I1F-MC-RHBX Protocol b

# A 52-Week Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ixekizumab (LY2439821) in bDMARD-Naive Patients with Nonradiographic Axial Spondyloarthritis

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# Protocol I1F-MC-RHBX(b)
# A 52-Week Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ixekizumab (LY2439821) in bDMARD-Naive Patients with Nonradiographic Axial Spondyloarthritis

## Confidential Information



Ixekizumab (LY2439821)

Study I1F-MC-RHBX is a Phase 3, multicenter, randomized, double-blind, and placebo-controlled, parallel-group, outpatient study examining the efficacy and safety of subcutaneous (SC) ixekizumab (LY2439821) treatment regimens (80 mg every 2 weeks [Q2W] and 80 mg every 4 weeks [Q4W] with an 80-mg or 160-mg starting dose) as compared to SC placebo in patients with active nonradiographic axial spondyloarthritis (axSpA) who are biological disease-modifying antirheumatic drug (bDMARD)-naive, during a 52-week treatment period.

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# 1. Protocol Synopsis

**Title of Study:**
A 52-Week Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ixekizumab (LY2439821) in bDMARD-Naive Patients with Nonradiographic 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). Compelling scientific evidence exists indicating an important role of the IL-23/IL-17 pathway in axial spondyloarthritis (axSpA) pathogenesis. Recently disclosed data from Phase 3 studies with secukinumab (Cosentyx®), a drug with a similar mechanism of action (MoA) as ixekizumab, have demonstrated the effectiveness of inhibiting IL-17A in patients with radiographic-axial spondyloarthritis (rad-axSpA, also called Ankylosing Spondylitis) who were biological disease-modifying antirheumatic drug (bDMARD)-naive or had previously received tumor necrosis factor (TNF) inhibitors. The present study evaluates the efficacy and safety of ixekizumab in nonradiographic-axSpA (nonrad-axSpA) patients who are bDMARD-naive.

**Objective(s)/Endpoints:**

There are 2 primary objectives in this study to accommodate regional regulatory requirements.

| Objectives | Endpoints |
|---|---|
| **Primary**<br>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 nonradiographic axial spondyloarthritis (nonrad-axSpA). | • Proportion of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response at Week 16<br>(for regulatory agencies that accept Week 16 as primary endpoint)<br>• Proportion of patients achieving an ASAS40 response at Week 52<br>(for regulatory agencies that require Week 52 as primary endpoint) |
| **Secondary**<br>**The major secondary objective is:**<br>• To compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W) versus placebo in patients with active nonrad-axSpA at Week 16 and Week 52 | • Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) at Week 16<br>• Change from baseline in ASDAS at Week 52<br>• Change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 16<br>• Change from baseline in BASFI at Week 52<br>• Proportion of patients achieving ASDAS inactive disease at Week 16<br>• Proportion of patients achieving ASDAS inactive disease at Week 52<br>• Change from baseline in magnetic resonance imaging (MRI) of the sacroiliac joints (SIJ) (Spondyloarthritis Research Consortium of Canada [SPARCC] score) at Week 16<br>• Percent of patients without clinically meaningful changes in background therapy at Week 52 |

**Summary of Study Design:**
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 2 SC ixekizumab treatment regimens (80 mg Q2W and 80 mg Q4W) as compared to SC placebo in patients with active nonrad-axSpA who are bDMARD-naive, during a double-blind, 52-week treatment period (Period 2). Patients will complete a Post-Study Follow-Up Period (Period 3) over a 12-week period.

**Treatment Groups and Duration:**
Study RHBX has 3 treatment groups during the 52-week Blinded Treatment Dosing Period: 80 mg ixekizumab Q4W, 80 mg ixekizumab Q2W, and placebo at a 1:1:1 ratio. In each ixekizumab treatment group, half of the patients will receive an 80-mg starting dose and half a 160-mg starting dose (1:1 randomization). Randomization will be stratified by country and screening MRI/CRP status (positive MRI and elevated C-reactive protein [CRP]; positive MRI and nonelevated CRP; negative MRI and elevated CRP). All doses are administered via SC injection. At baseline (Week 0), all patients will receive 2 injections. Patients assigned to an ixekizumab treatment regimen with a 160-mg ixekizumab starting dose will receive 160 mg of ixekizumab as two 80-mg SC injections. Patients assigned to an ixekizumab treatment regimen with an 80-mg starting dose will receive 80 mg of ixekizumab as 1 SC injection and 1 SC injection of placebo. Patients assigned to the placebo treatment group will receive 2 SC injections of placebo. After Week 0 and through Week 50, all patients will receive 1 injection every 2 weeks.

Beginning at Week 16 and up to Week 44, any patient, regardless of their original treatment group, may be identified by an investigator based on clinical judgment as an inadequate responder. At such time, changes in background therapy and/or addition of biologic rescue therapy (ixekizumab 80 mg Q2W) can be made at the discretion of the investigator, while remaining blinded to the original randomization treatment assignment. Changes in ongoing medications at that time can include changes in dose of nonsteroidal anti-inflammatory drugs (NSAIDs) or nonbiological disease-modifying antirheumatic drugs (DMARDs), including the introduction of new medications. The investigator may also decide to use biologic rescue with ixekizumab 80 mg Q2W with an 80-mg starting dose. General treatment guidelines recommend a minimum period of 12 weeks to evaluate effect of biologic treatment modifications; however, if in the opinion of the investigator, a patient does not show any clinical improvement after at least 8 weeks of the ixekizumab 80 mg Q2W rescue treatment, then the investigator may consider discontinuation of the patient from ixekizumab treatment. Such patients may then receive other medical therapies (potentially including a TNF inhibitor) that are prescribed by their physician and are to remain in the study. The study duration will be up to 1 year (52 weeks). Patients who have taken at least 1 study dose and who discontinue study treatment prior to Week 16 (Visit 8) or study participation (regardless of timing) are to complete an early termination visit (ETV) and enter into post-study follow-up for at least 12 weeks after the ETV date or the last regularly scheduled visit. Patients whose ETV or last regularly scheduled visit is longer than 12 weeks after their last investigational study medication dose are not required to enter into the Post-Study Follow-Up Period. Patients who complete Study RHBX, if eligible, may enroll in a long-term extension study for up to 2 additional years of ixekizumab treatment.

**Study Population:**
This study will include approximately 300 randomized patients. The study population will include patients with a physician's diagnosis of active nonrad-axSpA, who meet the ASAS classification criteria for nonrad-axSpA either by the presence of sacroiliitis on MRI (based on central reading) accompanied by at least 1 spondyloarthritis (SpA) feature OR by being human leukocyte antigen (HLA)-B27 positive and having at least 2 additional SpA features.

Patients will present with a history of back pain ≥3 months with age at onset <45 years and have active nonrad-axSpA defined as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4, and total back pain ≥4 on a numeric rating scale (NRS) at screening and baseline as well as objective signs of inflammation at screening by the presence of sacroiliitis on MRI (as defined by ASAS/OMERACT) and/or presence of elevated CRP (defined as CRP >5.00 mg/L). Patients must also have a history of inadequate response 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. Patients must also have a history of prior therapy for axSpA of at least 12 weeks prior to screening and not have received conventional

DMARDs (cDMARDs) and/or other therapies or other immunosuppressive agents for at least 4 weeks prior to baseline randomization, except for methotrexate [MTX] (oral or parenteral up to 25 mg/week), sulfasalazine (up to 3 g/day), hydroxychloroquine (up to 400 mg/day), or oral corticosteroids (not to exceed 10 mg/day of prednisone or equivalent) that may be allowed if treated at a stable dose for at least 4 weeks prior to baseline randomization. If used, cDMARDs are not to be in any combination with other cDMARDs.

**Statistical Analysis:**
Approximately 300 patients will be randomized at a 1:1:1 ratio in the Blinded Treatment Dosing Period (Period 2) to ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, and placebo. In the active treatment groups, half the patients will be given a 160-mg starting dose and the other half will be given an 80-mg starting dose. With 100 patients per treatment group, this study will have approximately 98% power to test the superiority of ixekizumab Q2W to placebo for 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: 46% for ixekizumab 80 mg Q2W treatment group and 18% for the placebo group. A 2-sided Fisher's exact test at the 0.05 level is assumed.

There is little data from similarly designed 52-week placebo-controlled trials regarding the ASAS40 response rate for active and placebo treated patients to guide power estimation at Week 52. With 100 patients per treatment group, this study will have approximately 66-99% power to test the superiority of ixekizumab Q2W to placebo for ASAS40 at Week 52, assuming various ASAS40 response rates for ixekizumab Q2W and placebo at Week 52. 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 will be performed for all analyses in the Blinded Treatment Dosing Period. Unless otherwise specified, the ixekizumab 80 mg Q2W and 80 mg 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 screening MRI/CRP status (positive MRI and elevated CRP; positive MRI and nonelevated CRP; negative MRI and elevated CRP) 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. NRI will be applied to Week 52 (Visit 15) in a similar method. Patients who are deemed as inadequate responders by the investigator after Week 16 but remain on blinded study treatment and only have modifications in concomitant medications will not be automatically imputed as nonresponders. However, patients who discontinue originally assigned blinded study treatment and use rescue ixekizumab 80 mg Q2W will be analyzed as nonresponders for the Week 52 analysis. Randomized patients without any postbaseline observation will also be defined as nonresponders for the NRI analysis.

A 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, screening MRI/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, screening MRI/CRP status, and baseline.

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 an ANCOVA with treatment and baseline value.

Patients who discontinue study treatment after Week 16 will continue to be followed for all regularly scheduled visits for safety and efficacy assessment. The data collected after discontinuation of study treatment will be summarized separately.

# 2. Introduction

## 2.1. Background

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease predominantly affecting the axial skeleton (sacroiliac joints and spine) with onset of symptoms that typically appear in the second or third decade of life (Poddubnyy 2013). AxSpA is recognized as a single disease entity, with a patient subset defined by the presence of radiographically defined structural damage of the sacroiliac joints (rad-axSpA) and a patient subset without clear structural damage radiographically (nonrad-axSpA) (Deodhar et al. 2014). 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 these subsets still represent 1 disease. AxSpA, in a similar fashion, can be considered a single disease, with rad-axSpA and nonrad-axSpA subsets (Deodhar et al. 2014).

AxSpA affects up to 1.4% of the Caucasian adult population worldwide (Braun and Sieper 2007; Reveille et al. 2012; Strand et al. 2013). The proportion of nonrad-axSpA patients among all axSpA patients ranges from 40% to 60% according to several national and international referral programs (Rudwaleit and Sieper 2012; Poddubnyy et al. 2012).

Until recently, axSpA patients without radiographically defined sacroiliitis but with evidence of sacroiliitis from magnetic resonance imaging (MRI) imaging or other characteristics of disease have been less well diagnosed despite sharing a similar burden of disease and the same common features as patients with rad-axSpA, such as spinal inflammation, chronic back pain, positivity for human leukocyte antigen (HLA)-B27, and extraarticular manifestations. Delays in the diagnosis of axSpA can postpone administration of suitable treatment by several years (Haibel et al. 2008; Landewé et al. 2012; Rudwaleit et al. 2009c; van der Heijde et al. 2006). The Assessment of Spondyloarthritis International Society (ASAS) criteria for axSpA (Rudwaleit et al. 2009a, 2009b) have been developed, in addition to a diagnostic algorithm (van den Berg et al. 2013), to facilitate earlier recognition of axSpA and to identify axSpA patients with and without radiographic sacroiliitis (Rudwaleit et al. 2004, 2005) using x-rays and MRI. Adoption of the ASAS criteria has the potential to lead to earlier identification of patients with axSpA (Rudwaleit et al. 2004), early in the disease course, and to result in more timely therapeutic intervention.

The subgroup of nonrad-axSpA patients with objective signs of inflammation (defined as active inflammation on MRI and/or elevated C-reactive protein [CRP]) is considered the appropriate target population for biologic treatment given the higher observed progression rates (up to 20% over a 2-year period) relative to approximately 10% progression rate over the same period in nonrad-axSpA patients without such objective signs of inflammation. In addition, studies from (TNF) inhibitors in nonrad-axSpA demonstrated that minimal to no treatment effect is observed in nonrad-axSpA patients without objective signs of inflammation at baseline (Poddubnyy et al. 2012; Rudwaleit and Sieper 2012; Sieper et al. 2013; Sieper and van der Heijde 2013).

Although the exact etiology is unknown, genetic factors and several loci are likely to be involved in susceptibility to axSpA (Reveille 2011). There is a strong association with the major histocompatibility complex, HLA–B27. The risk of developing axSpA is as high as about 5% in HLA-B27 positive individuals. Similar findings are obtained in the HLA-B27–positive relatives of such patients (Braun and Sieper 2007). Up to approximately 70% of patients with nonrad-axSpA have been reported to be positive for HLA-B27 (Gulfe et al. 2014). 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 nonrad-axSpA includes regular exercise, physical therapy, and nonsteroidal anti-inflammatory drugs (NSAIDs). TNF inhibitors have also demonstrated efficacy in nonrad-axSpA; however, they are not yet approved globally for this indication (Braun et al. 2011; Robinson et al. 2014; Ward et al. 2015), and approximately 40% of patients only obtain a partial response on TNF inhibitors (Sieper at al. 2012, 2013; Landewé et al. 2012; Dougados et al. 2014). 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) or systemic corticosteroids (Braun and Sieper 2009; Haibel and Specker 2009).

TNF inhibitors have demonstrated efficacy across the axSpA spectrum and may be prescribed for nonrad-axSpA when NSAID treatment has failed or cannot be tolerated (Braun et al. 2014) and where regulatory approval has been obtained for this population. To date few treatment options are globally available for nonrad-axSpA (van der Heijde et al. 2006; Heiberg et al. 2008; Inman et al. 2008; Glintborg et al. 2010).

TNF inhibitors, the only available biologic therapy for axSpA, have been associated in various diseases, including axSpA, with potential safety concerns, such as opportunistic infections, demyelinating disorders, blood dyscrasias, reactivation of tuberculosis (TB), and exacerbation of congestive heart failure (Singh et al. 2011; Ruderman 2012; Deepak et al. 2013; Maxwell et al. 2015). There remains, therefore, a significant unmet need for safer, more effective treatments for patients with axSpA (Dougados and Baeten 2011).

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 to date suggests an important role of the IL-23/IL-17 pathway in the pathogenesis of axSpA (Baeten et al. 2010; Maksymowych 2010; Baraliakos et al. 2011; Reveille 2011; Baeten et al. 2013, 2014; 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 have failed NSAIDs and for patients who have lost response, failed to respond, or are intolerant to current marketed drugs. Ixekizumab may offer a more favorable safety profile compared to currently marketed therapies.

## 2.2. Study Rationale

Lilly is investigating ixekizumab as a treatment option for nonrad-axSpA based on its mechanism of action, selectively blocking IL-17A (as 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 was evaluated in both Phase 2 psoriasis (Ps) and rheumatoid arthritis (RA) studies, and ixekizumab demonstrated efficacy in both indications (Leonardi et al. 2012, Genovese et al. 2014). The 80 mg Q2W and 80 mg Q4W treatment regimens with a 160-mg starting dose were evaluated in pivotal Phase 3 studies in Ps 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 mechanism of action (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 TNF inhibitors (Sanford and McKeage 2015). The ixekizumab clinical development program for axSpA also includes 2 previously initiated Phase 3 studies of ixekizumab in rad-axSpA patients (Study I1F-MC-RHBV and Study I1F-MC-RHBW).

# 3. Objectives and Endpoints

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

**Table RHBX.1. Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary**<br>The primary objective is to compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W) versus placebo in patients with active nonrad-axSpA | • Proportion of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response at Week 16 (for regulatory agencies that require Week 16 as the primary endpoint)<br>• Proportion of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response at Week 52 (for regulatory agencies that require Week 52 as the primary endpoint) |
| **Secondary**<br>**The major secondary objectives are:**<br>• To compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W versus placebo in patients with active nonrad-axSpA at Week 16 and Week 52 | • Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) at Week 16<br>• Change from baseline in ASDAS at Week 52<br>• Change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 16<br>• Change from baseline in BASFI at Week 52<br>• Proportion of patients achieving ASDAS inactive disease at Week 16<br>• Proportion of patients achieving ASDAS inactive disease at Week 52<br>• Change from baseline in magnetic resonance imaging (MRI) of the sacroiliac joints (SIJ) (Spondyloarthritis Research Consortium of Canada [SPARCC] score) at Week 16<br>• Percent of patients without clinically meaningful changes in background therapy at Week 52 |
| **Other secondary objectives are:**<br>• To compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W) to placebo during the 52-week period | • Proportion of patients who achieve ASAS20, ASAS40, ASAS5/6, and partial remission by ASAS criteria<br>• Change from baseline in the individual components of the ASAS criteria<br>• Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)<br>• Proportion of patients reaching BASDAI50<br>• Change from baseline in ASDAS<br>• Proportion of patients who experience clinically-important improvement (change of ASDAS from baseline ≥1.1), major improvement (change of ASDAS from baseline ≥2.0), or inactive |

| Objectives | Endpoints |
|---|---|
| | disease (ASDAS <1.3)<br>• Change from baseline in the measure of CRP<br>• Change from baseline in BASFI<br>• Change from baseline in mobility<br>o Bath Ankylosing Spondylitis Metrology Index (BASMI) (linear) and individual components<br>o Chest expansion<br>o Change from baseline in occiput to wall distance<br>• Change from baseline in MRI of the SIJ (SPARCC score)<br>• Change from baseline in SPARCC SIJ Structural Score (SSS)<br>• Change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)<br>• Change from baseline in SPARCC Enthesitis Score<br>• The incidence and severity of peripheral arthritis by tender and swollen joint count scores of 46/44 joints<br>• Incidence rate of anterior uveitis or uveitis flares<br>• 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 physical component [PCS] and mental component scores [MCS]), and Quick Inventory of Depressive Symptomatology–Self-Report (16 Items) (QIDS-SR16) score.<br>• NSAID intake (ASAS-NSAID score and % of patients taking NSAIDs) |
| • To explore the effect of starting dose (160 mg compared to 80 mg)<br>• To evaluate the incidence of anti-ixekizumab antibodies and its relationship to efficacy of ixekizumab | • Onset of action and treatment response (ASAS, ASDAS, CRP, BASFI)<br>• 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<br>o Proportion of patients achieving ASAS40<br>o Proportion of patients achieving ASAS20<br>o Proportion of patients achieving ASDAS inactive disease |
| • To measure ixekizumab exposure and assess the relationship between exposure and efficacy and exposure and immunogenicity | • Serum trough concentrations of ixekizumab<br>• Model parameters for the exposure-response relationship between ixekizumab serum trough concentrations and efficacy endpoints (for example, ASAS20, ASAS40) at Week 16 and/or Week 52<br>• Ixekizumab serum trough concentrations associated with anti-drug antibody (ADA) titer |
| **Exploratory Objective** | |

| Objectives | Endpoints |
| --- | --- |
| • CCI [redacted] | [redacted] |

# 4. Study Design

## 4.1. Overview of Study Design

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 2 ixekizumab treatment regimens (80 mg Q2W and 80 mg Q4W SC) as compared to placebo SC in patients with active nonrad-axSpA who are bDMARD-naive, during a double-blind, 52-week treatment period (Period 2).

Figure RHBX.1 illustrates the study design. Within the active treatment groups, half the patients will be given a 160-mg starting dose and the other half will be given an 80-mg starting dose. 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 before administration of the investigational product, as applicable.

For each patient, x-rays and magnetic resonance imaging (MRIs) will be collected according to Section 8.1.2.21.1 and the Schedule of Activities (Appendix 2).

Appendix 3 lists the specific laboratory tests that will be performed for this study. At or after Week 16, patients who are deemed inadequate responders may receive rescue therapies as described in Section 6.1.1. Patients discontinuing study treatment after Week 16 are to remain in the study and follow the regular visit schedule.

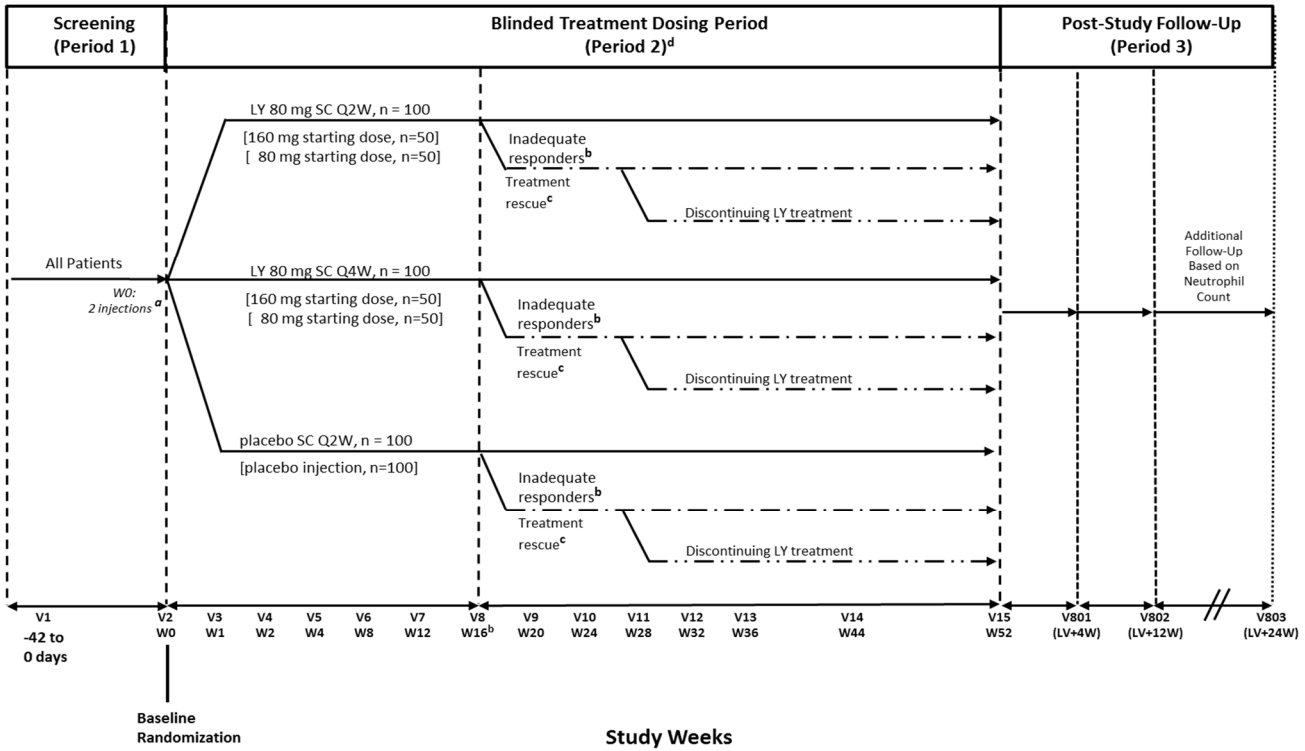
Patients who have taken at least 1 study dose and who discontinue study treatment prior to Week 16 or study participation (regardless of timing) are to complete an early termination visit (ETV) and enter into post-study follow-up for at least 12 weeks after the ETV date or the last regularly scheduled visit. Patients whose ETV or last regularly scheduled visit is longer than 12 weeks after their last investigational study medication dose are not required to enter into the Post-Study Follow-Up Period (Period 3). For the management of patient safety, patients are to be monitored through the Post-Study Follow-Up Period as indicated on the Schedule of Activities (Appendix 2).

Patients who complete Study RHBX may be eligible to enroll into a long-term extension study (Study I1F-MC-RHBY [RHBY]) for up to 2 additional years.

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.




Abbreviations: DMARD = disease-modifying antirheumatic drug; ETV = early termination visit; LV = last visit; LY = ixekizumab; n = number; NSAID = nonsteroidal anti-inflammatory drug; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; TNF = tumor necrosis factor; V = study visit; W = study week.

a All patients will receive 2 injections at baseline at Week 0 to maintain the blind with an 80-mg or 160-mg starting dose of ixekizumab or placebo.

b Beginning at Week 16 and up to Week 44, any patient, regardless of their original treatment group, may be identified by an investigator based on clinical judgment as an inadequate responder and receive rescue treatment. At such time changes in background therapy (including, but not limited to NSAIDs, nonbiological DMARDs or the use of rescue biologic treatment) can be made at the discretion of the investigator, while remaining blinded to the original randomization treatment assignment. Changes in ongoing medications at that time can include changes in dose of NSAIDS or nonbiological DMARDs, including the introduction of new medications. Investigator may also decide to use biologic rescue of ixekizumab 80 mg Q2W with an 80-mg starting dose.

[c] Following any treatment modifications, investigators are to reevaluate the clinical status of the patient as appropriate to assess effect of treatment modification. Treatment guidelines recommend a minimum period of 12 weeks to evaluate effect of biologic treatment modifications; however, if in the opinion of the investigator, a patient does not show any clinical improvement after at least 8 weeks of the ixekizumab 80 mg Q2W treatment modification, then the investigator may consider discontinuation of the patient from ixekizumab treatment. Such patients may then receive other medical therapies (potentially including a TNF inhibitor) that are prescribed by their physician and are to remain in the study until Week 52 per study schedule.

[d] Patients who have taken at least 1 study dose and who discontinue study treatment prior to Week 16 or study participation (regardless of timing) are to complete an ETV and enter into post-study follow-up for at least 12 weeks after the ETV date or the last regularly scheduled visit. Patients whose ETV or last regularly scheduled visit is longer than 12 weeks after their last investigational study medication dose are not required to enter into the Post-Study Follow-Up Period. V801 and V802 are required for patients in the Post-Study Follow-Up Period; V803 may be needed depending on neutrophil counts.

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

## 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. The dose justification is outlined in Section 4.4. The study blind is maintained as described in Section 6.3. The impact of ixekizumab starting dose on speed of onset and through the primary efficacy endpoint assessment at Week 16 will be evaluated by providing a 160-mg starting dose to half of the patients and an 80-mg starting dose to the remaining half of the patients.

The placebo-controlled Blinded Treatment Dosing Period is designed to minimize bias in the evaluation of ixekizumab in patients with nonrad-axSpA for both efficacy and safety assessments. Patients randomized to placebo 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 sections (Section 6.8). A placebo control period up to Week 52 is in accordance with United States (US) Regulatory advice for nonrad-axSpA and is considered globally acceptable given that as of Week 16, investigators may decide to offer rescue treatment based on their judgement of the appropriate clinical approach for the individual patient. Such rescue treatments may include changes in concomitant medications (as specified in Section 6.8) and/or the use of ixekizumab 80 mg Q2W. To maintain the blind, the rescue treatment of ixekizumab 80 mg Q2W will be given across all treatment groups. The use of rescue ixekizumab therapy 80 mg Q2W allows patients who were on placebo to receive active treatment, patients who were on ixekizumab 80 Q4W to increase dose, and patients who were on ixekizumab Q2W more time to further improve their response. Studies with TNF inhibitors indicate that there is a proportion of patients who have a delayed response and may benefit from more time to reach an optimal response (Maksymowych et al. 2015a).

General guidelines recommend a minimum period of 12 weeks to evaluate effect of biologic treatment modifications. However, if in the opinion of the investigator, a patient does not show any clinical improvement after at least 8 weeks of the ixekizumab 80 mg Q2W treatment modification, then the investigator may consider discontinuation of the patient from ixekizumab treatment. Such patients may then receive other medical therapies (potentially including a TNF inhibitor) that are prescribed by their physician and are to remain in the study.

The effectiveness of ixekizumab in treating nonrad-axSpA will be assessed primarily by the ASAS40 response rate at Week 16 for regulatory agencies that require Week 16 as the primary endpoint, and by the ASAS40 response rate at Week 52 for regulatory agencies that require Week 52 as the primary endpoint. The ASAS40 response at Week 16 endpoints are in alignment with efficacy endpoints for currently approved axSpA therapies and with regulatory guidance (EMEA 2009). The ASAS40 response at Week 52 and other Week 52 endpoints are in line with regulatory advice received by Lilly from the Food and Drug Administration for nonrad-axSpA (2015, 2018). Steady-state exposure of ixekizumab is expected to be reached by Week 16.

Based on previous studies with ixekizumab in patients with Ps, RA, and PsA, it is anticipated that maximum or near maximum clinical effect in nonrad-axSpA patients will be achieved for the majority of patients within this timeframe for both ixekizumab treatment regimens regardless of the starting dose.

Nonrad-axSpA patients with objective signs of inflammation, defined as sacroiliitis on MRI and/or elevated CRP, are at increased risk of disease progression. In the present study sacroiliitis on MRI is defined by ASAS/OMERACT criteria (Rudwaleit et al. 2009b, 2009d) and elevated CRP is defined as CRP >5.00 mg/L. In addition, biologic treatment of patients with these objective signs of inflammation has been reported to result in consistently better clinical responses (compared with placebo) relative to the subpopulation of nonrad-axSpA patients with no evidence of sacroiliitis by MRI and a normal CRP level at baseline (Poddubnyy et al. 2012; Sieper et al. 2013; Sieper et al. 2015; Maksymowych et al. 2014). Therefore the following strata (positive MRI and elevated CRP; positive MRI and nonelevated CRP; negative MRI and elevated CRP) have been defined to ensure balance across treatment groups and greater comparability of treatment groups at baseline.

The Post-Study Follow-Up Period is important for safety monitoring following administration of the last study treatment. The duration of the Post-Study Follow-Up Period (Period 3) is approximately 12 weeks to allow for monitoring during ixekizumab clearance and reflects a time period equivalent to approximately 5 half-lives of ixekizumab.

## 4.4. Justification for Dose

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

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The ixekizumab 80 mg Q2W and 80 mg Q4W treatment regimens with a 160-mg starting dose have also been tested in pivotal Phase 3 studies and demonstrated efficacy with favorable benefit-risk profile in Ps (Griffiths et al. 2015) and PsA (Gottlieb et al. 2015; Mease et al. 2015). Other therapies (most TNF inhibitors and secukinumab) have demonstrated efficacy using a similar treatment regimen across various rheumatological conditions (RA, PsA, axSpA) (Humira® package insert, 2015 [WWW]; Enbrel® package insert, 2015 [WWW]; Simponi® package insert, 2013 [WWW]; Cimzia® package insert, 2015 [WWW]; Cosentyx® package insert, 2015 [WWW], Sanford and McKeage 2015).

Treatment effect size has been reported to be similar between rad-axSpA and nonrad-axSpA patients treated with TNF-inhibitors compared with placebo comparator groups, using the same dose regimen across the axSpA spectrum (Callhoff et al. 2015).

The impact of an ixekizumab starting dose on speed of onset and through the primary efficacy endpoint assessment at Week 16 will be evaluated by providing a 160-mg starting dose to half of the patients and an 80-mg starting dose to the remaining half of the patients.

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 both rad-axSpA and nonrad-axSpA patients 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 a physician's diagnosis of active nonrad-axSpA, who meet the ASAS classification criteria for nonrad-axSpA either by the presence of sacroiliitis on MRI (based on central reading) accompanied by at least 1 spondyloarthropathy (SpA) feature OR by being HLA–B27 positive and having at least 2 additional SpA features (Appendix 5) and 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 randomization 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 before 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] Presence of sacroiliitis on MRI (according to ASAS/OMERACT criteria and based on central reading) (Rudwaleit et al. 2009d) and have at least 1 SpA feature

OR

Are positive for HLA-B27 and have at least 2 additional SpA features, according to the ASAS criteria (Sieper et al. 2009; Rudwaleit et al. 2009a); SpA features listed in Appendix 5.

[2] Patients have a history of back pain ≥3 months with age at onset <45 years.

[3] Have active nonrad-axSpA defined as BASDAI ≥4 and total back pain ≥4 on a NRS at screening and baseline (Sieper et al. 2009)

[4] Patients have objective signs of inflammation by presence of sacroiliitis on MRI (as defined by ASAS/OMERACT) or presence of elevated CRP (defined as CRP >5.00 mg/L).

[5] 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

[6] 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.

**Patient Characteristics**

[7] Are ambulatory male or female patients 18 years or older 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 including 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 follows:

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

  OR

  Women who are ≥60 years of age.

  OR

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

**Informed Consent**

[9] Are able and have given informed consent approved by Lilly, or its designee, and the Investigational Review Board/Ethical Review Board (IRB/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] Fulfillment of the modified New York (mNY) criteria (van der Linden et al. 1984) with sacroiliitis defined radiographically, based on central reading: sacroiliitis grade ≥2 bilaterally or grades 3 to 4 unilaterally

[11] 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 who 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 study entry criteria.

[12] Have active Crohn's disease (CD) or active ulcerative colitis (UC)

**Note**: Patients may be enrolled if they have had a history of inflammatory bowel disease (IBD), including CD and UC, but have had no exacerbation for ≥6 months prior to baseline, and, if currently on treatment, must be on stable treatment for ≥6 months prior to baseline.

[13] 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 ≥4 weeks after resolution of acute symptoms.

[14] 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

[15] 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

[16] 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

[17] Presence of any comorbid respiratory, hepatic, renal, gastrointestinal, endocrine, or 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

[18] Presence of any neurologic or neuropsychiatric 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 significant uncontrolled neuropsychiatric disorder; have a recent history of a suicide attempt (within 30 days prior to screening visit [Visit 1] and any time between screening visit [Visit 1] and baseline randomization [Visit 2]); 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.

[20] 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 antibiotics for an infection,
- 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
  - or had an infection that occurs with increased incidence in an immunocompromised host (including, but not limited to, Pneumocystis jirovecii pneumonia, symptomatic histoplasmosis, or coccidioidomycosis)

[21] Have a known immunodeficiency or who are immunocompromised to an extent such that participation in the study would pose an unacceptable risk to the patient

[22] Have or had a herpes zoster or any other clinically apparent varicella-zoster virus infection within 12 weeks of baseline randomization

[23] 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 once ≥4 weeks after resolution of symptoms.

[24] Have a known allergy or hypersensitivity to any biologic therapy that would pose an unacceptable risk to the patient if participating in this study

[25] 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

[26] 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**

[27] Patients who are taking NSAIDs or cyclooxygenase-2 (COX-2) inhibitors and are not on a stable dose for at least 2 weeks prior to baseline randomization are excluded.

[28] 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:** the following cDMARDs: 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, are not to 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.

[29] Current use of oral corticosteroids greater than 10 mg per day of prednisone or equivalent

**Note**: If patients are taking prednisone or its equivalent and the dose is less than or equal to 10 mg/day, the dose must be stable for at least 4 weeks prior to baseline randomization.

[30] 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 inhibitors, TNF inhibitors, IL-1, IL-6, IL-12/23, IL-17 [including ixekizumab], IL-17R, T cell, or B cell targeted therapies)

[31] Are currently enrolled in, have participated in, 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 wash-out period (described in criterion above).

[32] 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

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

[34] Have received any parenteral glucocorticoid administered by intraarticular, intramuscular, or intravenous injection within 6 weeks prior to baseline randomization; or are planning to receive a parenteral injection of glucocorticosteroids during the Blinded Treatment Dosing Period (Period 2) of the study

[35] Use of any opiate analgesic at average daily doses of >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.

[36] Had a live vaccination within 12 weeks prior to baseline randomization, 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 must 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.

[37] 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

**Diagnostics Assessments**

[38] Have a body temperature ≥38°C (100.5°F) at baseline randomization

**Note**: These patients may be rescreened once ≥4 weeks after documented resolution of elevated temperature.

[39] 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 criteria)

[40] Are positive for human immunodeficiency virus (HIV) serology; ie, positive for human immunodeficiency virus antibody (HIVAb)

[41] 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.

[42] 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).

[43] Have electrocardiogram (ECG) abnormalities that are considered clinically significant by the investigator and would pose an unacceptable risk to the patient if participating in the study

[44] Have 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 are not to 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 by study site personnel prior to randomization. For eligibility, the most recent lab test results must not meet any of the following criteria:

[45] At screening, have a neutrophil count <1500 cells/µL (<1.50x$10^3$/µL or <1.50 GI/L)

[46] At screening, have a lymphocyte count <800 cells/µL (<0.80x$10^3$/µL or <0.80 GI/L)

[47] At screening, have a platelet count <100,000 cells/µL (<100x$10^3$/µL or <100 GI/L)

[48] At screening, have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal (ULN)

[49] At screening, have a total white blood cell (WBC) count <3000 cells/µL (<3.00x$10^3$/µL or <3.00 GI/L)

[50] 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

[51] 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**

[52] Have donated blood of more than 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 1 time after ≥4 weeks have passed since initial screening.

[53] Are women who are lactating or breastfeeding

[54] 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.

[55] Are Lilly employees or its designee or are employees of third-party organizations (TPOs) involved in the study

[56] Are unwilling or unable to comply with the use of a data collection device to directly record data from the patient

[57] 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 [13], [23], [38], or [52] may be rescreened one time, ≥4 weeks after documented resolution of symptoms or from time of blood donation.

The screening MRI must be completed ≤30 days prior to baseline randomization (Visit 2). After consultation with Lilly medical, patients may be rescreened if screening MRI of the SIJ was >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 that 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 RHBX Screening of Patients Who Were Ineligible for Study RHBV

Study RHBV is a Phase 3, multicenter, randomized, double-blind, active- and placebo-controlled, parallel-group, outpatient study examining the efficacy and safety of ixekizumab compared to placebo SC in patients with active rad-axSpA who are bDMARD-naive. Patients **ineligible** for Study RHBV because of an absence of radiographic evidence of axSpA may be **eligible** for Study RHBX.

Patients who were initially screened for Study RHBV and were excluded because their x-ray of the SIJ did not meet mNY criteria but who may meet entry criteria for Study RHBX, may give consent for Study RHBX. Timeframe guidelines for screening procedures are as follows:

**MRI:**

- **If ≤30 days** between the Study RHBV screening MRI of the SIJ and Study RHBX randomization (Visit 2): MRI of the SIJ does not need to be repeated.
- **If >30 days** between the Study RHBV screening MRI of the SIJ and Study RHBX baseline randomization (Visit 2): MRI of the SIJ must be repeated.

**Other procedures:**

- **If ≤42 days** between the Study RHBV screening visit (Visit 1) and the Study RHBX baseline randomization (Visit 2): data collected at the Study RHBV screening visit (for example, laboratory data, TB testing, and patient questionnaires) may be used to determine eligibility for Study RHBX.
- **If >42 days** between the Study RHBV screening visit (Visit 1) and the Study RHBX 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 RHBV prior to entering into Study RHBX.

## 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 ixekizumab at 2 treatment regimens (80 mg Q2W and 80 mg Q4W) with placebo treatment. Each ixekizumab treatment regimen will include patients receiving an 80-mg or a 160-mg starting dose; patients will be randomized to a starting dose at a 1:1 ratio. All doses are administered via SC injection. Table RHBX.2 shows the treatment regimens.

At baseline (Week 0), all patients will be randomized to a treatment group and receive 2 injections. Patients assigned to an ixekizumab treatment regimen with a 160-mg ixekizumab starting dose will receive 160-mg of ixekizumab as 2 SC injections (80 mg per SC injection). Patients assigned to an ixekizumab treatment regimen with an 80-mg starting dose will receive 80 mg of ixekizumab as 1 SC injection and 1 SC injection of placebo. Patients assigned to the placebo treatment group will receive 2 SC injections of placebo. After Week 0 and through Week 50, all patients will receive 1 injection every 2 weeks. Details of the patient treatment regimens are provided in Table RHBX.2.

Beginning at Week 16 and up to Week 44, any patient, regardless of their original treatment group, may be identified by an investigator based on clinical judgment as an inadequate responder. At such time, changes in background therapy and/or addition of biologic rescue therapy (ixekizumab 80 mg Q2W) can be made at the discretion of the investigator, while remaining blinded to the original randomization treatment assignment. Changes in ongoing medications at that time can include changes in dose of NSAIDs or nonbiological disease-modifying antirheumatic drugs (DMARDs), including the introduction of new medications. The investigator may also decide to use biologic rescue of ixekizumab 80 mg Q2W with an 80-mg starting dose, which is a blinded decision as to whether the patient will be initiating ixekizumab, increasing the dose, or remaining on the same treatment regimen.

Investigators who believe a patient needs rescue ixekizumab 80 mg Q2W treatment will indicate such via interactive web-response system (IWRS), and these patients will receive ixekizumab 80 mg Q2W with an 80-mg starting dose. This option specifically means the following:

- Placebo inadequate responders will switch to ixekizumab 80 mg Q2W.
- Ixekizumab 80 mg Q4W inadequate responders will switch to ixekizumab 80 mg Q2W.
- Ixekizumab 80 mg Q2W inadequate responders will continue on the same regimen of ixekizumab 80 mg Q2W to allow more time to improve their response.

General treatment guidelines recommend a minimum period of 12 weeks to evaluate effect of biologic treatment modifications; however, if, in the opinion of the investigator, a patient does not show any clinical improvement after at least 8 weeks of the ixekizumab 80 mg Q2W rescue treatment, then the investigator may consider discontinuation of the patient from ixekizumab treatment. Such patients may then receive medical therapies as per local standard of care, which may include a TNF inhibitor, as prescribed by their physician, and are to remain in the study per the Schedule of Activities (Appendix 2). If an investigator decides to initiate a TNF inhibitor in

patients who fail rescue ixekizumab therapy, it is recommended that, for the timing of the first TNF inhibitor injection, investigators take into account the half-life of ixekizumab (approximately 13 days) and apply appropriate clinical judgement in balancing the need for treatment (eg, introducing a TNF inhibitor) with potential safety considerations. For patients who are prescribed a TNF inhibitor by the investigator after failing rescue ixekizumab therapy, the patient's specific TNF inhibitor may be provided to him/her during his/her participation in the trial up to Week 52 in an unblinded method either by direct supply or by reimbursement, depending upon local policy and procedures.

Details of the treatment regimens for patients responding to study treatment are summarized in Table RHBX.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) until the patient discontinues investigational product.

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

- explaining the correct use of the investigational product to the patient/patient caretaker
- 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 RHBX.2. Treatment Regimens from Week 0 to Week 50 (Blinded Treatment Dosing Period [Period 2])**

| Treatment Assignment | | Dose Week 0 (Day 0) | | Dose Week 2 to Week 50 (Remainder of Period 2)[a] |
|---|---|---|---|---|
| | **Total injections per patient:** | **2 injections** | | **1 injection Q2W** |
| ixekizumab 80 mg Q2W with 160-mg starting dose | Treatment dose | 2 ixekizumab 80-mg injections | → | 1 ixekizumab 80-mg Q2W injection (Beginning at Week 2, Q2W) |
| | Injections to maintain blinding | None | | |
| ixekizumab 80 mg Q2W with 80-mg starting dose | Treatment dose | 1 ixekizumab 80-mg injection | → | |
| | Injections to maintain blinding | 1 placebo for ixekizumab 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 | None | | |
| 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) |
| | Injections to maintain blinding | 1 placebo for ixekizumab injection | | |
| | | | | |
| Placebo | Injections to maintain blinding | 2 placebo for ixekizumab injections | | 1 placebo for ixekizumab injection Q2W (Beginning at Week 2, Q2W) |

Abbreviations: DMARDs = disease-modifying antirheumatic drug; NSAIDs = nonsteroidal anti-inflammatory drugs; Q2W = every 2 weeks; Q4W = every 4 weeks.

Note: Shaded cells represent ixekizumab treatment regimens with a 160-mg starting dose (given as 2 ixekizumab 80-mg injections at Week 0).

[a] Beginning at Week 16 and up to Week 44, any patient, regardless of their original treatment group, may be identified by an investigator based on clinical judgment as an inadequate responder. At such time changes in background therapy and/or addition of biologic ixekizumab rescue therapy can be made at the discretion of the investigator, while remaining blinded to the original randomization treatment assignment. Changes in ongoing medications at that time can include changes in dose of NSAIDS or nonbiological DMARDS, including the introduction of new medications. Investigator may also decide to use biologic rescue with ixekizumab 80 mg Q2W and an 80-mg starting dose.

### 6.1.1. Administration of Investigational Product

Injections will be self-administered SC by the patient or caregiver after training by the clinical staff.

**Training:** At Week 0 (baseline, Visit 2) each patient is scheduled to receive 2 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 injection 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 self-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 when the injections have to be done at the site for postdose 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 the investigational product. Note that in case a study drug injection is performed in an arm, it is not to be given in the same arm from which patient blood samples, including PK samples, are drawn at relevant visits.

Study Drug Administration Logs will be dispensed to each patient 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 *Manual Syringe Directions for Use*. The injection site may be rotated to another area for subsequent doses.

**Observation:** For safety monitoring patients are to remain under observation for at least 1 hour after dosing at Week 0 (Visit 2) and at any visit on or after Week 16 in which a patient receives the initial injection of ixekizumab as rescue therapy. This initial injection of rescue ixekizumab will be administered by the patient or caregiver at the clinical site to allow for observation for any AEs and for collection of postinjection 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 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

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 screening MRI/CRP status (positive MRI and elevated CRP; positive MRI and nonelevated CRP; negative MRI and elevated CRP). Elevated CRP is defined as >5.00 mg/L.

Target enrollment will be a minimum of approximately 20% for each of the MRI/CRP strata. 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 ≥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 will 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; patients, study site personnel, and study team will be blinded to study treatment randomization. If an investigator decides to use the treatment modification of ixekizumab Q2W for a patient, study site personnel, the patient, and the study team will remain blinded to the initial randomization.

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 a 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 requested to make every effort to contact the Lilly clinical research physician/clinical research scientist prior to unblinding a patient's treatment assignment. If the patient's treatment assignment is unblinded, Lilly 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 an injectable solution 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. 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 or shaken. 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 except where treatment modifications are recommended by the investigator because of inadequate response (refer to Section 6.1 for treatment modifications and 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 are to 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 the 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 anti-drug antibodies (ADA) and PK as soon as possible (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, etc.). 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 or 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 injection 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. Deviations from the prescribed dosage regimen are to be recorded in the case report form (CRF).

Compliance is defined in Section 9.3.4.

## 6.8. Concomitant Therapy

All concomitant medication taken during the study must be recorded in the electronic CRF (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.

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 relevant 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. 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-Study Follow-Up Period (Period 3), 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.

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.

*TNF alpha inhibitors:*

TNF alpha inhibitors are not to be used during any study period prior to discontinuation of investigational study medication and/or rescue ixekizumab 80 mg.

*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.

### *6.8.1. Concomitant Medications During Week 0 to Week 16*

*NSAIDs and Analgesics*:

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 (AE).

Short-acting analgesics with no anti-inflammatory action (such as paracetamol) are permitted. If administered ad hoc as needed, they are to be withheld within the 24-hour period prior to any

assessment. Aspirin (in a dose not exceeding 350 mg/day) may be taken to manage cardiovascular risk.

Opiate analgesic use is allowed but is not to exceed an average daily dose of 30 mg/day of morphine or its equivalent. 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.

*Conventional DMARDs:*

Discontinuation of excluded oral or injectable cDMARDs before study enrollment must occur at least 4 weeks prior to baseline. 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. These agents can only be used as single agent therapy 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, then cDMARD dose is to be lowered or the medication stopped. Local standard of care is to be followed for concomitant administration of folic or folinic acid if MTX is taken.

*Corticosteroids*:

*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. Treatment alteration in oral corticosteroid dose is not to occur prior to Week 16.

*Parenteral corticosteroids (intravenous, intramuscular, intra-articular)*: Treatment with any parenteral corticosteroids is not permitted within 6 weeks prior to baseline or up to Week 16.

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

### *6.8.2. Concomitant Medications at or after Week 16 for Treatment Modifications (after Completion of Week 16 Assessments)*

*General:*

Changes in therapy are discouraged in the last 8 weeks prior to 52 week assessments.

*NSAIDs and Analgesics*:

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 assessment. Any changes in frequency and/or dose must be recorded in the eCRF.

Short-acting analgesics with no anti-inflammatory action (such as paracetamol) are permitted. If administered ad hoc as needed, they 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: Use of variable doses of opiate analgesics is allowed but is not to exceed an average daily dose of 30 mg morphine or its equivalent.

*Conventional DMARDs:*

Adjustment of allowed cDMARDs (eg, 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 8 weeks is recommended. cDMARD can only be used as a single agent and not in combination with other cDMARDs. Any changes must be recorded in the eCRF.

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

*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 (intravenous, 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.

Any change in medication not addressed above is to be discussed with the clinical research physician or clinical research scientist. 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 RHBY) offering up to an additional 2 years of treatment, if enrollment criteria for Study RHBY are met. For patients who have completed Study RHBX through Week 52 and have exclusionary criteria for Study RHBY at Week 44 **and** Week 52, patients will complete the Post-Study Follow-Up Period (Period 3) in Study RHBX.

### *6.9.2. Continued Access*

Investigational product will not be made available to patients after conclusion of this study. However, patients who complete Study RHBX and who are eligible to continue in the long-term study (Study RHBY) may 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.

Patients who have taken at least 1 study dose and who discontinue study treatment prior to Week 16 or study participation (regardless of timing) are to complete an ETV and enter into post-study follow-up for at least 12 weeks after the ETV date or the last regularly scheduled visit. Patients whose ETV or last regularly scheduled visit is longer than 12 weeks after their last investigational study medication dose are not required to enter into the Post-Study Follow-Up Period. Patients who complete the study through Week 52 and who are not entering into Study RHBY are to enter into the Post-Study Follow-Up Period (Period 3) as shown in the Schedule of Activities (Appendix 2).

## 7.1. Discontinuation from Study Treatment

### *7.1.1. Permanent Discontinuation from Study Treatment*

The following criteria must be followed for discontinuation from study treatment.

[1] Discontinuation of the investigational product for abnormal liver tests should be considered by the investigator when a patient meets 1 of the following conditions after consultation with the Lilly designated medical monitor:

- ALT or AST >8 times ULN
- ALT or AST >5 times ULN for more than 2 weeks
- ALT or AST >3X ULN and total bilirubin level >2 times ULN or prothrombin time >1.5 times ULN
- ALT or AST >3 times ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase >2.5 times ULN and total bilirubin >2 times ULN
- alkaline phosphatase >2.5 times ULN 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/µL (<0.50x10$^3$/µL or <0.50 GI/L)
    - ≥500 and <1000 cells/µL (≥0.50x10$^3$/µL and <1.00x10$^3$/µL or ≥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)
    - ≥1000 and <1500 cells/µL (≥1.00x10$^3$/µL and <1.50x10$^3$/µL or ≥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/µL (<2.00x10$^3$/µL or <2.00 GI/L)
- Lymphocyte count <500 cells/µL (<0.50x10$^3$/µL or <0.50 GI/L)
- Platelet count <50,000 cells/µL (<50x10$^3$/µL 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 Adverse Events, 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] 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 in the following circumstances:

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.

[9] The investigator or attending physician decides that the patient is to be withdrawn from study treatment.

[10] The patient requests to be withdrawn from study treatment.

[11] 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).

[12] The patient becomes HBV DNA positive. The patient is to be referred to a specialist physician. Discussion of discontinuation from study treatment and from the study is provided in Section 8.4.10.2.

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

The criteria for enrollment must be followed explicitly. If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the sponsor clinical research physician 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 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 participation 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 due

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 ASAS5/6 (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 8.1.2.20.1), and
6) Spinal Mobility (lateral spinal flexion) (Section 8.1.2.6).

### *8.1.1. Primary Efficacy Assessments: ASAS40*

The ASAS40 response (Anderson et al. 2001; Brandt et al. 2004; Sieper et al. 2009) is derived from patient-reported assessments. The ASAS40 is defined as a ≥40% improvement and an absolute improvement from baseline of ≥2 units (range 0 to 10) in ≥3 of the following 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 ASAS5/6

The ASAS20, ASAS individual components, ASAS partial remission, and ASAS5/6 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 response is derived from patient-reported assessments. An ASAS20 response is defined as a ≥20% improvement and an absolute improvement from baseline of ≥1 units

(range 0 to 10) in ≥3 of the following 4 domains (Patient Global, Spinal Pain, Function, and Inflammation) and no worsening of ≥20% and ≥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 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. ASAS5/6*

The ASAS5/6 includes assessment of all 6 individual ASAS domains listed above (Section 8.1) and represents improvement of ≥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 a 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, 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 a NRS and are each rated between "0" (no pain) and "10" (most severe pain). The first question is used to calculate derived scores (ie, ASAS40, ASAS20, etc.) and defines the total back pain for inclusion criteria [3].

### 8.1.2.4. Bath Ankylosing Spondylitis Disease Activity Index

The BASDAI is a patient-reported assessment. The BASDAI is an instrument consisting of 6 questions that relate to 5 major symptoms relevant to 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). Higher score represents worse disease activity.

The BASDAI50 represents an improvement of ≥50% of the BASDAI score from baseline.

### 8.1.2.5. Bath Ankylosing Spondylitis Functional Index

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

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 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 which 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 encircled length by centimeter (cm) 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 (larger difference) measurement 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. Tip of nose and tragus must be at the same horizontal line to avoid neck extension. Then the distance from occiput to the 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 et al. 2011). The parameters used for the ASDAS (with high-sensitivity CRP [hsCRP] as acute phase reactant):

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

$ASDAS_{crp}$: 0.121 × total back pain + 0.110 × patient global + 0.073 × peripheral pain/swelling + 0.058 × duration of morning stiffness + 0.579 × Ln(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 ≤ ASDAS <2.1 defines moderate disease activity;
- 2.1≤ ASDAS ≤3.5 defines high disease activity; and
- ASDAS >3.5 defines very high disease activity.

Clinically important improvement is defined as change ≥1.1 units, and major improvement is defined as change ≥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 (Hueft-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 of scores: 0 to 13), higher scores indicate more severe enthesitis.

The MASES is to be assessed by a rheumatologist or health care provider who meets study qualifications for study assessment.

#### 8.1.2.11. SPARCC 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 of scores: 0 to 16). Higher scores indicate more severe enthesitis.

The SPARCC is to be assessed by a rheumatologist or health care provider who meets study 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) must be excluded from evaluation from the time of the injection to the conclusion of the study.

Joint assessments will be performed by an experienced rheumatologist or skilled and trained assessor. 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 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) must be excluded from evaluation from the time of the injection to the conclusion of the study.

Joint assessment is to be performed by an experienced 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 and will be excluded from evaluation during the study.

The SJC data will be collected electronically.

### 8.1.2.13. NSAID 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. Clinically Meaningful Changes in Concomitant Medication(s) or Background Therapy

Information regarding changes in concomitant medication or background therapy will be collected at baseline and through Week 52. A detailed definition of what are considered clinically meaningful changes in concomitant medication(s) or background therapy will be provided in the SAP.

### 8.1.2.15. 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 (ICFD) which has been published by World Health Organization (WHO). The ASAS has applied the ICFD as a basis to define a core set of items relevant for patients with axSpA. The 17-item instrument has scores ranging from 0 (good Health) to 17 (poor Health) (Kiltz et al. 2015). Each item consists of 1 question that the patient needs to respond to with either "I agree" (score 1) or "I do not agree

(score 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.

#### 8.1.2.16. 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 and Physical Component Summary 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).

#### 8.1.2.17. 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 1 number that describes their worst level of fatigue during the previous 24 hours.

#### 8.1.2.18. Work Productivity and Activity Impairment Questionnaire—Spondyloarthritis

The WPAI-SpA consists of 6 questions to determine employment status, hours missed from work because of spondyloarthritis, hours missed from work for other reasons, hours actually worked, the degree to which spondyloarthritis affected work productivity while at work, and the degree to which spondyloarthritis 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 Health Outcomes Research [WWW]).

#### 8.1.2.19. Jenkins Sleep 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 numbers 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).

#### 8.1.2.20. Laboratory Tests Used for Efficacy Measures and Disease Diagnosis

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

High-sensitivity C-reactive protein (hsCRP) 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 study blind.

### 8.1.2.21. Imaging Used for Efficacy Measures and Disease Diagnosis

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

For each patient, x-ray and MRI images will be collected according to the Schedule of Activities (Appendix 2) and Table RHBX.3 and will follow the study specific recommendations included in the site training materials for the study. The x-ray of the SIJ will be used to exclude patients with radiographic sacroiliitis as defined by the mNY criteria. MRI of the SIJ, collected at screening, Week 16, and Week 52 will generate objective data for the investigational drug on the anti-inflammatory effect as well as data on the evolution of structural changes in the SIJ. The screening x-ray of the spine will serve as baseline for later evaluation of change from baseline in structural progression in the long-term study (Study RHBY). All reading of x-ray and MRI images is done centrally.

**Table RHBX.3. Imaging Requirements for Sacroiliac Joints and Spine**

| Time Point[a] | Type of Image[b] | Purpose | Reading | Other Readers |
|---|---|---|---|---|
| Screening | X-ray of the SIJ[d] | Eligibility to exclude rad-axSpA (per mNY criteria)[a] | Centrally read[c] | Send to central reader. Results must be received from central reader prior to baseline randomization. |
| Screening | X-ray of the spine (cervical and lumbar) | Provides baseline for later evaluation of structural progression in spine | Centrally read | Send to central readers (as baseline for later structure assessments in LTE study). |
| Screening, Week 16, and Week 52 | MRI of the SIJ | Eligibility (to confirm sacroiliitis on MRI)[c] Assess efficacy | Centrally read | Send to central reader. Results must be received from central reader prior to baseline randomization. |

Abbreviations: LTE = long-term extension study; mNY = modified New York; MRI = magnetic resonance imaging; nonrad-axSpA = nonradiographic axial spondyloarthritis; 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 randomization.

c Patient cannot be randomized until centrally read results are received by site.

#### *8.1.2.21.2. 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. 2005). Scoring will be performed by central readers.

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

Structural lesions in MRIs of the SIJ were 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. 2015b). 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 a cardinal score. 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 outcome. The EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, may be converted into a single summary index by applying a formula that essentially attaches values (also called weights) to each of the levels in each dimension (The 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 follows: 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 are to 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 are not to 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 1 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 events (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.

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 will be collected as soon as possible for any patient who experiences an AE of a potential systemic allergic /hypersensitivity reaction 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, 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 an AE 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 signs measurements are to be conducted according to the Schedule of Activities (Appendix 2). Vital signs include BP, pulse, and temperature. Patients are to be resting for a minimum of 5 minutes prior to vital sign collection.

Any clinically significant findings from vital signs measurement 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 an AE via CRF.

### 8.4.3. Laboratory Tests

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

Urine pregnancy test and PPD/T-SPOT® will be collected and read/analyzed locally. QuantiFERON®-TB Gold test will be collected and read/analyzed either centrally or locally.

If required per local regulations, urine testing for pregnancy may occur at intervals as required during the study treatment period and/or follow-up period.

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 an AE 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 finding from a complete physical examination that results in a diagnosis and that occurs after the patient receives the first dose of study treatment is to be reported to Lilly or its designee as an AE via CRF.

### 8.4.5. Eye Symptom Assessment

At each study visit, study healthcare 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 is to be reported to Lilly or its designee as an AE via CRF.

**Patients with no TB test (Purified Protein Derivative [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 ≥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, 1 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 ≥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 1 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 ≤2xULN) upon retesting of serum ALT/AST prior to randomization. Such patients must complete appropriate latent TB infection (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 either no induration or induration measuring <5mm 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 latent TB treatment prior to baseline (Week 0, Visit 2) and continued treatment during the study is required to attain and maintain 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 contract 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 an AE 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 that 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 (IDS/QIDS home page [WWW]).

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

The C-SSRS (Posner et al. 2007, C-SSRS web site [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 1 question eCRF questionnaire that is completed at any visit, including baseline visits, asking for the number of suicidal or nonsuicidal self-injurious behaviors the patient experienced since last assessment. For each unique event identified, a

questionnaire (Self-Harm Follow-Up Form) which collects supplemental information on the self-injurious behavior must 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 will 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 ≥3xULN, alkaline phosphatase ≥2xULN, or elevated total bilirubin ≥2xULN, 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 (Period 2)*

**During treatment with investigational product**, patients with neutrophil counts <1500 cells/µL (<1.50x10$^3$/µL or <1.50 GI/L) are to be managed for neutropenia as follows:

- <500 cells/µL (<0.50x10$^3$/µL or <0.50 GI/L), see Discontinuation Criteria (Section 7.1)
- ≥500 cells/µL and <1000 cells/µL (≥0.50x10$^3$/µL and <1.00x10$^3$/µL or ≥0.50 GI/L and <1.00 GI/L), see Discontinuation Criteria (Section 7.1)
- ≥1000 cells/µL and <1500 cells/µL (≥1.00x10$^3$/µL and <1.50x10$^3$/µL or ≥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 ≥1500 cells/μL (≥1.50x10$^3$/μL or ≥1.50x10$^3$/μL) 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 ≥1000 cells/μL and <1500 cells/μL (≥1.00x10$^3$/μL and <1.50x10$^3$/μL or ≥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 ≥1000 cells/μL and <1500 cells/μL (≥1.00x10$^3$/μL and <1.50x10$^3$/μL or ≥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.

- ≥1000 cells/μL and <1500 cells/μL (≥1.00x10$^3$/μL and <1.50x10$^3$/μL or ≥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 ≥1500 cells/μL (≥1.50x10$^3$/μL or ≥1.50 GI/L). If the patient has 3 or more postbaseline neutrophil counts of ≥1000 cells/μL (≥1.00x10$^3$/μL or ≥1.00 GI/L) and <1500 cells/μL (<1.50x10$^3$/μL or <1.50 GI/L), no value of <1000 cells/μL (<1.00 x10$^3$/μL 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 RHBY*: If, at the last scheduled study visit, the patient's neutrophil count is <1500 cells/μL (<1.50x10$^3$/μL 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 must 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 the Post-Study Follow-Up Period (Period 3) design at Visits 801 (4 weeks post-resolution of infection), 802 (8 weeks after Visit 801 unless otherwise specified), and 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 above mentioned threshold at Week 52 who have already enrolled in Study RHBY, requirements for repeat test for neutrophil count will be specified in the Study RHBY 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-Study Follow-Up Period (Period 3) design, Visits 801 (4 weeks post-ETV or last regularly scheduled visit), 802, and 803 (if necessary); additional visits may be required depending on the degree of neutropenia.

#### *8.4.10.1.3. Post-Study Follow-Up*

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

- As long as a patient's neutrophil count is <1000 cells/μL (<1.00x$10^3$/μL 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 ≥1000 cells/μL and <1500 cells/μL (≥1.00x$10^3$/μL and <1.50x$10^3$/μL or ≥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 ≥1500 cells/μL (≥1.50x$10^3$/μL or ≥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/μL (<1.50x$10^3$/μL 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 who 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

who 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 who 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) should be consulted and potentially start antiviral therapy prior to discontinuation of any immunosuppressant therapy (including investigational drug). Timing of discontinuation from the study treatment and of any immunosuppressant therapy/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 ≥160 mm Hg plus ≥20 mm Hg increase from baseline [Week 0; Visit 2]; and/or diastolic BP at ≥100 mm Hg plus ≥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 antihypertensive 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.

Samples will not be used 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 and epigenetic changes thought to play a role in nonrad-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 following 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

CCI [redacted]

### *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).

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 ixekizumab.

## 8.9. Health Economics

Refer to Section 8.1.3.

# 9. Statistical Considerations and Data Analysis

## 9.1. Determination of Sample Size

Approximately 300 patients will be randomized at a 1:1:1 ratio in the Blinded Treatment Dosing Period (Period 2) to ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, and placebo. With 100 patients per treatment group, this study will have approximately 98% 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: 46% for ixekizumab 80 mg Q2W treatment group and 18% for the placebo group. A 2-sided Fisher's exact test at the 0.05 level is assumed. These assumptions are based on the data from historical clinical studies in nonrad-axSpA patients with objective signs of inflammation (etanercept, adalimumab, certolizumab, and golimumab [Sieper et al. 2013; Dougados et al. 2014; Landewé et al. 2014; Sieper et al. 2015]).

There is little data from similarly designed 52-week placebo-controlled trials regarding the ASAS40 response rate for active and placebo treated patients to guide power estimation at Week 52. Table RHBX.4 provides power estimates to test the superiority of ixekizumab Q2W to placebo for the ASAS40 at Week 52, assuming various ASAS40 response rates for ixekizumab Q2W and placebo at Week 52. A 2-sided Fisher's exact test at the 0.05 level is assumed.

**Table RHBX.4. Power Estimates for Week 52**

| ASAS40 Response Rates (%) at Week 52 | | |
|---|---|---|
| Ixekizumab Q2W (N = 100) | Placebo (N = 100) | Power (%) |
| 50 | 10 | 99 |
| 40 | 10 | 99 |
| 30 | 10 | 93 |
| 50 | 15 | 99 |
| 40 | 15 | 97 |
| 30 | 15 | 66 |

Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; N = number of subjects; Q2W = every 2 weeks.

## 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 2)*

Comparisons between each ixekizumab regimen (80 mg Q2W or 80 mg Q4W) 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 at Week 52 (Visit 15) or the ETV (between Weeks 0 and 52). For patients who are deemed as inadequate responders by investigators after Week 16 and for whom the investigator indicates the need to use ixekizumab 80 mg Q2W, only data prior to the assignment of modified treatment by ixekizumab 80 mg Q2W will be included in the Period 2 primary analyses to avoid falsely ascribing benefit from the modified biologic treatment to the initially randomized treatment. For patients who are deemed as inadequate responders by investigators after Week 16 and for whom the treatment modifications are limited to concomitant medication only, all data from Period 2 will be included (from time of first injection of study treatment at Week 0 [Visit 2] up to and including Week 52 [Visit 15] or the ETV [between Weeks 0 and 52]).

Baseline will be defined as the last available value before the first injection for efficacy, health outcome, 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 the 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 screening MRI/CRP status (positive MRI and elevated CRP; positive MRI and nonelevated CRP; negative MRI and elevated CRP) as described in Section 6.2. The countries will be categorized into geographic regions for analysis. Geographic regions will be defined in the SAP upon country finalization. Unless otherwise specified, the statistical analysis models will adjust for geographic region and screening MRI/CRP status.

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

The primary analysis method for treatment comparisons of categorical efficacy and health outcomes variables at specific time points will be made using a logistic regression analysis with treatment, geographic region, and screening MRI/CRP status in the model. The odds ratio and 95% confidence intervals (CIs) will be reported. Treatment difference and 95% CI 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, screening MRI/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), Week 52 (Visit 15), 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, 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, screening MRI/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), Week 52 (Visit 15), and all other visits will be tested.

When the ANCOVA is used, the model will include treatment, geographic region, screening MRI/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 (focusing on Week 4) and treatment response during Blinded Treatment Dosing Period 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 does 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.

Patients who discontinue study treatment after Week 16 will continue to be followed for the scheduled visits for safety and efficacy assessment. The data collected post discontinuation of study treatment will be summarized separately.

### *9.2.2. General Considerations for Analyses during Period 3 (Post-Study Follow-Up Period)*

For the safety analyses during Period 3, baseline is defined as the last nonmissing assessment on or prior to entering Period 3, that is, on or prior to Week 52 (Visit 15) or ETV.

Safety data collected will be summarized using descriptive statistics.

### *9.2.3. Analysis Populations*

The following analysis populations will be used; additional analysis populations will be specified in the SAP:

**Intent-to-Treat Population (ITT):** Unless otherwise specified, efficacy and health outcomes analyses for Period 2 (Blinded Treatment Dosing Period) 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 52 (Visit 15). 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 is 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 (Blinded Treatment Dosing Period). For patients who are deemed as inadequate responders by investigators after Week 16 and for whom the investigator indicates the need for modified treatment by the use of rescue ixekizumab 80 mg Q2W, the requirements for PPS only apply during the treatment period prior to the assignment of modified treatment by ixekizumab 80 mg Q2W.

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.

**Follow-up Population:** Safety analyses for Period 3 (Post-Study Follow-Up Period) 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 Post-Study Follow-Up Period. Patients will be analyzed according to the treatment they received before entering the follow-up period.

## *9.2.4. 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:

### 9.2.4.1. Nonresponder Imputation for Clinical Response

Analysis of categorical efficacy and health outcomes variables will be assessed using a nonresponder imputation (NRI) method. Patients will be considered a nonresponder 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. Similarly, all nonresponders at Week 52 (Visit 15), as well as patients who discontinue study treatment at any time prior to Week 52 for any reason, will be defined as nonresponders for the NRI analysis at Week 52. Patients who are deemed as inadequate responders by the investigator after Week 16 but remain on blinded study treatment and only have modifications in concomitant medications will not be automatically imputed as nonresponders. However, patients who discontinue originally assigned blinded study treatment and use rescue ixekizumab 80 mg Q2W will be analyzed as nonresponders for the Week 52 analysis. 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.

### 9.2.4.2. 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, with the following exception: for patients who discontinue originally assigned blinded study treatment and use rescue ixekizumab 80 mg Q2W, the last nonmissing observations prior to the use of rescue ixekizumab 80 mg Q2W will be carried forward to subsequent time points. 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.

#### 9.2.4.3. 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 1 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. For patients who discontinue originally assigned blinded study treatment and use rescue ixekizumab 80 mg Q2W, their last nonmissing observations prior to the use of rescue ixekizumab 80 mg Q2W will be carried forward to subsequent time points. Randomized patients without any postbaseline observation will not be included for evaluation.

### *9.2.5. Adjustment for Multiple Comparisons*

The primary outcome of ASAS40 at Week 16 will be tested for ixekizumab 80 mg Q2W versus placebo at a 2-sided $\alpha$=0.05. The primary outcome of ASAS40 at Week 52 will also be tested for ixekizumab 80 mg Q2W versus placebo at a 2-sided $\alpha$=0.05. Because this study has a different primary endpoint for different regulatory agencies, the significances of both primary endpoints will not be required in order for the study to be considered successful. No multiplicity adjustment will be made for the 2 primary endpoints. The comparison of ASAS40 for ixekizumab 80 mg Q4W versus placebo at Weeks 16 and Week 52 and the major secondary objectives (Section 3) will be tested using an appropriate multiple testing approach providing strong control of the familywise error rate (for the primary and major secondary tests) at a 2-sided $\alpha$=0.05. Details of the specific testing methodology (including testing order, interrelationships, type I error allocation, and the associated propagation) will be specified in the SAP.

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 discontinue from the study treatment and the study will be identified, and the extent of their participation in the study will be reported.

Patient disposition will be summarized with reasons for discontinuation. The reasons for discontinuation during Period 2 (Blinded Treatment Dosing Period) 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. Baseline characteristics will include sex, age, age category, weight, body mass index, race, geographic region, country, baseline disease activity (BASDAI), duration of disease, HLA-B27 positivity, baseline CRP (% of nonelevated or elevated), screening MRI status, screening MRI/CRP 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, spinal pain, inflammation (mean of questions 5 and 6 of BASDAI), MASES, enthesitis SPARCC, TJC, and SJC.

Treatment group comparisons in Period 2 (Blinded Treatment Dosing Period) will be conducted using Fisher's exact test for categorical data and an 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 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 (Blinded Treatment Dosing Period) 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 the treatment period. A patient will be considered overall compliant for treatment 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 (Blinded Treatment Dosing Period) 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 or at Week 52 treated with ixekizumab 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) or Week 52 (Visit 15) 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 9.2.4.

Secondary analyses for ASAS40 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 Weeks 16 and 52 will be based on the ITT population for Blinded Treatment Dosing Period (Period 2). The major secondary comparisons will be based on the multiple testing procedures described in Section 9.2.5. Treatment comparisons in the

proportion of patients achieving a categorical response at Week 16 (Visit 8) and Week 52 (Visit 15) 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 9.2.4. Treatment comparisons in the continuous measures will be analyzed using the MMRM model defined in Section 9.2.1.

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

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

| Outcomes Measure | Primary Analysis Method | Secondary Analysis Method |
|---|---|---|
| ASAS40 at Week 16 (primary efficacy outcome for regulatory agencies who accept Week 16 as the primary endpoint) | Logistic regression analysis with NRI | Categorical MMRM<br>Fisher's exact test with NRI<br>Logistic regression analysis with NRI on PPS |
| ASAS40 at Week 52 (primary efficacy outcome for regulatory agencies who require Week 52 as the primary endpoint) | Logistic regression analysis with NRI | Categorical MMRM<br>Fisher's exact test with NRI<br>Logistic regression analysis with NRI on PPS |
| Change from baseline in ASDAS at Week 16 (major secondary outcome) | MMRM | ANCOVA with mBOCF/LOCF |
| Change from baseline in ASDAS at Week 52 (major secondary outcome) | MMRM | ANCOVA with mBOCF/LOCF |
| Change from baseline in BASFI at Week 16 (major secondary outcome) | MMRM | ANCOVA with mBOCF/LOCF |
| Change from baseline in BASFI at Week 52 (major secondary outcome) | MMRM | ANCOVA with mBOCF/LOCF |
| ASDAS inactive disease at Week 16 (major secondary outcome) | Logistic regression analysis with NRI | Categorical MMRM<br>Fisher's exact test with NRI |
| ASDAS inactive disease at Week 52 (major secondary outcome) | Logistic regression analysis with NRI | Categorical MMRM<br>Fisher's exact test with NRI |
| Change from baseline in MRI of the SIJ [SPARCC Score] at Week 16 (major secondary outcome) | ANCOVA with observed case analysis[a] | Secondary analysis maybe specified in SAP |
| Percent of patients without clinically meaningful changes in background therapy at Week 52 (major secondary outcome) | Logistic regression analysis | Fisher's exact test |

Abbreviations: ANCOVA = analysis of covariance; ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; 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; SIJ = sacroiliac joints; SPARCC = Spondyloarthritis Research Consortium of Canada Score.

[a] 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 point 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 9.2.4.

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 analysis will be conducted using ANCOVA model defined in Section 9.2.1. Missing data will be imputed by the mBOCF method as described in Section 9.2.4.

### *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 on categorical safety data will be performed using Fisher's exact test as described in Section 9.2.1. Continuous safety data will be analyzed by an ANCOVA model as described in Section 9.2.1.

For patients who are deemed as inadequate responders by investigators after Week 16 and for whom the investigator indicates the need for modified treatment by the use of rescue ixekizumab 80 mg Q2W, safety data collected after initiation of modified treatment by ixekizumab 80 mg Q2W will be summarized separately.

Safety data collected after study treatment discontinuation will be summarized separately.

For post-study follow-up (Period 3), safety data will be summarized according to the treatment patients were on prior to entering the Post-Study Follow-Up Period.

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 and the date/time of the injection are considered when determining TEAEs. TEAEs 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 the treatment period, including the number and percentage of patients who experienced TEAE, TEAE by maximum severity, death, SAE, TEAE related to study drug, discontinuations from the treatment due to an AE, and treatment-emergent AESI. TEAEs (all, by maximum severity, and TEAEs possibly related to study drug by the investigator), SAEs including deaths, AEs that lead to treatment discontinuation will be summarized and analyzed by MedDRA system organ class (SOC) and preferred term (PT).

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

FEAEs, SAEs including deaths, AEs that lead to study discontinuation will be summarized for Period 3.

### *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) and postbaseline visits, 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 group, 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, ASAS20 or ASAS40) 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 developed 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 a specified time point 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 9.2.4.

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 analysis will be conducted using ANCOVA model defined in Section 9.2.1. Missing data will be imputed by the mBOCF method as described in Section 9.2.4.

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

### *9.7.2. Subgroup Analyses*

Subgroup analysis will be conducted for ASAS40 and selective major secondary outcomes (defined in SAP) at Week 16 (Visit 8) and Week 52 (Visit 15) 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, screening MRI/CRP status, and 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 9.2.4. 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 (eg, 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 mBOCF method as described in Section 9.2.4.

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 treatment-emergent positive anti-drug antibody (TE-ADA+) patient will be defined as any occurrence of a greater than or equal to 4-fold or 2 dilution increase in immunogenicity titer over

the baseline titer. This is equivalent to an increase in titer to ≥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 NAbs 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 the analysis will be performed at the time (that is, a cut-off date) the last patient completes Visit 15 (Week 52) or ETV. This interim database lock will include all data collected by the cut-off date including follow-up data from patients who have begun the Post-Study Follow-Up Period (Period 3). Because the study will still be ongoing for the Post-Study Follow-Up Period at the time of this database lock, the analysis will be referred to as an interim analysis. The analyses from the Week 52 lock will be treated as a primary analysis because all primary and major secondary study objectives will be assessed at this time.

In addition to the Week 52 lock, an internal Lilly data review committee or a data monitoring committee not in direct contact with the study sites may have access to unblinded data once all patients complete the Week 16 time point for regulatory submission or for a business purpose. The study will not be terminated early on the basis of efficacy assessment following the Week 16 analyses. Information that may unblind the study during the Week 16 analysis will not be reported to study sites or blinded study team until after the study has been unblinded at the Week 52 lock. All investigators, patients, and study team will remain blinded to treatment assignment until after all patients complete Week 52 or are discontinued from the study.

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
- 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 may 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. The ePRO 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, 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

Anderson JJ, Baron G, van der Heijde D, Felson DT, Dougados M. Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. *Arthritis Rheum.* 2001;44(8):1876-1886.

[APA] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: APA; 1994.

Appel H, Heydrich R, Loddenkemper C, Hempfing A, Sieper J. In situ detection of IL-17 secreting cells in the bone marrow of facet joints obtained from patients with ankylosing spondylitis. *Arthritis Rheum.* 2008;58(suppl):S351.

Aydin SZ, Maksymowych WP, Bennett AN, McGonagle D, Emery P, Marzo-Ortega H. Validation of the ASAS criteria and definition of a positive MRI of the sacroiliac joint in an inception cohort of axial spondyloarthritis followed up for 8 years. *Ann Rheum Dis*. 2012 71(1):56-60. doi: 10.1136/ard.2011.153064. Epub 2011 Sep 6.

Baeten D, Sieper J, Emery P, Braun J, Heijde D, McInnes I, van Laar JM, Landewe R, Wordsworth P, Wollenhaupt J, Kellner H, Paramarta J, Berolino AP, Wright AM, Hueber W. The anti-IL-17A monoclonal antibody secukinumab (AIN457) showed good safety and efficacy in the treatment of active ankylosing spondylitis [poster]. Poster presented at: Annual Meeting of the American College of Rheumatology; 10 November 2010; Atlanta, GA. Available at: http://www.abstracts2view.com/acr/view.php?nu=4350&type=abstract&sesId=541&num=APS&trk=). Accessed February 21, 2011.

Baeten D, Baraliakos X, Braun J, Sieper J, Emery P, van der Heijde D, McInnes I, van Laar JM, Landewé R, Wordsworth P, Wollenhaupt J, Kellner H, Paramarta J, Wei J, Brachat A, Bek S, Laurent D, Li Y, Wang YA, Bertolino AP, Gsteiger S, Wright AM, Hueber W. Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2013;382(9906):1705-1713. doi: 10.1016/S0140-6736(13)61134-4. Epub 2013 Sep 13. Erratum in: *Lancet*. 2014;383(9928):1548.

Baeten D, Braun J, Baraliakos X, Sieper J, Dougados M, Emery P, Deodhar A, Porter B, Martin R, Mpofu S, Richards H. Secukinumab, a monoclonal antibody to interleukin-17A, significantly improves signs and symptoms of active ankylosing spondylitis: results of a 52-week phase 3 randomized placebo-controlled trial with intravenous loading and subcutaneous maintenance dosing. In: ACR/ARHP Annual Meeting Abstract Supplement. 14-19. Nov 2014; Boston, MA. *Arthritis Rheum.* 2014;66(S10):S360. Abstract 819.

Baraliakos X, Braun J, Laurent DD, Baeten D, van der Heijde D, Sieper J, Emery P, McInnes I, van Laar J, Landewe R, Wordsworth P, Wollenhaupt J, Kellner H, Wright AM, Gsteiger S, Hueber W. Interleukin-17A blockade with secukinumab reduces spinal inflammation in patients with ankylosing spondylitis as early as week 6, as detected by magnetic resonance imaging. *Arthritis Rheum.* 2011;63(suppl 10):2486D. Presented at: *Annual Meeting of the American College of Rheumatology*; 4-9 November 2011; Chicago, IL.

Brandt J, Listing J, Sieper J, Rudwaleit M, van der Heijde D, Braun J. Development and preselection of criteria for short term improvement after anti-TNFa treatment in ankylosing spondylitis. *Ann Rheum Dis.* 2004;63:1438-1444.

Braun J, Baraliakos X, Heldmann F, Kiltz U. Tumor necrosis factor alpha antagonists in the treatment of axial spondyloarthritis. *Expert Opin Investig Drugs.* 2014 May;23(5):647-659. doi: 10.1517/13543784.2014.899351. Epub 2014 Mar 22.

Braun J and Sieper J. Ankylosing spondylitis. *Lancet.* 2007;369(9570):1379-1390.

Braun J and Sieper J. Treatment of rheumatoid arthritis and ankylosing spondylitis. *Clin Exp Rheumatol*. 2009;27(4 suppl 55):S146-S147.

Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, Dagfinrud H, Dijkmans B, Dougados M, Emery P, Geher P, Hammoudeh M, Inman RD, Jongkees M, Khan MA, Kiltz U, Kvien T, Leirisalo-Repo M, Maksymowych WP, Olivieri I, Pavelka K, Sieper J, Stanislawska-Biernat E, Wendling D, Ozgocmen S, van Drogen C, vanRoyen B, van der Heijde D. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis*. 2011;70:896-904.

Calin A, Jones SD, Garrett SL, Kennedy LG. Bath Ankylosing Spondylitis Functional Index. *Br J Rheumatol*. 1995;34(8):793-794.

Callhoff J, Sieper J, Weiß A, Zink A, Listing J. Efficacy of TNFα blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. *Ann Rheum Dis.* 2015;74(6):1241-8. doi: 10.1136/annrheumdis-2014-205322. Epub 2014 Apr 9.

CIMZIA [package insert]. Smyrna, Georgia: UCB; 2015. Available at: http://www.ucb-usa.com/_up/ucb_usa_com/documents/Prescribing_Information.pdf. Accessed October 19, 2015.

Columbia Suicide-Severity Rating Scale (C-SSRS) web site. Available at: http://www.cssrs.columbia.edu. Accessed January 13, 2016.

COSTENYX [package insert]. East Hanover, New Jersey: Novartis; 2015. Available at: http://www.pharma.us.novartis.com/product/pi/pdf/cosentyx.pdf. Accessed October 19, 2015.

Davis Jr. JC, van der Heijde D, Braun J, Dougados M, Cush J, Clegg DO, Kivitz A, Fleischmann R, Inman R, Tsuji W; Enbrel Ankylosing Spondylitis Study Group. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum*. 2003;48(11):3230-3236.

Deodhar A, Braun J, Inman RD, Mack M, Parasuraman S, Buchanan J, Hsu B, Gathany T, van der Heijde D. Golimumab reduces sleep disturbance in patients with active ankylosing spondylitis: results from a randomized, placebo-controlled trial. *Arthritis Care Res* (Hoboken). 2010;62(9):1266-1271.

Deodhar A, Deodhar A, Reveille JD, van den Bosch F, Braun J, Burgos-Vargas R, Caplan L, Clegg DO, Colbert RA, Gensler LS, van der Heijde D, van der Horst-Bruinsma IE, Inman RD, Maksymowych WP, Mease PJ, Raychaudhuri S, Reimold A, Rudwaleit M, Sieper J, Weisman MH, Landewé RB. The concept of axial spondyloarthritis: joint statement of the spondyloarthritis research and treatment network and the Assessment of SpondyloArthritis

International Society in response to the US Food and Drug Administration's comments and concerns. *Arthritis Rheumatol.* 2014;66(10):2649-2656.

Deepak P, Stobaugh DJ, Ehrenpreis ED. Infectious complications of TNF-α inhibitor monotherapy versus combination therapy with immunomodulators in inflammatory bowel disease: analysis of the Food and Drug Administration Adverse Event Reporting System. *J Gastrointestin Liver Dis.* 2013;22(3):269-276.

Diggle PJ, Heagerty P, Liang KY, Zeger SL. Analysis of Longitudinal Data. Oxford: Oxford University Press; 1994.

Dougados M, Baeten D. Spondyloarthritis. *Lancet*. 2011;377(9783):2127-2137.

Dougados M, Simon P, Braun J, Burgos-Vargas R, Maksymowych WP, Sieper J, van der HeijdeD. ASAS recommendations for collecting, analysing and reporting NSAID intake in clinicaltrials/epidemiological studies in axial spondyloarthritis. *Ann Rheum Dis*. 2011;70(2):249-251.

Dougados M, van der Heijde D, Sieper J, Braun J, Maksymowych WP, Citera G, Miceli-Richard C, Wei JC, Pederson R, Bonin R, Rahman MU, Logeart I, Wajdula J, Koenig AS, Vlahos B, Alvarwz D, Bukowski JF. Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol*. 2014;66:2091-3102.

[EMEA] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products for the treatment of ankylosing spondylitis. 2009. Available at: http://www.ema.europa.eu/docs/en_GB/ document_library/Scientific_guideline/2009/09/WC500003424.pdf. January 13, 2016.

ENBREL [package insert]. Thousand Oaks, California: Amgen Inc; 2015. Available at: http://pi.amgen.com/united_states/enbrel/derm/enbrel_pi.pdf. Accessed October 19, 2015.

EuroQol Group. EQ-5D-5L User Guide. Version 1.0. April 2011. Available at: http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/UserGuide_ EQ-5D-5L. Accessed January 13, 2016.

Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol*. 1994;21(12):2286-2291.

Genovese MC, Greenwald M, Cho C-S, Berman A, Jin L, Cameron GS, Benichou O, Xie L, Braun D, Berclaz P-Y, Banerjee S. A phase II randomized study of subcutaneous ixekizumab, an anti–interleukin-17 monoclonal antibody, in rheumatoid arthritis patients who were naive to biologic agents or had an inadequate response to tumor necrosis factor inhibitor. *Arthritis Rheum.* 2014;66(7):1693-1704.

Glintborg B, Ostergaard M, Krogh NS, Dreyer L, Kristensen HL, Hetland ML. Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years' surveillance in the Danish nationwide DANBIO registry. *Ann Rheum Dis*. 2010;69(11):2002-2008.

Gottlieb AB, Mease PJ, Cuchacovich RS, Shuler CL, Lin CY, Burge RT, Samanta S, Lee CH, Gladman DD. Ixekizumab improves physical function, quality of life, and work productivity in

biologic disease-modifying antirheumatic drug-naive patients with active psoriatic arthritis [abstract]. *Arthritis Rheumatol*. 2015;67(suppl 10).

Griffiths CE, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, Cameron GS, Erickson J, Zhang L, Secrest RJ, Ball S, Braun DK, Osuntokun OO, Heffernan MP, Nickoloff BJ, Papp K; UNCOVER-2 and UNCOVER-3 investigators. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet.* 2015;386(9993):541-51. doi: 10.1016/S0140-6736(15)60125-8. Epub 2015 Jun 10.

Gulfe A, Kapetanovic MC, Kristensen LE. Efficacy and drug survival of anti-tumour necrosis factor-alpha therapies in patients with non-radiographic axial spondyloarthritis: an observational cohort study from Southern Sweden. *Scand J Rheumatol*. 2014;43(6):493-7. doi: 10.3109/03009742.2014.918173. Epub 2014 Aug 22.

Haibel H, Rudwaleit M, Listing J, Heldmann F, Wong RL, Kupper H, Braun J, Sieper J. Efficacy of adalimumab in the treatment of axial spondyloarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. *Arthritis Rheum.* 2008;58(7):1981-1991.

Haibel H and Specker C. Disease-modifying anti-rheumatic drugs in rheumatoid arthritis and ankylosing spondylitis. *Clin Exp Rheumatol*. 2009:(4 suppl 55):S159-S163.

Heiberg MS, Koldingsnes W, Mikkelsen K, Rødevand E, Kaufmann C, Mowinckel P, Kvien TK. The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. *Arthritis Rheum.* 2008;59(2):234-240.

Hueft-Dorenbosch L, Spoorenberg A, van Tubergen A, Landewé R, van ver Tempel H, Mielants H, Dougados M, van der Heijde D. Assessment of enthesitis in ankylosing spondylitis. *Ann Rheum Dis.* 2003;62(2):127-132.

HUMIRA [package insert]. North Chicago, IL: AbbVie Inc; 2015. Available at: http://www.rxabbvie.com/pdf/humira.pdf. Accessed October 19, 2015.

IDS/QIDS home page. IDS/QIDS web site. Available at: http://www.ids-qids.org/. Accessed January 14, 2016.

Inman RD, Davis JC Jr, van der Heijde D, Diekman L, Sieper J, Kim SI, Mack M, Han J, Visvanathan S, Xu Z, Hsu B, Beutler A, Braun J. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. *Arthritis Rheum.* 2008;58(11):3402-3412.

Jandus C, Bioley G, Rivals JP, Dudler J, Speiser D, Romero P. Increased numbers of circulating polyfunctional Th17 memory cells in patients with seronegative spondyloarthritides. *Arthritis Rheum*. 2008;58(8):2307-2317.

Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. *J Rheumatol.* 1994;21(9):1694-1698.

Kiltz U, van der Heijde D, Boonen A, Cieza A, Stucki G, Khan MA, Maksymowych WP, Marzo-Ortega H, Reveille J, Stebbings S, Bostan C, Braun J. Development of a health index in patients with ankylosing spondylitis (ASAS HI): final result of a global initiative based on the ICF guided by ASAS. *Ann Rheum Dis.* 2015;74(5)830-835; doi:10.1136/annrheumdis-2013-203967.

Landewé R, Rudwaleit M, van der Heijde D, Dougados M, Maksymowych WP, Braun J, Deodhar AA. Effect of certolizumab pegol on signs and symptoms of ankylosing spondyltitis and non-radiographic axial spondyloarthritis: 24 week results of a double blind randomized placebo-controlled phase 3 axial spondyloarthritis study [abstract]. *Arthritis Rheum.* 2012;64(Suppl 10):777.

Landewé R, Dougados M, Maksymowych WP, Mease PJ, Reveille JD, Rudwaleit M, van der Heijde D, Stach C, Hoepken B, Fichtner A, Coteur G, de Longueville M, Sieper J. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a doubleblind randomised placebo-controlled Phase 3 study. *Ann Rheum Dis*. 2014;73:39-47.

Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson-Heredia E, Braun D, Banerjee S. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N Engl J Med.* 2012 Mar 29;366(13):1190-1199.

Machado P, Castrejon I, Katchamart W, Koevoets R, Kuriya B, Schoels M, Silva-Fernández L, Thevissen K, Vercoutere W, Villeneuve E, Aletaha D, Carmona L, Landewé R, van der Heijde D, Bijlsma JW, Bykerk V, Canhão H, Catrina AI, Durez P, Edwards CJ, Mjaavatten MD, Leeb BF, Losada B, Martín-Mola EM, Martinez-Osuna P, Montecucco C, Müller-Ladner U, Østergaard M, Sheane B, Xavier RM, Zochling J, Bombardier C. Multinational evidence-based recommendations on how to investigate and follow-up undifferentiated peripheral inflammatory arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis*. 2011a;70(1):15-24.

Machado PM, Landewé RB, van der Heijde DM. Endorsement of definitions of disease activity states and improvements scores for the Ankylosing Spondylitis Disease Activity Score: results of OMERACT 10. *J Rheumatol.* 2011b;38(7);1502-1506.

Machado PM, Landewé RB, Lie E, Kvien, TK, Braun J, Baker D, van der Heijde D. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis*. 2011c;70:47-53.

Machado PM, Navarro-Compán V, Landewé R, Floris A, van Gaalen A, Roux C, van der Heijde D. Calculating the Ankylosing Spondylitis Disease Activity Score if the conventional C-reactive protein level is below the limit of detection or if high-sensitivity C-reactive protein is used: an analysis in the DESIR cohort. *Arthritis Rheum*. 2015;67(2):408-413.

Maksymowych WP, Inman RD, Salonen D, Dhillon SD, Williams M, Stone M, Conner-Spady B, Palsat J, Lambert RGW. Spondyloarthritis Research Consortium of Canada magnetic resonance imaging index for assessment of sacroiliac joint inflammation in ankylosing spondylitis. *Arthritis Rheum*. 2005;53(4):502-509.

Maksymowych WP, Mallon C, Morrow S, Shojania K, Olszynski WP, Wong RL, Sampalis J, Conner-Spady B. Development and validation of the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index. *Ann Rheum Dis*. 2009;68:948-953.

Maksymowych WP. Disease modification in ankylosing spondylitis. *Nat Rev Rheumatol*. 2010;6(2):7581.

Maksymowych WP, van der Heijde D, Dougados M, Sieper J, Braun J, Citera G, Miceli-Richard C, Wei JC-C, Pederson R, Bonin R, Logeart I, Wajdula J, Rahman MU, Vlahos b, Bukowski J. Clinical and imaging efficacy of etanercept in early non-radiographic axial spondyloarthritis: 48-week treatment data. *Ann Rheum Dis.* 2014;73(suppl 2):728. doi:10.1136/annrheumdis-2014-eular.1138.

Maksymowych WP, Bukowski JF, Marshall L, Szumski A, Jones H. Baseline characteristics of early, delayed, and non-responders in a non-radiographic axial spondyloarthritis study. *ACR/ARHP Annual Meeting* 2015a. Date of first publication: September 29, 2015.

Maksymowych WP, Wichuk S, Chiowchanwisawakit P, Lambert RG, Pedersen SJ. Development and preliminary validation of the spondyloarthritis research consortium of Canada magnetic resonance imaging sacroiliac joint structural score. *J Rheumatol*. 2015b;42(1):79-86.

Maxwell LJ, Zochling J, Boonen A, Singh JA, Veras MM, Tanjong Ghogomu E, Benkhalti Jandu M, Tugwell P, Wells GA. TNF-alpha inhibitors for ankylosing spondylitis. *Cochrane Database Syst Rev.* 2015;4:CD005468.

Mease PJ, van der Heijde D, Ritchlin CT, Cuchacovich R, Shuler CL, Lee CH, Samanta S, Lin CY, Gladman DD, Vangerow H. A randomized, double-blind, active- and placebo-controlled phase 3 study of efficacy and safety of ixekizumab, adalimumab, and placebo therapy in patients naive to biologic disease modifying anti-rheumatic drugs with active psoriatic arthritis [abstract]. *Arthritis Rheumatol*. 2015;67(suppl 10).

Mei Y, Pan F, Gao J, Ge R, Duan Z, Zeng Z, Liao F, Xia G, Wang S, Xu S, Xu J, Zhang L, Ye D. Increased serum IL-17 and IL-23 in the patient with ankylosing spondylitis. *Clin Rheumatol.* 2011; 30(2):269-273.

Naegeli AN, Flood E, Tucker J, Devlen J, Edson-Heredia E. The patient experience with fatigue and content validity of a measure to assess fatigue severity: qualitative research in patients with ankylosing spondylitis (AS). *Health Qual Life Outcomes.* 2013;11:192.

Poddubnyy D, Brandt H, Vahldiek J, Spiller I, Song I-H, Rudwaleit M, Sieper J. The frequency of non-radiographic axial spondyloarthritis in relation to symptom duration in patients referred because of chronic back pain: results from the Berlin early spondyloarthritis clinic. *Ann Rheum Dis.* 2012;71(12):1998-2001.

Poddubnyy D. Axial spondyloarthritis: is there a treatment of choice?. *Ther Adv Musculoskelet Dis*. 2013;5(1):45-54

Posner K, Oquendo MA, Gould M, Stanley B, and Davies M. Columbia classification algorithm of suicide assessment (C-CASA): Classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Pyschiatry*. 2007;164:1035-1043.

Reilly MC, Gooch KL, Wong RL, Kupper H, van der Heijde D. Validity, reliability and responsiveness of the Work Productivity and Activity Impairment Questionnaire in ankylosing spondylitis. *Rheumatology* (Oxford). 2010;49(4):812-819.

Reilly Associates Health Outcomes Research web site. Available at: http://www.reillyassociates.net/. Accessed January 13, 2016.

Reveille JD. The genetic basis of spondyloarthritis. *Ann Rheum Dis*. 2011:70(suppl 1):i44-i50.

Reveille JD, Witter JP, Weisman MH. Prevalence of axial spondylarthritis in the United States: estimates from a cross-sectional survey. *Arthritis Care Res*. 2012;64(6): 905–910.

Robinson PC, Bird P, Lim I, Saad N, Schachna L, Taylor AL, Whittle SL, Brown MA. Consensus statement on the investigation and management of non-radiographic axial spondyloarthritis (nr-axSpA). *Int J Rheum Dis.* 2014;17(5):548-56. doi: 10.1111/1756-185X.12358. Epub 2014 Mar 28.

Ruderman EM. Overview of safety of non-biologic and biologic DMARDs. *Rheumatology*. 2012;51(Suppl 6):vi37-43.

Rudwaleit M, van der Heijde D, Khan MA, Braun J, Sieper J. How to diagnose axial spondyloarthritis early. *Ann Rheum Dis.* 2004;63(5):535–543.

Rudwaleit M, Khan MA, Sieper J. The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria? *Arthritis Rheum.* 2005;52:1000–1008.

Rudwaleit M, Landewé R, van der Heijde D, Listing J, Braun J, Burgos-Vargas R, Collantes-Estevez E, Davis J, Dijkmans B, Dougados M, Emery P, van der Horst-Bruinsma E, Inman R, Khan MA, Leirisalo-Repo M, van der Linden S, Maksymowych WP, Mielants H, Olivieri I, Sturrock R, de Vlam K, Sieper J. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis.* 2009a;68(6):770–776.

Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, Braun J, Chou CT, Collantes-Estevez E, Dougados M, Huang F, Gu J, Khan MA, Kirazli Y, Maksymowych WP, Mielants H, Sørensen IJ, Ozgocmen S, Roussou E, Valle-Oñate R, Weber U, Wei J, Sieper J. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis*. 2009b;68(6):777-7783.

Rudwaleit M, Haibel H, Baraliakos X, Listing J, Marker-Hermann E, Zeidler H, Braun J, Sieper J. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. *Arthritis Rheum.* 2009c;60(3):717–727.

Rudwaleit M, Jurik AG, K-G A Hermann K-GA, Landewe´R, van der Heijde D, Baraliakos X, Marzo-Ortega H, Østergaard M, Braun J, Sieper J. Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. *Ann Rheum Dis.* 2009d;68(10):1520–1527.

Rudwaleit M,Sieper J. Referral strategies for early diagnosis of axial spondyloarthritis. *Nat Rev Rheumatol.* 2012;8:262–268.

Sanford M and McKeage K. 2015 Secukinumab: First Global Approval. *Drugs.* 2015;75(3):329-328.

Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, Dougados M, Hermann KG, Landewé R, Maksymowych W, van der Heijde D. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis*. 2009;68(suppl 2):ii1–ii44.

Sieper J, van der Heijde D. Review: Nonradiographic axial spondyloarthritis: new definition of an old disease? *Arthritis Rheum.* 2013;65(3):543–551.

Sieper J, van der Heijde, Dougados M, Brown LS, Lavie F, Pangan AL. Early response to adalimumab predicts long-term remission through 5 years of treatment in patients with ankylosing spondylitis. *Ann Rheum Dis.* 2012;71:700-706 doi:10.1136/annrheumdis-2011-200358.

Sieper J, van der Heijde D, Dougados M, Mease PJ, Maksymowych WP, Brown MA, Arora V, Pangan AL. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis*. 2013;72(6):815-822.

Sieper J, van der Heiijde D, Dougados M, Maksymowych WP, Scott BB, Bioce JJ, Berd Y, Bergman G, Curtis S, Tzontcheva A, Huyck S, Weng HH. A Randomized, Double-Blind, Placebo-Controlled, Sixteen-Week Study of Subcutaneous Golimumab in Patients With Active Nonradiographic Axial Spondyloarthritis. *Arthritis Rheumatol.* 2015;67(10):2702–2712.

SIMPONI [package insert]. Horsham, PA: Janssen Biotech; 2015. Available at: http://www.simponi.com/shared/product/simponi/prescribing-information.pdf. Accessed January 13, 2016.

Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, Filippini G, Skoetz N, Francis D, Lopes LC, Guyatt GH, Schmitt J, La Mantia L, Weberschock T, Roos JF, Siebert H, Hershan S, Lunn MP, Tugwell P, Buchbinder R. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev*. 2011;16(2):CD008794.

Strand V, Rao SA, Shillington AC, Cifaldi MA, McGuire M, Ruderman EM. Prevalence of Axial Spondyloarthritis in United States Rheumatology Practices: Assessment of SpondyloArthritis International Society Criteria versus Rheumatology Expert Clinical Diagnosis. *Arthritis Care Res.* 2013;65(8):1299-1306.

van den Berg R, de Hooge M, Rudwaleit M, Sieper J, van Gaalen F, Reijnierse M, Landewé R, Huizinga T, van der Heijde D. ASAS modification of the Berlin algorithm for diagnosing axial spondyloarthritis: results from the SPondyloArthritis Caught Early (SPACE)-cohort and from the Assessment of SpondyloArthritis international Society (ASAS)-cohort. *Ann Rheum Dis.* 2013;72(10):1646–1653.

van der Heijde D, Kivitz A, Schiff MH, Sieper J, Dijkmans BA, Braun J, Dougados M, Reveille JD, Wong RL, Kupper H, Davis JC Jr. ATLAS Study Group. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2006;54(7):2136-2146.

van der Heijde D, Landewé R, Feldtkeller E. Proposal of a linear definition of the Bath Ankylosing Spondylitis Metrology Index (BASMI) and comparison with the 2-step and 10-step definitions. *Ann Rheum Dis.* 2008; 67(4):489-493.

van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis, A proposal for modification of the New York criteria. *Arthritis Rheum.* 1984;27(4):361-368.

Ward MM, Deodhar A, Akl EA, Lui A, Ermann J, Gensler LS, Smith JA, Borenstein D, Hiratzka J, Weiss PF, Inman RD, Majithia V, Haroon N, Maksymowych WP, Joyce J, Clark BM, Colbert RA, Figgie MP, Hallegua DS, Prete PE, Rosenbaum JT, Stebulis JA, van den Bosch F, Yu DT, Miller AS, Reveille JD, Caplan L. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. *Arthritis Rheumatol.* 2015. doi: 10.1002/art.39298 [Epub ahead of print].

Ware JE Jr. SF-36 health survey update. *Spine.* 2000;25(24):3130-3139.

Wendling D, Cedoz JP, Racadot E, Dumoulin G. Serum IL-17, BMP-7, and bone turnover markers in patients with ankylosing spondylitis. *Joint Bone Spine.* 2007;74(3):304-305.

Yeremenko N, Paramarta JE, Baeten D. The interleukin-23/interleukin-17 immune axis as a promising new target in the treatment of spondyloarthritis. *Curr Opin Rheumatol*. 2014;26(4):361-370.

Zochling J. Measures of symptoms and disease status in ankylosing spondylitis: Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), and Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S). *Arthritis Care Res*. 2011;63(suppl 11)S47-S58.

# Appendix 1. Abbreviations and Definitions

| Term | Definition |
|---|---|
| **ADA** | anti-drug antibody |
| **AE** | adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product |
| **AESI** | adverse events of special interest |
| **ALT** | alanine aminotransferase |
| **ANCOVA** | analysis of covariance |
| **AS** | ankylosing spondylitis: currently referred to as radiographic axial spondyloarthritis (rad-axSpA) |
| **ASDAS** | Ankylosing Spondylitis Disease Activity Score |
| **ASAS** | Assessment of Spondyloarthritis International Society |
| **ASAS-HI** | Assessment of Spondyloarthritis International Society Health Index |
| **AST** | aspartate aminotransferase |
| **axSpA** | 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) |
| **BASDAI** | Bath Ankylosing Spondylitis Disease Activity Index |
| **BASDAI50** | Bath Ankylosing Spondylitis Disease Activity Index 50 |
| **BASFI** | Bath Ankylosing Spondylitis Functional Index |
| **BASMI** | Bath Ankylosing Spondylitis Metrology Index |
| **BCG** | Bacillus Calmette- Guérin |
| **bDMARD** | biological disease-modifying antirheumatic drug |

| Term | Definition |
|---|---|
| **blinding/masking** | 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.<br>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. |
| **BP** | blood pressure |
| **CD** | Crohn's disease |
| **cDMARD** | conventional disease-modifying antirheumatic drug |
| **CEC** | clinical events committee |
| **cGMP** | current Good Manufacturing Practices |
| **CI** | confidence interval |
| **COA** | Clinical Outcome Assessment |
| **complaint** | A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system. |
| **COX-2** | cyclooxygenase-2 |
| **CRF/eCRF** | case report form/electronic case report form |
| **CRP** | C-reactive protein |
| **CSR** | clinical study report |
| **C-SSRS** | Columbia-Suicide Severity Rating Scale |
| **DMARD** | disease-modifying antirheumatic drug |
| **ECG** | electrocardiogram |
| **enroll** | The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment. |
| **enter** | Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives. |
| **ePRO** | electronic patient-reported outcome |
| **EQ-5D-5L** | European Quality of Life–5 Dimensions 5-Level |
| **ETV** | early termination visit |
| **FEAE** | follow-up emergent adverse event |

| Term | Definition |
|---|---|
| **FSH** | follicle stimulating hormone |
| **GCP** | good clinical practice |
| **HBC** | hepatitis C virus |
| **HBcAb+** | anti-hepatitis B core antibody positive |
| **HBsAg+** | hepatitis B virus surface antigen |
| **HBV** | hepatitis B virus |
| **HIV** | human immunodeficiency virus |
| **HIVAb** | human immunodeficiency virus antibody |
| **HLA** | human leukocyte antigen |
| **hsCRP** | high-sensitivity C-reactive protein |
| **IB** | Investigator's Brochure |
| **IBD** | inflammatory bowel disease (eg, Crohn's disease and ulcerative colitis) |
| **IBP** | inflammatory back pain |
| **ICF** | informed consent form |
| **ICFD** | International Classification of Functioning Disability and Health |
| **ICH** | International Conference on Harmonisation |
| **IgG4** | immunoglobulin G subclass 4 |
| **IL-17A** | interleukin-17A, also known as IL-17 |
| **inadequate responder** | patient who, as determined by the investigator, shows inadequate improvement in disease signs or symptoms or a failure to adequately respond following treatment with a therapeutic agent |
| **interim analysis** | An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked. |
| **investigational product** | A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. |
| **IRB/ERB** | Investigational Review Board/Ethical Review Board |

| Term | Definition |
|---|---|
| **ITT** | 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. |
| **IWRS** | interactive web-response system |
| **JSEQ** | Jenkins Sleep Evaluation Questionnaire |
| **LOCF** | last observation carried forward |
| **LS** | least-squares |
| **MAb** | monoclonal antibody |
| **MASES** | Maastricht Ankylosing Spondylitis Enthesitis Score |
| **mBOCF** | modified baseline observation carried forward |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **MI** | myocardial infarction |
| **MMRM** | mixed-effects model of repeated measures |
| **mNY** | modified New York criteria |
| **MOA** | mechanism of action |
| **MRI** | magnetic resonance imaging |
| **MTX** | methotrexate |
| **NAb** | neutralizing anti-drug antibody |
| **nonrad-axSpA** | nonradiographic axial spondyloarthritis: a subset of axSpA in which there is no clear structural damage as defined by conventional radiographic imaging. |
| **NRI** | nonresponder imputation |
| **NRS** | numeric rating scale |
| **NSAIDS** | nonsteroidal anti-inflammatory drugs |
| **OMERACT** | outcome measures in rheumatology |
| **PK/PD** | pharmacokinetics/pharmacodynamics |
| **PPD** | purified protein derivative |

| Term | Definition |
|---|---|
| **PPS** | 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. |
| **PRO/ePRO** | patient-reported outcomes/electronic patient-reported outcomes |
| **Ps** | psoriasis |
| **PsA** | psoriatic arthritis |
| **PT** | preferred term |
| **Q2W** | every 2weeks |
| **Q4W** | every 4 weeks |
| **QIDS-SR16** | Quick Inventory of Depressive Symptomatology–Self-Report (16 Items) |
| **RA** | rheumatoid arthritis |
| **rad-axSpA** | radiographic axial spondyloarthritis: a subset of axSpA in which there is evidence of disease features on radiographic imaging |
| **SAE** | serious adverse event |
| **SAP** | statistical analysis plan |
| **SC** | subcutaneous |
| **screen** | The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. |
| **SF-36 MCS** | Short Form 36 mental component score |
| **SF-36 PCS** | Short Form 36 physical component score |
| **SIJ** | sacroiliac joints |
| **SJC** | swollen joint count |
| **SOC** | system organ class |
| **SpA** | spondyloarthritis |
| **SPARCC** | Spondyloarthritis Research Consortium of Canada |
| **SPARCC SSS** | Spondyloarthritis Research Consortium of Canada–SIJ Structural Score |
| **SUSARs** | suspected unexpected serious adverse reactions |
| **TB** | tuberculosis |

| Term | Definition |
|---|---|
| **TE-ADA** | treatment-emergent anti-drug antibody |
| **TEAE** | treatment-emergent adverse event: Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment. |
| **TJC** | tender joint count |
| **TNF inhibitor** | tumor necrosis factor inhibitor |
| **TPO** | third-party organization |
| **UC** | ulcerative colitis |
| **ULN** | upper limit of normal |
| **US** | United States |
| **VAS** | visual analog scale |
| **WBC** | white blood count |
| **WHO** | World Health Organization |
| **WPAI-SpA** | Work Productivity Activity Impairment—Spondyloarthritis |

# Appendix 2. Schedule of Activities

**Schedule of Activities, Protocol I1F-MC-RHBX (Periods 1-2)**

| | Screening (Period 1) | Baseline Randomization | Blinded Treatment Dosing Period (Period 2)[a] | | | | | |
|---|---|---|---|---|---|---|---|---|
| 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 |
| Informed consent | X | | | | | | | |
| Demographics[b] | X | | | | | | | |
| Physical examination[c] | X | | | | | | | X |
| Vital signs (BP and pulse)[d] | X | X[d] | X | X | X | X | X | X[d] |
| Weight[bb] | X | X | | | X | X | X | X |
| Height | | X | | | | | | |
| Habits[e] | | X | | | | | | |
| Body temperature | | X | | | | | | |
| Posterior anterior chest x-ray[f] | X | | | | | | | |
| Inclusion/exclusion criteria[g] | X | X | | | | | | |
| Evaluate presence of SpA features | X | X | | | | | | |
| Randomization | | X | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X |
| NSAID use | X | X | X | X | X | X | X | X |
| Preexisting conditions & medical history[h] | X | X | X | X | X | X | X | X |
| Adverse events | X | X | X | X | X | X | X | X |
| Eye symptom assessment[i] | X | X | X | X | X | X | X | X |
| Treatment modification[j] | | | | | | | | X |
| Administer IP on site[j] | | X | | | | | | |
| Dispense IP | | X | | X | X | X | 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-RHBX (Periods 1-2)**

| | Screening (Period 1) | Baseline Randomization | Blinded Treatment Dosing Period (Period 2)[a] | | | | | |
|---|---|---|---|---|---|---|---|---|
| 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 |
| **Clinical Efficacy/Health Outcomes** | | | | | | | | |
| MRI of the SIJ[dd] | X[ee] | | | | | | | X[k] |
| X-ray of the SIJ[l] | X | | | | | | | |
| X-ray of the spine[m] | 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/SHFU[n] | | 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-RHBX (Periods 1-2)**

| | Screening (Period 1) | Baseline Randomization | Blinded Treatment Dosing Period (Period 2)[a] | | | | | |
|---|---|---|---|---|---|---|---|---|
| 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 |
| **Laboratory Tests** | | | | | | | | |
| HLA-B27[o] | X | | | | | | | |
| CRP | X[p] | X | X | X | X | X | X | X |
| Administer TB test(s)[q] | X | | | | | | | |
| ECG | X | | | | | | | |
| FSH[r] | X | | | | | | | |
| HIV/HCV | X | | | | | | | |
| HBV | X[s] | X[s] | | | | | X[s] | |
| Serum pregnancy test[t] | X | | | | | | | |
| Urine pregnancy test[t] | | X | | | | | X | |
| Serum chemistry | X | X | | | X | X | X | X |
| PTT, PT/INR | X | | | | | | | X |
| Lipid panel (fasting)[u] | | 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)[v] | | X | X[w] | X[w] | X | X[w] | X[w] | X |
| Pharmacogenetic exploratory sample (DNA)[v,cc] | | X | | | | | | |
| Immunogenicity testing[x] | | X | X | X | X | X | X | X |
| PK sampling[x,y] | | X | X | X | X | X | X | X |

**Schedule of Activities, Protocol I1F-MC-RHBX (Period 2)**

| | Blinded Treatment Dosing Period (Period 2)[a] | | | | | | | 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[c] | | | | | | | X | X |
| Vital signs (BP and pulse)[d] | X[d] | X[d] | X[d] | X[d] | X[d] | X[d] | X | X |
| Weight[bb] | 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 & medical history[h] | X | X | X | X | X | X | X | X |
| Adverse events | X | X | X | X | X | X | X | X |
| Eye symptom assessment[i] | X | X | X | X | X | X | X | X |
| Treatment modification[j] | X | X | X | X | X | X | | |
| Dispense IP | X | X | X | X | X | X | | |
| IP compliance[j] | 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 |
| **Clinical Efficacy/Health Outcomes** | | | | | | | | |
| MRI of the SIJ[dd] | | | | | | | X[z] | X[k] |
| 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 |

| | Blinded Treatment Dosing Period (Period 2)[a] | | | | | | | 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 | |
| SF-36 | | | | | X | | X | X |
| ASAS-HI | | | | | X | | X | X |
| QIDS-SR16 | | | | | X | | X | X |
| C-SSRS/SHFU[n] | X | X | X | X | X | X | X | X |
| EQ-5D-5L | | | | | | | X | X |
| WPAI-SpA | | | | | | | X | X |
| JSEQ | | | | | X | | X | X |
| **Laboratory Tests** | | | | | | | | |
| CRP | X | X | X | X | X | X | X | X |
| HBV | | X[s] | | | X[s] | X[s] | X[s] | X[s] |
| Urine pregnancy test[t] | | X | | | X | X | X | X |
| Serum chemistry | X | X | X | X | X | X | X | X |
| PTT, PT/INR | | X | | | X | | X | |
| Lipid panel (fasting)[u] | | X | | | X | | X | |
| Hematology | X | X | X | X | X | X | X | X |
| Urinalysis | | X | | | X | | X | X |
| CCI [redacted] | | [redacted] | [redacted] | | [redacted] | | [redacted] | |
| Immunogenicity testing[x] | | X | X | | X | | X | X |
| PK sampling[x,y] | | X | X | | X | | X | X |

**Schedule of Activities, Protocol I1F-MC-RHBX (Period 3)**

| | Post-Study Follow-Up Period (Period 3)[aa] | | |
|---|---|---|---|
| | Required Follow-Up Visits | | As-Needed Follow-Up Visits |
| CRF (V) Visit Number | V801 | V802 | V803 |
| | LV + 4W | LV + 12W | LV + 24 W |
| Study Days | ±14d | ±14d | ±14d |
| Concomitant medications | X | X | X |
| Vital signs (BP and pulse) | X | X | X |
| Weight [bb] | X | X | X |
| Preexisting conditions and medical history[h] | X | X | X |
| Adverse events | X | X | X |
| C-SSRS/SHFU[n] | X | X | X |
| HBV | X[s] | X[s] | |
| Serum chemistry | X | X | X |
| Hematology | X | X | X |
| Nonpharmacogenetic biomarker exploratory storage samples (urine, serum, plasma, RNA, and whole blood)[v] | X[w] | X[w] | |
| Immunogenicity testing[x] | X | X | |
| PK sampling[x,y] | X | X | |

**Abbreviations:** AE = adverse event; ASAS = Assessment of Spondyloarthritis International Society; 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 or Early Term Visit = 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 normalised ratio; IP = investigational product; JSEQ = Jenkins Sleep Evaluation Questionnaire; LV= last visit; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; mNY = modified New York; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drugs; NRS = numeric rating scale; PK = pharmacokinetic; PPD = purified protein derivative; PT = prothrombin time; PTT = partial thromboplastin time; QIDS-SR16 = Quick Inventory of Depressive Symptomatology-self report (16 items); RNA = ribonucleic acid; SDAL = Study Drug Administration Log; SF-36 = Short Form 36; SHFU = Self-Harm Supplement Form; SIJ = sacroiliac joints; 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] Patients who have taken at least 1 study dose and who discontinue study treatment prior to Week 16 or study participation (regardless of timing) are to complete an ETV and enter into post-study follow-up for at least 12 weeks after the ETV date or the last regularly scheduled visit. Patients whose ETV or last

regularly scheduled visit is longer than 12 weeks after their last investigational study medication dose are not required to enter into the Post-Study Follow-Up Period (Period 3).

[b] Demographics includes recording of year of birth, sex, race, and ethnicity.

[c] One complete physical examination (excluding pelvic, rectal examination) will be performed at screening. All physical examinations throughout the study are to include a symptom-directed physical as well as examination of heart, lungs, abdomen, eyes and visual examination of the skin.

[d] Patients are to be resting for a minimum of 5 minutes prior to vital sign collection. Blood pressure and pulse will be measured in sitting position and will be recorded before IP dosing at all visits (Section 8.4.2). For safety monitoring, patients are to remain under observation for at least 1 hour after dosing at Week 0 (Visit 2) and at any visit on or after Week 16 in which a patient receives the initial injection of ixekizumab as rescue therapy. This initial injection of rescue ixekizumab will be administered by the patient or caregiver at the clinical site to allow for observation for any AEs and for collection of postinjection BP and pulse measurements approximately 1 hour after administration of the IP (Section 8.4.2).

[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 both historical events as well as preexisting conditions which are assessed after Visit 2 to determine any treatment-emergent worsening of 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. Note that at or after Week 16, treatment modifications may occur per the investigator decision by a change in concomitant medication and/or a decision to use ixekizumab 80 mg Q2W. The treatment modification of ixekizumab 80 mg Q2W requires that the dose is administered on site; patients to stay an additional hour for on-site observation after the initial injection of rescue ixekizumab therapy.

[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. If patients discontinue study participation prior to Week 16, MRI of the SIJ should be collected at ETV. For ETV, MRI requirements are dependent on the timing of study discontinuation. If discontinuation is:

- at or before Visit 5, no MRI is required at ETV.
- after Visit 5 up to and including Visit 8 (Week 16), MRI is required at ETV.
- after Visit 8, MRI is required only if ETV occurs on or after Visit 12.

[l] An x-ray of the SIJ will be performed during the Screening Period (Period 1) unless an x-ray taken within 6 months prior to screening is available and of good quality. All x-rays require central reading ONLY, regardless of date taken. Central reading will define eligibility using the mNY criteria to exclude patients with definite sacroiliitis on x-ray.

[m] Cervical and lumbar spine only; serves as baseline for potential later assessments of structural changes. X-ray does not need to be repeated if one is available that was taken ≤3 months prior to screening (Visit 1; refer to Sections 5.2 and 5.3) and has passed quality assessment by central reading vendor.

[n] A Self-Harm Follow-Up Form must be completed for each discrete event identified on the Self-Harm Supplement Form.

[o] HLA-B27 test will be performed centrally.

[p] 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.

[q] TB test(s) include PPD, QuantiFERON®-TB Gold, and T-SPOT®. See Section 8.4.6 for detailed description of TB testing. 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 to 3 days after Visit 1.

[r] For female patients ≥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 nonchildbearing potential (FSH ≥40 mIU/mL). FSH test will be performed centrally.

[s] All patients will be tested for HBV at screening. Patients who are HBcAb+ at screening, regardless of HBsAb status, will have a serum HBV DNA obtained by the central laboratory. Patients who are found to be HBV DNA positive (detectable) at screening will be excluded from the trial. Patients who 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 must be discontinued from the study treatment and should receive appropriate follow-up medical care (refer to Section 8.4.10.2 for further information regarding the timing of discontinuation).

[t] 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 designated scheduled visits through Week 52. Additional urine pregnancy testing can be performed at the investigator's discretion. If required per local regulations, urine testing for pregnancy may occur at intervals as required during the study treatment period and/or follow-up period.

[u] For the fasting lipid profile patients are to not eat or drink anything except water for 12 hours prior to test.

[v] Where collection is allowed by local regulations.

[w] Only serum and plasma are collected at this visit..

[x] 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.

[y] PK samples are to be collected before investigational product injection.

[z] The Week 52 MRI may be collected up to 10 days **prior** to Week 52 (Visit 15).

[aa] Patients who have taken at least 1 study dose and who discontinue study treatment prior to Week 16 or study participation (regardless of timing) are to complete an ETV and enter into post-study follow-up for at least 12 weeks after the ETV date or the last regularly scheduled visit. Patients whose ETV or last regularly scheduled visit is longer than 12 weeks after their last investigational study medication dose are not required to enter into the Post-Study Follow-Up Period (Period 3). Patients who complete the study through Week 52 and who are not entering into Study RHBY are to enter into the Post-Study Follow-Up Period (Period 3). Visits 801 and 802 are scheduled at 4 and 12 weeks (respectively) after the date of the last patient 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 MRI of the SIJ must be completed ≤30 days prior to randomization (refer to Sections 5.3 and 5.4).

# Appendix 3. Clinical Laboratory Tests

**Clinical Laboratory Tests**

| **Hematology[a]:** | **Serum Chemistry[a]:** |
|---|---|
| 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 |
| **Absolute counts of:** | 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 |
| **Urinalysis (dipstick)[a]:** | Glucose |
| Color | Albumin |
| Specific gravity | Cholesterol (total) |
| pH | Total protein |
| Protein | Calculated creatinine clearance |
| Glucose | Creatine phosphokinase (CPK) |
| Ketones | Triglycerides |
| Bilirubin | Gamma-glutamyl transferase (GGT) |
| Urobilinogen | |
| Blood | **Lipid Panel[c]** |
| Nitrite | Low density lipoprotein (LDL) |
| Urine creatinine | High density lipoprotein (HDL) |
| Leukocyte esterase | Very low density lipoprotein (VLDL) |
| **Other Tests:** | |
| Human immunodeficiency virus antibody (HIV)[f] | Pregnancy test (serum)[d] |
| Hepatitis B surface antigen (HBsAg)[f] | Follicle-stimulating hormone (FSH)[e] |
| Anti–hepatitis B surface antibody (HBsAb)[f] | Thyroid-stimulating hormone (TSH) and free T4 |
| Anti–hepatitis B core antibody (HBcAb)[f] | Ixekizumab serum concentration (pharmacokinetic) |
| Anti–hepatitis C antibody[f,h] | Partial thromboplastin time (PTT) |
| HBV DNA[g] | Prothrombin time/international normalized ratio |
| High-sensitivity C-reactive protein (hsCRP) | Exploratory storage samples (urine, serum, plasma, |
| Purified protein derivative (PPD)[i] | RNA, and whole blood) |
| Urine pregnancy test[d] (assayed by clinical study site) | Pharmacogenetic sample (DNA) |
| QuantiFERON®-TB Gold test[i] | Immunogenicity testing (anti-ixekizumab Ab) |
| T-SPOT®[i] | |
| HLA-B27 | |

**Clinical Laboratory Tests**

Abbreviations: Ab = antibody; DNA = deoxyribonucleic acid; HBV = hepatitis B virus; HCV = hepatitis C virus; IgA = immunoglobulin A; 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.

[d] Serum pregnancy test for all women <60 years of age who are still of childbearing potential at Visit 1; after Visit 1, urine pregnancy test performed locally for women of childbearing potential.

[e] Women ≥40 and <60 years of age who have had a cessation of menses for ≥12 months will have an FSH test confirming nonchildbearing potential (≥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 HBcAb+ at any time

[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.

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

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

**Hepatic Monitoring Tests**

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

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

[a] Assayed by Lilly-designated or local laboratory.

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

# Appendix 5. Spondyloarthritis Features

To be included in Study RHBX, patients must fulfill the ASAS criteria for nonrad-axSpA either by:

(a) presence of sacroiliitis on MRI (according to ASAS/OMERACT criteria and based on central reading) (Rudwaleit et al. 2009d) and have at least 1 SpA feature from the bulleted list below.

**OR**

(b) being HLA-B27 positive and have at least 2 additional SpA features from the bulleted list below.

**SpA features:**

- **Inflammatory back pain (IBP):** IBP according to experts: four out of five of the following parameters present: (1) onset before the age of 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):** Heel enthesitis: 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 h 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) ankylosing spondylitis, (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. 2009d; Sieper et al. 2009; Aydin et al. 2012.

# Appendix 6. Protocol Amendment I1F-MC-RHBX(b) Summary: A 52-Week Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ixekizumab (LY2439821) in bDMARD-Naive Patients with Nonradiographic Axial Spondyloarthritis

Protocol I1F-MC-RHBX, A 52-Week Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ixekizumab (LY2439821) in bDMARD-Naive Patients with Nonradiographic 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 overall changes and rationale for the changes made to this protocol are as follows:

- There are now two primary objectives to accommodate regional regulatory requirements.
- Proportion of patients achieving ASAS40 response at Week 52 is removed from the secondary objective and added as a primary objective. Power estimations were added for this objective.
- Clarified that we will use screening MRI/CRP status and not baseline.

Other minor typographical corrections and clarifications not affecting content have been made in the document.

# Revised Protocol Sections

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

## Section 1. Protocol Synopsis

**Objective(s)/Endpoints:**
There are 2 primary objectives in this study to accommodate regional regulatory requirements.

| Objectives | Endpoints |
|---|---|
| **Primary**<br>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 nonradiographic axial spondyloarthritis (nonrad-axSpA) ~~at Week 16.~~ | • Proportion of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response at Week 16 (for regulatory agencies that accept Week 16 as primary endpoint)<br>• Proportion of patients achieving an ASAS40 response at Week 52 (for regulatory agencies that require Week 52 as primary endpoint) |
| **Secondary**<br>**The major secondary objective is:**<br>• To compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W) versus placebo in patients with active nonrad-axSpA at Week 16 and Week 52 | • ~~Proportion of patients achieving an ASAS40 response at Week 52~~<br>• Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) at Week 16<br>• Change from baseline in ASDAS at Week 52<br>• Change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 16<br>• Change from baseline in BASFI at Week 52<br>• Proportion of patients achieving ASDAS inactive disease at Week 16<br>• Proportion of patients achieving ASDAS inactive disease at Week 52<br>• Change from baseline in magnetic resonance imaging (MRI) of the sacroiliac joints (SIJ) (Spondyloarthritis Research Consortium of Canada [SPARCC] score) at Week 16<br>• Percent of patients without clinically meaningful changes in background therapy at Week 52 |

**Treatment Groups and Duration:**
Study RHBX has 3 treatment groups during the 52-week Blinded Treatment Dosing Period: 80 mg ixekizumab Q4W, 80 mg ixekizumab Q2W, and placebo at a 1:1:1 ratio. In each ixekizumab treatment group, half of the patients will receive an 80 mg starting dose and half a 160 mg starting dose (1:1 randomization). Randomization will be stratified by country and ~~baseline~~ screening MRI/CRP status (positive MRI and elevated C-reactive protein [CRP]; positive MRI and nonelevated CRP; negative MRI and elevated CRP). All doses are administered via SC injection. At baseline (Week 0), all patients will receive 2 injections. Patients assigned to an ixekizumab treatment regimen with a 160 mg ixekizumab starting dose will receive 160 mg of ixekizumab as two 80 mg SC injections. Patients assigned to an ixekizumab treatment regimen with an 80 mg starting dose will receive 80 mg of ixekizumab

as 1 SC injection and 1 SC injection of placebo. Patients assigned to the placebo treatment group will receive 2 SC injections of placebo. After Week 0 and through Week 50, all patients will receive 1 injection every 2 weeks.

**Statistical Analysis:**
Approximately 300 patients will be randomized at a 1:1:1 ratio in the Blinded Treatment Dosing Period (Period 2) to ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, and placebo. In the active treatment groups, half the patients will be given a 160 mg starting dose and the other half will be given an 80 mg starting dose. With 100 patients per treatment group, this study will have approximately 98% power to test the superiority of ixekizumab Q2W to placebo for 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: 46% for ixekizumab 80 mg Q2W treatment group and 18% for the placebo group. A 2-sided Fisher's exact test at the 0.05 level is assumed.

There is little data from similarly designed 52-week placebo-controlled trials regarding the ASAS40 response rate for active and placebo treated patients to guide power estimation at Week 52. With 100 patients per treatment group, this study will have approximately 66-99% power to test the superiority of ixekizumab Q2W to placebo for ASAS40 at Week 52, assuming various ASAS40 response rates for ixekizumab Q2W and placebo at Week 52. 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 will be performed for all analyses in the Blinded Treatment Dosing Period. Unless otherwise specified, the ixekizumab 80 mg Q2W and 80 mg 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~~ screening MRI/CRP status (positive MRI and elevated CRP; positive MRI and nonelevated CRP; negative MRI and elevated CRP) 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. NRI will be applied to Week 52 (Visit 15) in a similar method. Patients who are deemed as inadequate responders by the investigator after Week 16 but remain on blinded study treatment and only have modifications in concomitant medications will not be automatically imputed as nonresponders. However, patients who discontinue originally assigned blinded study treatment and use rescue ixekizumab 80 mg Q2W will be analyzed as nonresponders for the Week 52 analysis. Randomized patients without any postbaseline observation will also be defined as nonresponders for the NRI analysis.

A 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~~ screening MRI/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~~ screening MRI/CRP status, and baseline.

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 an ANCOVA with treatment and baseline value.

Patients who discontinue study treatment after Week 16 will continue to be followed for all regularly scheduled visits for safety and efficacy assessment. The data collected after discontinuation of study treatment will be summarized separately.

## Section 3. Objectives and Endpoints

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

**Table RHBX.1. Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary**<br>The primary objective is to compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W) versus placebo in patients with active nonrad-axSpA ~~at Week 16~~ | • Proportion of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response at Week 16 (for regulatory agencies that require Week 16 as the primary endpoint)<br>• Proportion of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response at Week 52 (for regulatory agencies that require Week 52 as the primary endpoint) |
| **Secondary**<br>**The major secondary objectives are:**<br>• To compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W versus placebo in patients with active nonrad-axSpA at Week 16 and Week 52 | • ~~Proportion of patients achieving an ASAS40 response at Week 52~~<br>• Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) at Week 16<br>• Change from baseline in ASDAS at Week 52<br>• Change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 16<br>• Change from baseline in BASFI at Week 52<br>• Proportion of patients achieving ASDAS inactive disease at Week 16<br>• Proportion of patients achieving ASDAS inactive disease at Week 52<br>• Change from baseline in magnetic resonance imaging (MRI) of the sacroiliac joints (SIJ) (Spondyloarthritis Research Consortium of Canada [SPARCC] score) at Week 16<br>• Percent of patients without clinically meaningful changes in background therapy at Week 52 |
| **Other secondary objectives are:**<br>• To compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W) to placebo during the 52-week period | • Proportion of patients who achieve ASAS20, ASAS40, ASAS5/6, and partial remission by ASAS criteria<br>• Change from baseline in the individual components of the ASAS criteria<br>• Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) |

| Objectives | Endpoints |
|---|---|
| | • Proportion of patients reaching BASDAI50<br>• Change from baseline in ASDAS<br>• Proportion of patients who experience clinically-important improvement (change of ASDAS from baseline ≥1.1), major improvement (change of ASDAS from baseline ≥2.0), or inactive disease (ASDAS <1.3)<br>• Change from baseline in the measure of CRP<br>• Change from baseline in BASFI<br>• Change from baseline in mobility<br>  o Bath Ankylosing Spondylitis Metrology Index (BASMI) (linear) and individual components<br>  o Chest expansion<br>  o Change from baseline in occiput to wall distance<br>• Change from baseline in MRI of the SIJ (SPARCC score)<br>• Change from baseline in SPARCC SIJ Structural Score (SSS)<br>• Change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)<br>• Change from baseline in SPARCC Enthesitis Score<br>• The incidence and severity of peripheral arthritis by tender and swollen joint count scores of 46/44 joints<br>• Incidence rate of anterior uveitis or uveitis flares<br>• 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 physical component [PCS] and mental component scores [MCS]), and Quick Inventory of Depressive Symptomatology–Self-Report (16 Items) (QIDS-SR16) score.<br>• <u>NSAID intake (ASAS-NSAID score and % of patients taking NSAIDs)</u> |
| • To explore the effect of starting dose (160 mg compared to 80 mg)<br><br>• To evaluate the incidence of anti-ixekizumab antibodies and its relationship to efficacy of ixekizumab | • ~~NSAID intake (ASAS-NSAID score and % of patients taking NSAIDs)~~<br>• Onset of action and treatment response (ASAS, ASDAS, CRP, BASFI)<br>• 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<br>  o Proportion of patients achieving ASAS40<br>  o Proportion of patients achieving ASAS20<br>  o Proportion of patients achieving ASDAS inactive disease |

| Objectives | Endpoints |
|---|---|
| • To measure ixekizumab exposure and assess the relationship between exposure and efficacy and exposure and immunogenicity | • Serum trough concentrations of ixekizumab<br>• Model parameters for the exposure-response relationship between ixekizumab serum trough concentrations and efficacy endpoints (for example, ASAS20, ASAS40) at Week 16 and/or Week 52<br>• Ixekizumab serum trough concentrations associated with anti-drug antibody (ADA) titer |

### Section 4.3. Scientific Rationale for Study Design

The effectiveness of ixekizumab in treating nonrad-axSpA will be assessed primarily by the ASAS40 response rate at Week 16 for regulatory agencies that require Week 16 as the primary endpoint, and by the ASAS40 response rate at Week 52 for regulatory agencies that require Week 16 as the primary endpoint, and by the ASAS40 response rate at Week 52 for regulatory agencies that require Week 52 as the primary endpoint. The ASAS40 response at ~~This measure and the other~~ Week 16 endpoints are in alignment with efficacy endpoints for currently approved axSpA therapies and with regulatory guidance (EMEA 2009). The ASAS40 response at Week 52 ~~(first major secondary endpoint)~~ and other Week 52 endpoints are in line with regulatory advice received by Lilly from the Food and Drug Administration for nonrad axSpA (2015, 2018). Steady-state exposure of ixekizumab is expected to be reached by Week 16. Based on previous studies with ixekizumab in patients with Ps, RA, and PsA, it is anticipated that maximum or near maximum clinical effect in nonrad axSpA patients will be achieved for the majority of patients within this timeframe for both ixekizumab treatment regimens regardless of the starting dose.

### Section 6.2. Method of Treatment Assignment

To achieve between-group comparability, the randomization will be stratified by country and ~~baseline~~ screening MRI/CRP status (positive MRI and elevated CRP; positive MRI and nonelevated CRP; negative MRI and elevated CRP). Elevated CRP is defined as >5.00 mg/L.

### Section 8.1.2.9. Ankylosing Spondylitis Disease Activity Score

ASDAScrp: 0.121~~6~~ × total back pain + 0.110~~6~~ × patient global + 0.073~~6~~ × peripheral pain/swelling + 0.058~~6~~ × duration of morning stiffness + 0.579~~6~~ × Ln(CRP+1) (Machado et al. 2015).

### Section 9.1. Determination of Sample Size

Approximately 300 patients will be randomized at a 1:1:1 ratio in the Blinded Treatment Dosing Period (Period 2) to ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, and placebo. With 100 patients per treatment group, this study will have approximately 98% 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: 46% for ixekizumab 80 mg Q2W treatment group and 18% for the placebo group. A 2-sided Fisher's exact test at the 0.05 level is assumed. These assumptions are based on the data from historical clinical studies in nonrad-axSpA patients with objective signs

of inflammation (etanercept, adalimumab, certolizumab, and golimumab [Sieper et al. 2013; Dougados et al. 2014; Landewé et al. 2014; Sieper et al. 2015]).

There is little data from similarly designed 52-week placebo-controlled trials regarding the ASAS40 response rate for active and placebo treated patients to guide power estimation at Week 52. Table RHBX .4. provides power estimates to test the superiority of ixekizumab Q2W to placebo for the ASAS40 at Week 52, assuming various ASAS40 response rates for ixekizumab Q2W and placebo at Week 52. A 2-sided Fisher's exact test at the 0.05 level is assumed.

**Table RHBX.4. Power Estimates for Week 52**

| ASAS40 Response Rates (%) at Week 52 | | |
|---|---|---|
| Ixekizumab Q2W (N = 100) | Placebo (N = 100) | Power (%) |
| 50 | 10 | 99 |
| 40 | 10 | 99 |
| 30 | 10 | 93 |
| 50 | 15 | 99 |
| 40 | 15 | 97 |
| 30 | 15 | 66 |

Abbreviations: ASAS = Assessment of Spondyloarthritis International Society; N = number of subjects; Q2W = every 2 weeks.

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

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

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

The primary analysis method for treatment comparisons of categorical efficacy and health outcomes variables at specific time points will be made using a logistic regression analysis with treatment, geographic region, and ~~baseline~~ screening MRI/CRP status in the model. The odds ratio and 95% confidence intervals (CIs) will be reported. Treatment difference and 95% CI 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~~ screening MRI/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), Week 52 (Visit 15), 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, 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~~ screening MRI/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), Week 52 (Visit 15), and all other visits will be tested.

When the ANCOVA is used, the model will include treatment, geographic region, ~~baseline~~ screening MRI/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 (focusing on Week 4) and treatment response during Blinded Treatment Dosing Period 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 does 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.

Patients who discontinue study treatment after Week 16 will continue to be followed for the scheduled visits for safety and efficacy assessment. The data collected post discontinuation of study treatment will be summarized separately.

### Section 9.2.5. Adjustment for Multiple Comparisons

The primary outcome of ASAS40 at Week 16 will be tested for ixekizumab 80 mg Q2W versus placebo at a 2-sided $\alpha$=0.05. The primary outcome of ASAS40 at Week 52 will also be tested for ixekizumab 80 mg Q2W versus placebo at a 2-sided $\alpha$=0.05. Because this study has a different primary endpoint for different regulatory agencies, the significances of both primary endpoints will not be required in order for the study to be considered successful. No multiplicity adjustment will be made for the 2 primary endpoints. The comparison of ASAS40 for ixekizumab 80 mg Q4W versus placebo at Weeks 16 and Week 52 and the major secondary objectives (Section 3) will be tested using an appropriate multiple testing approach providing strong control of the familywise error rate (for the primary and major secondary tests) at a 2-sided $\alpha$=0.05. Details of the specific testing methodology (including testing order, interrelationships, type I error allocation, and the associated propagation) will be specified in the SAP.

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

### Section 9.3.2. Patient Characteristics

Patient characteristics and baseline clinical measures will be summarized. Baseline characteristics will include sex, age, age category, weight, body mass index, race, geographic region, country, baseline disease activity (BASDAI), duration of disease, HLA-B27 positivity, baseline CRP (% of nonelevated or elevated), ~~baseline~~ screening MRI status, ~~baseline~~ screening MRI/CRP 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, spinal pain, inflammation (mean of questions 5 and 6 of BASDAI), MASES, enthesitis SPARCC, TJC, and SJC.

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

### Section 9.4.1. Primary Analyses

The primary analysis, the proportion of patients with ASAS40 at Week 16 or at Week 52, 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) or Week 52 (Visit 15) 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 9.2.4.

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.

### Section 9.4.2.1. Major Secondary Analyses

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

| Outcomes Measure | Primary Analysis Method | Secondary Analysis Method |
|---|---|---|
| ASAS40 at Week 16 (primary efficacy outcome for regulatory agencies who accept Week 16 as the primary endpoint) | Logistic regression analysis with NRI | Categorical MMRM<br>Fisher's exact test with NRI<br>Logistic regression analysis with NRI on PPS |
| ASAS40 at Week 52 (primary efficacy outcome for regulatory agencies who require Week 52 as the primary endpoint) | Logistic regression analysis with NRI | Categorical MMRM<br>Fisher's exact test with NRI<br>Logistic regression analysis with NRI on PPS |
| Change from baseline in ASDAS at Week 16 (major secondary outcome) | MMRM | ANCOVA with mBOCF/LOCF |
| Change from baseline in ASDAS at Week 52 (major secondary outcome) | MMRM | ANCOVA with mBOCF/LOCF |
| Change from baseline in BASFI at Week 16 (major secondary outcome) | MMRM | ANCOVA with mBOCF/LOCF |
| Change from baseline in BASFI at Week 52 (major secondary outcome) | MMRM | ANCOVA with mBOCF/LOCF |
| ASDAS inactive disease at Week 16 (major secondary outcome) | Logistic regression analysis with NRI | Categorical MMRM<br>Fisher's exact test with NRI |
| ASDAS inactive disease at Week 52 (major secondary outcome) | Logistic regression analysis with NRI | Categorical MMRM<br>Fisher's exact test with NRI |
| Change from baseline in MRI of the SIJ [SPARCC Score] at Week 16 (major secondary outcome) | ANCOVA with observed case analysis[a] | Secondary analysis maybe specified in SAP |
| Percent of patients without clinically meaningful changes in background therapy at Week 52 (major secondary outcome) | Logistic regression analysis | Fisher's exact test |

Abbreviations: ANCOVA = analysis of covariance; ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; 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; SIJ = sacroiliac joints; SPARCC = Spondyloarthritis Research Consortium of Canada Score.

[a] Only patients with both baseline and Week 16 MRI scores will be included in the observed case analysis.

### Section 9.7.2. Subgroup Analyses

Subgroup analysis will be conducted for ASAS40 and selective major secondary outcomes (defined in SAP) at Week 16 (Visit 8) and Week 52 (Visit 15) 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, ~~baseline~~ screening MRI/CRP status, and presence of HLA-B27.

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