

I1F-MC-RHBV(b) Clinical Protocol

A Multicenter, Randomized, Double-Blind, Active and Placebo-Controlled 16-Week Study Followed by Long-Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in bDMARD-Naive Patients with Radiographic Axial Spondyloarthritis.

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**Protocol I1F-MC-RHBV(b)**  
**A Multicenter, Randomized, Double-Blind, Active and**  
**Placebo-Controlled 16-Week Study Followed by Long-Term**  
**Evaluation of Efficacy and Safety of Ixekizumab (LY2439821)**  
**in bDMARD-Naive Patients with Radiographic Axial**  
**Spondyloarthritis**

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**Ixekizumab (LY2439821)**

Study I1F-MC-RHBV is a Phase 3, multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group, outpatient study examining the efficacy and safety of ixekizumab (LY2439821) compared to placebo over 16 weeks in biological disease-modifying antirheumatic drug (bDMARD)-naive patients with radiographic axial spondyloarthritis (rad-axSpA). Patients will be randomized to subcutaneous (SC) placebo, or 1 of 2 treatment regimens of ixekizumab (80 mg every 2 weeks [Q2W] or every 4 weeks [Q4W]), or adalimumab (Humira®, Abbott Laboratories). This study will also evaluate long-term efficacy and safety of ixekizumab during an Extended Treatment Period (36 weeks). All patients entering into the Extended Treatment Period from the placebo treatment or adalimumab treatment groups will be rerandomized to ixekizumab 80 mg Q2W or Q4W.

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## 1. Protocol Synopsis

### Title of Study:

A Multicenter, Randomized, Double-Blind, Active and Placebo-Controlled 16-Week Study Followed by Long-Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in bDMARD-Naive Patients with Radiographic Axial Spondyloarthritis.

### Rationale:

Ixekizumab (LY2439821) is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody (MAb) that neutralizes the cytokine interleukin-17A (IL-17A, also known as IL-17). Strong scientific evidence exists indicating an important role of the IL23/IL-17 pathway in axial spondyloarthritis (axSpA) pathogenesis (Baeten et al. 2010, 2014a; Maksymowych 2010; Barkaliakos et al. 2011; Reveille 2011; Yeremenko et al. 2014). Pivotal studies of secukinumab (Cosentyx®), another IL-17A MAb, have recently demonstrated the efficacy of blocking IL-17A in the treatment of radiographic axial spondyloarthritis (rad-axSpA; ankylosing spondylitis [AS]) in biological disease-modifying antirheumatic drug (bDMARD)-naive as well as in tumor necrosis factor (TNF) inhibitor-experienced patients (Sanford and McKeage 2015).

### Objective(s)/Endpoints:

Objectives	Endpoints
<p><b>Primary</b> The primary objective is to compare both ixekizumab regimens (80 mg every 2 weeks [Q2W] or 80 mg every 4 weeks [Q4W]) versus placebo in patients with active radiographic axial spondyloarthritis (rad-axSpA) <u>at Week 16.</u></p> <p><b>Secondary</b> <b><u>The major secondary objective is:</u></b></p> <ul style="list-style-type: none"> <li>• To compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W) to placebo <u>at Week 16</u></li> </ul>	<ul style="list-style-type: none"> <li>• Proportion of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response.</li> <li>• Proportion of patients achieving an ASAS20 response</li> <li>• Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS)</li> <li>• Proportion of patients achieving Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI50) response</li> <li>• Change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI)</li> <li>• Proportion of patients achieving ASDAS inactive disease</li> <li>• Change from baseline in magnetic resonance imaging (MRI) of the spine (Spondyloarthritis Research Consortium of Canada [SPARCC] score)</li> <li>• Change from baseline in Short Form 36 (SF-36) physical component score (PCS)</li> <li>• Change from baseline in ASAS Health Index (ASAS HI)</li> </ul>

**Summary of Study Design:**

Study I1F-MC-RHBV (RHBV) is a Phase 3, multicenter, randomized, double-blind, active- and placebo-controlled, parallel-group, outpatient study examining the efficacy and safety of 2 treatment regimens of ixekizumab, 80 mg Q2W and 80 mg Q4W subcutaneous (SC), as compared to placebo SC in patients with rad-axSpA, during a 16-week Blinded Treatment Dosing Period. Adalimumab at the approved dose of 40 mg (SC) and the approved regimen of Q2W has been selected as the active control for comparison with placebo to provide the study with internal evidence of assay sensitivity (i.e., generate data on an approved and well characterized anti-TNF treatment and ixekizumab treatment concurrently in one trial setting rather than comparing with historically observed data with adalimumab).

**Treatment Groups and Duration:**

Study RHBV has 4 treatment groups during the 16-week Blinded Treatment Dosing Period; ixekizumab 80 mg Q4W, ixekizumab 80 mg Q2W, placebo, and adalimumab 40 mg Q2W at 1:1:1:1 ratio. Randomization will be stratified by country and baseline high sensitivity C-reactive protein (CRP) status (nonelevated or elevated, elevated defined as  $>5.00$  mg/L). All patients randomized to an ixekizumab treatment group will receive a starting dose of ixekizumab 80 mg or 160 mg (1:1 ratio) at Week 0 followed by ixekizumab 80 mg Q4W or Q2W thereafter; all patients randomized to adalimumab will receive adalimumab 40 mg Q2W from Week 0 to Week 14. All administrations are SC. At Week 16, placebo patients will be rerandomized at a 1:1 ratio to ixekizumab 80 mg Q2W or Q4W with a 160 mg starting dose. At Week 16, adalimumab patients will be re-randomized to ixekizumab 80 mg Q4W or Q2W. All patients will be on an ixekizumab regimen for the Extended Treatment Period (Weeks 16 to 52) (for safety reasons, adalimumab patients will have a 6-week washout period before receiving ixekizumab). As needed, investigators can modify concomitant medication during the wash-out period to maintain symptom control. The study duration will be up to 1 year for ixekizumab administration, and up to 1 year and approximately 4 months for study participation over 4 periods ([1] Screening Period: up to 42 days; [2] Blinded Treatment Dosing Period: 16 weeks; [3] Extended Treatment Period: 36 weeks; [4] Post-Treatment Follow-Up Period: at least 12 weeks after the date of the patient's early termination visit [ETV] or last regularly scheduled visit). Patients who complete Study RHBV may have the opportunity to continue into a long term study instead of the Post-Treatment Follow-Up Period.

**Study Population:**

This study will include approximately 320 randomized patients. Patients are eligible to be included in the study if they have an established diagnosis of rad-axSpA with sacroiliitis defined radiographically according to the modified New York (mNY) criteria, based on central reading, associated with  $\geq 1$  spondyloarthritis (SpA) feature, and have active disease defined as BASDAI  $\geq 4$  and back pain  $\geq 4$  on a numeric rating scale (NRS). Patients must have had an inadequate response, as determined by the investigator, to 2 or more nonsteroidal anti-inflammatory drugs (NSAIDs) at the therapeutic dose range (for a total duration of at least 4 weeks) and a history of prior rad-axSpA therapy for at least 3 months. Only bDMARD-naïve patients can be enrolled.

**Statistical Analysis:**

Approximately 320 patients will be randomized at a 1:1:1:1 ratio in the Blinded Treatment Dosing Period (Period 2) to ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, adalimumab 40 mg Q2W, and placebo. With 80 patients per treatment group, this study will have approximately 96% power to test the superiority of ixekizumab Q2W to placebo for the ASAS40 at Week 16. The following assumptions were used for the power calculations for ASAS40 response rates at Week 16 regardless of ixekizumab starting dose: 44% for ixekizumab 80mg Q2W treatment group and 16% for the placebo group. A 2-sided Fisher's exact test at the 0.05 level is assumed. The efficacy analyses for the Blinded Treatment Dosing Period will be conducted on the intent-to-treat (ITT) population and safety analyses will be conducted on the safety population.

Comparisons between each ixekizumab treatment group (80 mg Q2W or 80 mg Q4W) and placebo as well as between adalimumab and placebo will be performed for all analyses in the Blinded Treatment Dosing Period. Unless otherwise specified, the ixekizumab 80 mg Q2W and Q4W groups will be analyzed without regard to

starting dose. The primary analysis method for treatment group comparisons of categorical efficacy and health outcomes variables will be a logistic regression analysis with treatment, geographic region, and baseline CRP status (nonelevated or elevated) as factors, using the nonresponder imputation (NRI) method. Under NRI, all nonresponders at Week 16 (Visit 8), as well as all patients who discontinue study treatment at any time prior to Week 16 for any reason, will be defined as nonresponders for the NRI analysis at Week 16. Randomized patients without any postbaseline observation will also be defined as nonresponders for the NRI analysis. A graphical multiple testing strategy for the primary and major secondary objectives will be implemented to control the family-wise type I error rate at a 2-sided  $\alpha$  level of 0.05.

The primary analyses for the continuous efficacy and health outcomes variables will be made using mixed-effects model of repeated measures (MMRM) analysis with treatment, geographic region, baseline CRP status, baseline value, visit, baseline value-by-visit, and treatment-by-visit interactions as fixed factors.

A secondary analysis for continuous efficacy and health outcomes variables will be made using analysis of covariance (ANCOVA) with treatment, geographic region, baseline CRP status and baseline value in the model.

Fisher's exact test will be used for all adverse events (AEs), baseline, discontinuation, and other categorical safety data. Continuous vital sign and laboratory values will be analyzed by ANCOVA with treatment and baseline values in the model.

Efficacy, health outcomes, and safety variables during the Extended Treatment Period will also be summarized.

## 2. Introduction

### 2.1. Background

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease predominantly affecting the axial skeleton (sacroiliac joints [SIJ] and spine) (Poddubnyy 2013). AxSpA is now recognized as a single disease entity, with a subset defined by the presence of radiographically defined structural damage of the SIJ (rad-axSpA) and a subset without clear structural damage defined radiographically (nonrad-axSpA). When comparing axSpA with rheumatoid arthritis (RA), it can be noted that while RA can be divided into erosive and nonerosive or seropositive and seronegative subsets, it is well accepted that it is still one disease. AxSpA, in a similar fashion, also has subsets, and thus can be considered a single disease (Deodhar et al. 2014).

Radiographic axSpA (rad-axSpA), formerly called ankylosing spondylitis (AS), represents a disease in which there is evidence of disease features on radiographic imaging. It is a chronic inflammatory disease characterized by chronic inflammation of the axial and SIJ and variable involvement of the peripheral joints (Braun and Sieper 2007). As the disease progresses, it can lead to new bone formation in the form of syndesmophytes and joint ankylosis, primarily in the axial skeleton. Patients with rad-axSpA may also have extra-articular manifestations of the disease such as enthesitis, anterior uveitis, psoriasis, and inflammatory bowel disease (IBD) as well as comorbidities of aortitis or cardiac conduction abnormalities. Compared with the general population, patients with rad-axSpA have increased rates of work disability, unemployment, and mortality (Boonen and van der Linden 2006).

AxSpA affects up to 1.4% of the adult population worldwide (Braun and Sieper 2007; Reveille et al. 2012; Strand et al. 2013). Although the exact etiology is unknown, it has been indicated that genetic factors and several loci are likely to be involved in susceptibility to the disease (Reveille 2011). There is a strong association with the major histocompatibility complex, human leukocyte antigen (HLA)–B27. About 90% to 95% of patients with rad-axSpA are positive for HLA-B27, and the risk of this disease developing is as high as about 5% in HLA-B27 positive individuals and substantially higher in HLA-B27–positive relatives of patients (Braun and Sieper 2007). Most of the other known genetic susceptibility comes from genes involved in cytokine production, specifically including genes in the T helper (Th)17 pathway (Maksymowych 2010; Reveille 2011).

Current standard of care for rad-axSpA includes regular exercise, physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), and tumor necrosis factor (TNF) alpha inhibitors (Braun et al. 2011; Ward et al. 2015). Corticosteroid injections may also be of some benefit. Though NSAIDs are the first line of drug treatment for axSpA, they are not effective or well tolerated in all patients (Braun and Sieper 2009). In contrast to patients with RA, patients with axSpA do not respond well to conventional disease-modifying antirheumatic drugs (cDMARDs) including methotrexate (MTX) or systemic corticosteroids (Braun and Sieper 2009; Haibel and Specker 2009).

Tumor necrosis factor inhibitors are effective and frequently prescribed when NSAID treatment has failed or cannot be tolerated (Zochling et al. 2006). While TNF inhibitors have proven to be

effective treatments for axSpA, an unmet need remains, as not all patients respond well to or tolerate TNF inhibitor treatments (van der Heijde et al. 2006; Heiberg et al. 2008; Inman et al. 2008; Glinborg et al. 2010). While TNF inhibitors have demonstrated significant impact on signs and symptoms, function, and quality of life, they have not been able to demonstrate significant effect on structural progression in prospective clinical studies. The use of these biologic therapies in various diseases also is associated with safety concerns, such as opportunistic infections, demyelinating disorders, blood dyscrasias, reactivation of tuberculosis (TB), and exacerbation of congestive heart failure (Moreland 2005; Smith et al. 2009). There remains, therefore, a significant unmet need for safer, more effective treatments for patients with axSpA (Dougados and Baeten 2011). Ixekizumab may offer an alternative treatment approach to TNF inhibitor therapy in patients with axSpA.

Ixekizumab (LY2439821) is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody (MAb) that neutralizes the cytokine interleukin-17A (IL-17A, also known as IL-17). Ixekizumab treatment is administered by subcutaneous (SC) injections. Compelling scientific information exists to date suggesting an important role of the IL-23/IL-17 pathway in the pathogenesis of axSpA (Baeten et al. 2010, 2014a; Maksymowych 2010; Baraliakos et al. 2011; Reveille 2011; Yeremenko et al. 2014). The demonstration of increased IL-17 producing Th17 lymphocyte numbers and serum IL-17 levels in rad-axSpA is consistent with a direct role of Th17 lymphocytes in this disease (Wendling et al. 2007; Jandus et al. 2008; Mei et al. 2011). IL-17 secreting cells have also been detected in situ in the bone marrow of facet joints obtained from patients with rad-axSpA (Appel et al. 2008).

Selectively targeting IL-17A with ixekizumab is hypothesized to provide therapeutic benefit without unduly impacting host defenses. As such, ixekizumab may offer a therapeutic option for patients who are candidates for initial systemic treatment as well as those patients who have lost response, failed to respond, or are intolerant to currently marketed drugs, and may also offer a more favorable safety profile compared to currently marketed therapies.

## 2.2. Study Rationale

Eli Lilly and Company (hereafter Lilly) is investigating ixekizumab as a treatment option for rad-axSpA based on its mechanism of action (MoA), selectively blocking IL-17A (detailed in the Investigator's Brochure [IB]). The following 2 SC ixekizumab treatment regimens will be studied in this trial: 80 mg every 4 weeks (Q4W) or 80 mg every 2 weeks (Q2W). Starting doses of 80 mg and 160 mg (at Week 0) will be evaluated for each ixekizumab regimen. A wide range of dosing regimens were evaluated in Phase 2 psoriasis and RA studies and demonstrated efficacy. The 80 mg Q2W and Q4W treatment regimens with a 160 mg starting dose were evaluated in pivotal Phase 3 studies in psoriasis and psoriatic arthritis (PsA) and demonstrated efficacy, with a favorable benefit/risk profile (Gottlieb et al. 2015; Griffiths et al. 2015; Mease et al. 2015). Recently disclosed data from Phase 3 studies with secukinumab (Cosentyx®), a drug with a similar MoA as ixekizumab, selectively inhibiting IL-17A, have demonstrated the effectiveness of inhibiting IL-17A in patients with rad-axSpA who were biological disease-modifying antirheumatic drug (bDMARD)-naive or had previously received anti-TNF agents (Sanford and McKeage 2015).

### 3. Objectives and Endpoints

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

**Table RHBV.1. Objectives and Endpoints**

Objectives	Endpoints
<p><b>Primary</b> The primary objective is to compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W) versus placebo in patients with active rad-axSpA <u>at Week 16</u></p> <p><b>Secondary</b> <b><u>The major secondary objective is:</u></b></p> <ul style="list-style-type: none"> <li>• To compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W) to placebo <u>at Week 16</u></li> </ul>	<ul style="list-style-type: none"> <li>• Proportion of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response</li> <li>• Proportion of patients achieving an ASAS20 response</li> <li>• Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS)</li> <li>• Proportion of patients achieving Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI50) response</li> <li>• Change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI)</li> <li>• Proportion of patients achieving ASDAS inactive disease</li> <li>• Change from baseline in magnetic resonance imaging (MRI) of the spine (Spondyloarthritis Research Consortium of Canada [SPARCC] score)</li> <li>• Change from baseline in Short Form 36 (SF-36) physical component score (PCS)</li> <li>• Change from baseline in ASAS Health Index (ASAS-HI)</li> </ul>



Objectives	Endpoints
<i>Secondary objectives continued</i>	
<p><b><u>Other secondary objectives are:</u></b></p> <ul style="list-style-type: none"> <li>• To compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W) to placebo <u>during</u> the 16-week placebo controlled period (Period 2)</li> </ul>	<ul style="list-style-type: none"> <li>• Proportion of patients who achieve ASAS20, ASAS40, ASAS 5/6, and partial remission by ASAS criteria</li> <li>• Change from baseline in the individual components of the ASAS criteria</li> <li>• Change from baseline in BASDAI</li> <li>• Proportion of patients reaching BASDAI50</li> <li>• Change from baseline in ASDAS</li> <li>• Proportion of patients who experience clinically-important improvement (change of ASDAS from baseline <math>\geq 1.1</math>), major improvement (change of ASDAS from baseline <math>\geq 2.0</math>), or inactive disease (ASDAS score <math>&lt; 1.3</math>)</li> <li>• Change from baseline in the measure of high sensitivity C-reactive protein (CRP)</li> <li>• Change from baseline in BASFI</li> <li>• Change from baseline in mobility               <ul style="list-style-type: none"> <li>○ Bath Ankylosing Spondylitis Metrology Index (BASMI) (linear) and individual components</li> <li>○ Chest expansion</li> <li>○ Change from baseline in occiput to wall distance</li> </ul> </li> <li>• Change from baseline in MRI of the SIJ (SPARCC score)</li> <li>• Change from baseline in SPARCC SIJ Structural Score (SSS)</li> <li>• Change from baseline in MRI of the spine (Ankylosing Spondylitis Spinal Magnetic Resonance Imaging activity–Berlin Score [ASSpiMRI-Berlin])</li> <li>• Change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)</li> <li>• Change from baseline in SPARCC Enthesitis Score</li> <li>• Incidence and severity of peripheral arthritis by tender (TJC) and swollen joint count scores (SJC) of 46/44 joints.</li> <li>• Incidence rate of anterior uveitis or uveitis flares</li> <li>• Change from baseline in the following health outcomes measures: Fatigue NRS score, ASAS-HI score, Jenkins Sleep Evaluation Questionnaire (JSEQ), Work Productivity Activity Impairment—Spondyloarthritis (WPAI-SpA) scores, SF-36 (both PCS and mental component scores [MCS]) and Quick Inventory of Depressive Symptomatology—Self Report 16 items (QIDS-SR16) score.</li> </ul>

Objectives	Endpoints
<i>Secondary objectives continued</i>	
<ul style="list-style-type: none"> <li>To determine if the effect of either ixekizumab regimen is maintained through Week 52</li> </ul>	<p>All endpoints assessed at Week 16 (above) and during the 16-week placebo-controlled period (above) will continue to be assessed through Week 52.</p> <p>In addition the following endpoint is added: NSAID intake (ASAS-NSAID score and % of patients taking NSAIDs)</p>
<ul style="list-style-type: none"> <li>To explore effect of starting dose (160 mg compared to 80 mg)</li> <li>To evaluate the incidence of anti-ixekizumab antibodies and their relationship to efficacy of ixekizumab</li> <li>To measure ixekizumab exposure and assess the relationship between exposure and efficacy, and exposure and immunogenicity</li> <li>To test assay sensitivity by comparing adalimumab 40 mg Q2W with placebo treatment at Week 16</li> </ul>	<ul style="list-style-type: none"> <li>Onset of action and treatment response (ASAS, ASDAS, CRP, BASFI) during the placebo-controlled period</li> <li>Efficacy response rates listed below at Weeks 16 and 52 by treatment-emergent anti-drug antibody (TE-ADA) status and by neutralizing anti-drug antibody (NAb) status                             <ul style="list-style-type: none"> <li>Proportion of patients achieving ASAS40</li> <li>Proportion of patients achieving ASAS20</li> <li>Proportion of patients achieving ASDAS inactive disease</li> </ul> </li> <li>Serum trough concentrations of ixekizumab</li> <li>Model parameters for the exposure-response relationship between ixekizumab serum trough concentrations and efficacy endpoints (for example, ASAS20, ASAS40) at Week 16 and/or 52</li> <li>Ixekizumab serum trough concentrations associated with ADA titer sub groups</li> <li>Proportion of patients achieving an ASAS 40 response</li> </ul>
<p><b>Exploratory</b></p> <ul style="list-style-type: none"> <li>CCI [REDACTED]</li> </ul>	<ul style="list-style-type: none"> <li>[REDACTED]</li> </ul>

## 4. Study Design

### 4.1. Overview of Study Design

Study IIF-MC-RHBV is a Phase 3, multicenter, randomized, double-blind, active and placebo-controlled, parallel-group, outpatient study examining the efficacy and safety of ixekizumab treatment regimens (80 mg Q2W and 80 mg Q4W SC), as compared to placebo SC in patients with active rad-axSpA who are bDMARD-naive, during a double-blind, 16-week treatment period.

Starting doses of 80 mg and 160 mg (at Week 0) will be evaluated for each ixekizumab regimen. Adalimumab (at the approved dosing regimen of 40 mg SC Q2W) has been selected as the active control for comparison with placebo.

Study RHBV will also evaluate long-term efficacy and safety of ixekizumab during the Extended Treatment Period (Period 3) for a total treatment duration of 1 year (52 weeks). Patients that complete Study RHBV may be eligible to enroll into a long-term study (Study IIF-MC-RHBY [RHBY]) for up to 2 additional years. Patients that do not enroll into Study RHBY will complete the Post-Treatment Follow-Up Period (Period 4) in Study RHBV.

[Figure RHBV.1](#) illustrates the study design, and all treatment groups and administration of the investigational product are described in [Section 6.1](#), and the Study Drug Administration Log is described in [Section 6.2.1](#).

All procedures to be conducted during the study, including timing of all procedures, are indicated in the Schedule of Activities ([Appendix 2](#)). Selected study procedures are to be performed prior to administration of the investigational product, as applicable.

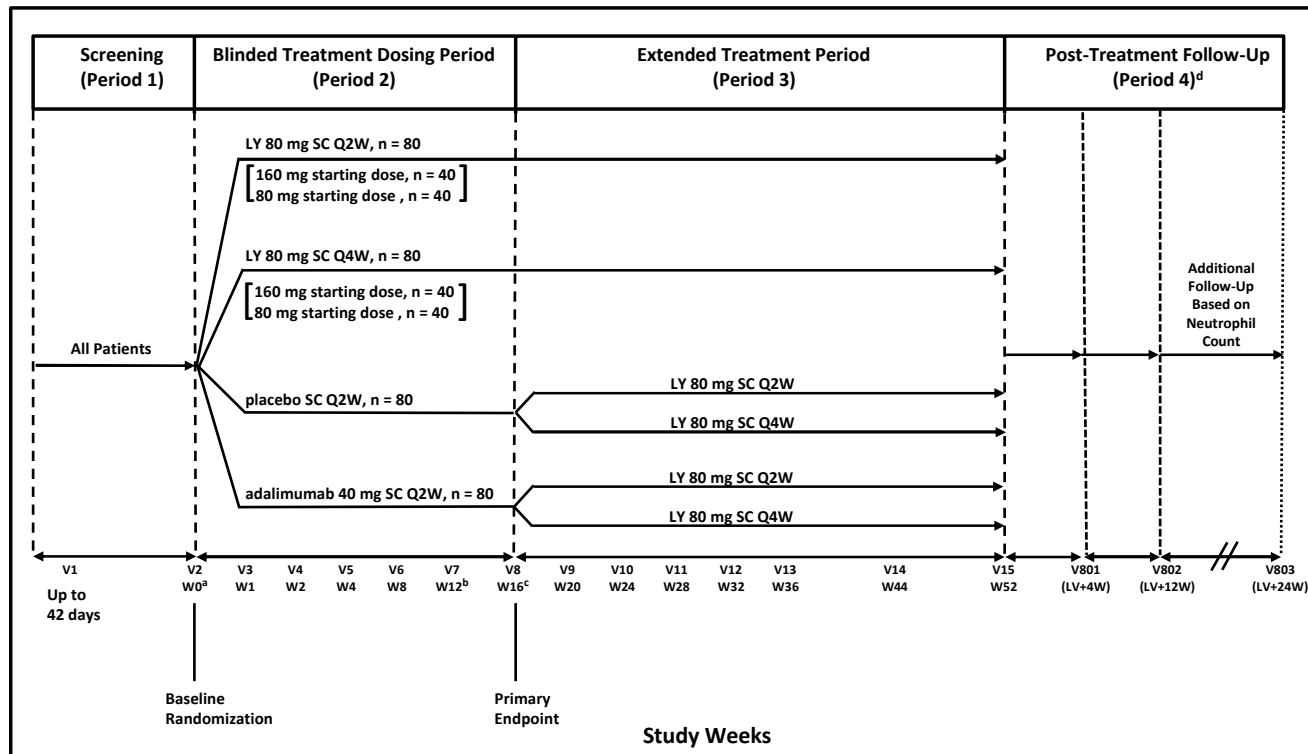
For each patient, x-rays and magnetic resonance imaging (MRIs) will be collected according to [Section 8.1.2.20.1](#) and the Schedule of Activities ([Appendix 2](#)). [Appendix 3](#) lists the specific laboratory tests that will be performed for this study.

Patients discontinuing from study treatment who have received at least 1 dose of investigational product will continue to the early termination visit (ETV) prior to proceeding to the Post-Treatment Follow-Up Period. For the management of patient safety, all patients are to be monitored through the Post-Treatment Follow-Up Period at least as frequently as indicated in the Schedule of Activities ([Appendix 2](#)).

Excluded and concomitant medications are detailed in [Section 6.8](#).

Pharmacokinetic (PK) sampling is detailed in [Section 8.5](#).

[Section 9.8](#) outlines the information regarding the interim analyses including the primary database lock at Week 16.



**Abbreviations:** LV = last visit; LY = ixekizumab; n = number; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; V = study visit; W = study week

<sup>a</sup> All patients will receive 3 injections at baseline, as detailed in Section 6.1. Patients randomized to an ixekizumab regimen will be randomized to a 160 mg starting dose or 80 mg starting dose at a 1:1 ratio (within each ixekizumab regimen).

<sup>b</sup> Patients in the adalimumab treatment group will be re-randomized at Week 16 to ixekizumab 80 mg Q4W or Q2W. They will receive their last adalimumab dose at Week 14. There will be a 6-week wash-out period. Patients will receive their first ixekizumab dose at Week 20. Please refer to Section 6.1 for more details.

<sup>c</sup> All patients will receive 2 injections at Week 16, as detailed in Section 6.1. Patients randomized to placebo at Week 0 will begin ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W at Week 16 with a 160 mg starting dose (Section 6.1).

<sup>d</sup> Patients who discontinue from study treatment for any reason and who have received at least 1 dose of investigational product will continue to the early termination visit (ETV) before entering the Post-Treatment Follow-Up Period. V801 and V802 are required for all patients; V803 may be needed depending on neutrophil counts (Section 8.4.10.1).

**Figure RHBV.1. Illustration of study design for Clinical Protocol I1F-MC-RHBV.**

## 4.2. End of Trial Definition

End of the trial is the date of the last visit or last scheduled procedure shown in the Schedule of Activities ([Appendix 2](#)) for the last patient in the trial.

## 4.3. Scientific Rationale for Study Design

Two treatment regimens of ixekizumab 80 mg (Q2W and Q4W) will be studied as detailed in Section [6.1](#), and the effect of an 80 mg and a 160 mg starting dose will be evaluated for treatment outcomes. Dose justification is outlined in Section [4.4](#). The study blind is maintained as described in Section [6.3](#).

The placebo-controlled Blinded Treatment Dosing Period (Period 2) is designed to minimize bias in the evaluation of ixekizumab in patients with rad-axSpA for both efficacy and safety. All patients may still receive treatment in the form of the allowed concomitant medications as described in the study inclusion and exclusion criteria (Sections [5.1](#) and [5.2](#)), and concomitant therapy (Section [6.8](#)). Patients can be discontinued from study treatment at any time by investigator or patient decision if they are considered to be receiving insufficient benefit from study treatment (Section [7.1.1](#)).

As of Week 16 (after completion of Period 2) investigators are allowed to adjust some concomitant medications, if needed, as specified in Section [6.8](#), across all treatment groups.

Patients originally assigned to placebo during Period 2 will be rerandomized at a 1:1 ratio to ixekizumab 80 mg Q2W or Q4W with a 160 mg starting dose at Week 16.

Adalimumab 40 mg Q2W will provide the active control for comparison with placebo during Blinded Treatment Dosing Period 2 to determine assay sensitivity in the context of study implementation. Adalimumab has been selected because it is an approved therapy for the treatment of AS (rad-axSpA) in countries in which this study will be conducted, and its approved dosing regimen fits well with the frequency of dosing of ixekizumab regimens in this study.

Patients assigned to adalimumab at Week 0 will have the last adalimumab injection at Week 14, be re-randomized to ixekizumab 80 mg Q2W or Q4W at Week 16, and start ixekizumab at Week 20 to allow a 6-week washout period for safety reasons. The length of the washout period takes into account the half-life of adalimumab (mean terminal half-life is approximately 2 weeks, hence majority of adalimumab will be cleared after 6 weeks), the desire to minimize risk of relapse, and the study visit schedule.

Ixekizumab 80 mg Q2W and 80 mg Q4W treatment regimens are continued beyond Week 16 to further assess safety and efficacy during the Extended Treatment Period (Period 3).

The effectiveness of ixekizumab in treating rad-axSpA will be assessed primarily by the ASAS40 response rate at Week 16. ASAS20 response will also be assessed at Week 16. These measures and the Week 16 endpoint are in alignment with efficacy endpoints for currently approved rad-axSpA therapies and with regulatory guidance (EMA 2009). Steady-state exposure of ixekizumab is expected to be reached by Week 16. Based on previous studies with ixekizumab in patients with psoriasis, RA, and PsA, it is anticipated that maximum or near

maximum clinical effect in rad-axSpA will be achieved within this timeframe for both ixekizumab treatment regimens as well as for the active control treatment group.

Baseline CRP has been reported as a predictor of response in patients with rad-axSpA treated with TNF inhibitors (Inman et al. 2008; de Vries et al. 2009; Sieper et al. 2011; Vastesaeger et al. 2011); hence by including it as a stratification factor, it ensures balance in baseline CRP levels resulting in greater comparability across treatment groups at baseline.

The Extended Treatment Period (Period 3) will permit collection of data for the assessments of maintenance of efficacy and long term safety with ixekizumab.

The Post-Treatment Follow-Up Period (Period 4) is important for safety and efficacy monitoring following administration of the last study treatment.

#### 4.4. Justification for Dose

Lilly considers it appropriate to evaluate 2 treatment regimens in Study RHBV to enable appropriate evaluation of the relative benefit/risk associated with continuous ixekizumab therapy in axSpA.

CCI [REDACTED]

As referred to above, the current internal (ixekizumab) and external (TNF inhibitors and secukinumab) scientific data in this area support the rationale for studying ixekizumab in patients with rad-axSpA with the proposed treatment regimens.

#### 4.5. Benefit/Risk Assessment

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

## 5. Study Population

The study population will include patients with active rad-axSpA (with sacroiliitis defined radiographically according to the modified New York [mNY] criteria, based on central reading, associated with at least 1 SpA feature [Appendix 5]), who have given written informed consent.

Study investigator(s) will review patient history and screening test results from Visit 1 (all criteria), and Visit 2 as per the Schedule of Activities (Appendix 2) to determine if the patient meets all inclusion and none of the exclusion criteria to qualify for participation in the study. All screening activities must be completed and reviewed before the patient is randomized. Patients may be rescreened in the circumstances described in Section 5.3.

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

In this protocol section, the following definitions apply:

- Screening is defined as Visit 1, up to 42 days prior to baseline randomization.
- Baseline randomization visit is defined as Visit 2 (Week 0).

### 5.1. Inclusion Criteria

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

#### Type of Patient and Disease Characteristics

- [1] Have an established diagnosis of rad-axSpA with sacroiliitis defined radiographically according to the mNY criteria (van der Linden et al. 1984) based on central reading: sacroiliitis grade  $\geq 2$  bilaterally or grades 3 to 4 unilaterally.  
  
AND  
  
At least 1 SpA feature, according to ASAS criteria (Rudwaleit et al. 2009; Sieper et al. 2009), listed in Appendix 5.
- [2] Patients have a history of back pain  $\geq 3$  months with age at onset  $< 45$  years
- [3] Have active rad-axSpA defined as BASDAI  $\geq 4$  and total back pain  $\geq 4$  (Sieper et al. 2009, Box 25 Spinal Pain) on an NRS at screening and baseline.
- [4] Must have had an inadequate response, as determined by the investigator, to 2 or more NSAIDs at the therapeutic dose range for a total duration of at least 4 weeks OR have a history of intolerance to NSAIDs.
- [5] Patients must have a history of prior therapy for axSpA of at least 12 weeks prior to screening. Examples of prior therapy may include but are not limited to physical therapy and NSAID treatment.
- [6] If taking NSAIDs or cyclooxygenase-2 (COX-2) inhibitors, the dose must be stable for at least 2 weeks prior to baseline randomization.

**Patient Characteristics**

[7] Are ambulatory male or female patients  $\geq 18$  years of age at time of screening.

[8] Must agree to use a reliable method of birth control

- If a male patient, patient agrees to use a reliable method of birth control during the study and for at least 12 weeks following the last dose of investigational product, whichever is longer. Methods of birth control include, but are not limited to, condoms with spermicide and male sterilization.

OR

- If a female patient is a woman of childbearing potential who tests negative for pregnancy and agrees to use a reliable method of birth control or remain abstinent during the study and for at least 12 weeks following the last dose of investigational product, whichever is longer. Methods of contraception include, but are not limited to:

oral contraceptives, contraceptive patch, injectable or implantable contraceptives, intrauterine device, vaginal ring, diaphragm with contraceptive gel, or condom with contraceptive foam.

OR

- If a female patient is a woman of nonchildbearing potential, she is not required to use any method of birth control. Nonchildbearing potential is defined as:

Women who have had surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation).

- or -

Women who are  $\geq 60$  years of age.

- or -

Women  $\geq 40$  and  $< 60$  years of age who have had a cessation of menses for  $\geq 12$  months and a follicle stimulating hormone (FSH) test confirming nonchildbearing potential ( $\geq 40$  mIU/mL or  $\geq 40$  IU/L).

**Informed Consent**

[9] Have given written informed consent approved by Lilly, or its designee, and the Investigational Review Board (IRB)/Ethical Review Board (ERB) governing the site.

**5.2. Exclusion Criteria**

Patients will be excluded from study enrollment if they meet any of the following criteria at screening or as specified:



**Medical Conditions**

- [10] Have total ankylosis of the spine, as assessed locally, based on lateral radiographs of the cervical and lumbar spine.
- [11] Have any condition or contraindication as addressed in the local labeling for adalimumab that would preclude the patient from participating in this protocol.
- [12] Have a history of other systemic inflammatory diseases (such as but not limited to: lupus, vasculitis or RA), or other chronic pain conditions (such as but not limited to fibromyalgia) that might confound the evaluations of benefit from ixekizumab therapy.

**Note:** Patients with psoriasis that have never received and do not require systemic treatment for psoriasis, such as but not limited to oral agents or biologic therapies, can be included provided these patients fulfill the entry criteria.

- [13] Have active Crohn's disease (CD) or active ulcerative colitis (UC).

**Note:** Patients may be enrolled if they have had a history of IBD, including CD and UC, but have had no exacerbation for  $\geq 6$  months prior to baseline randomization and, if currently on treatment, must be on stable treatment for  $\geq 6$  months prior to baseline randomization.

- [14] Have evidence of active anterior uveitis (an acute episode) within the last 4 weeks prior to baseline randomization.

**Note:** These patients may be rescreened only one time  $\geq 4$  weeks after resolution of acute symptoms.

- [15] Have current or a history of lymphoproliferative disease, or signs or symptoms of lymphoproliferative disease within 5 years prior to baseline randomization; or have active or history of malignant disease within 5 years prior to baseline randomization.
- [16] Have a history of fluid overload, myocardial infarction (MI), uncompensated heart failure, or evidence of new-onset ischemic heart disease or in the opinion of the investigator other serious cardiac disease, within 12 weeks prior to baseline randomization.
- [17] Presence of significant uncontrolled cerebrocardiovascular events (for example, unstable angina, unstable arterial hypertension, moderate-to-severe heart failure [New York Heart Association class III/IV], or cerebrovascular accident) at screening that, in the opinion of the investigator, pose an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.

- [18] Presence of any comorbid respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic disorders, at screening that, in the opinion of the investigator, pose an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.
- [19] Presence of any neurologic or neuropsychiatric disorders, at screening that, in the opinion of the investigator, poses an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.
- [20] Presence of significant uncontrolled neuropsychiatric disorder; have recent history (within 30 days prior to screening visit [Visit 1] and any time between screening visit [Visit 1] and baseline randomization [Visit 2]) of a suicide attempt; or have a score of 3 on Item 12 (Thoughts of Death or Suicide) of the Quick Inventory of Depressive Symptomatology-self report (16 items) (QIDS-SR16) at screening or baseline randomization or are clinically judged by the investigator to be at risk for suicide.
- [21] Have presence or personal history or family history (1st degree relative) of demyelinating disorder.
- Note:** 1st degree means child, parent, or sibling, provided a blood relationship exists.
- [22] Patients who have:
- in the past 12 weeks prior to baseline randomization:
    - had a serious infection (for example, pneumonia, cellulitis),
    - have been hospitalized for an infection,
    - or have received intravenous (IV) antibiotics for an infection,
  - or in the past 24 weeks prior to baseline randomization had a serious bone or joint infection
  - or have ever had,
    - an infection of an artificial joint,
    - an infection that occurs with increased incidence in an immunocompromised host (including, but not limited to, Pneumocystis jirovecii pneumonia, symptomatic histoplasmosis, or coccidioidomycosis)
- [23] Have a known immunodeficiency or are immunocompromised to an extent such that participation in the study would pose an unacceptable risk to the patient.
- [24] Have or had a herpes zoster or any other clinically apparent varicella-zoster virus infection within 12 weeks of baseline randomization.

- [25] Have any other active or recent infection within 4 weeks of baseline randomization that in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study.
- Note:** These patients may be rescreened one time  $\geq 4$  weeks after resolution of symptoms.
- [26] Have known allergy to rubber or latex.
- [27] Have a known allergy or hypersensitivity to any biologic therapy that would pose an unacceptable risk to the patient if participating in this study.
- [28] Have had surgical treatment of a joint that is to be assessed in the study within 8 weeks prior to baseline randomization or will require surgical treatment of a joint that is to be assessed in the study during the first 16 weeks of the trial.
- [29] Have had any major surgery within 8 weeks prior to baseline randomization, or will require major surgery during the study that in the opinion of the investigator and in consultation with Lilly or its designee would pose an unacceptable risk to the patient.

#### **Prior/Concurrent Therapy or Clinical Trial Experience**

- [30] Have received cDMARDs and/or other therapies such as but not limited to: gold salts, cyclosporine, azathioprine, dapsone, 6-mercaptopurine, mycophenolate mofetil, or any other immunosuppressive agents within 4 weeks prior to baseline randomization.

Exception: MTX (oral or parenteral up to 25 mg/week), sulfasalazine (up to 3 g/day), or hydroxychloroquine (up to 400 mg/day) may be allowed IF at stable dose for at least 4 weeks prior to baseline randomization.

AND

if used, must not be in any combination with other cDMARDs.

**Note:** If MTX is used, local standard of care is to be followed for concomitant administration of folic or folinic acid with MTX.

- [31] Use of oral corticosteroids  $>10$  mg/day prednisone or its equivalent.
- Note:** If patients are taking prednisone or its equivalent and the dose is  $\leq 10$  mg/day, the dose must be stable for at least 4 weeks prior to baseline randomization.
- [32] Have received any prior, or are currently receiving, treatment with biologic or other immunomodulatory agents, including investigational therapies (such as but not limited to Janus kinase (JAK) inhibitors, TNF inhibitors, IL-1, IL-6, IL-23, IL-17 (including ixekizumab), IL-17R, T cell, or B cell targeted therapies).

[33] Are currently enrolled in, have participated, or discontinued from a clinical trial involving an investigational product or nonapproved use of a drug or device within the last 30 days prior to screening or a period of at least 5 half-lives of the last administration of the drug, whichever is longer.

**Note:** Investigational products that are biologic or other immunomodulatory agents are not permitted regardless of washout period (described in criterion above).

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

[35] Are currently receiving or have received treatment with denosumab within 6 months prior to baseline randomization.

[36] Have received any parenteral glucocorticoid administered by intra-articular, intramuscular, or IV injection within 6 weeks prior to baseline randomization, or for whom a parenteral injection of glucocorticosteroids is anticipated during the Blinded Treatment Dosing Period (Period 2) of the study.

[37] Use of any opiate analgesic at average daily doses >30 mg/day of morphine or its equivalent or use of variable doses of any opiate analgesic within 6 weeks prior to baseline randomization. Exception for patients with pain that may interfere with undergoing an MRI: patient may receive premedication of ≤30 mg of morphine or equivalent, on the day of the MRI, for significant pain as judged by the investigator.

[38] Had a live vaccination within 12 weeks prior to baseline randomization, or intend to have a live vaccination during the course of the study, or within 12 weeks of completing treatment in this study, or have participated in a vaccine clinical study within 12 weeks prior to baseline randomization. Investigators are to review the vaccination status of their patients and follow the local guidelines for adult vaccination with nonlive vaccines intended to prevent infectious disease prior to therapy.

**Note:** Killed/inactive or subunit vaccines are expected to be safe; however, their efficacy with concomitant ixekizumab treatment is unknown.

[39] Had a vaccination with Bacillus Calmette-Guérin (BCG) within 12 months prior to baseline randomization, or intend to have this vaccination with BCG during the course of the study, or within 12 months of completing treatment in this study.

### Diagnosics Assessments

[40] Have a body temperature  $\geq 38^{\circ}\text{C}$  ( $100.5^{\circ}\text{F}$ ) at baseline randomization.

**Note:** These patients may be rescreened one time  $\geq 4$  weeks after documented resolution of elevated temperature.

- [41] Have evidence or suspicion of active or latent TB (refer to Section 5.3 for rescreening and Section 8.4.6 for details on determining full TB exclusion criterion).
- [42] Are positive for human immunodeficiency virus serology (HIV); that is, positive for human immunodeficiency virus antibody (HIVAb).
- [43] Have evidence of or test positive for hepatitis B virus (HBV) by testing positive for: 1) HBV surface antigen (HBsAg+), OR 2) anti-hepatitis B core antibody positive (HBcAb+) and are HBV DNA positive.

**Note:** Patients who are HBcAb+ and HBV DNA negative may be enrolled in the study. Patients who meet these criteria at screening will be identified by the central laboratory and monitored during the study as detailed in Section 8.4.10.2.

- [44] Have evidence of or test positive for hepatitis C virus (HCV). A positive test for HCV is defined as: 1) positive for hepatitis C antibody (anti-HCV Ab); and 2) positive via a confirmatory test for HCV (for example, HCV-polymerase chain reaction).
- [45] Have electrocardiogram (ECG) abnormalities that are considered clinically significant and would pose an unacceptable risk to the patient if participating in the study.
- [46] Patients having contraindications to MRI (for example, claustrophobia, pacemakers, aneurysm clips, intraocular metallic fragments).

**Note:** For claustrophobia, premedication with benzodiazepine is allowed (investigator should assess for potential interactions with other concomitant medication(s) such as opiates).

**Laboratory tests may not be repeated unless there is a technical error or clinical reason to believe a result may need to be retested within the screening period.** Laboratory tests can be repeated a maximum of 1 time, and results must be received and reviewed prior to randomization. For eligibility, the most recent lab panel must not meet any of the following criteria:

- [47] At screening, have a neutrophil count  $<1500$  cells/ $\mu\text{L}$  ( $<1.50 \times 10^3/\mu\text{L}$  or  $<1.50$  GI/L).
- [48] At screening, have a lymphocyte count  $<800$  cells/ $\mu\text{L}$  ( $<0.80 \times 10^3/\mu\text{L}$  or  $<0.80$  GI/L).
- [49] At screening, have a platelet count  $<100,000$  cells/ $\mu\text{L}$  ( $<100 \times 10^3/\mu\text{L}$  or  $<100$  GI/L).
- [50] At screening, have aspartate aminotransferase (AST) or alanine aminotransferase (ALT)  $>2.5$  times the upper limit of normal ( $>2.5 \times \text{ULN}$ ).
- [51] At screening, have a total white blood cell (WBC) count  $<3000$  cells/ $\mu\text{L}$  ( $<3.00 \times 10^3/\mu\text{L}$  or  $<3.00$  GI/L).

- [52] At screening, have hemoglobin <8.5 g/dL (85.0 g/L) for male patients and <8.0 g/dL (80 g/L) for female patients.
- [53] Have other clinical laboratory test results at screening that are outside the normal reference range for the population and are considered clinically significant, per investigator assessment.

### Other Exclusions

- [54] Have donated blood >450 mL within the last 4 weeks prior to screening, or intend to donate blood during the course of the study.  
**Note:** Patients who have donated blood may be rescreened one time  $\geq 4$  weeks have passed since initial screening.
- [55] Are women who are lactating or breastfeeding.
- [56] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
- [57] Are Lilly employees or its designee or are employees of third-party organizations involved in the study.
- [58] Are unwilling or unable to comply with the use of a data collection device to directly record data from the patient.
- [59] Have any other condition that precludes the patient from following and completing the protocol, in the opinion of the investigator.

### 5.3. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened in the following circumstances: patients who test positive for latent TB at screening may be rescreened following appropriate treatment as described in Section 8.4.6; patients who do not qualify at screening under Exclusion Criteria [14], [25], [40], or [54], may be rescreened one time,  $\geq 4$  weeks after documented resolution of symptoms or from time of blood donation.

Screening MRIs must be performed  $\leq 30$  days prior to baseline randomization (Visit 2). After consultation with Lilly medical, patients may be rescreened if screening MRI(s) of the spine and/or SIJ were performed  $> 30$  days prior to baseline randomization.

If a patient is unable to complete all screening procedures within the screening period, the patient may be rescreened after consultation with Lilly medical.

When rescreening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number. To ensure all eligibility criteria are met, all screening procedures must be repeated unless previously conducted within timeframes specified in the Schedule of Activities ([Appendix 2](#)).

#### 5.4. Study RHBV Screening of Patients Who Were Ineligible for Study RHBX

Study I1F-MC-RHBX (RHBX) is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study examining the efficacy and safety of ixekizumab compared to placebo SC in patients with active nonrad-axSpA who are bDMARD-naive. Patients **ineligible** for Study RHBX because they fulfill mNY criteria (thus do not qualify as “nonrad-axSpA”) may be **eligible** for Study RHBV.

Patients who were initially screened for Study RHBX and were excluded because central reading indicated that the patient fulfills mNY criteria, but who may meet entry criteria for Study RHBV, may give consent for Study RHBV. Timeframe guidelines for screening procedures are as follows:

##### **MRIs:**

- **Within 30 days** prior to Study RHBV baseline randomization (Visit 2): patients must undergo an initial screening MRI of the spine (and SIJ if not performed for Study RHBX).
- **If ≤30 days** between the Study RHBX screening MRI of the SIJ and Study RHBV baseline randomization (Visit 2): MRI of the SIJ does not need to be repeated.
- **If >30 days** between the Study RHBX screening MRI of the SIJ and Study RHBV baseline randomization (Visit 2): MRI of the SIJ must be repeated.

##### **Other procedures:**

- **If ≤42 days** between Study RHBX screening visit (Visit 1) and Study RHBV baseline randomization (Visit 2): data collected at the Study RHBX screening visit (for example, laboratory data, TB testing, and patient questionnaires) may be used to determine eligibility for Study RHBV.
- **If >42 days** between Study RHBX screening visit (Visit 1) and Study RHBV baseline randomization (Visit 2): laboratory tests will need to be repeated, but x-rays may not need to be repeated if conducted within timeframes specified in the Schedule of Activities ([Appendix 2](#)).

Patients must have discontinued from screening of Study RHBX prior to entering into Study RHBV.

#### 5.5. Lifestyle and/or Dietary Requirements

Not applicable.

## 6. Treatment

### 6.1. Treatments Administered

The Blinded Treatment Dosing Period (Period 2) involves a comparison of 2 treatment regimens of ixekizumab, 80 mg Q2W and 80 mg Q4W to placebo. Each ixekizumab treatment regimen will include patients receiving an 80 mg or a 160 mg starting dose at a 1:1 ratio; patients will be randomized to a starting dose at a 1:1 ratio. Adalimumab 40 mg Q2W, the approved dose for AS, is the active control for comparison with placebo (Table RHBV.2). All doses are administered via SC injection. Table RHBV.2 shows the treatment regimens.

This is a double dummy design in which each active treatment has its own matched placebo to preserve the blind.

At baseline (Week 0) all patients will receive 3 injections, and will be randomized to a treatment regimen. Patients assigned to an ixekizumab treatment regimen with a 160 mg starting dose will receive 160 mg of ixekizumab as 2 SC injections, in addition to 1 SC adalimumab placebo. Patients assigned to an ixekizumab treatment regimen with an 80 mg starting dose will receive 80 mg of ixekizumab as 1 SC injection, and 2 placebo injections SC (1 adalimumab placebo, 1 ixekizumab placebo). Patients assigned to the adalimumab treatment group will receive 2 SC injections of ixekizumab placebo and 1 SC injection of adalimumab 40 mg. Patients assigned to the placebo treatment group will receive 2 SC injections of ixekizumab placebo and 1 SC adalimumab placebo. During the remainder of the Blinded Treatment Dosing Period (Period 2; Week 0 to Week 16) all patients will receive 2 injections every 2 weeks. Details are provided in Table RHBV.2.

During the Extended Treatment Period (Period 3; Week 16 to Week 52), patients originally assigned to either ixekizumab treatment regimen will remain on the same treatment regimen through Period 3. At Week 16, patients originally assigned to placebo will be rerandomized at a 1:1 ratio to ixekizumab 80 mg Q2W or Q4W with a 160 mg starting dose (as two 80 mg SC injections). To maintain the blind, all patients, regardless of treatment group, will receive 2 SC injections at Week 16. Treatment groups in this period are described in Table RHBV.3.

Patients assigned to adalimumab during Period 2 will receive their last adalimumab dose at Week 14 and will be re-randomized to either ixekizumab 80 mg Q2W or Q4W at Week 16. These patients will receive their first ixekizumab 80 mg injection at Week 20 after a 6-week washout period and thereafter follow their assigned ixekizumab regimen from Week 20 through Week 52. Treatment groups in this period are described in Table RHBV.2.

To maintain blinding throughout the study, each patient will receive at least 1 SC injection Q2W regardless of his/her assigned treatment regimen (that is, placebo will be administered every other week as necessary for the Q4W treatment group).

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

- explaining the correct use of the investigational product to the patient/patient caregiver



- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing, collection, and administration
- returning all unused medication to Lilly or its designee at the end of the study.

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.

Further instructions and special considerations for the administration of the investigational product are provided in Sections [6.1.1](#), [6.2.1](#), and [6.6.1](#).

**Table RHBV.2. Treatment Regimens from Week 0 to Week 14 (Period 2)**

<b>Initial Regimen</b>		<b>Dose Week 0 (Day 0)</b>		<b>Dose Week 2 to Week 14<sup>a</sup> (Period 2)</b>
	<b>Total injections per patient</b>	<b>3 injections</b>		<b>2 injections Q2W</b>
ixekizumab 80 mg Q2W with 160 mg starting dose	Treatment dose	2 ixekizumab 80 mg injections	↘	1 ixekizumab 80 mg Q2W (Beginning at Week 2, Q2W)
	Injections to maintain blinding	1 placebo for adalimumab injection		
ixekizumab 80 mg Q2W with 80 mg starting dose	Treatment dose	1 ixekizumab 80 mg injection	↘	1 placebo for adalimumab injection Q2W (Beginning at Week 2, Q2W)
	Injections to maintain blinding	1 placebo for ixekizumab injection 1 placebo for adalimumab injection		
ixekizumab 80 mg Q4W with 160 mg starting dose	Treatment dose	2 ixekizumab 80 mg injections	↘	1 ixekizumab 80 mg Q4W injection (Beginning at Week 4, Q4W)
	Injections to maintain blinding	1 placebo for adalimumab injection		
ixekizumab 80 mg Q4W with 80 mg starting dose	Treatment dose	1 ixekizumab 80 mg injection	↘	1 placebo for ixekizumab injection (Beginning at Week 2, Q4W) and 1 placebo for adalimumab injection Q2W (Beginning at Week 2, Q2W)
	Injections to maintain blinding	1 placebo for ixekizumab injection 1 placebo for adalimumab injection		
adalimumab 40 mg Q2W (comparator)	Treatment dose	1 adalimumab 40 mg injection		1 adalimumab 40 mg Q2W injection (Beginning at Week 2, Q2W)
	Injections to maintain blinding	2 placebo for ixekizumab injections		1 placebo for ixekizumab injection Q2W (Beginning at Week 2, Q2W)
placebo	Injections to maintain blinding	2 placebo for ixekizumab injections 1 placebo for adalimumab injection		1 placebo for ixekizumab injection Q2W (Beginning at Week 2, Q2W) and 1 placebo for adalimumab injection Q2W (Beginning at Week 2, Q2W)

Abbreviations: Q2W = every 2 weeks; Q4W = every 4 weeks.

<sup>a</sup> Patients on adalimumab will receive their last adalimumab dose at Week 14.

Note: Shaded cells represent ixekizumab regimens with a starting dose (ixekizumab 160 mg).

**Table RHBV.3. Treatment Regimens from Week 16 to Week 50**

Initial Regimen		Dose Week 16 <sup>a</sup>	Dose Week 18 to Week 50 (Period 3)
	<b>Total injections per patients</b>	<b>2 injections</b>	<b>1 injection Q2W</b>
ixekizumab 80 mg Q2W	Treatment dose	1 ixekizumab 80 mg injection	1 ixekizumab 80 mg injection Q2W (Beginning at Week 18, Q2W)
	Injections to maintain blinding	1 placebo for ixekizumab injection	None
ixekizumab 80 mg Q4W	Treatment dose	1 ixekizumab 80 mg injection	1 ixekizumab 80 mg injection Q4W (Beginning at Week 20, Q4W)
	Injections to maintain blinding	1 placebo for ixekizumab injection	1 placebo for ixekizumab injection Q4W (Beginning at Week 18, Q4W)
adalimumab 40 mg Q2W (comparator)		rerandomized to ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W <sup>b</sup>	
	Treatment dose	None	ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W beginning at Week 20
	Injections to maintain blinding	2 placebo for ixekizumab injections	1 placebo injection at Week 18 only (ixekizumab 80 mg Q2W regimen) or 1 placebo for ixekizumab injection Q4W beginning at Week 18 (ixekizumab 80 mg Q4W regimen)
placebo		rerandomized to ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W	
	Treatment dose	2 ixekizumab 80 mg injections (starting dose)	ixekizumab 80 mg Q2W beginning at Week 18 or ixekizumab 80 mg Q4W beginning at Week 20
	Injections to maintain blinding	None	None (ixekizumab 80 mg Q2W regimen) or 1 placebo for ixekizumab injection Q4W beginning at Week 18 (ixekizumab 80 mg Q4W regimen)

<sup>a</sup> Patients on placebo will receive a starting dose of 160 mg ixekizumab (2 ixekizumab 80 mg injections) at Week 16. All other patients will receive placebo injections as needed to maintain blinding.

<sup>b</sup> Patients assigned to the adalimumab treatment group at Week 0 will be re-randomized to an ixekizumab regimen at Week 16, but they will not receive an ixekizumab injection at Week 16. These patients will receive 2 placebo for ixekizumab injections at Week 16 to maintain the blind. Patients will receive their first ixekizumab dose (a single 80 mg injection) at Week 20, after the wash out period is complete. Patients will then maintain the ixekizumab regimen they were re-randomized to (ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W), with placebo injections as needed to maintain blinding.

### 6.1.1. Administration of Investigational Product

Injections will be administered subcutaneously by the patient or caregiver after training by the clinical staff.

**Training:** At Week 0 (baseline, Visit 2) each patient is scheduled to receive 3 injections of blinded investigational product. For training purposes, the proper procedures for administration of the initial injection will be performed by clinical staff and the second and third injections of investigational product at that visit will be administered by the patient or caregiver under the supervision of clinical staff. If additional training is necessary, an injection may be administered by the patient or caregiver under the supervision of clinical staff at Week 2 (Visit 4).

**Administration:** If the patient is unable to perform the injection, a caregiver, who will also be trained under supervision of site staff, may administer the investigational product. All subsequent injections of investigational product will be administered, unsupervised, by the patient or caregiver. It is recommended that these injections be administered away from the investigational site, except for Weeks 0, 16, and 20 when the injections have to be done at the site for post-dose monitoring. If the patient or caregiver is not able to administer the second injection of the starting dose, or any dose throughout the study, study site staff may administer that injection.

Refer to the appropriate *Manual Syringe Directions for Use* provided by the sponsor for each investigational product. Note that injections are not to be given in the same arm from which patient blood samples, including PK/PD samples, are being drawn at relevant visits.

Study Drug Administration Logs will be dispensed to each patient as needed for recording pertinent data about each injection; details of the use of these logs are provided in Section 6.2.1.

Possible injection sites are identified in the syringe *Directions for Use*. The injection site is to be rotated to another area for subsequent doses.

**Observation:** Patients are to remain under observation for at least 1 hour after dosing at Week 0 (Visit 2), Week 16 (Visit 8) and Week 20 (Visit 9) to monitor for safety since some patients will be receiving ixekizumab for the first time at these visits. Therefore, at Week 16 (Visit 8) and Week 20 (Visit 9) injections of the investigational product will be administered by the patient or caregiver at the clinical site to allow for observation for any AEs and collection of post injection blood pressure (BP) and pulse measurements approximately 1 hour after administration of the investigational product (Section 8.4.2 and [Appendix 2](#)).

## 6.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Week 0 (Visit 2). Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign double-blind investigational product to each patient. Site personnel will confirm that they have located the correct assigned investigational product package by entering a confirmation number found on the package into the IWRS.

To achieve between-group comparability, the randomization will be stratified by country and baseline CRP (nonelevated or elevated). Elevated CRP is defined as CRP > 5.00 mg/L.

Once a specific stratum is fully enrolled, the sponsor may stop further enrollment of patients fitting the criteria of that stratum.

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

Investigational product is to be administered at approximately the same time each day, as much as possible. If an injection is missed, the missed dose should be administered as soon as possible. Injection(s) for missed dose(s) should not be given within 5 days of the next scheduled dose; injections should be  $\geq 5$  days apart. Dates of subsequent study visits are not to be modified according to this delay.

A paper Study Drug Administration Log will be completed by randomized patients for each injection throughout study participation. The data from the Study Drug Administration Log must be transcribed into the electronic case report form (eCRF) by site personnel.

Patients will be instructed to contact their study site in the event of an injection problem. In addition, site personnel review all Study Drug Administration Logs at each visit to identify any product complaints and they will complete a Product Complaint Form for each operation failure reported on a Study Drug Administration Log (see Section 8.2.3 for additional instructions regarding complaint handling).

### **6.3. Blinding**

This is a double-blind study.

Initial randomization (study treatment administered between Weeks 0 and 16) will remain blinded to study site personnel and patients until the final clinical trial database lock has occurred. The study treatment in the Extended Treatment Period (Period 3) will remain blinded to study site personnel and patients until final clinical trial database lock or patients entering Study RHBV, whichever comes first.

Initial randomization will remain blinded to sponsor until the clinical trial database through Week 16 has been locked. Subsequent randomization at Week 16 for adalimumab and placebo patients (to ixekizumab 80 mg Q2W or Q4W) may be blinded to sponsor until the clinical trial database through Week 52 has locked.

Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All actions 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 is to be discontinued from the study treatment. In cases where there are ethical reasons to have the patient remain on study treatment, the investigator must obtain specific approval from a Lilly

clinical research physician or Lilly clinical research scientist for the patient to continue on study treatment.

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 is to make every effort to contact the Lilly clinical research physician/clinical research scientist prior to unblinding a patient's treatment assignment. If a patient's treatment assignment is unblinded, the Lilly clinical research physician/clinical research scientist must be notified immediately.

#### 6.4. Packaging and Labelling

The investigational products will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practices (cGMP).

Clinical trial materials will be labeled according to the country's regulatory requirements. All investigational products will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

**Ixekizumab and placebo to match** will be supplied as injectable solutions in 1-mL, single-dose, prefilled, disposable manual syringes with study specific labels. Each syringe of ixekizumab is designed to deliver ixekizumab 80 mg. The syringes (and contents) containing either ixekizumab or placebo will be visibly indistinguishable from each other, and visibly different from adalimumab and its matching placebo. Syringes will be supplied in cartons, with the appropriate quantity of syringes specific to the planned dispensing schedule of the investigational product.

**Commercially purchased adalimumab (Humira™) and placebo to match** adalimumab will be supplied as an injectable solution in single-dose, prefilled, disposable manual syringes; commercial labels will have been removed and replaced with study-specific labels. Each syringe of adalimumab is designed to deliver adalimumab 40 mg. The syringes (and contents) containing either adalimumab or placebo to match adalimumab will be visibly indistinguishable from each other and visibly different from ixekizumab and its matching placebo. Syringes will be supplied in cartons, with the appropriate quantity of syringes specific to the planned dispensing schedule of the investigational product.

#### 6.5. Preparation/Handling/Storage

Investigational products will be supplied by Lilly or its representative, in accordance with cGMP and will be supplied with lot numbers, expiry dates, and certificates of analysis, as applicable.

The investigational product is to be stored at 2°C to 8°C (36°F to 46°F) in its original carton to protect from light. Investigational product must not be frozen. Sites will be required to monitor temperature of the on-site storage conditions of the investigational product.

## 6.6. Dose Modification

No investigational product dose modifications are permitted (refer to Section 8.4.10.1.1 for instances where drug may be withheld).

### 6.6.1. Special Treatment Considerations

Patients will be screened for eligibility in the study as described in Sections 5.1 and 5.2 and will be informed of the study-specific restrictions and requirements of the study. Patients who are not willing to comply with the study restrictions and requirements of the study will not be eligible for enrollment.

All biological agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include, but are not limited to:

- skin rash
- pruritus (itching)
- urticaria (hives)
- angioedema (for example, swelling of the lips and/or tongue)
- anaphylactic reaction.

Sometimes these reactions can be life threatening. Proteins may also cause redness, itching, swelling, or pain locally at the injection site; therefore, all patients should be closely monitored for signs or symptoms that could result from such reactions, educated on the signs or symptoms of these types of reactions, and instructed to contact the study site immediately if any of these symptoms are experienced following an injection. If a patient experiences an acute allergic/hypersensitivity reaction after an injection of investigational product, he or she is to be managed appropriately and given instruction to receive relevant supportive care. Additionally, for an event judged by the investigator to be a potential systemic allergic/hypersensitivity reaction, a blood sample is to be drawn to test for ADA and PK as soon as possible (see Section 8.4.9).

For patients who experience a potential allergic/hypersensitivity reaction, consideration for any premedication for future injections will be agreed upon between the investigator and sponsor. Examples of potential allergic/hypersensitivity reactions that might merit premedication include mild-to-moderate skin rashes, mild-to-moderate generalized pruritus and/or urticaria, and mild-to-moderate injection site reactions (for example, injection site erythema, injection site pruritus, and so on). Patients who develop clinically significant systemic allergic/hypersensitivity reactions following administration of investigational product that do not respond to symptomatic medication or result in clinical sequelae (for example, hospitalization) are to be discontinued from study treatment and not receive further doses of investigational product, with or without premedication (see Section 7.1.1). Medications considered appropriate for premedication include, but are not restricted to, acetaminophen/paracetamol up to 1000 mg and antihistamines (for example, oral diphenhydramine 50 mg) given after all efficacy assessments have been completed for a given visit, and 30 to 60 minutes prior to investigational product SC injections for visits where injections are administered at the clinic. For all other



injections, patients may self-premedicate at home prior to administration of investigational product, as directed by the investigator. All such premedications will be recorded as concomitant medications. Corticosteroids are not permitted as agents for premedication.

### 6.7. Treatment Compliance

Patient compliance with study medication will be assessed at each visit. Compliance will be assessed by review of the Study Drug Administration Log, return of empty or unused investigational product packaging, and/or direct questioning. Deviation(s) from the prescribed dosage regimen are to be recorded in the eCRF.

Compliance is defined in Section 9.3.4.

### 6.8. Concomitant Therapy

All concomitant medication taken during the study must be recorded in the eCRF. Patients will maintain their usual medication regimen throughout the study unless specifically excluded in the protocol. Patients taking permitted medications are to be on stable doses at the baseline visit (Week 0; Visit 2) through Week 16 as specified in inclusion/exclusion criteria (Sections 5.1 and 5.2). Up to Week 16, patients should not start new medications or make any changes to concomitant medications unless changes need to be made for an AE or for safety reasons. Beyond Week 16, some flexibility is allowed in concomitant medication as outlined below.

#### **Vaccines:**

Live vaccines are not allowed during any of the study periods. Use of nonlive seasonal vaccinations and/or emergency vaccination (such as rabies or tetanus vaccinations) is allowed.

#### **NSAIDs and Analgesics:**

##### Blinded Treatment Dosing Period (Period 2):

NSAIDs, including COX-2 inhibitors, will be allowed up to the maximum recommended doses for pain. Patients must be on a stable dose of NSAIDs/COX-2 inhibitors for at least 2 weeks prior to baseline randomization. Introduction of a new NSAID or dose adjustment to an existing NSAID is not permitted, unless required for safety reasons.

Short-acting analgesics with no anti-inflammatory action (such as paracetamol) are permitted and may be administered ad hoc as needed and are to be withheld within the 24-hour period prior to any assessment. Aspirin (dose not exceeding 350 mg/day) may be taken to manage cardiovascular risk.

Opiate analgesic use is allowed but not to exceed >30 mg/day of morphine or its equivalent. Patients are to be on stable dose during Period 2. Introduction of a new opiate analgesic or dose adjustment to an existing opiate analgesic is not permitted, unless required for safety reasons or as premedication for MRIs.



Extended Treatment and Post-Treatment Follow-Up Periods (Periods 3 and 4):

After completion of the Week 16 assessments, alterations of NSAIDs, including COX-2 inhibitors (dose change, introduction, or withdrawal) are allowed. Doses are recommended to be stable in the 2 weeks prior to an arthritis assessment.

Short-acting analgesics with no anti-inflammatory action (such as paracetamol) are permitted and may be administered ad hoc as needed but are to be withheld within the 24-hour period prior to any assessment. Aspirin (dose not exceeding 350 mg/day) may be taken to manage cardiovascular risk.

Use of variable doses of opiate analgesics is allowed, but not to exceed an average daily dose of 30 mg morphine or its equivalent.

**Conventional DMARDs:**Blinded Treatment Dosing Period (Period 2):

Discontinuation of excluded oral or injectable cDMARDs before study enrollment must occur at least 4 weeks prior to baseline. Methotrexate (oral or parenteral up to 25 mg/week), sulfasalazine (up to 3 g/day), or hydroxychloroquine (up to 400 mg/day) may be allowed IF at stable dose for at least 4 weeks prior to baseline randomization.

During Period 2, alteration of cDMARD dose or route, and/or introduction of a new cDMARD are not permitted, unless required for safety reasons. Conventional DMARDs can only be used as single agents and not in combination with other cDMARDs. If, at any time, the investigator believes that side effects or laboratory abnormalities may be attributable to the cDMARD, the cDMARD dose is to be lowered or the medication stopped.

Extended Treatment and Post-Treatment Follow-Up Periods (Periods 3 and 4):

During Periods 3 and 4, adjustment of allowed cDMARDs (for example, dose change, introduction, withdrawal of cDMARDs, or replacement of a current cDMARD with the introduction of a new cDMARD) is allowed after all assessments at Week 16 are completed. Not more than 1 adjustment of cDMARDs at 1 time within 12 weeks is recommended. Conventional DMARDs can only be used as single agents and not in combination with other cDMARDs. Any changes must be recorded in the eCRF.

For all study periods, the maximum allowed doses are 25 mg/week MTX, 400 mg/day hydroxychloroquine and 3 g/day sulfasalazine. Local standards of care are to be followed for concomitant administration of folic or folinic acid if MTX is taken, and for administration of other cDMARDs.

**Corticosteroids:**Blinded Treatment Dosing Period (Period 2):

*Oral corticosteroids:* If on oral corticosteroids, the dose must not exceed 10 mg/day of prednisone or its equivalent and must be stable for at least 4 weeks prior to baseline

randomization. During Period 2, treatment alterations in oral corticosteroid dose are strongly discouraged.

*Parenteral corticosteroids (IV, intramuscular, intra-articular):* Treatment with any parenteral corticosteroids is not permitted within 6 weeks prior to baseline or during Period 2.

*Inhaled and topical steroids:* Regular use of inhaled or topical steroids will be permitted during any study period.

Extended Treatment and Post-Treatment Follow-Up Periods (Periods 3 and 4):

*Oral corticosteroids:* As of Week 16, adjustments of oral corticosteroids are allowed, however the maximum dose is not to exceed 10 mg/day of prednisone or its equivalent at any time during these periods.

*Parenteral corticosteroids (IV, intramuscular, intra-articular):* As of Week 16, intra-articular injection of corticosteroid may be allowed, as needed. The joint injected must be designated along with the medication in the eCRF and must be recorded as unevaluable on the TJC/SJC assessment.

*Inhaled and topical steroids:* Regular use of inhaled or topical steroids will be permitted during any study period.

**Other Concomitant Medications (Periods 2, 3, and 4):**

Patients requiring surgery at any time during the study are to interrupt administration of the investigational product beginning 8 weeks prior to the surgery, or as early as possible within 8 weeks of surgery, and resume administration of the investigational product only after complete wound healing.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem. If the need for concomitant medication arises, the investigator is to base decisions on the patient and on clinical factors. Any additional medication, whether prescription or over-the-counter, used at baseline (Week 0, Visit 2) and/or during the course of the study, must be documented with the start and stop dates in the eCRF.

Additional systemic drugs are to be avoided during the study, unless required to treat an AE. Other medications may be allowed, if approved by the sponsor or its designee.

Only for patients who discontinued study treatment and have entered the Post-Treatment Follow-Up Period, axSpA therapy with another agent previously excluded during the treatment period of the study may be allowed, as determined appropriate by the investigator and approved by Lilly medical.

Any changes in medications not addressed above are to be discussed with the investigator. Patients must be instructed to consult the investigator or other appropriate study personnel at the site before taking any new medications or supplements.

## **6.9. Treatment After Study Completion**

### **6.9.1. Study Extensions**

Patients who complete this study through Visit 15 (Week 52) may be eligible to participate in a long-term study (Study RHBV) offering up to an additional 2 years of treatment, if enrollment criteria for Study RHBV are met. For patients who have completed Study RHBV through Week 52 and meet exclusion criteria at Week 44 **and** Week 52, patients will complete the Post-Treatment Follow-Up Period (Period 4) in Study RHBV.

### **6.9.2. Continued Access**

Investigational product will not be made available to patients after conclusion of this study. However, patients who complete Study RHBV and continue in the long term study (RHBV) will have access to investigational product for up to an additional 2 years.

## 7. Discontinuation Criteria

The reason for and date of discontinuation from study treatment (investigational product) and reason for and date of discontinuation from study participation will be collected for all randomized patients.

For any patient permanently discontinuing from study treatment, the investigational product will be withheld, and the patient will complete the ETV and the Post-Treatment Follow-Up Period (Period 4), as shown in the Schedule of Activities ([Appendix 2](#)). For patients discontinuing prior to Week 16, the patient will complete additional assessments as described in Section 7.1.1.1 and shown in the Schedule of Activities ([Appendix 2](#)).

### 7.1. Discontinuation from Study Treatment

#### 7.1.1. Discontinuation from Study Treatment

The following criteria must be followed for discontinuation from study treatment. Patients will enter into the Post-Treatment Follow-Up Period (Period 4) if they discontinue from study treatment.

- [1] 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 >8xULN
  - ALT or AST >5xULN for more than 2 weeks
  - ALT or AST >3xULN and total bilirubin level >2xULN or prothrombin time >1.5xULN
  - ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - alkaline phosphatase >2.5xULN and total bilirubin >2xULN
  - alkaline phosphatase >2.5xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- [2] Other laboratory tests (**Note:** Laboratory test(s) that may result in discontinuation based on a single result may be repeated only once if there is a technical error or clinical reason to believe a result may need to be retested. Laboratory tests can only be repeated after consultation with Lilly medical. Investigational product should not be administered in these cases until retest result is available.):
  - Neutrophil (segmented) counts (see safety monitoring for neutropenia in Section [8.4.10.1](#)):

- $<500$  cells/ $\mu\text{L}$  ( $<0.50 \times 10^3/\mu\text{L}$  or  $<0.50$  GI/L)
  - $\geq 500$  and  $<1000$  cells/ $\mu\text{L}$  ( $\geq 0.50 \times 10^3/\mu\text{L}$  and  $<1.00 \times 10^3/\mu\text{L}$  or  $\geq 0.50$  GI/L and  $<1.00$  GI/L) (based on 2 test results; the second test performed within 1 week from knowledge of the initial result)
  - $\geq 1000$  and  $<1500$  cells/ $\mu\text{L}$  ( $\geq 1.00 \times 10^3/\mu\text{L}$  and  $<1.50 \times 10^3/\mu\text{L}$  or  $\geq 1.00$  GI/L and  $<1.50$  GI/L) (based on 3 test results as specified in Section 8.4.10.1)
    - AND - a concurrent infection
  - Total WBC count  $<2000$  cells/ $\mu\text{L}$  ( $<2.00 \times 10^3/\mu\text{L}$  or  $<2.00$  GI/L).
  - Lymphocyte count  $<500$  cells/ $\mu\text{L}$  ( $<0.50 \times 10^3/\mu\text{L}$  or  $<0.50$  GI/L).
  - Platelet count  $<50,000$  cells/ $\mu\text{L}$  ( $<50 \times 10^3/\mu\text{L}$  or  $<50$  GI/L).
- [3] The patient experiences a severe AE, an SAE, or a clinically significant change in a laboratory value that, in the opinion of the investigator, merits the discontinuation of the investigational product and appropriate measures being taken. In this case, Lilly or its designee is to be notified immediately. Refer to Section 8.2.
- [4] Clinically significant systemic hypersensitivity reaction following SC administration of investigational product that does not respond to symptomatic medication or results in clinical sequelae.
- [5] The patient becomes pregnant.
- [6] The patient develops a malignancy.

**Note:** Patients may be allowed to continue if they develop no more than 2 nonmelanoma skin cancers during the study.

- [7] Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- [8] The patient, at any time during the study, scores a 3 for Item 12 (Thoughts of Death or Suicide) on the QIDS-SR16

-OR-

develops active suicidal ideation with some intent to act with or without a specific plan (yes to question 4 or 5 on the “Suicidal Ideation” portion of the Columbia–Suicide Severity Rating Scale [C-SSRS])

-OR-

develops suicide-related behaviors as recorded on the C-SSRS.

It is recommended that the subject be assessed by a psychiatrist or

appropriately trained professional to assist in deciding whether the subject is to be discontinued from the study.

- [9] The patient develops any condition or contraindication as addressed in the local labeling for adalimumab that would preclude the patient from continuing in this protocol.
- [10] The investigator or attending physician decides that the patient is to be withdrawn from study treatment.
- [11] The patient requests to be withdrawn from study treatment.
- [12] Lilly or its designee stops the patient's participation in the study or Lilly stops the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- [13] The patient becomes HBV DNA positive, at which time the patient is to be referred to a specialist physician. Discussion of the timing of discontinuation from the study and from study treatment is provided in Section 8.4.10.2.

#### **7.1.1.1. Discontinuation of Study Treatment Prior to Week 16**

Patients who discontinue prior to Week 16 will complete the ETV and the Post-Treatment Follow-Up Period (Period 4). In addition, patients will complete several additional assessments, as detailed in the Schedule of Activities ([Appendix 2](#)).

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

The criteria for enrollment must be followed explicitly. If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the sponsor clinical research physician/clinical research scientist and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor clinical research physician/clinical research scientist to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product.

#### **7.1.3. Permanent Discontinuation from the Study**

Some possible reasons that may lead to permanent discontinuation include:

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- Patient decision: The patient requests to be withdrawn from the study

Patients who discontinue the study early will have end-of-study procedures performed as shown in the Schedule of Activities ([Appendix 2](#)).

**7.1.4. Patients 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.

## 8. Study Assessments and Procedures

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

[Appendix 3](#) lists the laboratory tests that will be performed for this study.

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

### 8.1. Efficacy Assessments

Below are brief descriptions on key aspects of scales used in the study. Complete assessments are included in site training materials.

The following ASAS domains are used to determine ASAS20, ASAS40, ASAS partial remission, and ASAS 5/6 (Sieper et al. 2009, ASAS Handbook):

- 1) Patient Global (Section [8.1.2.2](#))
- 2) Spinal Pain (Section [8.1.2.3](#))
- 3) Function (Section [8.1.2.5](#))
- 4) Inflammation (mean of BASDAI questions 5 and 6)(Section [8.1.2.4](#))
- 5) CRP (Section [8.1.2.19.1](#)) and
- 6) Spinal mobility (lateral spinal flexion) (Section [8.1.2.6](#))

#### 8.1.1. Primary Efficacy Assessment: ASAS40

The ASAS40 (Anderson et al. 2001; Brandt et al. 2004; Sieper et al. 2009) is derived from patient-reported assessments. An ASAS40 response is defined as a  $\geq 40\%$  improvement and an absolute improvement from baseline of  $\geq 2$  units (range 0 to 10) in  $\geq 3$  of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation) without any worsening in the remaining domain.

#### 8.1.2. Secondary Efficacy Assessments

##### 8.1.2.1. ASAS20, ASAS Individual Components, ASAS Partial Remission, and ASAS 5/6

The ASAS20, ASAS individual components, ASAS partial remission and ASAS 5/6 responses (Davis et al. 2003; Sieper et al. 2009) are secondary efficacy assessments that are calculated as improvements in respective response rates in multiple disease domains.

Complete definitions of each assessment are provided below.

##### 8.1.2.1.1. ASAS20

The ASAS20 is derived from patient-reported assessments. An ASAS20 response is defined as a  $\geq 20\%$  improvement and an absolute improvement from baseline of  $\geq 1$  units (range 0 to 10) in



$\geq 3$  of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation), and no worsening of  $\geq 20\%$  and  $\geq 1$  unit (range 0 to 10) in the remaining domain.

#### **8.1.2.1.2. ASAS Partial Remission**

The ASAS partial remission is derived from patient-reported assessments. An ASAS partial remission response is defined as a value not above 2 units (range 0 to 10, NRS) in each of the following 4 domains: Patient Global, Spinal Pain, Function, and Inflammation.

#### **8.1.2.1.3. ASAS 5/6**

The ASAS 5/6 includes assessment of all 6 individual ASAS domains listed in Section 8.1 and represents improvement of  $\geq 20\%$  in at least 5 domains.

#### **8.1.2.2. Patient Global (Assessment of Disease Activity)**

From the ASAS Handbook (Sieper et al. 2009), the patient is asked to respond to the following question: “How active was your spondylitis on average during the last week?” The answer is recorded on an NRS and is rated between “0” (not active) and “10” (very active).

#### **8.1.2.3. Spinal Pain**

From the ASAS Handbook (Sieper et al. 2009), the patient is asked to respond to the following 2 questions (on average during the last week):

1. “How much pain of your spine due to ankylosing spondylitis do you have?”
2. “How much pain of your spine due to ankylosing spondylitis do you have at night?”

The answers are recorded on an NRS and are each rated between “0” (no pain) and “10” (most severe pain). The first question is used to derive responses (that is, ASAS40, ASAS20, and so on).

#### **8.1.2.4. Bath Ankylosing Spondylitis Disease Activity Index**

The BASDAI is a patient-reported assessment consisting of 6 questions that relate to 5 major symptoms relevant to rad-axSpA (Garrett et al. 1994; Sieper et al. 2009): 1) Fatigue, 2) Spinal pain, 3) Peripheral arthritis, 4) Enthesitis, 5) Intensity, and 6) Duration of morning stiffness. Patients need to score each item with a score from 0 to 10 (NRS).

BASDAI50 represents an improvement of  $\geq 50\%$  of the BASDAI score from baseline.

#### **8.1.2.5. Bath Ankylosing Spondylitis Functional Index**

The BASFI is a patient-reported assessment that establishes a patient’s functional baseline and subsequent response to treatment (Calin et al. 1995). To complete the BASFI, a patient is asked to rate the difficulty associated with 10 individual basic functional activities. Patients respond to each question using an NRS scale (range 0 to 10) with a higher score indicating worse function.

The patient’s final BASFI score is the mean of the 10 item scores completed on an NRS.

#### **8.1.2.6. Bath Ankylosing Spondylitis Metrology Index—Spinal Mobility**

The BASMI is a combined index comprising the following 5 clinical measurements of spinal mobility in patients with rad-axSpA (Jenkinson et al. 1994):

- Lateral spinal flexion
- Tragus-to-wall distance
- Lumbar flexion (modified Schrober)
- Maximal intermalleolar distance
- Cervical rotation.

The BASMI includes these 5 measurements that are each scaled to a score of 0 to 10 depending on the result of the assessment (BASMI linear function). The average score of the 5 assessments gives the BASMI linear result (van der Heijde et al. 2008; Sieper et al. 2009).

The BASMI must be assessed by a rheumatologist or health care provider who meets the qualifications for study assessment.

#### **8.1.2.7. Chest Expansion**

While patients have their hands resting on or behind the head, the assessor will measure the chest's encircled length by centimeter at the fourth intercostal level anteriorly. The difference between maximal inspiration and expiration in centimeters will be recorded. Two tries will be recorded. The better measurement (larger difference) of 2 tries (in centimeters) will be used for analyses.

The measurement of chest expansion must be assessed by a rheumatologist or health care provider who meets the qualifications for study assessment.

#### **8.1.2.8. Occiput to Wall Distance**

The patient is to make a maximum effort to touch the head against the wall when standing with heels and back against the wall (occiput). Then the distance from occiput to wall is measured. Two tries will be recorded. The better (smaller) measurement of 2 tries (in centimeters) will be used for analyses .

The measurement of occiput to wall distance must be assessed by a rheumatologist or health care provider who meets the qualifications for study assessment.

#### **8.1.2.9. Ankylosing Spondylitis Disease Activity Score**

The ASDAS is a composite index to assess disease activity in AS (Machado et al. 2011a, 2011b; Zochling 2011). The parameters used for the ASDAS (with CRP as acute phase reactant) are the following:

- 1) Total back pain (BASDAI question 2)
- 2) Patient global (Section [8.1.2.2](#))
- 3) Peripheral pain/swelling (BASDAI question 3)
- 4) Duration of morning stiffness (BASDAI question 6)
- 5) CRP in mg/L

The  $ASDAS_{crp}$  is calculated with the following equation:  $0.1216 \times \text{total back pain} + 0.1106 \times \text{patient global} + 0.0736 \times \text{peripheral pain/swelling} + 0.0586 \times \text{duration of morning stiffness} + 0.5796 \times \text{Ln}(\text{CRP}+1)$  (Machado et al. 2015). (Note: CRP is in mg/liter, the range of other variables is from 0 to 10; Ln represents the natural logarithm.)

Four disease activity states have been defined by ASAS consensus (Machado et al. 2011c):

- ASDAS <1.3 defines inactive disease
- $1.3 \leq \text{ASDAS} < 2.1$  defines moderate disease activity
- $2.1 \leq \text{ASDAS} \leq 3.5$  defines high disease activity
- ASDAS > 3.5 defines very high disease activity.

Clinically important improvement is defined as change  $\geq 1.1$  units, and major improvement is defined as change  $\geq 2.0$  units (Machado et al. 2011b).

#### **8.1.2.10. Maastricht Ankylosing Spondylitis Enthesitis Score**

The MASES is an index used to measure the severity of enthesitis (Heuft-Dorenbosch et al. 2003). The MASES assesses 13 sites for enthesitis using a score of “0” for no activity or “1” for activity. Sites assessed include costochondral 1 (right/left), costochondral 7 (right/left), spinal iliaca anterior superior (right/left), crista iliaca (right/left), spina iliaca posterior (right/left), processus spinosus L5, and Achilles tendon proximal insertion (right/left). The MASES is the sum of all site scores (range 0 to 13); higher scores indicate more severe enthesitis.

The MASES must be assessed by a rheumatologist or health care provider who meets the qualifications for study assessments.

#### **8.1.2.11. Spondyloarthritis Research Consortium of Canada–Enthesitis Score**

The SPARCC enthesitis is an index used to measure the severity of enthesitis (Maksymowych et al. 2009). The SPARCC assesses 16 sites for enthesitis using a score of “0” for no activity or “1” for activity. Sites assessed include Medial epicondyle (left/right [L/R]), Lateral epicondyle (L/R), Supraspinatus insertion into greater tuberosity of humerus (L/R), Greater trochanter (L/R), Quadriceps insertion into superior border of patella (L/R), Patellar ligament insertion into inferior pole of patella or tibial tubercle (L/R), Achilles tendon insertion into calcaneum (L/R), and Plantar fascia insertion into calcaneum (L/R). The SPARCC is the sum of all site scores (range 0 to 16). Higher scores indicate more severe enthesitis.

The SPARCC must be assessed by a rheumatologist or health care provider who meets the qualifications for study assessments.

#### **8.1.2.12. Peripheral Arthritis**

##### **8.1.2.12.1. Tender Joint Count**

The number of tender and painful joints will be determined by examination of 46 joints (23 joints on each side of the patient’s body). The 46 joints to be assessed and classified as tender or not tender are detailed in site training materials. Any joints that require intra-articular injections during the study (according to Section 6.8) are to be excluded from evaluation from the time of the injection to the conclusion of the study.

Joint assessments must be assessed by a rheumatologist or health care provider who meets the qualifications for study assessments. To minimize interobserver variation, particularly during the Blinded Treatment Dosing Period (Period 2), it is recommended that the same assessor performs the TJC for a given patient. Missing, replaced, ankylosed, or arthrodesed joints will be

identified by the investigator at the screening visit (Visit 1) and will be excluded from evaluation during the study.

The TJC data will be collected electronically.

#### **8.1.2.12.2. Swollen Joint Count**

The number of swollen joints will be determined by examination of 44 joints (22 joints on each side of the patient's body). The 44 joints to be assessed and classified as swollen or not swollen are detailed in site training materials. Any joints that require intra-articular injections during the study (according to Section 6.8) are to be excluded from evaluation from the time of the injection to the conclusion of the study.

Joint assessments must be assessed by a rheumatologist or health care provider who meets the qualifications for study assessments. To minimize interobserver variation, particularly during the Blinded Treatment Dosing Period (Period 2), it is recommended that the same assessor performs the SJC for a given patient. Missing, replaced, ankylosed, or arthrodesed joints will be identified by the investigator at the screening visit (Visit 1) and will be excluded from evaluation during the study.

The SJC data will be collected electronically.

#### **8.1.2.13. Nonsteroidal Anti-Inflammatory Drug Intake**

Information regarding NSAIDs intake will be collected in the eCRF and the ASAS-NSAID score will be calculated at baseline and through Week 52 (Dougados et al. 2011).

#### **8.1.2.14. Assessment of Spondyloarthritis International Society Health Index**

The ASAS HI is a disease-specific health-index instrument designed to assess the impact of interventions for SpA, including axSpA. This broader concept of health is included in the International Classification of Functioning, Disability, and Health, which has been published by the World Health Organization (WHO). The ASAS has applied this classification as a basis to define a core set of items relevant for patients with rad-axSpA. The 17-item instrument has scores ranging from 0 (good health) to 17 (poor health) (Kiltz et al. 2013). Each item consists of one question that the patient needs to respond to with either "I agree" (score of 1) or "I do not agree" (score of 0). A score of "1" is given where the item is affirmed, indicating adverse health. All item scores are summed to give a total score or index.

#### **8.1.2.15. Medical Outcomes Study 36-Item Short-Form Health Survey**

The SF-36 is a 36-item patient-administered measure designed to be a short, multipurpose assessment of health in the areas of physical functioning, role – physical, role – emotional, bodily pain, vitality, social functioning, mental health, and general health. The 2 overarching domains of mental well-being and physical well-being are captured by the mental component summary (MCS) and physical component summary (PCS) scores. The summary scores range from 0 to 100; higher scores indicate better levels of function and/or better health. Items are answered on Likert scales of varying lengths. The SF-36 version 2 (acute version) will be used, which utilizes a 1-week recall period (Ware 2000).

### **8.1.2.16. Fatigue Severity Numeric Rating Scale**

The Fatigue Severity NRS is a patient-administered, single-item, 11-point horizontal scale anchored at 0 and 10, with 0 representing “no fatigue” and 10 representing “as bad as you can imagine” (Naegeli et al. 2013). Patients rate their fatigue (**feeling tired or worn out**) by circling the one number that describes their worst level of fatigue during the previous 24 hours.

### **8.1.2.17. Work Productivity and Activity Impairment Questionnaire— Spondyloarthritis**

The WPAI-SpA consists of 6 questions to determine employment status, hours missed from work because of SpA, hours missed from work for other reasons, hours actually worked, the degree to which SpA affected work productivity while at work, and the degree to which SpA affected activities outside of work. The WPAI-SpA has been validated in the rad-axSpA patient population (Reilly et al. 2010). Four scores are derived: percentage of absenteeism, percentage of presenteeism (reduced productivity while at work), an overall work impairment score that combines absenteeism and presenteeism, and percentage of impairment in activities performed outside of work. Greater scores indicate greater impairment (Reilly Associates [WWW]).

### **8.1.2.18. Jenkins Sleep Evaluation Questionnaire**

The JSEQ is a 4-item scale designed to estimate sleep problems in clinical research. The JSEQ assesses the frequency of sleep disturbance in 4 categories: 1) trouble falling asleep, 2) waking up several times during the night, 3) having trouble staying asleep (including waking up far too early), and 4) waking up after the usual amount of sleep feeling tired and worn out. Patients report the number of days they experience each of these problems in the past month on a 6-point Likert scale ranging from 0 = “no days” to 5 = “22-30 days.” The total JSEQ score ranges from 0 to 20, with higher scores indicating greater sleep disturbance (Deodhar et al. 2010).

### **8.1.2.19. Laboratory Tests Used for Efficacy Measures and Disease Diagnosis**

#### **8.1.2.19.1. High Sensitivity C-Reactive Protein**

High sensitivity CRP will be the measure of acute phase reactant. It will be measured with a high sensitivity assay at the central laboratory to help assess the effect of ixekizumab on disease activity. The results will not be shared with the investigative sites after baseline randomization to maintain the study blind.

### **8.1.2.20. Imaging Used for Efficacy Measures and Disease Diagnosis**

#### **8.1.2.20.1. Imaging of Sacroiliac Joints and Spine**

For each patient, x-ray and MRI images will be collected according to the Schedule of Activities ([Appendix 2](#)), [Table RHBV.4](#), and will follow the study specific recommendations included in site training materials for the study. The SIJ x-ray will be used to confirm patients have radiographic sacroiliitis as defined by the mNY criteria. Magnetic resonance imaging of the SIJ and spine, collected at screening, Week 16, and Week 52 will generate objective data on the anti-inflammatory effect of the investigational drug. The screening x-ray of the spine will also serve as baseline for later evaluation of change from baseline in structural progression in the long-term study (RHBV).

The site will read the screening x-ray of the spine (cervical+lumbar) for presence or absence of total ankylosis to determine study eligibility. The site will then send the x-ray to the central reader to be maintained as a baseline for later structure assessments. All other images (x-ray of the SIJ and MRIs) are centrally read for eligibility and/or for assessment of treatment effect.

**Table RHBV.4. Imaging Requirements for Sacroiliac Joints and Spine**

Time Point <sup>a</sup>	Type of Image <sup>b</sup>	Purpose	Reading	Requirements
Screening	X-ray of the SIJ	Eligibility to determine rad-axSpA (per mNY criteria)	Centrally read <sup>c</sup>	Send to central reader; results must be received from central reader prior to baseline randomization
Screening	X-ray of the spine (cervical and lumbar)	Eligibility to determine total ankylosis	Locally read (by investigator) <sup>d</sup>	Send to central reader (as baseline for later structure assessments)
Screening, Week 16, and Week 52	MRI of the spine plus SIJ	Assess efficacy	Centrally read	Send to central reader

Abbreviations: mNY = modified New York; MRI = magnetic resonance imaging; rad-axSpA = radiographic axial spondyloarthritis; SIJ = sacroiliac joints.

- a Screening procedures must be conducted within timeframes specified in the Schedule of Activities (Appendix 2).
- b Imaging to be reviewed and approved for quality; imaging that does not pass the quality assessment must be repeated prior to baseline randomization.
- c Patient cannot be randomized until centrally read results are received by site.
- d Patient can be enrolled by investigator for this inclusion/exclusion criterion of ankylosis.

#### **8.1.2.20.2. Spondyloarthritis Research Consortium of Canada–MRI Score for Spine**

All 23 disco-vertebral units (DVUs) of the spine (from C2 to S1) are scored for bone marrow edema. A single DVU has a scoring range of 0 to 18, bringing the maximum total score to 414, with higher scores reflecting worse disease (Maksymowych et al. 2005a). Scoring will be performed by central readers.

#### **8.1.2.20.3. Spondyloarthritis Research Consortium of Canada–MRI Score for Sacroiliac Joints**

Both left and right SIJ are scored for bone marrow edema. Total SIJ SPARCC scores can range from 0 to 72 with higher scores reflecting worse disease (Maksymowych et al. 2005b). Scoring will be performed by central readers.

#### **8.1.2.20.4. Spondyloarthritis Research Consortium of Canada–SIJ Structural Score (SSS)**

Structural lesions in MRIs of the SIJ are assessed using the SPARCC SSS method in which the presence or absence of lesions is scored in SIJ quadrants (for fat metaplasia and erosion) or SIJ halves (for backfill and ankylosis). Scoring ranges are fat metaplasia (0 to 40), erosions (0 to 40), backfill (0 to 20), and ankylosis (0 to 20) (Maksymowych et al. 2015). Scoring will be performed by central readers.

### **8.1.2.20.5. Ankylosing Spondylitis Spinal Magnetic Resonance Imaging Activity–Berlin Score**

All 23 DVUs of the spine (from C2 to S1) are scored for bone marrow edema. The Berlin method score range is between 0 and 3 per vertebral unit, bringing the maximum total score to 69 with higher scores reflecting worse disease (Braun et al. 2003; Lukas et al. 2007). Scoring will be performed by central readers.

## **8.1.3. Other Assessments**

### **8.1.3.1. European Quality of Life—5 Dimensions 5-Level**

The European Quality of Life—5 Dimensions- 5- Level (EQ-5D-5L) is a standardized measure of health status used 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 visual analog scale (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/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 are not to be used as ordinal scores. The VAS records the respondent's self-rated health on a vertical VAS in which the endpoints are labeled "best imaginable health state" and "worst imaginable health state." This information can be used as a quantitative measure of health outcomes. 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 2011).

### **8.1.3.2. Healthcare Resource Utilization**

Healthcare resource utilization data regarding the number of visits to medical care providers, such as general practitioners, specialists, physical, or occupational therapists, and other nonphysical care providers for services outside of the clinical trial; emergency room admissions; hospital admissions; and concomitant medications will be recorded by the investigator in the study's CRF. These data will be collected to support economic evaluations of treatment.

## **8.2. Adverse Events**

An AE is defined as: 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 AE 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.

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



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

Investigators must document their review of each laboratory safety report.

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

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

After the ICF is signed, study site personnel will record via CRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record via CRF any change in the condition(s) and any new conditions as AEs. Investigators must record their assessment of the potential relatedness of each AE to protocol procedure, investigational product, via CRF.

The investigator decides whether he or she interprets each AE as reasonably possibly related to the study product, study procedure, disease under study, or other concomitant medications, or pathologies. To assess the relationship of the AEs, the following is defined:

Reasonably Possibly **Related**: Reasonable possibility that there is a cause and effect relationship between the study product 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 electronic data entry, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

Accurate start and stop dates (and times, where required) are to be reported via electronic data entry for all AEs. Only AEs that are ongoing at the last study visit and/or communication are to be documented as "ongoing."

### **8.2.1. Serious Adverse Events**

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect



- 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.

If an SAE occurs after signing the ICF, but prior to receiving investigational product, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

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

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

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient summary 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/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

#### **8.2.1.1. Suspected Unexpected Serious Adverse Reactions**

Lilly has procedures that will be followed for the recording and expedited reporting of suspected unexpected serious adverse reactions (SUSARs) that are consistent with global regulations and the associated detailed guidances.

#### **8.2.2. Adverse Events of Special Interest**

The following adverse events of special interest (AESIs) will be used to determine the safety and tolerability of ixekizumab over the range of doses selected for this clinical study.

The AESIs for ixekizumab are:

- cytopenias (leukopenia, neutropenia, and thrombocytopenia)
- clinically significant hepatic events and/or significant elevations in liver function test changes/enzyme elevations (ALT, AST, bilirubin, and alkaline phosphatase)
- infections
- injection-site reactions
- allergic reactions/hypersensitivities
- cerebrocardiovascular events
- malignancies
- IBD
- depression.

Sites will provide details on some of these AEs as instructed on the CRF. Investigators will also educate patients and/or caregivers about the symptoms of allergic/hypersensitivity reactions and will provide instructions on dealing with these reactions (see also Section 6.6.1). A blood sample is to be collected as soon as possible for any patient who experiences an AE of a potential systemic allergic /hypersensitivity reactions during the study as judged by the investigator.

Data on preferred terms associated with cerebrocardiovascular events (defined as death, cardiac ischemic events including MI and hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, coronary revascularization procedure, stroke/transient ischemic attack, peripheral revascularization procedure, and peripheral arterial event and hospitalization for hypertension) will be collected, and these events and any deaths will be adjudicated by an external Clinical Events Committee (CEC) made up of a chairman, 2 cardiologists, and a neurologist.

Data on suspected IBD, as identified by events possibly indicative of ulcerative colitis and Crohn's disease, will be collected and the events will be adjudicated by an external CEC with expertise in IBD.

The role of external CECs is to adjudicate defined clinical events in a blinded, consistent, and unbiased manner throughout the course of a study. The purpose of the CEC for adjudication of cerebrocardiovascular events and the CEC for adjudication of suspected IBD events is to ensure that all reported events are evaluated uniformly by a single group.

### **8.2.3. Complaint Handling**

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

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

## **8.3. Treatment of Overdose**

Refer to the IB.

## **8.4. Safety Assessments**

### **8.4.1. Electrocardiograms**

For each patient, 12-lead ECGs must be collected locally at screening ([Appendix 2](#)). Patients are to be resting for 5 minutes prior to the ECG. It is recommended that patients be in a supine position.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational treatment are to be reported to Lilly or its designee as AEs via CRF. Any clinically significant ECG findings prior to receiving drug are to be reported as a preexisting condition.

### **8.4.2. Vital Signs**

For each patient, vital sign measurements are to be conducted according to the Schedule of Activities ([Appendix 2](#)). Vital signs include BP and pulse. Patients are to be resting for a minimum of 5 minutes prior to vital sign collection.

Any clinically significant findings from vital sign measurements that result in a diagnosis and that occur after the patient receives the first dose of study treatment are to be reported to Lilly or its designee as AEs via CRF.

### **8.4.3. Laboratory Tests**

For each patient, laboratory tests detailed in ([Appendix 3](#)) will be sent to a central laboratory for processing and must be conducted according to the Schedule of Activities ([Appendix 2](#)). Please reference the central laboratory manual for specific instructions.

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

### **8.4.4. Physical Examination**

For each patient, a complete physical examination must be conducted according to the Schedule of Activities ([Appendix 2](#)).

Any clinically significant findings from a complete physical examination that result in a diagnosis and that occur after the patient receives the first dose of study treatment are to be reported to Lilly or its designee as AEs via CRF.

### **8.4.5. Eye Symptom Assessment**

At each study visit, study health care providers will evaluate the patient for any symptoms of anterior uveitis as specified in the Schedule of Activities ([Appendix 2](#)). If the patient has no prior ophthalmologist-diagnosed anterior uveitis and develops eye pain or discomfort, eye redness, blurring of vision, or any other symptoms suggestive of anterior uveitis, the patient must be evaluated by an ophthalmologist. If a patient has prior history of ophthalmologist-diagnosed anterior uveitis, then she/he must be evaluated by a physician for recurrence of anterior uveitis (whenever possible, diagnosis is to be confirmed by an ophthalmologist).

### **8.4.6. Chest X-Ray and Tuberculosis Testing**

For each patient, a posterior anterior chest x-ray and TB testing must be conducted according to the Schedule of Activities ([Appendix 2](#)).

The posterior anterior chest x-ray or results will be reviewed by the investigator or designee prior to baseline randomization to exclude patients with active TB infection.

Any clinically significant findings from a posterior anterior chest x-ray or TB testing that result in a new diagnosis and that occur after the patient receives the first dose of study treatment are to be reported to Lilly or its designee as AEs via CRF.

**Patients with no TB test (PPD and/or Interferon-Gamma Release Assay) results on file:**

These patients will be tested at screening as indicated on the Schedule of Activities ([Appendix 2](#)) for evidence of active or latent TB indicated by a positive PPD skin test response, defined as  $\geq 5$  mm diameter of induration, between approximately 2 and 3 days after test application, regardless of BCG vaccination history. In countries where the Interferon-Gamma Release Assay (QuantiFERON®-TB Gold test, or T-SPOT®) is available and in the judgment of the investigator preferred as an alternative to the PPD skin test for the evaluation of TB infection, it may be used instead of the PPD test (positive tests excluded). The QuantiFERON®-TB Gold test may be read locally or centrally, while the T-SPOT® must be read locally. If the QuantiFERON®-TB Gold test is indeterminate, or the T-SPOT® is invalid or borderline, one retest is allowed. If the retest for the QuantiFERON®-TB Gold test is indeterminate, or the retest for the T-SPOT® is invalid or borderline, then the patient is excluded from enrolling in the study.

However, patients with a PPD skin test  $\geq 5$  mm induration or a positive QuantiFERON®-TB Gold or positive T-SPOT® test at screening, but no other evidence of active TB may be rescreened one time and may be enrolled without repeating a PPD or QuantiFERON®-TB Gold test or T-SPOT® (TB test) if the following conditions are met:

- after receiving at least 4 weeks of appropriate latent TB infection (LTBI) therapy.
- with no evidence of hepatotoxicity (ALT/AST must remain  $\leq 2$ xULN) upon retesting of serum ALT/AST prior to randomization. Such patients must complete appropriate LTBI therapy during the course of the study in order to remain eligible.
- meet all other inclusion/exclusion criteria for participation.

If rescreening occurs within 6 months of the initial screening posterior anterior chest x-ray, there is no necessity for repeat of the chest x-ray for considering enrollment.

**Patients with negative TB test results on file:** Patients with documentation of a negative test result within 3 months prior to baseline (Week 0; Visit 2) do not need a TB screen at Visit 1. Documentation of a PPD test result must include a record of the size of the induration response documenting no induration or induration measuring  $< 5$  mm in diameter. A PPD test recorded as negative without documenting the size of induration will result in a required test at screening to determine patient eligibility.

**Patients with positive TB test results on file:** Patients with prior history of a positive TB test are not to have a TB test at Visit 1. Documentation of this history and of at least 4 weeks of appropriate LTBI prior to baseline (Week 0, Visit 2) is required for study eligibility. Patients who have a documented history of completing an appropriate TB treatment regimen with no history of re-exposure to TB since their treatment was completed and no evidence of active TB are eligible to participate in the study. Patients who have had household contact with a person with active TB are excluded, unless appropriate and documented prophylaxis for TB was completed.

#### **8.4.7. Quick Inventory of Depressive Symptomatology—Self-Report (16 Items)**

For each patient, a QIDS-SR16 assessment will be collected according to the Schedule of Activities ([Appendix 2](#)).

Any clinically significant findings from the QIDS-SR16 assessment that result in a diagnosis and that occur after the patient receives the first dose of study treatment are to be reported to Lilly or its designee as AEs via CRF.

The QIDS-SR16 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, 4th Edition (APA 1994). 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 are (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. Additional information and the QIDS-SR16 questions may be found at the University of Pittsburgh IDS/QIDS internet page (<http://www.ids-qids.org/>).

#### **8.4.8. Columbia Suicide Severity Rating Scale**

The C-SSRS (Posner et al. 2007, Columbia University Medical Center [WWW]) is a scale that captures the occurrence, severity, and frequency of suicide-related ideations and behaviors during the assessment period. The C-SSRS must be administered by appropriately trained site personnel. The tool was developed by the National Institute of Mental Health (NIMH) Treatment of Adolescent Suicide Attempters (TASA) trial group for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) categorization of suicidal events. Patients will be assessed according to the Schedule of Activities ([Appendix 2](#)).

The Self-Harm Supplement Form is a one-question form that is completed, at any visit, including baseline visits, that asks for the number of suicidal or nonsuicidal self-injurious behaviors the patient has experienced since the last assessment. For each unique event identified, a questionnaire (Self-Harm Follow-up Form) which collects supplemental information on the self-injurious behavior is to be completed. This information is then documented in the eCRF.

#### **8.4.9. Immunogenicity**

For each patient, an immunogenicity sample will be collected according to the Schedule of Activities ([Appendix 2](#)).

Additionally, a blood sample is to be collected, as soon as possible, for any patient who experiences a potential systemic allergic/hypersensitivity reaction during the study as judged by

the investigator. These samples will be tested for immunogenicity and PK, while other laboratory tests may be performed as needed to elucidate the cause of the allergic/hypersensitivity reaction.

#### **8.4.10. Safety Monitoring**

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

If a study patient experiences elevated ALT  $\geq 3$ xULN, alkaline phosphatase  $\geq 2$ xULN, or elevated total bilirubin  $\geq 2$ xULN, clinical and laboratory monitoring is to be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. For other AESIs or abnormal lab results, please refer to the appropriate protocol section that addresses these topics. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly clinical research physician/clinical research scientist regarding collection of specific recommended clinical information and follow-up laboratory tests (see [Appendix 4](#)).

##### **8.4.10.1. Neutropenia**

###### **8.4.10.1.1. During Treatment (Periods 2 and 3)**

**During treatment with investigational product**, patients with neutrophil counts  $<1500$  cells/ $\mu$ L ( $<1.50 \times 10^3/\mu$ L or  $<1.50$  GI/L) are to be managed for neutropenia as follows:

- $<500$  cells/ $\mu$ L ( $<0.50 \times 10^3/\mu$ L or  $<0.50$  GI/L), see Discontinuation Criteria (Section 7.1)
- $\geq 500$  cells/ $\mu$ L and  $<1000$  cells/ $\mu$ L ( $\geq 0.50 \times 10^3/\mu$ L and  $<1.00 \times 10^3/\mu$ L or  $\geq 0.50$  GI/L and  $<1.00$  GI/L), see Discontinuation Criteria (Section 7.1)
- $\geq 1000$  cells/ $\mu$ L and  $<1500$  cells/ $\mu$ L ( $\geq 1.00 \times 10^3/\mu$ L and  $<1.50 \times 10^3/\mu$ L or  $\geq 1.00$  GI/L and  $<1.50$  GI/L), and the patient has a concurrent infection that requires systemic anti-infective therapy (for example, antibiotic, antifungal agent, antiviral agent):
  - The dose of investigational product is to be withheld, the patient is to receive appropriate medical care, and a repeat test for neutrophil count is to be performed within 4 weeks from knowledge of the initial report. If the repeat neutrophil count has returned to  $\geq 1500$  cells/ $\mu$ L ( $\geq 1.50 \times 10^3/\mu$ L or  $\geq 1.50 \times 10^3/\mu$ L) and the infection has resolved or is resolving, the patient may resume dosing of investigational product and evaluation at scheduled visits. If the neutrophil count remains  $\geq 1000$  cells/ $\mu$ L and  $<1500$  cells/ $\mu$ L ( $\geq 1.00 \times 10^3/\mu$ L and  $<1.50 \times 10^3/\mu$ L or  $\geq 1.00$  GI/L and  $<1.50$  GI/L), investigational product is to continue to be withheld and a repeat neutrophil count is to again be performed within another 4 weeks. If, after 2 repeat tests, the neutrophil count still remains  $\geq 1000$  cells/ $\mu$ L and  $<1500$  cells/ $\mu$ L ( $\geq 1.00 \times 10^3/\mu$ L and  $<1.50 \times 10^3/\mu$ L or  $\geq 1.00$  GI/L and  $<1.50$  GI/L), and:

- the infection has not fully resolved, the patient will be discontinued from the study treatment.
- the infection has resolved, the patient may resume dosing and evaluation at scheduled visits. However, if resumption of dosing is not deemed appropriate by the investigator, the patient will be discontinued from the study treatment.
- $\geq 1000$  cells/ $\mu\text{L}$  and  $< 1500$  cells/ $\mu\text{L}$  ( $\geq 1.00 \times 10^3/\mu\text{L}$  and  $< 1.50 \times 10^3/\mu\text{L}$  or  $\geq 1.00$  GI/L and  $< 1.50$  GI/L), and the patient has no concurrent infection that requires systemic anti-infective therapy (for example, antibiotic, antifungal agent, antiviral agent):
  - Dosing may continue, and a repeat neutrophil count is to be performed 4 to 8 weeks from knowledge of the initial report. Testing may be at a regularly scheduled visit or at an unscheduled visit, as necessary.

Repeat testing is to be performed at 4- to 8-week intervals until the neutrophil count has returned to  $\geq 1500$  cells/ $\mu\text{L}$  ( $\geq 1.50 \times 10^3/\mu\text{L}$  or  $\geq 1.50$  GI/L). If the patient has 3 or more postbaseline neutrophil counts of  $\geq 1000$  cells/ $\mu\text{L}$  ( $\geq 1.00 \times 10^3/\mu\text{L}$  or  $\geq 1.00$  GI/L) and  $< 1500$  cells/ $\mu\text{L}$  ( $< 1.50 \times 10^3/\mu\text{L}$  or  $< 1.50$  GI/L), no value of  $< 1000$  cells/ $\mu\text{L}$  ( $< 1.00 \times 10^3/\mu\text{L}$  or  $< 1.00$  GI/L), and no postbaseline infection requiring systemic anti-infective therapy, the patient may continue or resume further evaluation at scheduled visits, as deemed appropriate by the investigator.

If a patient without initial concurrent infection develops an infection that requires systemic anti-infective therapy, then the patient is to be managed as indicated above for patients with concurrent infection.

#### **8.4.10.1.2. At Early Termination Visit**

*For patients not enrolling in Study RHBV:* If, at the last scheduled study visit, the patient's neutrophil count is  $< 1500$  cells/ $\mu\text{L}$  ( $< 1.50 \times 10^3/\mu\text{L}$  or  $< 1.50$  GI/L) and less than the patient's baseline neutrophil count, the following measures are to be taken:

- *Patients with Concurrent Infection:* If there is a concurrent infection that requires systemic anti-infective therapy, the patient is to receive appropriate medical care and a repeat test for neutrophil count is to be performed at least Q4W (or sooner as appropriate) until resolution of infection. Upon resolution of infection, the neutrophil count is to be monitored using the required study visits in Post-Treatment Follow-Up Period (Period 4): Visit 801 (4 weeks post-resolution of infection), Visit 802 (8 weeks after Visit 801 unless otherwise specified), and Visit 803 (if necessary; 12 weeks after Visit 802); additional visits may be required depending on the degree of neutropenia. For patients with a neutrophil count below the abovementioned threshold at Week 52 who have already enrolled in Study RHBV, requirements for repeat test for neutrophil count will be specified in the Study RHBV protocol.

- *Patients without Concurrent Infection:* If there is no concurrent infection that requires systemic anti-infective therapy, the neutrophil count is to be monitored using the required study visits in the Post-Treatment Follow-Up Period (Period 4): Visit 801 (4 weeks post-ETV or last regularly scheduled visit), Visit 802, and Visit 803 (if necessary); additional visits may be required depending on the degree of neutropenia.

#### **8.4.10.1.3. Post-Treatment Follow-Up Period**

For patients not enrolling in Study RHBV, at Visit 801 and subsequent visits, the following monitoring applies:

- As long as a patient's neutrophil count is  $<1000$  cells/ $\mu\text{L}$  ( $<1.00 \times 10^3/\mu\text{L}$  or  $<1.00$  GI/L) at any follow up visit, the patient is to return for visits at least Q4W (may require unscheduled visits).
- As long as a patient's neutrophil count is  $\geq 1000$  cells/ $\mu\text{L}$  and  $<1500$  cells/ $\mu\text{L}$  ( $\geq 1.00 \times 10^3/\mu\text{L}$  and  $<1.50 \times 10^3/\mu\text{L}$  or  $\geq 1.00$  GI/L and  $<1.50$  GI/L) at any follow-up visit, the patient is to return for additional visit(s) at least every 4 to 8 weeks (may require unscheduled visits).
- If, at Visit 802 or Visit 803, the patient's neutrophil count is  $\geq 1500$  cells/ $\mu\text{L}$  ( $\geq 1.50 \times 10^3/\mu\text{L}$  or  $\geq 1.50$  GI/L) or greater than or equal to the patient's baseline neutrophil count (whichever is lower), the patient's participation in the study will be considered complete unless the investigator deems additional follow-up may be necessary.

If, at Visit 803, the patient's neutrophil count remains  $<1500$  cells/ $\mu\text{L}$  ( $<1.50 \times 10^3/\mu\text{L}$  or  $<1.50$  GI/L) and less than the patient's baseline neutrophil count, or if the investigator deems additional follow-up may be necessary, the investigator in consultation with Lilly, or qualified designee, will determine the appropriate management of the patient and the appropriate timing of additional contact(s) or visit(s).

#### **8.4.10.2. Hepatitis B Monitoring**

Patients that are HBcAb+ at screening, regardless of other hepatitis B testing results, will have a serum HBV DNA specimen obtained to be analyzed by the central laboratory. Such patients that are determined to be HBV DNA negative (undetectable) may be enrolled into the study with required HBV DNA monitoring every 3 to 4 months during treatment and 12 weeks after the last dose of ixekizumab. Patients that are found to be HBV DNA positive (detectable) at screening will be excluded from the trial.

If the result of any subsequent HBV DNA testing is positive, the patient is to be discontinued from the study treatment, is to continue safety follow up, and is to receive appropriate follow-up medical care, including consideration for antiviral therapy. A specialist physician in the care of patients with hepatitis (for example, infectious disease or hepatologist subspecialists) is to be consulted and potentially start antiviral therapy prior to discontinuation of any immunosuppressant or immunomodulatory therapy (including investigational drug). Timing of discontinuation from the study and of any immunosuppressant/immunomodulatory therapy



(including investigational product) needs to be based on the recommendations of the consulting specialist physician in conjunction with the investigator and medical guidelines/standard of care.

#### 8.4.10.3. Hypertension

Patients who experience changes in BP (systolic BP at  $\geq 160$  mm Hg plus  $\geq 20$  mm Hg increase from baseline [Week 0; Visit 2]; and/or diastolic BP at  $\geq 100$  mm Hg plus  $\geq 10$  mm Hg increase from baseline) on 2 consecutive visits are to receive intervention for the management of hypertension. Intervention could include the maximal intervention of withholding the dose of investigational product and/or the introduction of anti-hypertensive agent(s) as medically appropriate.

### 8.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities ([Appendix 2](#)), blood samples of approximately 4 mL each will be collected to determine the serum concentrations of ixekizumab. These blood samples for PK analysis are matched to the timing of samples for the assessment of immunogenicity. It is expected that these PK samples will allow sufficient description of ixekizumab PK profiles at steady state throughout the study. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Samples collected for PK analysis will be tested at a laboratory approved by Lilly or its designee. Concentrations of immunoreactive ixekizumab in human serum will be determined by a validated method.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last patient visit for the study.

### 8.6. Pharmacodynamics

Refer to Section [9.6](#).

### 8.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities ([Appendix 2](#)) where local regulations and ERBs allow. These samples are not being collected to create a biobank for conducting unspecified disease or population genetic research either now or in the future. Samples may be used to investigate variable response to ixekizumab and to investigate genetic variants thought to play a role in axSpA and/or associated autoimmune/inflammatory conditions. Assessment of variable response may include evaluation of AEs or differences in efficacy. These studies may include but are not limited to axSpA and/or associated autoimmune/inflammatory conditions to evaluate their association with observed response to ixekizumab.

All pharmacogenetic 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 destroyed according to a process consistent with local regulations.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by the sponsor. 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 drug development or when the drug is commercially available.

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

## 8.8. Biomarkers

Urine, serum, plasma, RNA, and whole blood for epigenetics samples will be collected for non-genetic biomarker research at the times specified in the Schedule of Activities ([Appendix 2](#)) where local regulations and ERBs allow. Samples will be used for research on the drug target, disease process, pathways associated with axSpA and/or associated autoimmune/inflammatory conditions, MoA of ixekizumab, and/or research method, or in validating diagnostic tools or assay(s) related to axSpA and/or associated autoimmune/inflammatory conditions.

All biomarker 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 destroyed according to a process consistent with local regulations.

Samples will be retained for a maximum 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits, at a facility selected by the sponsor. 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 drug development or when the drug is commercially available.

### 8.8.1. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine antibody production against the investigational product(s) as specified in the Schedule of Activities ([Appendix 2](#)). Immunogenicity will be assessed using a validated assay designed to detect ADA in the presence of the investigational product(s). Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the investigational product(s). Anti-drug antibodies against active comparators may also be assessed.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if regulations and ERBs impose shorter time limits, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the ixekizumab.

## 8.9. Health Economics

Refer to Section [8.1.2](#).

## 9. Statistical Considerations and Data Analysis

### 9.1. Determination of Sample Size

Approximately 320 patients will be randomized at a 1:1:1:1 ratio in the Blinded Treatment Dosing Period (Period 2) to ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, adalimumab 40 mg Q2W, and placebo. With 80 patients per treatment group, this study will have approximately 96% power to test the superiority of ixekizumab Q2W to placebo for the ASAS40 at Week 16. The following assumptions were used for the power calculations for ASAS40 response rates at Week 16 regardless of starting dose: 44% for ixekizumab 80mg Q2W treatment group and 16% for the placebo group. A 2-sided Fisher's exact test at the 0.05 level is assumed. These assumptions are based on the review of historical clinical studies in rad-axSpA (etanercept, adalimumab, infliximab, certolizumab, and golimumab [Davis et al. 2003; van der Heijde et al. 2005 and 2006; Inman et al. 2008; Landewe et al. 2014]) and recent secukinumab data in patients who are TNF-naive (Baeten et al. 2014b; Sieper et al. 2014).

### 9.2. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly.

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

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 (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

Complete details of the planned analyses will be documented in the SAP.

#### 9.2.1. General Considerations for Analyses during the Blinded Treatment Dosing Period (Period 2)

Comparisons between each ixekizumab regimen (80 mg Q2W or 80 mg Q4W) and placebo, as well as comparisons between adalimumab and placebo, will be performed for all analyses in Period 2.

Period 2 starts at the first injection of study treatment at Week 0 (Visit 2) and ends prior to the first injection of study treatment at Week 16 (Visit 8) or the ETV (between Weeks 0 and 16).

Baseline will be defined as the last available value before the first injection for efficacy, health outcomes and safety analyses. In most cases, this will be the measure recorded at Week 0 (Visit 2). For efficacy measures, if the patient does not take any injection, the last available value on or prior to randomization date will be used. Change from baseline will be calculated as the visit value of interest minus the baseline value. For safety analyses using a baseline period, the baseline period is defined as the time from Visit 1 to the date/time of the first injection.

The randomization to treatment groups is stratified by country and baseline CRP status (nonelevated or elevated) as described in Section 6.2. The countries will be categorized into geographic regions for analysis. Geographic regions will be defined in SAP upon country finalization. Unless otherwise specified, the statistical analysis models will adjust for geographic region and baseline CRP status.

Unless otherwise specified, treatment groups of ixekizumab 80 mg Q2W and Q4W will be analyzed without regard to starting dose.

The primary analysis method for treatment comparisons of categorical efficacy, health outcomes variables at specific time points will be made using a logistic regression analysis with treatment, geographic region, and baseline CRP status in the model. The odds ratio and 95% confidence intervals (CIs) will be reported; treatment difference and 95% CIs will also be reported. Secondary analysis will be conducted using a Fisher's exact test.

As a secondary analysis for the primary and major secondary categorical efficacy measures, a categorical mixed-effects model of repeated measures (categorical MMRM) estimating the percentage of patients achieving response across postbaseline visits may be used. The model will include treatment, geographic region, baseline CRP status, visit, treatment-by-visit as fixed factors, as well as the continuous, fixed covariate of baseline value and baseline value-by-visit interaction (when appropriate). The binomial distribution and the logit link will be used. An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The Newton-Raphson with ridging optimization technique will be used to aid with convergence. The probability of response, the corresponding 2-sided 95% CI, and the p-value for treatment comparisons at Week 16 (Visit 8) and all other postbaseline visits will be reported.

If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, followed by the compound symmetry, will be used. This order is specified according to a decreasing number of covariance parameters in the structure. The sandwich estimator (Diggle et al. 1994) for the covariance estimation will be used by specifying the EMPIRICAL option in SAS PROC MIXED. When sandwich estimation is used, the Kenward-Roger approximation for denominator degrees of freedom cannot be used. Instead, the DDFM=BETWITHIN option will be used to estimate denominator degrees of freedom.

The primary analyses for continuous efficacy and health outcomes variables will be made using MMRM. A secondary analysis for continuous efficacy and health outcomes variables will be made using analysis of covariance (ANCOVA).

When the MMRM is used, the model will include treatment, geographic region, baseline CRP status, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors. The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the similar approach specified above for categorical MMRM will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III tests for the least-squares (LS) means

will be used for the statistical comparison; the 95% CI will also be reported. Treatment group comparisons with placebo at Week 16 (Visit 8) and all other visits will be tested.

When the ANCOVA is used, the model will include treatment, geographic region, baseline CRP status and baseline value. Type III sums of squares for the LS means will be used for the statistical comparison; the 95% CI will also be reported.

The impact of ixekizumab starting dose of 160 mg versus 80 mg on time to onset (focus on Week 4) and treatment response during Period 2 (focus on Week 16) will be summarized and evaluated; details will be specified in the SAP.

For variables that are not collected at each postbaseline visit, data may exist at visits where the variable was not scheduled to be collected, due to early discontinuation visits. In these situations, data from the early discontinuation visit that do not correspond to the planned collection schedule will be excluded from the MMRM and categorical MMRM analyses. However, the data will still be used in other analyses, including shift analyses, change from baseline to last observation carried forward (LOCF) or modified baseline observation carried forward (mBOCF) endpoint analyses, and other categorical analyses.

Fisher's exact test will be used for all AE, baseline, discontinuation, and other categorical safety data. Continuous vital sign and laboratory values will be analyzed by an ANCOVA with treatment and baseline value in the model.

### **9.2.2. General Considerations for Analyses during the Extended Treatment Period (Period 3)**

Unless otherwise specified, Period 3 starts at the first injection of study treatment at Week 16 (Visit 8) and ends on the date of Week 52 (Visit 15) or the ETV (between Weeks 16 and 52).

For the efficacy and health outcomes analyses, baseline is defined as the last available value before the first injection in Period 2 and, in most cases, will be the value recorded at Week 0 (Visit 2).

Unless otherwise specified, for the safety analyses during Period 3, baseline is defined as the last available value before first injection of ixekizumab in Period 3. In most cases, this will be the measure recorded at Week 16 (Visit 8).

All efficacy and safety data collected will be summarized using descriptive statistics.

### **9.2.3. General Considerations for Analyses during the Post-Treatment Follow-Up (Period 4)**

For the safety analyses during Period 4, baseline is defined as the last nonmissing assessment on or prior to entering Period 4, that is, on or prior to Week 52 (Visit 15), or ETV.

Safety data collected will be summarized using descriptive statistics.

### 9.2.4. *Analysis Populations*

The following analysis populations will be used:

**Intent-to-Treat Population (ITT):** Unless otherwise specified, efficacy and health outcomes analyses for Period 2 will be conducted on the ITT population, defined as all randomized patients, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Patients will be analyzed according to the treatment to which they were assigned.

**Per-Protocol Set (PPS):** In addition, the primary efficacy analysis will be repeated using the PPS, which is defined as all randomized patients who are compliant with therapy, who do not have significant protocol deviations, and whose investigator site does not have significant GCP issues that require a report to the regulatory agencies prior to Week 16 (Visit 8). Compliance with therapy is defined to be missing no more than 20% of expected doses, not missing 2 consecutive doses (all injections at a visit are counted as 1 dose) and not have any occurrence of double-dosing (that is, took more injections at the same time point than specified in the protocol) during Period 2.

Significant protocol deviations will be described in the SAP. Patients will be analyzed according to the treatment to which they were assigned.

**Safety Population:** Safety analyses for Period 2 will be conducted on the Safety Population, defined as all randomized patients who received at least 1 dose of study treatment. Patients will be analyzed according to the treatment to which they were assigned in that period.

**Extended Treatment Period Population:** Efficacy, health outcomes, and safety analyses for Period 3 will be conducted on the Extended Treatment Period Population, defined as all patients who received at least 1 dose of ixekizumab treatment during Period 3.

**Follow-Up Population:** Safety analyses for Period 4 will be conducted on the Follow-Up Population, defined as all randomized patients who received at least 1 dose of study treatment and have entered the Period 4. Patients will be analyzed according to the treatment they received before entering the Period 4.

### 9.2.5. *Missing Data Imputation*

In accordance with precedent set with other Phase 3 axSpA trials (van der Heijde et al. 2006; Inman et al. 2008), the following methods for imputation of missing data will be used:

#### 9.2.5.1. **Nonresponder Imputation**

Analysis of categorical efficacy and health outcomes variables will be assessed using a nonresponder imputation (NRI) method. Patients will be considered nonresponders for the NRI analysis if they do not meet the clinical response criteria or have missing clinical response data at the primary analysis time point. All nonresponders at Week 16 (Visit 8), as well as all patients who discontinue study treatment at any time prior to Week 16 for any reason, will be defined as nonresponders for the NRI analysis at Week 16. Randomized patients without at least 1 postbaseline observation will also be defined as nonresponders for the NRI analysis.

The NRI may be applied at any time point specified for analysis.

#### **9.2.5.2. Modified Baseline Observation Carried Forward**

An mBOCF analysis will be performed on efficacy and health outcomes variables in the major and other secondary objectives. For patients discontinuing study drug due to an AE, the baseline observation will be carried forward to the corresponding time point for evaluation. For patients discontinuing study drug for any other reason, the last nonmissing observation before discontinuation will be carried forward to the corresponding time point for evaluation. Randomized patients without at least 1 postbaseline observation will not be included for evaluation with the exception of patients discontinuing study treatment because of an AE.

#### **9.2.5.3. Last Observation Carried Forward**

A LOCF analysis will be performed on continuous efficacy and health outcomes variables in the major secondary objectives. This approach is identical to the mBOCF approach, with one exception: For patients discontinuing study drug because of an AE, the last nonmissing postbaseline observation before discontinuation will be carried forward to the corresponding endpoint for evaluation. Randomized patients without any postbaseline observation will not be included for evaluation.

#### **9.2.6. Adjustment for Multiple Comparisons**

A multiple testing strategy for the primary and major secondary objectives will be implemented to control the overall family-wise type I error rate at a 2-sided  $\alpha$  level of 0.05. A graphical multiple testing procedure (Bretz et al. 2011) will be used (Figure RHBV.2). The graphical approach is a closed testing procedure, hence it strongly controls the family-wise error rate (Alosh et al. 2014). The following is a list of primary and major secondary outcomes to be tested for both ixekizumab 80 mg Q2W and Q4W regimens at Week 16:

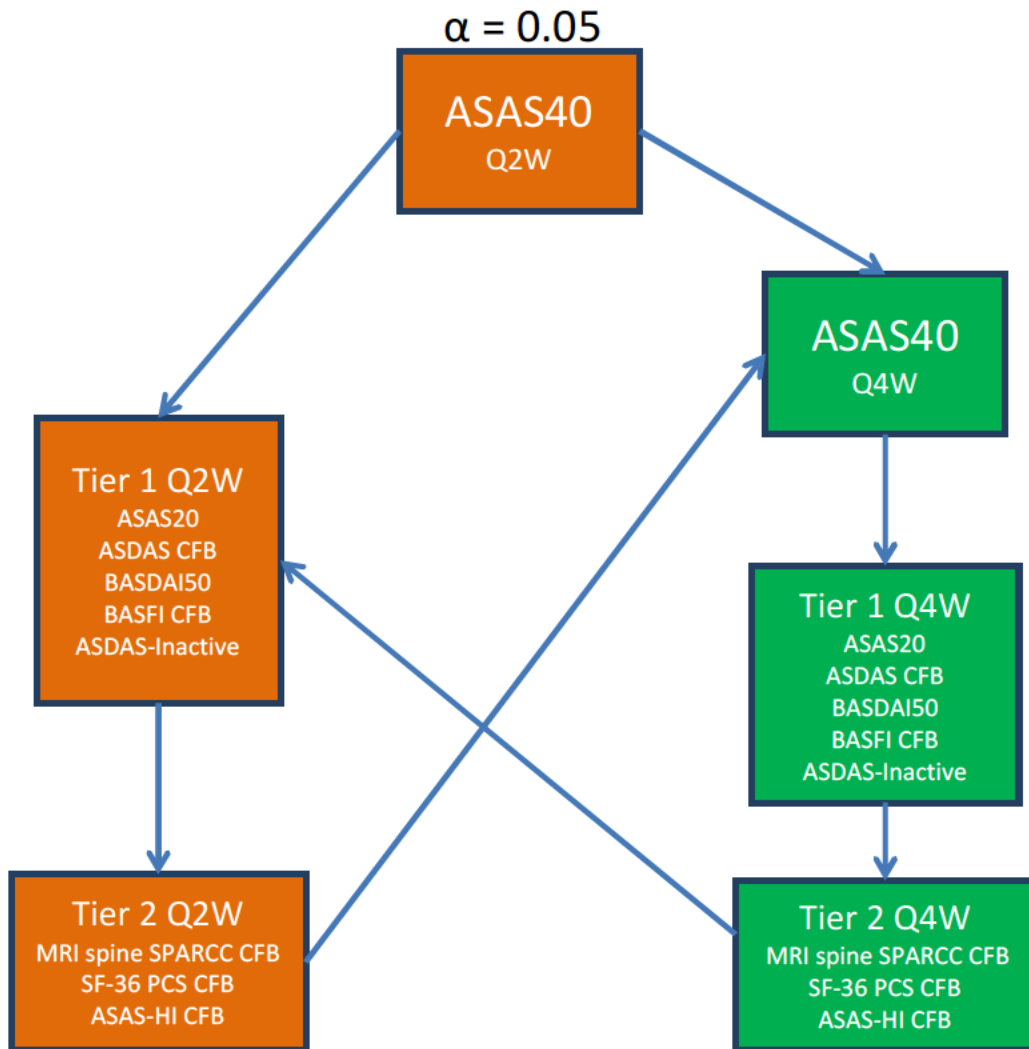
- Primary: proportion of patients achieving an ASAS40 response [ASAS40]
- Secondary 1: proportion of patients achieving an ASAS20 response [ASAS20]
- Secondary 2: change from baseline in ASDAS score [ASDAS CFB]
- Secondary 3: proportion of patients achieving BASDAI50 [BASDAI50]
- Secondary 4: change from baseline in BASFI [BASFI CFB]
- Secondary 5: proportion of patients achieving ASDAS inactive disease [ASDAS inactive]
- Secondary 6: change from baseline in MRI of the spine [MRI spine SPARCC score CFB]
- Secondary 7: change from baseline in SF-36 PCS score [SF-36 PCS CFB]
- Secondary 8: change from baseline in ASAS-HI [ASAS-HI CFB]

The 8 secondary outcomes are grouped into 2 tiers (Figure RHBV.2) based on the clinical importance as well as statistical significance observed in historical axSpA studies.

Figure RHBV.2 shows a general form of the graphical testing scheme. The primary outcome of ASAS40 will be tested for ixekizumab 80 mg Q2W versus placebo at a 2-sided  $\alpha=0.05$ . If the null hypothesis is not rejected, no further testing is conducted as the  $\alpha$  for that test is considered

“spent” and cannot be passed to other endpoints. If the null hypothesis is rejected, the  $\alpha$  will be distributed to the Tier 1 set of secondary outcomes for ixekizumab 80 mg Q2W and ASAS40 for ixekizumab 80 mg Q4W. The testing process continues for the remaining outcomes by allocating the remaining  $\alpha$  to the next set of outcomes as long as at least one hypothesis can be rejected. Each time a hypothesis is rejected, the graph is updated to reflect the reallocation of  $\alpha$ , which is considered “recycled” (Alosh et al. 2014). This iterative process of updating the graph and reallocating  $\alpha$  is repeated until all major secondary hypotheses have been tested or when no remaining hypotheses can be rejected at their corresponding  $\alpha$  levels. The weights along the edges for  $\alpha$  allocation between ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W outcomes as well as within each of the tiers will be prespecified in the SAP prior to the first patient randomization of the study.





Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; ASAS HI = ASAS Health Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CFB = change from baseline; SF-36 PCS = Short Form 36 physical component score; SPARCC = Spondyloarthritis Research Consortium of Canada; Q2W = every 2 weeks; Q4W = every 4 weeks.

**Figure RHBV.2. Illustration of graphical multiple testing procedure.**

There will be no adjustment for multiple comparisons for any other analyses.

### **9.3. Treatment Group Comparability**

#### **9.3.1. Patient Disposition**

All patients who prematurely discontinue from the study treatment and/or from the study will be identified, and the extent of their participation in the study will be reported.

Patient disposition will be summarized for each treatment period with reasons for discontinuation. The reasons for discontinuation during Period 2 will be compared between treatment groups using Fisher's exact test.

#### **9.3.2. Patient Characteristics**

Patient characteristics and baseline clinical measures will be summarized for each treatment period. Baseline characteristics will include sex, age, age category, weight, body mass index (BMI), race, geographic region, country, baseline disease activity (BASDAI), duration of disease, HLA-B27 positivity, baseline CRP (% of nonelevated or elevated), baseline MRI status, and history of extra-axial disease manifestations. Baseline clinical measurements may include ASDAS, CRP, BASFI, BASMI, chest expansion, Fatigue NRS, Patient Global NRS, total back pain, spinal pain at night due to AS, spinal pain due to AS, inflammation (mean of questions 5 and 6 of BASDAI), MASES, SPARCC Enthesitis, TJC, and SJC.

Treatment group comparisons in Period 2 will be conducted using Fisher's exact test for categorical data and an analysis of variance (ANOVA) with treatment as a factor for continuous data.

#### **9.3.3. Concomitant Therapy**

Previous and concomitant medications will be summarized for patients who enter each treatment period and will be presented by WHO Anatomic Therapeutic Class Level 4 and WHO preferred term. Concomitant DMARDs, concomitant oral corticosteroids, and concomitant NSAIDs will also be summarized. Treatment group comparisons in Period 2 will be conducted using Fisher's exact test.

#### **9.3.4. Treatment Compliance**

Treatment compliance with investigational product will be summarized for patients who enter each treatment period. A patient will be considered overall compliant for each study period if he/she is missing no more than 20% of the expected doses, does not miss 2 consecutive doses and does not over-dose (that is, take more injections at the same time point than specified in the protocol).

Proportions of patients compliant by visit and overall will be compared between treatment groups during Period 2 using Fisher's exact test.

## 9.4. Primary and Secondary Analyses

### 9.4.1. Primary Analyses

The primary analysis, the proportion of patients with ASAS40 at Week 16 compared with placebo, will be based on the ITT Population. In addition, an analysis of the PPS Population will be used to support the primary efficacy analysis.

Treatment comparisons between each ixekizumab treatment group and placebo in the proportion of patients achieving an ASAS40 response at Week 16 (Visit 8) will be analyzed using the logistic regression model defined in Section 9.2.1. Missing data will be imputed using the NRI method described in Section 9.2.5.

Secondary analyses for ASAS40 at Week 16 will be conducted using categorical MMRM and Fisher's exact test as described in Section 9.2.1.

### 9.4.2. Secondary Analyses

#### 9.4.2.1. Major Secondary Analyses

The major secondary analyses at Week 16 will be based on the ITT population for Period 2. The major secondary comparisons will be based on the multiple testing procedure detailed in Section 9.2.6. Treatment comparisons in the proportion of patients achieving a categorical response at Week 16 (Visit 8) will be analyzed using the logistic regression model defined in Section 9.2.1. For categorical responses, missing data will be imputed using the NRI method described in Section 9.2.5. Treatment comparisons in the continuous measures will be analyzed using the MMRM model defined in Section 9.2.1.

Table RHBV.5 summarizes the primary and major secondary outcomes and analysis methods. All analyses listed will be performed based on the ITT Population unless otherwise specified.

**Table RHBV.5. Primary and Major Secondary Outcome Analyses**

Outcome Measure	Primary Analysis Method	Secondary Analysis Method
ASAS40 (primary efficacy outcome)	Logistic regression analysis with NRI	Categorical MMRM Fisher's exact test with NRI Logistic regression analysis with NRI on PPS
ASAS20 (major secondary outcome)	Logistic regression analysis with NRI	Categorical MMRM Fisher's exact test with NRI Logistic regression analysis with NRI on PPS
Change from baseline in ASDAS (major secondary outcome)	MMRM	ANCOVA with mBOCF/LOCF
BASDAI50 (major secondary outcome)	Logistic regression analysis with NRI	Categorical MMRM Fisher's exact test with NRI
Change from baseline in BASFI (major secondary outcome)	MMRM	ANCOVA with mBOCF/LOCF
ASDAS inactive disease (major secondary outcome)	Logistic regression analysis with NRI	Categorical MMRM Fisher's exact test with NRI
Change from baseline in MRI of spine [SPARCC score] (major secondary outcome)	ANCOVA with observed case analysis <sup>a</sup>	Secondary analysis maybe specified in SAP
Change from baseline in SF-36 PCS (major secondary outcome)	MMRM	ANCOVA with mBOCF/LOCF
Change from baseline in the ASAS-HI (major secondary outcome)	MMRM	ANCOVA with mBOCF/LOCF

Abbreviations: ANCOVA = analysis of covariance; ASAS = Assessment of Spondyloarthritis International Society; ASAS HI = Assessment of Spondyloarthritis International Society Health Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI50 = Bath Ankylosing Spondylitis Disease Activity Index 50; BASFI = Bath Ankylosing Spondylitis Functional Index; LOCF = last observation carried forward; mBOCF = modified baseline observation carried forward; MMRM = mixed-effects model of repeated measures; MRI = magnetic resonance imaging; NRI = nonresponder imputation; PPS = per-protocol set; SAP = statistical analysis plan; SF-36 PCS = Short Form-36 physical component scores; SPARCC = Spondyloarthritis Research Consortium of Canada.

<sup>a</sup> Only patients with both baseline and Week 16 MRI scores will be included in the observed case analysis.

#### **9.4.2.2. Other Secondary Efficacy Analyses**

There will be no adjustment for multiple comparisons. Analyses will be conducted for the other secondary efficacy objectives defined in Section 3. Specific details of analyses will be specified in the SAP.

##### **9.4.2.2.1. Period 2 (Blinded Treatment Dosing Period)**

Unless otherwise specified, the other secondary analyses during Period 2 will be based on the ITT Population.

Treatment comparisons in the proportion of patients achieving a categorical response at specified time points will be analyzed using the logistic regression model defined in Section 9.2.1.

Missing data will be imputed using the NRI method described in Section 9.2.5.

For all continuous efficacy variables that are collected at repeated visits, treatment group comparisons will be analyzed using the MMRM model defined in Section 9.2.1. No imputation methods are applied to MMRM analysis. Additional analyses will be conducted using the ANCOVA model defined in Section 9.2.1; missing data will be imputed by the mBOCF method as described in Section 9.2.5. For continuous efficacy variables that are collected only once within Period 2, analyses will be made using the ANCOVA model with the mBOCF method.

#### **9.4.2.2.2. Period 3 (Extended Treatment Period)**

Data collected in this study period will be summarized for the Extended Treatment Period Population. The within-treatment group comparisons may be conducted as appropriate.

#### **9.4.3. Other Exploratory Analyses**

Details about exploratory analyses will be included in the SAP or appropriate biomarker analysis plan.

### **9.5. Safety Analyses**

Safety will be assessed by summarizing and analyzing AEs including adjudicated cerebrocardiovascular events, laboratory analytes including neutrophil counts, QIDS-SR16, C-SSRS, and vital signs. The duration of treatment exposure will also be summarized

For Period 2 (Blinded Treatment Dosing Period), safety data will be summarized for the Safety Population. Treatment group comparisons will be performed on categorical safety data using Fisher's exact test as described in Section 9.2.1; continuous safety data will be analyzed by an ANCOVA model.

For Period 3 (Extended Treatment Period), the safety data will be summarized and no treatment group comparisons will be performed.

For Period 4 (Post-Treatment Follow-Up Period), safety data will be summarized according to the treatment patients were on prior to entering Period 4.

The categorical safety measures will be summarized with incidence rates. The mean change of the continuous safety measures will be summarized by visits.

Further details will be described in the SAP.

#### **9.5.1. Adverse Events**

Adverse events are classified based upon the Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline and on or prior to the date of the last visit within the treatment period. Both the date/time of the event onset and the date/time of the first study drug injection are considered when determining TEAEs. Treatment-emergent adverse events will be assigned to the treatment period in which they first occurred or worsened. A follow-up emergent adverse event (FEAE) is defined as an event that first occurred or worsened in severity after the date of Week 52 (Visit 15) or the ETV. For events that are gender specific, the denominator and computation of the percentage will include only patients from the given gender.

An overall summary of AEs will be provided for each of the treatment periods, including the number and percentage of patients who experienced TEAEs, TEAEs by maximum severity, deaths, SAEs, TEAEs related to study drug, discontinuations from the treatment due to an AE, and treatment-emergent AESIs. Treatment-emergent adverse events (all, by maximum severity, and TEAEs possibly related to study drug by the investigator), SAEs including deaths, and AEs that lead to treatment discontinuation will be summarized and analyzed by MedDRA system organ class (SOC) and preferred term.

In addition to general safety parameters, safety information on specific topics of AESIs will also be presented. Potential AESIs will be identified by a standardized MedDRA query (SMQ) or a Lilly defined MedDRA preferred term listing.

Follow-up emergent adverse events, SAEs including deaths, and AEs that lead to study discontinuation will be summarized for Period 4.

### **9.5.2. Clinical Laboratory Tests**

Laboratory assessments will be presented as mean changes from baseline, and as incidence of treatment-emergent abnormal, high, or low laboratory values (see below). Shift tables will be presented for selected parameters.

- For categorical lab tests:
  - Treatment-emergent **abnormal** value = a change from normal at all baseline visits to abnormal at any time postbaseline.
- For continuous lab tests:
  - Treatment-emergent **high** value = a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time postbaseline.
  - Treatment-emergent **low** value = a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time postbaseline.

### **9.5.3. Vital Signs, Physical Findings, and Other Safety Evaluations**

Vital signs will be presented as mean changes from baseline and as incidence of treatment-emergent high or low values (see below) and will be summarized both pre- and postdose at Week 0 (Visit 2), Week 16 (Visit 8) and Week 20 (Visit 9) as applicable.

- For treatment-emergent high and low:

- A treatment-emergent high result is defined as a change from a value less than or equal to the high limit at baseline to a value greater than the high limit at any time that meets the specified change criteria during the treatment period.
- A treatment-emergent low result is defined as a change from a value greater than or equal to the low limit at baseline to a value less than the low limit at any time that meets the specified change criteria during the treatment period.

The maximum postbaseline QIDS-SR16 total score will be summarized by treatment group, and a shift table will be produced for the change from baseline in QIDS-SR16 total score category.

Suicide-related thoughts and behaviors and self-injurious behavior with no suicidal intent, based on the C-SSRS, will be listed by patient.

## 9.6. Pharmacokinetic/Pharmacodynamic/Immunogenicity Analyses

Observed ixekizumab serum concentrations will be summarized by treatment regimen, visits and corresponding time when sampling occurred.

As appropriate, the PK and the exposure-response relationship between ixekizumab exposure and clinically important efficacy measures (for example, ASAS40 or ASAS20) may be explored using graphical methods and/or a modeling approach. Pharmacokinetic and/or exposure-response data from this study may be combined with existing PK and/or exposure-response data from other studies, if considered appropriate.

If a trend or statistically significant difference between the ixekizumab dose cohorts and/or the placebo cohort is noted in any safety endpoint, the exposure relationship for this endpoint may be explored graphically.

In addition, the potential impact of immunogenicity on ixekizumab exposure and/or efficacy responses may be evaluated by graphical assessments, as appropriate, to compare drug exposure or efficacy responses between ADA negative and ADA positive patients at corresponding visits, or before and after ADA development for patients who develop ADA. Both treatment-emergent only and all ADA positive/negative patients may be explored. A similar approach may be taken if patients become NAb positive. The effect of immunogenicity may be evaluated as a covariate in the population PK and exposure-response analyses, if applicable.

## 9.7. Other Analyses

### 9.7.1. Health Economics

There will be no adjustment for multiple comparisons. Analyses will be conducted for the other secondary health outcomes objectives as defined in Section 3.

#### Period 2 (Blinded Treatment Dosing Period):

Unless otherwise specified, the other secondary analyses during Period 2 will be based on the ITT population.

Treatment comparisons in the proportion of patients achieving a categorical response at specified time points will be analyzed using the logistic regression model defined in Section 9.2.1. Missing data will be imputed using the NRI method described in Section 9.2.5.

For all continuous health outcomes variables that are collected at repeated visits, treatment group comparisons will be analyzed using the MMRM model defined in Section 9.2.1. No imputation methods are applied to MMRM analysis. Additional analyses will be conducted using the ANCOVA model defined in Section 9.2.1; missing data will be imputed by the mBOCF method as described in Section 9.2.5. For continuous health outcomes variables that are collected only once within the Period 2, analyses will be made using the ANCOVA model with the mBOCF method.

### **Period 3 (Extended Treatment Period):**

Data collected in Period 3 will be summarized for the Extended Treatment Period Population. The within-treatment group comparisons may be conducted as appropriate.

Additional analyses of health outcomes measures will be specified in the SAP.

### **9.7.2. Subgroup Analyses**

Subgroup analyses will be conducted for ASAS40 and selective major secondary outcomes (defined in the SAP) at Week 16 (Visit 8) using the ITT Population.

Subgroup analyses may be conducted based on gender, age category, race, baseline disease severity, country, geographic region, baseline CRP status, baseline MRI status, presence of HLA-B27.

For ASAS40, a logistic regression model with treatment, subgroup, and the interaction of subgroup-by-treatment included as factors will be used. The subgroup-by-treatment interaction will be tested at the significance level of 0.10. Treatment group differences will be evaluated within each category of the subgroup using Fisher's exact test, regardless of whether the interaction is statistically significant. Missing data will be imputed using NRI as described in Section 9.2.5. If any group within the subgroup is <10% of the total population, only summaries of the efficacy data will be provided (that is, no inferential testing).

For continuous efficacy outcome (for example, mean change from baseline in ASDAS), an ANCOVA model with treatment, baseline value, subgroup, and the interaction of subgroup-by-treatment will be used. The subgroup-by-treatment interaction will be tested at the significance level of 0.10. Treatment group differences will be evaluated within each category of the subgroup using an ANCOVA model with treatment and baseline value as a covariate, regardless of whether the interaction is statistically significant. Missing data will be imputed using the mBOCF method as described in Section 9.2.5.

Detailed description of the subgroup variables will be provided in the SAP. Additional subgroup analyses on efficacy or subgroup analyses on safety may be performed as deemed appropriate and necessary.



### 9.7.3. Immunogenicity

The analyses of ADA effects will be conducted on all evaluable patients within the defined safety population. Evaluable patients will be defined as either a) patients with an evaluable baseline sample and at least 1 evaluable postbaseline sample (that is, sample after administration of study drug); or b) patients with no evaluable baseline sample whose evaluable postbaseline samples were all ADA negative.

A TE-ADA positive patient will be defined as any occurrence of a  $\geq 4$ -fold or 2 dilution increase in immunogenicity titer over the baseline titer. This is equivalent to an increase in titer to  $\geq 1:10$ , in the case of a negative result at baseline. The frequency and percentage (incidence) of patients with positive, negative, or inconclusive ADA at baseline and postbaseline (and NAb at baseline and postbaseline) will be summarized by treatment group. Patients who are TE-ADA positive, TE-ADA persistent positive, and TE-ADA transient positive will also be summarized.

The potential impact of immunogenicity on ixekizumab exposure and/or efficacy responses will be evaluated, as appropriate.

Assessment of immunogenicity with respect to safety will include comparison of patients who experience TEAEs of systemic allergy/hypersensitivity and of injection-site reactions and who also develop treatment-emergent anti-ixekizumab antibody positivity with patients who experience the same types of TEAEs but who remain treatment-emergent anti-ixekizumab antibody negative. Anti-ixekizumab antibody titers will also be evaluated in anti-ixekizumab antibody positive patients who experience these events.

## 9.8. Interim Analyses

An interim database lock and unblinding will occur, and interim analyses will be performed at the time (that is, a cutoff date) the last patient completes Visit 8 (Blinded Dosing Treatment Period [Period 2], Week 16) or ETV. This interim database lock will include all data collected by the cutoff date including the data from the Extended Treatment Period (Period 3) and follow-up data from patients that have begun the Post-Treatment Follow-Up Period (Period 4). The analyses from the Week 16 lock will be treated as a primary analysis because all primary and major secondary study objectives will be assessed at this time.

Additional analyses and snapshots of study data may be performed during the Period 3 or after completion of Period 4 to fulfill the need for regulatory interactions or publication purposes.

Unblinding details are specified in the blinding/unblinding plan.

## 10. Study Governance Considerations

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

#### 10.1.1. Informed Consent

The investigator is responsible for ensuring:

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

#### 10.1.2. Ethical Review

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

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

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

- the current IB and updates during the course of the study
- adalimumab package insert
- ICF
- relevant curricula vitae

#### 10.1.3. Regulatory Considerations

This study will be conducted in accordance with:

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

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

#### **10.1.4. Investigator Information**

Licensed physicians with a specialty in rheumatology (for Japan: specialty in rheumatology or orthopedic surgery) will participate as investigators in this clinical trial.

#### **10.1.5. Protocol Signatures**

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

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

#### **10.1.6. Final Report Signature**

The 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 CSR coordinating investigator will be selected by the sponsor. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

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

### **10.2. Data Quality Assurance**

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

- provide instructional material to the study sites, as appropriate.
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the 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.

### **10.2.1. Data Capture System**

An electronic data capture system and an electronic source 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. Some or all of a patient's data will be directly entered into the eCRF at the time that the information is obtained. In instances where direct data entry is not used, the site will maintain source documentation in the trial files, and the patient's data will be transcribed into the eCRF. Paper documentation provided by the patient will serve as the source document, including a study drug administration log and an event-medication diary, that will be identified and documented by each site in that site's study file.

In this study, patient-rated scales/questionnaires will be collected at office visits (or even at home) directly via an electronic patient-reported outcome (ePRO) tablet device as part of an ePRO/Clinical Outcome Assessment (COA) system. Data entered into the ePRO/COA system will serve as the source data. Electronic PRO records are stored at a third party site. Investigator sites will have continuous access to the source data during the study and will receive an archival copy at the end of the study for retention. Any data collected within the ePRO instrument will serve as the source data and will be identified and documented by each site in that site's study file.

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

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

## **10.3. Study and Site Closure**

### **10.3.1. Discontinuation of Study Sites**

Study site participation may be discontinued if Lilly 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.

### **10.3.2. 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.

## 11. References

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## Appendix 1. Abbreviations and Definitions

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Term	Definition
<b>AE</b>	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.
<b>AESI</b>	adverse event of special interest
<b>ALT</b>	alanine aminotransferase
<b>ANCOVA</b>	analysis of covariance
<b>AS</b>	ankylosing spondylitis: currently referred to as radiographic axial spondyloarthritis (rad-axSpA)
<b>ASAS</b>	Assessment of Spondyloarthritis International Society
<b>ASAS HI</b>	Assessment of Spondyloarthritis International Society Health Index
<b>ASDAS</b>	Ankylosing Spondylitis Disease Activity Score. In this study, it refers to the ASDAS <sub>crp</sub> score which includes high sensitivity C-reactive protein (CRP).
<b>ASSpiMRI-Berlin</b>	Ankylosing Spondylitis Spinal Magnetic Resonance Imaging Activity–Berlin Score
<b>AST</b>	aspartate aminotransferase
<b>axSpA</b>	axial spondyloarthritis: a single disease entity with a subset defined by the presence of clear structural damage (rad-axSpA) and a subset with no clear structural damage as defined by conventional x-rays (nonrad-axSpA)
<b>BASDAI50</b>	Bath Ankylosing Spondylitis Disease Activity Index 50
<b>BASFI</b>	Bath Ankylosing Spondylitis Functional Index
<b>BASMI</b>	Bath Ankylosing Spondylitis Metrology Index
<b>bDMARD</b>	biological disease-modifying antirheumatic drug
<b>blinding</b>	<p>A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not.</p> <p>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.</p>
<b>cDMARD</b>	conventional disease-modifying antirheumatic drug

<b>Term</b>	<b>Definition</b>
<b>CEC</b>	Clinical Events Committee
<b>complaint</b>	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.
<b>CRP</b>	C-reactive protein
<b>C-SSRS</b>	Columbia–Suicide Severity Rating Scale
<b>DMARD</b>	disease-modifying antirheumatic drug
<b>DVU</b>	disco-vertebral unit
<b>ECG</b>	electrocardiogram
<b>enroll</b>	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
<b>enter</b>	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
<b>EQ-5D-5L</b>	European Quality of Life–5 Dimensions–5 Level
<b>GCP</b>	good clinical practice
<b>IB</b>	Investigator’s Brochure
<b>IBD</b>	inflammatory bowel disease (eg, Crohn’s disease and ulcerative colitis)
<b>ICF</b>	informed consent form
<b>investigational product</b>	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.
<b>ITT</b>	intent-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
<b>IWRS</b>	interactive web-response system
<b>JSEQ</b>	Jenkins Sleep Evaluation Questionnaire
<b>LOCF</b>	last observation carried forward
<b>MASES</b>	Maastricht Ankylosing Spondylitis Enthesitis Score

Term	Definition
<b>mBOCF</b>	modified baseline observation carried forward
<b>MMRM</b>	mixed-effects model of repeated measures
<b>mNY</b>	modified New York criteria
<b>MRI</b>	magnetic resonance imaging
<b>nonrad-axSpA</b>	nonradiographic axial spondyloarthritis: a subset of axSpA in which there is no clear structural damage as defined by conventional imaging
<b>NRI</b>	nonresponder imputation
<b>NRS</b>	numeric rating scale
<b>NSAID</b>	nonsteroidal anti-inflammatory drug
<b>PK/PD</b>	pharmacokinetics/pharmacodynamics
<b>PPS</b>	per-protocol set: The set of data generated by the subset of patients who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
<b>Q2W</b>	every 2 weeks
<b>Q4W</b>	every 4 weeks
<b>rad-axSpA</b>	radiographic axial spondyloarthritis: a subset of axSpA in which there is evidence of disease features on radiographic imaging
<b>SAE</b>	serious adverse event
<b>SAP</b>	statistical analysis plan
<b>screen</b>	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.
<b>SF-36 MCS</b>	Short Form 36 mental component score
<b>SF-36 PCS</b>	Short Form 36 physical component score
<b>SIJ</b>	sacroiliac joints
<b>SpA</b>	spondyloarthritis
<b>SPARCC</b>	Spondyloarthritis Research Consortium of Canada
<b>SPARCC SSS</b>	Spondyloarthritis Research Consortium of Canada–SIJ Structural Score
<b>TEAE</b>	treatment-emergent adverse event: Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.

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<b>Term</b>	<b>Definition</b>
<b>TNFi</b>	tumor necrosis factor inhibitor
<b>WPAI-SpA</b>	Work Productivity Activity Impairment–Spondyloarthritis

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## **Appendix 2. Schedule of Activities**

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## Schedule of Activities, Protocol I1F-MC-RHBV (Periods 1-2)

	Screening (Period 1)	Baseline Randomization	Blinded Treatment Dosing Period (Period 2) <sup>a</sup>					
	V1	V2	V3	V4	V5	V6	V7	V8
Weeks since Randomization		W0	W1	W2	W4	W8	W12	W16
Study Days	Up to -42 d	0	7 ± 2d	14 ± 2d	28 ± 2d	56 ± 4d	84 ± 4d	112 ± 4d
Informed consent	X							
Demographics <sup>b</sup>	X							
Physical examination <sup>c</sup>	X							X
Vital signs (BP and pulse) <sup>d</sup>	X	X <sup>d</sup>	X	X	X	X	X	X <sup>d</sup>
Weight <sup>bb</sup>	X	X			X	X	X	X
Height		X						
Habits <sup>e</sup>		X						
Body temperature		X						
Posterior anterior chest x-ray <sup>f</sup>	X							
Inclusion/exclusion criteria <sup>g</sup>	X	X						
Evaluate presence of SpA features	X	X						
Randomization		X						X
Concomitant medications	X	X	X	X	X	X	X	X
NSAID use	X	X	X	X	X	X	X	X
Preexisting conditions and medical history <sup>h</sup>	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
Eye Symptom Assessment <sup>i</sup>	X	X	X	X	X	X	X	X
Dispense IP		X		X	X	X	X	X
Administer IP on site <sup>j</sup>		X						X
IP compliance				X	X	X	X	X
Dispense SDAL		X		X	X	X	X	X
Collect, review, and enter data from SDAL		X		X	X	X	X	X

## Schedule of Activities, Protocol I1F-MC-RHBV (Periods 1-2)

CRF Visit (V) Number	Screening (Period 1)	Baseline Randomization	Blinded Treatment Dosing Period (Period 2) <sup>a</sup>					
	V1	V2	V3	V4	V5	V6	V7	V8
Weeks since Randomization		W0	W1	W2	W4	W8	W12	W16
Study Days	Up to -42 d	0	7 ± 2d	14 ± 2d	28 ± 2d	56 ± 4d	84 ± 4d	112 ± 4d
<b>Clinical Efficacy/Health Outcomes</b>								
MRIs of spine plus SIJ <sup>dd</sup>	X <sup>ee</sup>							X <sup>k</sup>
X-ray of the SIJ <sup>i</sup>	X							
X-ray of the spine <sup>m</sup>	X							
Linear BASMI		X				X		X
Chest expansion		X				X		X
Occiput to wall distance		X				X		X
Enthesitis (MASES and SPARCC)		X				X		X
Assessment of TJC/SJC (46/44)		X				X		X
Healthcare resource utilization		X				X		X
Patient Global Assessment of Disease Activity NRS	X	X	X	X	X	X	X	X
Spinal pain	X	X	X	X	X	X	X	X
BASFI	X	X	X	X	X	X	X	X
BASDAI	X	X	X	X	X	X	X	X
Fatigue NRS	X	X				X		X
SF-36	X	X			X	X		X
ASAS-HI	X	X			X	X		X
QIDS-SR16	X	X						X
C-SSRS <sup>n</sup>		X	X	X	X	X	X	X
Self-Harm Supplement Form <sup>n</sup>		X	X	X	X	X	X	X
EQ-5D-5L		X						X
WPAI-SpA		X						X
JSEQ		X				X		X

## Schedule of Activities, Protocol I1F-MC-RHBV (Periods 1-2)

	Screening (Period 1)	Baseline Randomization	Blinded Treatment Dosing Period (Period 2) <sup>a</sup>					
	V1	V2	V3	V4	V5	V6	V7	V8
CRF Visit (V) Number	V1	V2	V3	V4	V5	V6	V7	V8
Weeks since Randomization		W0	W1	W2	W4	W8	W12	W16
Study Days	Up to -42 d	0	7 ± 2d	14 ± 2d	28 ± 2d	56 ± 4d	84 ± 4d	112 ± 4d
<b>Laboratory Tests</b>								
HLA-B27 <sup>o</sup>	X							
CRP	XP	X	X	X	X	X	X	X
Administer PPD/Collect QuantiFERON®-TB Gold/ T-SPOT® <sub>q</sub>	X							
ECG	X							
FSH <sup>r</sup>	X							
HIV/HCV	X							
HBV	X <sup>s</sup>	X <sup>s</sup>					X <sup>s</sup>	
Serum pregnancy test <sup>t</sup>	X							
Urine pregnancy test <sup>t</sup>		X					X	
Serum chemistry	X	X			X	X	X	X
PTT, PT/INR	X							X
Lipid panel (fasting) <sup>u</sup>		X						X
Hematology	X	X			X	X	X	X
Urinalysis	X							X
TSH and freeT4	X							
Nonpharmacogenetic biomarker exploratory storage samples (urine, serum, plasma, RNA, and whole blood) <sup>v</sup>		X	X <sup>w</sup>	X <sup>w</sup>	X	X <sup>w</sup>	X <sup>w</sup>	X
Pharmacogenetic exploratory sample-(DNA) <sup>v, cc</sup>		X						
Immunogenicity testing <sup>x</sup>		X	X	X	X	X	X	X
PK sampling <sup>x,y</sup>		X	X	X	X	X	X	X

## Schedule of Activities, Protocol I1F-MC-RHBV (Period 3)

	Extended Treatment Period (Period 3) <sup>a</sup>							ETV
CRF Visit (V) Number	V9	V10	V11	V12	V13	V14	V15	ETV
Weeks since Randomization	W20	W24	W28	W32	W36	W44	W52	
Study Days	140 ± 4d	168 ± 4d	196 ± 4d	224 ± 4d	252 ± 4d	308 ± 7d	364 ± 7d	
Physical examination <sup>c</sup>							X	X
Vital signs (BP and pulse) <sup>d</sup>	X <sup>d</sup>	X	X	X	X	X	X	X
Weight <sup>bb</sup>	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
NSAID use	X	X	X	X	X	X	X	X
Preexisting conditions and medical history <sup>h</sup>	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
Eye Symptom Assessment <sup>i</sup>	X	X	X	X	X	X	X	X
Dispense IP	X	X	X	X	X	X		
Administer IP on site <sup>j</sup>	X							
IP compliance	X	X	X	X	X	X	X	X
Dispense SDAL	X	X	X	X	X	X		
Collect, review, and enter data from SDAL	X	X	X	X	X	X	X	X

## Schedule of Activities, Protocol I1F-MC-RHBV (Period 3)

	Extended Treatment Period (Period 3) <sup>a</sup>							ETV
CRF Visit (V) Number	V9	V10	V11	V12	V13	V14	V15	ETV
Weeks since Randomization	W20	W24	W28	W32	W36	W44	W52	
Study Days	140 ± 4d	168 ± 4d	196 ± 4d	224 ± 4d	252 ± 4d	308 ± 7d	364 ± 7d	
<b>Clinical Efficacy/Health Outcomes</b>								
MRI of spine plus SIJ <sup>dd</sup>							X <sup>z</sup>	X <sup>k</sup>
Linear BASMI		X			X		X	X
Chest expansion		X			X		X	X
Occiput to wall distance		X			X		X	X
Enthesitis (MASES and SPARCC)		X			X		X	X
Assessment of TJC/SJC (46/44)		X			X		X	X
Healthcare resource utilization			X		X		X	X
Patient Global Assessment of Disease Activity NRS	X	X	X	X	X	X	X	X
Spinal pain	X	X	X	X	X	X	X	X
BASFI	X	X	X	X	X	X	X	X
BASDAI	X	X	X	X	X	X	X	X
Fatigue NRS					X		X	X
SF-36					X		X	X
ASAS-HI					X		X	X
QIDS-SR16					X		X	X
C-SSRS <sup>n</sup>	X	X	X	X	X	X	X	X
Self-Harm Supplement Form <sup>n</sup>	X	X	X	X	X	X	X	X
EQ-5D-5L							X	X
WPAI-SpA							X	X
JSEQ					X		X	X

## Schedule of Activities, Protocol I1F-MC-RHBV (Period 3)

	Extended Treatment Period (Period 3) <sup>a</sup>							ETV
CRF Visit (V) Number	V9	V10	V11	V12	V13	V14	V15	ETV
Weeks since Randomization	W20	W24	W28	W32	W36	W44	W52	
Study Days	140 ± 4d	168 ± 4d	196 ± 4d	224 ± 4d	252 ± 4d	308 ± 7d	364 ± 7d	
<b>Laboratory Tests</b>								
CRP	X	X	X	X	X	X	X	X
HBV		X <sup>s</sup>			X <sup>s</sup>	X <sup>s</sup>	X <sup>s</sup>	X <sup>s</sup>
Urine pregnancy test <sup>t</sup>		X			X	X	X	X
Serum chemistry	X	X	X	X	X	X	X	X
PTT, PT/INR		X			X		X	
Lipid panel (fasting) <sup>u</sup>		X			X		X	
Hematology	X	X	X	X	X	X	X	X
Urinalysis		X			X		X	X
Nonpharmacogenetic biomarker exploratory storage samples (urine, serum, plasma, RNA, and whole blood) <sup>v</sup>		X	X <sup>w</sup>		X <sup>w</sup>		X	
Immunogenicity testing <sup>x</sup>		X	X		X		X	X
PK sampling <sup>x,y</sup>		X	X		X		X	X

## Schedule of Activities, Protocol I1F-MC-RHBV (Period 4)

	Post-Treatment Follow-Up for Patients Discontinuing Treatment at or after Week 16 (Period 4) <sup>aa</sup>		
	Required Follow-Up Visits		As-Needed Follow-Up Visits
CRF (V) Visit Number	V801	V802	V803 and onwards
Study Weeks	LV + 4W	LV + 12W	LV + 24 W
Study Days	±14d	±14d	±14d
Concomitant medications	X	X	X
Vital signs (BP and pulse) <sup>d</sup>	X	X	X
Weight <sup>bb</sup>	X	X	X
Preexisting conditions and medical history <sup>h</sup>	X	X	X
Adverse events	X	X	X
C-SSRS <sup>n</sup>	X	X	X
Self-Harm Supplement Form <sup>n</sup>	X	X	X
HBV		X <sup>s</sup>	
Serum chemistry	X	X	X
Hematology	X	X	X
Nonpharmacogenetic biomarker exploratory storage samples (urine, serum, plasma, RNA, and whole blood) <sup>v</sup>	X <sup>w</sup>	X <sup>w</sup>	
Immunogenicity testing <sup>x</sup>	X	X	
PK sampling <sup>x,y</sup>	X	X	



**Schedule of Activities, Protocol I1F-MC-RHBV (Period 4)**

Patients who discontinue treatment **prior** to Week 16 are to use the time table below to schedule activities for Post-Treatment Follow-Up visits.

<b>Discontinued Week No. (Visit No.)</b>	<b>Corresponding V801 (LV + 4 weeks)</b>	<b>Corresponding V802</b>	<b>Corresponding V803 (LV + 24 weeks)</b>
Week 1 (Visit 3)	Week 5	Week 16	Week 25
Week 2 (Visit 4)	Week 6	Week 16	Week 26
Week 4 (Visit 5)	Week 8	Week 16	Week 28
Week 8 (Visit 6)	Week 12	Week 16	Week 32
Week 12 (Visit 7)	Week 16	Week 24	Week 36

	<b>Post-Treatment Follow-Up for Patients Discontinuing Treatment prior to Week 16 (Period 4)<sup>aa</sup></b>		
	<b>Required Follow-Up Visits</b>		<b>As-Needed Follow-Up Visits</b>
CRF (V) Visit Number	V801	V802	V803 and onwards
Study Days	±14d	±14d	±14d
Concomitant medications	X	X	X
Vital signs (BP and pulse) <sup>d</sup>	X	X	X
Weight <sup>bb</sup>	X	X	X
Preexisting conditions and medical history <sup>h</sup>	X	X	X
Adverse events	X	X	X
C-SSRS <sup>a</sup>	X	X	X
Self-Harm Supplement Form <sup>n</sup>	X	X	X
HBV	X <sup>s</sup>	X <sup>s</sup>	
Serum chemistry	X	X	X
Hematology	X	X	X
Nonpharmacogenetic biomarker exploratory storage samples (urine, serum, plasma, RNA, and whole blood) <sup>v</sup>	X <sup>w</sup>	X <sup>w</sup>	
Immunogenicity testing <sup>x</sup>	X	X	
PK sampling <sup>x,y</sup>	X	X	
Patient Global Assessment of Disease Activity NRS	X	X	
Spinal pain	X	X	
BASFI	X	X	
BASDAI	X	X	
CRP	X	X	

## Schedule of Activities, Protocol 11F-MC-RHBV

**Abbreviations:** ASAS HI = ASAS Health Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; BP = blood pressure; CRF = case report form; CRP = high sensitivity C-reactive protein; C-SSRS = Columbia–Suicide Severity Rating Scale; d = days; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EQ-5D-5L = European Quality of Life–5 Dimensions–5 Level; ETV = early termination visit; FSH = follicle stimulating hormone; HBcAb+ = positive for anti-hepatitis B core antibody; HBsAb = anti-hepatitis B surface antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; INR = international normalized ratio; IP = investigational product; JSEQ = Jenkins Sleep Evaluation Questionnaire; LV = last visit; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MRI = magnetic resonance imaging; NRS = numeric rating scale; NSAID = nonsteroidal anti-inflammatory drug; PK = pharmacokinetic; PPD = purified protein derivative; PT = prothrombin time; PTT = partial thromboplastin time; QIDS-SR16 = Quick Inventory of Depressive Symptomatology-self report (16 items); rad-axSpA = radiographic axial spondyloarthritis; RNA = ribonucleic acid; SDAL = Study Drug Administration Log; SF-36 = Short Form 36; SJC = swollen joint count; SpA = spondyloarthritis; SPARCC = Spondyloarthritis Research Consortium of Canada; T4 = thyroxine; TB = tuberculosis; TJC = tender joint count; TSH = thyroid stimulating hormone; V = study visit; W = study week; WPAI-SpA = Work Productivity Activity Impairment Questionnaire–Spondyloarthritis

- a If a patient who has received at least 1 dose of IP discontinues from study treatment early, the patient will complete the ETV and then enter the Post-Treatment Follow-Up Period (Period 4). If a patient discontinues prior to Week 16, the patient will complete additional activities during Period 4.
- b Demographics includes recording of year of birth, gender, race, and ethnicity.
- c One complete physical examination (excluding pelvic, rectal examination) will be performed at screening. All physical examinations throughout the study must include a symptom-directed physical as well as examination of heart, lungs, abdomen, eyes, and visual examination of the skin.
- d BP and pulse will always be measured in sitting position and will be recorded before IP dosing at all visits; in addition, BP and pulse will be recorded approximately 1 hour post-dosing at baseline (Week 0), Week 16, and Week 20. Refer to Section 8.4.2 for more details.
- e Habits include recording of caffeine, alcohol, and tobacco consumption.
- f A posterior anterior chest x-ray will be taken locally at screening unless one has been obtained within 6 months of screening (Visit 1) (provided the x-ray and/or report are available for review). Refer to Section 8.4.6 for more details.
- g Refer to rescreening guidance as appropriate (Section 5.3).
- h Evaluation includes historical events and preexisting conditions.
- i Patients need to be asked about presence of eye symptoms; if eye symptoms are present then an eye examination is required. Refer to Section 8.4.5 for specific instructions.
- j Refer to Section 6.1.1 for specific IP administration instructions.
- k The Week 16 MRI may be collected up to 10 days **prior** to Week 16 (Visit 8). It is strongly recommended that the Week 16 MRI be collected prior to the Week 16 (Visit 8) dosing. For ETV, MRI requirements are dependent on the timing of study discontinuation. If discontinuation is:
  - at or before Visit 5, no repeat MRI is required at ETV.
  - after Visit 5 up to and including Visit 8 (Week 16), repeat MRI is required at ETV.
  - after Visit 8, repeat MRI is required only if ETV occurs on or after Visit 12.

- <sup>l</sup> An x-ray of the SIJ will be performed during the Screening Period (Period 1) unless an x-ray taken prior to screening is available for central reading, is of good quality, and confirms diagnosis of rad-axSpA. All x-rays require central reading ONLY, regardless of date taken. Central reading will define eligibility using the mNY criteria. If central reading of a preexisting x-ray is not consistent with rad-axSpA by central reading, a new x-ray of the SIJ may be taken during Period 1 and sent in for central reading.
- <sup>m</sup> Cervical and lumbar spine only; serves: 1) as baseline for later assessments of structural changes and 2) to evaluate presence of total ankylosis at screening (Refer to Section 5.2, exclusion criterion [10]). X-ray of the spine does not need to be repeated if one is available that was taken  $\leq 3$  months prior to screening (Visit 1; refer to Sections 5.2 and 5.3) and has passed quality assessment by central reading vendor.
- <sup>n</sup> A Self-Harm Follow-Up Form is to be completed for each discrete self-harm event identified on C-SSRS and the Self-Harm Supplement Form
- <sup>o</sup> HLA-B27 test will be performed centrally
- <sup>p</sup> Approval from the Lilly clinical research physician or clinical research scientist must be obtained before a CRP retest is permitted. If the CRP lab is retested, the most recent value will be used for randomization.
- <sup>q</sup> In countries where the QuantiFERON®-TB Gold test or T-SPOT® is available, either test may be used instead of the PPD TB test. The QuantiFERON®-TB Gold test may be performed locally or centrally; the T-SPOT® must be performed locally. PPD tests must be read 2-3 days after Visit 1. Refer to Section 8.4.6 for more details.
- <sup>r</sup> For female patients  $\geq 40$  and  $< 60$  years of age who have had a cessation of menses for at least 12 months, an FSH test will be performed to confirm non-childbearing potential (FSH  $\geq 40$  mIU/mL or  $\geq 40$  IU/L). FSH test will be performed centrally.
- <sup>s</sup> All patients will be tested for HBV at screening. Patients that are HBcAb+ at screening, regardless of HBsAb status, will have a serum HBV DNA obtained by the central laboratory. Patients that are found to be HBV DNA positive (detectable) at screening will be excluded from the trial. Patients that are HBV DNA negative (undetectable) may be enrolled into the study with required HBV DNA monitoring every 3 months during treatment and 12 weeks after the last dose of ixekizumab. If the result of the HBV DNA testing is positive, the patient is to be discontinued from the study and is to receive appropriate follow-up medical care (refer to Section 8.4.10.2 for further information regarding the timing of discontinuation).
- <sup>t</sup> Only for females of childbearing potential. Serum pregnancy test will be done at Visit 1 only, and will be performed centrally. Patients determined to be pregnant will be discontinued from treatment and will no longer be administered investigational product (see Section 7.1). Patients will undergo urine pregnancy testing at the clinic during scheduled visits through Week 52. Additional urine pregnancy testing can be performed at the investigator's discretion. If required per local regulations, testing can occur at other intervals during the study treatment period and/or follow up period. Patients determined to be pregnant will be discontinued from treatment and will no longer be administered investigational product (see Section 7.1).
- <sup>u</sup> For the fasting lipid profile patients are not to eat or drink anything except water for 12 hours prior to test.
- <sup>v</sup> Where collection is allowed by local regulations.
- <sup>w</sup> Only serum and plasma are collected at this visit.
- <sup>x</sup> Immunogenicity samples may also be analyzed for ixekizumab serum concentration to facilitate in the interpretation of immunogenicity data. An additional blood sample will be collected, when possible, for any patient who experiences a potential systemic allergic/hypersensitivity reaction during the study as judged by the investigator.
- <sup>y</sup> PK samples are to be collected before investigational product injection.
- <sup>z</sup> The Week 52 MRI may be collected up to 10 days **prior** to Week 52 (Visit 15).

- aa Patients receiving investigational product who discontinue at any time prior to the end of the study or who complete the study (Week 52) and do not choose to enroll in Study RHBV, will have safety Follow-Up Visits 801 and 802 at 4 and 12 weeks (respectively) after the date of their last visit. Visit 803 will occur if a patient's neutrophil counts have not returned to the criteria defined in Section [8.4.10.1](#).
- bb Weight is only captured on eCRF at V2, V8, V10, V15, and/or ETV. Body weight collected at other visits is used only for calculation of creatinine clearance.
- cc If not completed at Visit 2, the sample should be collected as soon as possible at the next scheduled visit.
- dd If MRI is conducted on the same day as study visit, ensure that any scales/questionnaires are completed prior to administering any premedication to facilitate patient undergoing an MRI (for example, morphine or equivalent for significant pain as judged by the investigator or a benzodiazepine for claustrophobia).
- ee For all patients, screening MRIs of the spine and SIJ must be completed  $\leq 30$  days prior to randomization (refer to Sections [5.3](#) and [5.4](#)).

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## Appendix 3. Clinical Laboratory Tests

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### Clinical Safety Laboratory Tests to be Performed by Sponsor-Designated Laboratory

Hematology <sup>a</sup> :	Serum Chemistry <sup>a</sup> :
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume (MCV)	Chloride
Mean cell hemoglobin concentration (MCHC)	Phosphorus
Leukocytes (WBC)	Total bilirubin
Platelets	Direct bilirubin
<b>Absolute counts of:</b>	Alkaline phosphatase
Neutrophils, segmented	Alanine aminotransferase (ALT/SGPT)
Neutrophils, juvenile (bands)	Aspartate aminotransferase (AST/SGOT)
Lymphocytes	Blood urea nitrogen (BUN)
Monocytes	Uric acid
Eosinophils	Creatinine
Basophils	Calcium
<b>Urinalysis (dipstick)<sup>a</sup>:</b>	Glucose
Color	Albumin
Specific gravity	Cholesterol (total)
pH	Total protein
Protein	Calculated creatinine clearance <sup>b</sup>
Glucose	Creatine phosphokinase (CPK)
Ketones	Triglycerides
Bilirubin	Gamma-glutamyl transferase (GGT)
Urobilinogen	
Blood	<b>Lipid panel<sup>c</sup></b>
Nitrite	Low density lipoprotein (LDL)
Urine creatinine	High density lipoprotein (HDL)
Leukocyte esterase	Very low density lipoprotein (VLDL)
<b>Other Tests:</b>	
Human immunodeficiency virus antibody (HIV) <sup>f</sup>	Pregnancy test (serum) <sup>d</sup>
Hepatitis B surface antigen (HBsAg) <sup>f</sup>	Follicle-stimulating hormone (FSH) <sup>e</sup>
Anti-hepatitis B surface antibody (HBsAb) <sup>f</sup>	Thyroid-stimulating hormone (TSH) and free T4
Anti-hepatitis B core antibody (HBcAb) <sup>f</sup>	Ixekizumab serum concentration (pharmacokinetic)
Anti-hepatitis C antibody <sup>f,h</sup>	Partial thromboplastin time (PTT)
HBV DNA <sup>g</sup>	Prothrombin time/international normalized ratio
High sensitivity C-reactive protein (CRP)	Exploratory storage samples (urine, serum, plasma, RNA, and whole blood)
Purified protein derivative (PPD) <sup>i</sup>	Pharmacogenetic sample (DNA)
Urine pregnancy test <sup>d</sup> (assayed by clinical study site)	Immunogenicity testing (anti-ixekizumab Ab)
QuantiFERON®-TB Gold test <sup>i</sup>	
T-SPOT® <sup>i</sup>	
HLA-B27	

**Clinical Safety Laboratory Tests**

Abbreviations: Ab = antibody; DNA = deoxyribonucleic acid; HBV = hepatitis B virus; RNA = ribonucleic acid; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; T4 = thyroxine; WBC = white blood cells.

- a Unscheduled blood chemistry, hematology, and urinalysis panels may be performed at the discretion of the investigator.
- b Cockcroft-Gault calculation is used for the calculated creatinine clearance.
- c For the fasting lipid profile, patients are not to eat or drink anything except water for 12 hours prior to test. Fasting is not required for the screening visit (Visit 1).
- d Serum pregnancy test for all women <60 years of age who are still of childbearing potential at Visit 1 only and will be performed centrally; after Visit 1, urine pregnancy test performed locally for women of childbearing potential.
- e Women  $\geq 40$  and <60 years of age who have had a cessation of menses for  $\geq 12$  months will have an FSH test confirming nonchildbearing potential ( $\geq 40$  mIU/mL).
- f Test required at Visit 1 to determine eligibility of patient for the study.
- g HBV DNA testing will be done in those patients who are HBcAb+ at screening.
- h See exclusion criteria (Section 5.2) specific to Hepatitis C antibody. A confirmatory test for HCV will be performed if the patient is positive for HCV antibody.
- i In countries where the QuantiFERON®-TB Gold test or T-SPOT® is available, either test may be used instead of the PPD TB test. The QuantiFERON®-TB Gold test may be performed locally or centrally; the T-SPOT® must be performed locally.

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## Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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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 clinical research physician, or its designee.

### Hepatic Monitoring Tests

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#### Hepatic Hematology<sup>a</sup>

Hemoglobin  
Hematocrit  
RBC  
WBC  
Neutrophils, segmented  
Lymphocytes  
Monocytes  
Eosinophils  
Basophils  
Platelets

#### Hepatic Chemistry<sup>a</sup>

Total bilirubin  
Direct bilirubin  
Alkaline phosphatase  
ALT  
AST  
GGT

#### CPK

#### Haptoglobin<sup>a</sup>

#### Hepatic Coagulation<sup>a</sup>

Prothrombin time  
Prothrombin time, INR

#### Hepatic Serologies<sup>a,b</sup>

Hepatitis A antibody, total  
Hepatitis A antibody, IgM  
Hepatitis B surface antigen  
Hepatitis B surface antibody  
Hepatitis B Core antibody  
Hepatitis C antibody  
Hepatitis E antibody, IgG  
Hepatitis E antibody, IgM

#### Anti-nuclear antibody<sup>a</sup>

#### Anti-smooth muscle antibody

#### Alkaline phosphatase isoenzymes<sup>a</sup>

#### Anti-Actin<sup>a</sup>

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

<sup>a</sup> Assayed by Lilly-designated or local laboratory.

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

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## Appendix 5. Spondyloarthritis Features

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To be included in Study RHBV, patients must have sacroiliitis defined radiographically according to the mNY criteria based on central reading

AND

at least one of the spondyloarthritis features (from Box 4, ASAS criteria for classification of axSpA [to be applied in patients with chronic back pain  $\geq 3$  months and age at onset of back pain <45 years]) bulleted below:

- **Inflammatory back pain (IBP):** According to experts, 4 out of 5 of the following parameters present: (1) age at onset <40 years, (2) insidious onset, (3) improvement with exercise, (4) no improvement with rest, (5) pain at night (with improvement upon getting up).
- **Arthritis:** Past or present active synovitis diagnosed by a doctor.
- **Enthesitis (heel):** Past or present spontaneous pain or tenderness at examination at the site of the insertion of the Achilles tendon or plantar fascia at the calcaneus.
- **Uveitis:** Past or present uveitis anterior, confirmed by an ophthalmologist.
- **Dactylitis:** Past or present dactylitis diagnosed by a doctor.
- **Psoriasis:** Past or present psoriasis diagnosed by a doctor.
- **Crohn's/Colitis:** Past or present Crohn's disease or ulcerative colitis diagnosed by a doctor.
- **Good response to NSAIDs:** At 24 to 48 hours after a full dose of NSAID, the back pain was not present anymore or much better.  
Note: As patients enrolling into the study should have failed 2 NSAIDs or be intolerant to NSAIDs, a doctor should assess whether patients had "good" prior response to NSAIDs.
- **Family history for SpA:** Presence in first-degree or second-degree relatives of any of the following: (a) AS, (b) psoriasis, (c) uveitis, (d) reactive arthritis, (e) IBD.  
Note: A doctor should confirm with his/her patient there was a clear diagnosis (not self-diagnosis) for any of these in first- or second-degree relatives.
- **HLA-B27:** Positive testing according to standard laboratory techniques.
- **Elevated CRP:** CRP >5.00 mg/L in the presence of back pain, after exclusion of other causes for elevated CRP concentration.

References: Rudwaleit et al. 2009; Sieper et al. 2009.



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**Appendix 6. Protocol Amendment I1F-MC-RHBV(b)  
Summary: A Multicenter, Randomized, Double-Blind,  
Active and Placebo-Controlled 16-Week Study Followed  
by Long-Term Evaluation of Efficacy and Safety of  
Ixekizumab (LY2439821) in bDMARD-Naive Patients with  
Radiographic Axial Spondyloarthritis**

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## Overview

Protocol I1F-MC-RHBV, A Multicenter, Randomized, Double-Blind, Active and Placebo-Controlled 16-Week Study Followed by Long-Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in bDMARD-Naive Patients with Radiographic Axial Spondyloarthritis, has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The change and rationale for the change made to this protocol are as follows:

### **Section 6.2. Method of Treatment Assignment**

At the time of initial protocol development the aim was to enroll relatively equal numbers of patients with elevated vs nonelevated CRP to facilitate subgroup analyses based on CRP (elevated/nonelevated). Based on enrollment to date it is clear that spontaneously it is likely that sufficient patients will enroll for each of these CRP cohorts. Therefore, the purpose of this amendment is to remove this specific limitation such that all patients who meet protocol eligibility criteria can be enrolled independent of having elevated or nonelevated CRP.

## Revised Protocol Sections

<b>Note:</b> Deletions have been identified by <del>striketroughs</del> . Additions have been identified by the use of <u>underscore</u> .
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### Section 6.2. Method of Treatment Assignment

To achieve between-group comparability, the randomization will be stratified by country and baseline CRP (nonelevated or elevated). ~~The study will enroll approximately 50% of patients with baseline CRP elevated (>5.00 mg/L).~~ Elevated CRP is defined as CRP>5.00 mg/L.

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