Objectives	Endpoints
• To evaluate in patients having achieved a state of sustained remission whether the ixekizumab 80 mg Q2W treatment group or ixekizumab 80 mg Q4W treatment group is superior to placebo in maintaining response after randomized withdrawal	• Time to flare for patients in the randomized withdrawal population during Period 2

Objectives	Endpoints
Other Secondary	
• To evaluate in patients having achieved a state of sustained remission whether the combined ixekizumab treatment group is superior to the placebo group in maintaining response during Period 2	• The proportion of patients in the randomized withdrawal population with Assessment of Spondyloarthritis International Society (ASAS)20, ASAS40, ASAS 5/6, ASAS partial remission, clinically-important improvement (change of Ankylosing Spondylitis Disease Activity Score [ASDAS] ≥1.1 units), major improvement (change of ASDAS ≥2.0 units), and inactive disease (ASDAS <1.3) during Period 2 • Change from baseline in the individual components of the ASAS criteria • Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) • Proportion of patients with Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI50) response • Change from baseline in ASDAS • Change from baseline in the measure of high sensitivity C-reactive protein (CRP) • Change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) • Change from baseline in the measures of spinal mobility o Bath Ankylosing Spondylitis Metrology Index (BASMI) (linear), and BASMI individual components o Chest expansion o Change from baseline in occiput to wall distance • Change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and Spondyloarthritis Research Consortium of Canada Score (SPARCC) • The incidence and severity of peripheral arthritis by tender and swollen joint counts of 46/44 joints • The incidence rate of anterior uveitis or uveitis flares

	Lead-In Period (Period 1)				Extension Period, Including Blinded, Randomized Withdrawal–Retreatment (Period 2)										Long-Term Extension Period (Period 3)					ETV
Visit No (Group A)[c]	V1[a]	V2	V3	V4	V5[c]	-	V6	-	V7	-	V8	-	V9	-	V10	V11	V12	V13	V14	ETV
Visit No (Group B)[c]					V505[c]	V506	V507	V508	V509	V510	V511	V512	V513	V514	V515	V516	V517	V518	V519	
Study Week	W0	W8	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W56	W60	W64	W76	W88	W100	W104	
Study Day	[b]	56 ± 5d	112 ± 5d	140 ± 5d	168 ± 5d	196 ± 5d	224 ± 5d	252 ± 5d	280 ± 5d	308 ± 5d	336 ± 5d	364 ± 5d	392 ± 5d	420 ± 5d	448 ± 5d	532 ± 5d	616 ± 5d	700 ± 5d	728 ± 5d	
Collect, review, and enter data from SDAL		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Efficacy/Health Outcomes																				
MRI of spine plus SIJ[m]					X[m]															
x-ray—spine[n]													X							X[n]
Linear BASMI	X		X		X				X				X		X		X		X	X
Chest expansion	X		X		X				X				X		X		X		X	X
Occiput to wall distance	X		X		X				X				X		X		X		X	X
Enthesitis (MASES and SPARCC)	X		X		X				X				X		X		X		X	X
Assessment of TJC/SJC (46/44)	X		X		X				X				X		X		X		X	X
Patient Global Assessment of Disease Activity NRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spinal pain	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BASFI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BASDAI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Healthcare resource utilization	X				X				X						X		X		X	X

Objectives	Endpoints
Other Secondary	
• To evaluate in patients having achieved a state of sustained remission whether the combined ixekizumab treatment group is superior to the placebo group in maintaining response during Period 2	• The proportion of patients in the randomized withdrawal population with ASAS20, ASAS40, ASAS 5/6, ASAS partial remission, clinically important improvement (change of Ankylosing Spondylitis Disease Activity Score [ASDAS] ≥1.1 units), major improvement (change of ASDAS ≥2.0 units), and inactive disease (ASDAS <1.3) during Period 2 • Change from baseline in the individual components of the ASAS criteria • Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) • Proportion of patients with Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI50) response • Change from baseline in (ASDAS) • Change from baseline in the measure of high sensitivity C-reactive protein (CRP) • Change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) • Change from baseline in the measures of spinal mobility: o Bath Ankylosing Spondylitis Metrology Index (BASMI) (linear), and BASMI individual components o Chest expansion o Change from baseline in occiput to wall distance • Change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and Spondyloarthritis Research Consortium of Canada Score (SPARCC) • The incidence and severity of peripheral arthritis by tender and swollen joint counts of 46/44 joints • The incidence rate of anterior uveitis or uveitis flares • Change from baseline in the following health outcomes measures: o Fatigue numeric rating scale (NRS) score o Quick Inventory of Depressive Symptomatology Self-Report-16 (QIDS-SR16) o SF-36 (both physical and mental component scores) o Assessments of Spondyloarthritis

- Patients in the ixekizumab 80 mg Q2W treatment group will be re-randomized to either ixekizumab 80 Q2W or placebo at 2:1 ratio and will be stratified by geographic region and originating study.
- Patients in the ixekizumab 80 mg Q4W treatment group will be re-randomized to either ixekizumab 80 mg Q4W or placebo at 2:1 ratio and will be stratified by geographic region and originating study.

After completion of the 40-week randomized withdrawal–retreatment period, patients will continue the same treatment that they were receiving at the end of Period 2, and will continue in the Long-Term Extension Period (Period 3). All treatment groups and administration of the investigational product are described in Section 7.1, and the Study Drug Administration Log is described in Section 7.2.1.

All procedures to be conducted during the study, including timing of all procedures, are indicated in the Schedule of Activities (Section 2). Selected study procedures are to be performed before administration of the investigational product, as applicable. Appendix 2 lists the specific laboratory tests that will be performed for this study.

Patients who have taken at least 1 study dose and who discontinue study treatment are to complete an ETV and enter into Post-Treatment Follow-Up Period (Period 4) for at least 12 weeks and up to 24 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 study dose are not required to enter into the Post-Treatment Follow-Up Period. For the management of patient safety, patients are to be monitored through the Post-Treatment Follow-Up Period as indicated on the Schedule of Activities (Section 2). Excluded and concomitant medications are detailed in Section 7.7. Immunogenicity testing and pharmacokinetic (PK) sampling are detailed in Section 9.4.9 and Section 9.5, respectively. Section 10.3.7 outlines the information regarding the interim analyses.

The Long-Term Extension Period (Period 3) allows for collection of data for the continued assessment of longer-term safety data and maintenance of efficacy with ixekizumab treatment.

The Post-Treatment Follow-Up Period (Period 4) is important for safety monitoring following administration of the last study treatment. The duration of the Post-Treatment Follow-Up Period is at least 12 weeks and up to 24 weeks to allow for monitoring during ixekizumab clearance and reflects a time period equivalent to approximately 5 half-lives of ixekizumab.

A repeat x-ray of the cervical and lumbar spine will be taken at Week 56 in Study RHBY (approximately 2 years after baseline of the originating study) to evaluate the potential effect of ixekizumab treatment on structural progression. The x-ray at Week 56 is only needed for patients initially enrolled in Studies RHBV or RHBW (see Schedule of Activities, Section 2). As structural progression in axSpA is slow, a 2-year time interval between consecutive x-rays is appropriate for such evaluation in patients with radiographic axSpA and avoids radiographic overexposure for patients.

5.5. Justification for Dose

Study RHBY is a long-term extension study for patients who have completed Week 52 of any of the following originating studies: RHBV, RHBW, or RHBX. The ixekizumab dose regimens used in Study RHBY (ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W) are the same as those used in studies RHBV, RHBW, and RHBX.

Secondary efficacy assessments will include evaluation of patients who meet the criteria for inactive disease (ASDAS <1.3; Machado et al. 2011c), clinically important improvement (defined as change ≥1.1 units), and major improvement (defined as change ≥2.0 units; Machado et al. 2011b).

9.1.2.2. Imaging Used for Efficacy Measures and Disease Diagnosis

9.1.2.2.1. Radiographic Imaging of the Spine

The radiographic image (x-ray) of the spine is used to evaluate structure progression.

At Week 56, a spinal x-ray, plain radiograph of the lateral views of cervical and lumbar spine, will be centrally read; the x-ray at Week 56 is only needed for patients initially enrolled in Studies RHBV or RHBW. The data set will be scored by the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS; Wanders 2004; Creemers 2005).

By the scoring system of mSASSS of the spinal x-rays, a total of 24 sites are scored on the lateral cervical and lumbar spine: the anterior corners of the vertebrae from lower border of C2 to upper border T1 (inclusive), and from lower border of T12 to upper border of S1 (inclusive). Each corner can be scored from 0 to 3, resulting in a range from 0 to 72 for the total mSASSS. The example of scoring according to the mSASSS, 0 = normal; 1 = sclerosis, squaring or erosion; 2 = syndesmophyte; 3 = bony bridge.

9.1.2.2.2. Spondyloarthritis Research Consortium of Canada MRI Score for Sacroiliac Joints

At Week 24 (Group B: Visit 505), an MRI of both left and right SIJ is collected. Both left and right SIJ are scored for bone marrow edema. Total SIJ Spondyloarthritis Research Consortium of Canada (SPARCC) scores can range from 0 to 72 with higher scores reflecting worse disease. Scoring will be performed by a central reader.

9.1.2.2.3. Ankylosing Spondylitis Spinal Magnetic Resonance Imaging Activity

At Week 24 (Group B: Visit 505), an MRI of the spine is collected. All 23 disco-vertebral units of the spine (from C2 to S1) are scored for bone marrow edema with a validated scoring method. Scoring will be performed by a central reader.

9.1.2.3. ASAS20, ASAS40, ASAS5/6, ASAS Partial Remission

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

1) Patient Global (Section 9.1.2.4)
2) Spinal Pain (Section 9.1.2.5)
3) Function (Section 9.1.2.6)
4) Inflammation (mean of BASDAI questions 5 and 6) (Section 9.1.2.7)
5) CRP (Section 9.1.2.14.1)
6) Spinal mobility (lateral spinal flexion) (Section 9.1.2.8)

9.1.2.3.1. 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 (from originating

study) 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.

9.1.2.3.2. 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 (from originating study) 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.

9.1.2.3.3. ASAS5/6

The ASAS5/6 includes assessment of all 6 individual ASAS domains listed above (Section 9.1.2.3) and represents improvement of ≥20% in at least 5 domains.

9.1.2.3.4. 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, numeric rating scale [NRS]) in each of the following 4 domains: Patient Global, Spinal Pain, Function, and Inflammation.

9.1.2.4. Patient Global (Assessment of Disease Activity)

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

9.1.2.5. Spinal Pain

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

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

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

9.1.2.6. 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.

9.1.2.7. 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)

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.

9.1.2.15.5. 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).

9.1.2.15.6. Work Productivity and Activity Impairment Questionnaire—Spondyloarthritis

The Work Productivity Activity Impairment Questionnaire-Spondyloarthritis (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]).

9.1.2.15.7. Jenkins Sleep Questionnaire

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

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."

9.2.1. Serious Adverse Events

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

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

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

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

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

Investigators are not obligated to actively seek AEs or SAEs in patients 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 patient 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.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

9.2.2. 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.

Adverse events of special interest for ixekizumab are as follows:

- 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
- inflammatory bowel disease
- 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 7.1.2). 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. The role of the CEC will be to adjudicate these defined clinical events in a blinded, consistent, and unbiased manner throughout the course of a study and ensure that all events that have been reported are evaluated uniformly by a single group (the CEC).

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 the CEC will be to adjudicate defined clinical events, in a blinded, consistent, and unbiased manner throughout the course of a study and ensure that all events that have been reported are evaluated uniformly by a single group.

9.2.3. Complaint Handling

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

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

9.3. Treatment of Overdose

Refer to the IB and/or the product label where applicable.

9.4. Safety

9.4.1. Electrocardiograms

For each patient, electrocardiograms (ECGs) should be collected according to the Schedule of Activities (Section 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 should be reported to Lilly or its designee as an AE via CRF.

9.4.2. Vital Signs

For each patient, vital signs measurements (sitting) should be conducted according to the Schedule of Activities (Section 2). Vital signs include blood pressure (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 should be reported to Lilly or its designee as an AE via CRF.

9.4.3. Laboratory Tests

For each patient, laboratory tests detailed in (Appendix 2) should be conducted according to the Schedule of Activities (Section 2). Please reference the central laboratory manual for specific instructions.

Urine pregnancy test will be collected and read/analyzed locally. Urine testing for pregnancy may occur at intervals more frequently than according to the Schedule of Activities during the study treatment period and/or follow up period if required per local regulation.

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

9.4.4. Physical Examination

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

comparing the radiographic progression of the Ixekizumab Structure Population to the Historical Control Population.

Important patient characteristics, such as age at baseline, baseline syndesmophytes, baseline CRP, age at onset, sex, smoking history and duration of disease, will be compared between the Ixekizumab Structure Population and the Historical Control Population. The primary analysis will be ANCOVA to compare the 2-year radiographic progression in spine measured by change in modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). The ANCOVA model will include population and baseline mSASSS score.

Fisher's exact test will be used to compare the proportion of nonprogressors measured by change in Total mSASSS <2 and by mSASSS=0, the proportion of progressors measured by change in Total mSASSS ≥0, and the proportion of patients with no new syndesmophytes.

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

For the safety analyses during Period 4, baseline is defined as the last nonmissing assessment prior to entering Period 4, that is, on or prior to Week 104 (Group A: Visit 14/Group B: Visit 519), or ETV. Safety data collected will be summarized using descriptive statistics.

10.3.1.5. Missing Data Imputation

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

10.3.1.5.1. 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 at any specified analysis time point. All nonresponders at any specified time point as well as all patients who discontinue study treatment before the specified analysis time point, for any reason, will be defined as a nonresponder for the NRI analysis. Patients without at least 1 observation on study treatment will also be defined as a nonresponder for the NRI analysis. The NRI may be applied at any time point specified for analysis.

10.3.1.5.2. Modified Nonresponder Imputation for Clinical Response

Analysis of categorical efficacy and health outcome variables for long-term ixekizumab treatment analysis will be assessed using a modified nonresponder imputation (mNRI) method. Patients will be considered as nonresponders if they discontinue study drug due to a flare, an AE, or lack of efficacy. For patients discontinuing study drug for any other reason, the data will be imputed using multiple imputation method (as described in Section 10.3.1.5.4). Patients without at least 1 observation will also be defined as nonresponders for the mNRI analysis.

10.3.1.5.3. Modified Baseline Observation Carried Forward

The primary analyses for all continuous efficacy and health outcome variables will be based on an mBOCF approach. For patients discontinuing study drug due to an AE, the baseline (from the

Period 2 (Extension Period, Including Blinded, Randomized Withdrawal–Retreatment):

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

Treatment comparisons in the proportion of patients achieving a categorical response at specified time points will be analyzed using the logistic regression model defined in Section 10.3.1.2.1. Missing data will be imputed using the NRI method described in Section 10.3.1.5.1.

For all continuous health outcomes variables, treatment group comparisons will be analyzed using the ANCOVA model defined in Section 10.3.1.2.1; missing data will be imputed by the mBOCF method as described in Section 10.3.1.5.3.

Combined Periods 1, 2, and 3:

Data collected in combined Periods 1, 2, and 3 will be summarized for the Long-Term Ixekizumab Treatment Efficacy Population. The within-treatment group comparisons may be conducted as appropriate.

10.3.6.2. Subgroup Analyses

Subgroup analyses will be conducted for time to flare and the proportion of patients who experienced a flare for the Randomized Withdrawal ITT Population.

Subgroup analyses may be conducted based on gender, age category, race, geographic region, population (radiographic and nonradiographic axSpA), origination study, and CRP status at the time of randomization in Period 2. Additional subgroups may be described in the SAP.

The Kaplan-Meier product limit method will be used to estimate the survival curves or time to flare. Analyses will be performed using a log-rank test with treatment, subgroup, and the interaction of treatment-by-subgroup included as factors in the model.

For the proportion of patients who experience a flare, a logistic regression model will be used with treatment, subgroup, and the interaction of treatment-by-subgroup included as factors. Missing data will be imputed using NRI.

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, regardless of whether the interaction is statistically significant.

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.

10.3.6.3. Immunogenicity

The analyses of anti-drug antibody (ADA) effects will be conducted on all evaluable patients within the defined Randomized Withdrawal Safety Population. Evaluable patients will be defined as either: a) patients with an evaluable baseline sample and at least 1 evaluable postbaseline sample (i.e., sample after administration of study drug); or b) patients with no evaluable baseline sample whose evaluable postbaseline samples were all ADA negative.

Lead-In Period (Period 1): Patients who were previously receiving ixekizumab treatment during Studies RHBV and RHBW will, as of Week 0 in Study RHBY, continue to receive the same ixekizumab treatment regimen they were on at the end of the originating study, but now in open-label fashion.

For patients in Study RHBX, treatment during the Lead-In Period will be assigned as follows:

- Patients who were rescued to ixekizumab 80 mg Q2W will remain on ixekizumab 80 mg Q2W in open-label fashion.
- Patients who were receiving blinded treatment with either ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W will continue on their ixekizumab dose regimen in blinded fashion.
- Patients who were receiving blinded treatment with placebo will be assigned to receive blinded treatment with ixekizumab 80 mg Q4W.

Note: Patients from Study RHBX on blinded therapy in Period 1 of Study RHBY will continue on blinded treatment until at least the Week 52 datalock has occurred for Study RHBX.

Patients, site personnel, and the Sponsor will remain blinded to the initial treatment patients were assigned to in Studies RHBV, RHBW, and RHBX until after completion of datalock for the respective originating study (i.e., Week 16 datalock for Studies RHBV and RHBW, and Week 52 datalock for Study RHBX).

Screening for eligibility for Study RHBY should occur during the last visit (Week 52) of the originating study. However, in particular circumstances, entry into Study RHBY may occur after Week 52 of the originating study after consultation with the sponsor (see Section 6.1). More details on treatment groups and administration of the investigational product are described in Section 7.1.

Extension Period, Including Blinded, Randomized Withdrawal–Retreatment (Period 2):

Eligibility criteria for participation in randomized withdrawal are defined as one of the following:

- ASDAS <1.3 at Weeks 16 and 20,

OR

- ASDAS <1.3 at Week 16 and ASDAS <2.1 at Week 20,

OR

- ASDAS <2.1 at Week 16 and ASDAS <1.3 at Week 20.

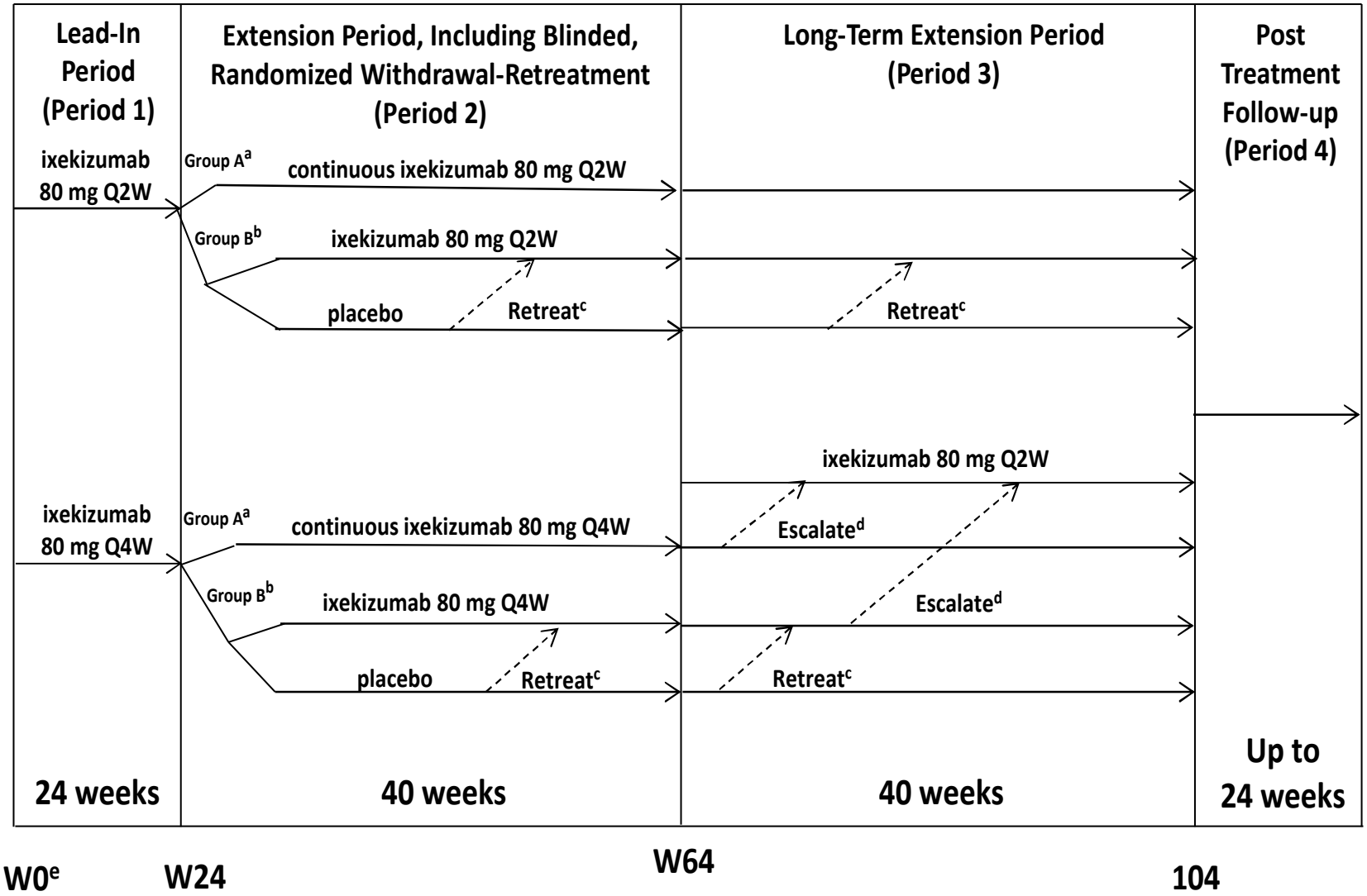
Patients who DO NOT meet entry criteria for participation in the 40-week double-blind, placebo-controlled, randomized withdrawal–retreatment period (i.e., patients who have not achieved a state of sustained remission) will continue to receive uninterrupted ixekizumab therapy and are referred to as Group A.

Term	Definition
BP	blood pressure
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	High sensitivity 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
FSH	follicle stimulating hormone
GCP	good clinical practice
HBV	hepatitis B virus
HLA	human leukocyte antigen
IB	Investigator's Brochure

Objectives	Endpoints
	• Change from baseline in the following health outcomes measures o Fatigue numeric rating scale (NRS) score o Quick Inventory of Depressive Symptomatology Self-Report-16 (QIDS-SR16) o SF-36 (both physical and mental component scores) o Assessments of Spondyloarthritis International Society–Health Index (ASAS-HI) o European Quality of Life – 5 Dimensions 5 Level (EQ-5D-5L) o Work Productivity Activity Impairment-Spondyloarthritis (WPAI-SpA) o Jenkins Sleep Evaluation Questionnaire (JSEQ)
• To assess the efficacy of retreatment with ixekizumab following a flare during Period 2	• Proportion of patients who regain ASDAS <1.3 within 16 weeks after ixekizumab retreatment • Proportion of patients who regain ASDAS <2.1 within 16 weeks after ixekizumab retreatment • Proportion of patients who achieve/maintain an ASAS20, ASAS40, ASAS5/6, ASAS partial remission, ASDAS major improvement, and ASDAS clinically important improvement within 16 weeks after ixekizumab retreatment • Proportion of patients who achieve an ASAS20, ASAS40, ASAS5/6, ASAS partial remission, ASDAS major improvement, ASDAS clinically important improvement, and ASDAS-inactive disease through Week 64
• To determine the long-term treatment effect of 80 mg ixekizumab Q2W and 80 mg ixekizumab Q4W through Week 104	• The proportion of patients with ASAS20, ASAS40, ASAS 5/6, ASAS partial remission, clinically important improvement, major improvement, and inactive disease • Change from baseline in the individual components of the ASAS criteria • Change from baseline in BASDAI • Proportion of patients with BASDAI50 response • Change from baseline in ASDAS • Change from baseline in the measure of CRP • Change from baseline in BASFI • Change from baseline in the measures of spinal mobility o BASMI (linear), and BASMI

	Lead-In Period (Period 1)				Extension Period, Including Blinded, Randomized Withdrawal–Retreatment (Period 2)										Long-Term Extension Period (Period 3)					ETV
Visit No (Group A)[c]	V1[a]	V2	V3	V4	V5[c]	-	V6	-	V7	-	V8	-	V9	-	V10	V11	V12	V13	V14	ETV
Visit No (Group B)[c]					V505[c]	V506	V507	V508	V509	V510	V511	V512	V513	V514	V515	V516	V517	V518	V519	
Study Week	W0	W8	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W56	W60	W64	W76	W88	W100	W104	
Study Day	[b]	56 ± 5d	112 ± 5d	140 ± 5d	168 ± 5d	196 ± 5d	224 ± 5d	252 ± 5d	280 ± 5d	308 ± 5d	336 ± 5d	364 ± 5d	392 ± 5d	420 ± 5d	448 ± 5d	532 ± 5d	616 ± 5d	700 ± 5d	728 ± 5d	
Fatigue NRS	X				X				X						X		X		X	X
SF-36	X				X				X						X		X		X	X
ASAS-HI	X				X				X						X		X		X	X
EQ-5D-5L	X				X				X						X		X		X	X
WPAI-SpA	X				X				X						X		X		X	X
JSEQ	X				X				X						X		X		X	X
QIDS-SR16	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Supplement Form[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Tests																				
CRP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer TB test(s)[p]	TB testing required only based on clinical assessment of TB risk (symptoms/signs/known or suspected TB exposure), and according to local regulations and/or local standard of care.																			
ECG	X												X						X	X
HBV DNA[q]	X	X	X		X		X		X		X		X		X	X	X	X		X
Urine pregnancy test[r]	X	X	X		X		X		X		X		X		X	X	X	X	X	X
Serum chemistry	X	X	X		X		X		X		X		X		X	X	X	X	X	X
PTT, PT/INR	X												X						X	X
Fasting lipid panel[s]	X				X		X				X				X	X	X	X	X	
Hematology	X	X	X		X		X		X		X		X		X	X	X	X	X	X

Objectives	Endpoints
	International Society–Health Index (ASAS-HI) o European Quality of Life - 5 Dimensions 5 Level (EQ-5D-5L) o Work Productivity Activity Impairment-Spondyloarthritis (WPAI-SpA) o Jenkins Sleep Evaluation Questionnaire (JSEQ)
• To assess the efficacy of retreatment with ixekizumab following a flare during Period 2	• Proportion of patients who regain ASDAS <1.3 within 16 weeks after ixekizumab retreatment • Proportion of patients who regain ASDAS <2.1 within 16 weeks after ixekizumab retreatment • Proportion of patients who achieve/maintain an ASAS20, ASAS40, ASAS5/6, ASAS partial remission, ASDAS major improvement, and ASDAS clinically important improvement within 16 weeks after ixekizumab retreatment • Proportion of patients who achieve an ASAS20, ASAS40, ASAS5/6, ASAS partial remission, ASDAS major improvement, ASDAS clinically important improvement, and ASDAS-inactive disease through Week 64
• To determine the long-term treatment effect of 80 mg ixekizumab Q2W and 80 mg ixekizumab Q4W through Week 104	• The proportion of patients with ASAS20, ASAS40, ASAS 5/6, ASAS partial remission, clinically important improvement, major improvement, and inactive disease • Change from baseline in the individual components of the ASAS criteria • Change from baseline in BASDAI • Proportion of patients with BASDAI50 response • Change from baseline in ASDAS • Change from baseline in the measure of CRP • Change from baseline in BASFI • Change from baseline in the measures of spinal mobility: o BASMI (linear), and BASMI individual components o Chest expansion o Change from baseline in occiput to wall distance • Change from baseline in MASES and SPARCC • The incidence and severity of peripheral arthritis by tender and swollen joint counts of 46/44 joints • The incidence rate of anterior uveitis or uveitis flares


Lead-In Period (Period 1)
Extension Period, Including Blinded, Randomized Withdrawal-Retreatment (Period 2)
Long-Term Extension Period (Period 3)
Post Treatment Follow-up (Period 4)
ixekizumab 80 mg Q2W
Group A[a]
continuous ixekizumab 80 mg Q2W
Group B[b]
ixekizumab 80 mg Q2W
placebo
Retreat[c]
Retreat[c]
ixekizumab 80 mg Q2W
ixekizumab 80 mg Q4W
Group A[a]
continuous ixekizumab 80 mg Q4W
Escalate[d]
Group B[b]
ixekizumab 80 mg Q4W
Escalate[d]
placebo
Retreat[c]
Retreat[c]
24 weeks
40 weeks
40 weeks
Up to 24 weeks
W0[e]
W24
W64
104

6. Study Population

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

6.1. Inclusion Criteria

The study population for Study RHBY will include patients from any of the originating studies (RHBV, RHBW, or RHBX), and will therefore include patients with rad-axSpA and patients with nonrad-axSpA, with or without prior use of TNF inhibitors.

For most patients, Week 52 of the originating study (RHBV, RHBW, or RHBX) will coincide with Week 0 (Visit 1) for Study RHBY. Study investigator(s) will review patient data from Week 52 in the respective originating study to determine if the patient meets all inclusion and none of the exclusion criteria to qualify for participation in Study RHBY. If, at Week 52 in the originating study, a patient is not able to enter Study RHBY (e.g., due to unresolved safety concerns), investigational product will be temporarily interrupted and the patient will be evaluated in the originating study for up to 12 weeks beyond Week 52 (i.e., Visit 802 in the originating study) to determine whether treatment with investigational product can resume. If, in the opinion of the investigator, restarting ixekizumab does not pose an unacceptable risk, the patient can begin participation in Study RHBY (Visit 1 [Week 0]).

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

[1.] Have completed the final study visit in Study RHBV, RHBW, or RHBX. (Note: Patients from Study RHBX are not eligible if they permanently discontinued ixekizumab and were receiving a TNF inhibitor).

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

- If the patient is male, the patient must agree 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 the patient is female and is a woman of childbearing potential who tests negative for pregnancy, the patient must agree 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 birth control include, but are not limited to, oral contraceptives, contraceptive patch, injectable or implantable contraceptives, intrauterine device, vaginal ring, or diaphragm with contraceptive gel.

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.

9.1.2.8. Bath Ankylosing Spondylitis Metrology Index—Spinal Mobility

The Bath Ankylosing Spondylitis Metrology Index (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.

9.1.2.9. 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 cm 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.

9.1.2.10. Occiput to Wall Distance

The patient is to make a maximum effort to touch the head against the wall when standing with heels and back against the wall (occiput). Then the distance from occiput to wall is measured. Two tries will be recorded. The better (smaller) measurement of 2 tries in centimeters will be used for analyses (Sieper et al. 2009).

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

9.1.2.11. Maastricht Ankylosing Spondylitis Enthesitis Score

The Maastricht Ankylosing Spondylitis Enthesitis Score (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

9.2. 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 should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

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

After the informed consent form (ICF) is signed, study site personnel will record via case report form (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 any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, investigational product, via CRF.

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

> Reasonably Possibly **Related**: Reasonable possibility that there is a cause and effect relationship between the study product and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

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

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.

9.4.5. 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 (Section 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).

9.4.6. Tuberculosis Testing

Tuberculosis testing will be conducted based on clinical assessment of TB risk (symptoms/signs/known or suspected TB exposure), and as required by local regulations and/or local standard of care.

Patients with a positive TB test and/or other evidence of active TB should be discontinued (Section 8.1.1).

In patients with a positive TB test indicating TB test conversion since prior testing (based on patient medical history), but no other evidence of active TB, study treatment should be withheld. These patients may continue in Study RHBY and resume study treatment without repeating TB testing if all of the following conditions are met:

- a specialist in the care of patients with TB (e.g., infectious disease or pulmonary medicine subspecialists) is consulted and does not identify evidence of active TB, and the patient is assessed as having latent TB infection
- a posterior-anterior view chest x-ray or results from a chest x-ray obtained within 30 days prior to the positive TB test does not indicate active TB infection
- after receiving at least the initial 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
- meet all other inclusion/exclusion criteria for participation

Such patients must complete appropriate LTBI therapy in order to remain in compliance and continue to participate in the study.

If a positive TB test result is believed to represent a false-positive result based on thorough medical assessment of the patient, the investigator should discuss further testing and management with Lilly medical.

Any findings of a positive TB test that occurs after the patient receives the first dose of study treatment are to be reported to Lilly or its designee as an AE via CRF.

originating study) observation will be carried forward to the corresponding primary endpoint for evaluation. For patients discontinuing study drug for any other reason, the last nonmissing observation before discontinuation will be carried forward to the corresponding primary endpoint for evaluation with the following exception; for patients who experience a flare in Period 2 and are retreated with ixekizumab 80 mg Q2W or Q4W, the last nonmissing observations prior to the ixekizumab re-treatment 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.

10.3.1.5.4. Multiple Imputation

Analysis of continuous efficacy and health outcome variables for long-term ixekizumab treatment analysis will be assessed using multiple imputation method. In the multiple imputation analyses, missing data will be imputed so as to estimate what observations would have been if the patient had not discontinued. Specifically, multiple imputation is the partial imputation of nonmonotone missing data using Markov chain Monte Carlo method with the simple imputation model, followed by a sequential regression imputation with the baseline score.

10.3.1.6. Adjustment for Multiple Comparisons

The primary outcome of proportion of patients who do not experience a flare will be tested for ixekizumab versus placebo at a 2-sided α=0.05. The comparison of major secondary objectives (Section 4) 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 α=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.

10.3.2. Treatment Group Comparability

10.3.2.1. 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 for each treatment period. Reasons for discontinuation from the study will be summarized. The reason for discontinuation during Period 2 for the Randomized Withdrawal ITT Population will be tested between treatment groups using Fisher's exact test.

10.3.2.2. Patient Characteristics

Patient characteristics and baseline clinical measures will be summarized. Baseline characteristics will include gender, age, age category, weight, race, geographic region, originating study, abnormal/normal CRP. Baseline clinical measurements may include BASDAI, BASFI, BASMI, chest expansion, Fatigue NRS, Patient Global NRS, total back pain, spinal pain at night, spinal pain, inflammation, MASES, enthesitis SPARCC, TJC, and SJC.

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 efficacy responses will be evaluated, as appropriate.

Assessment of immunogenicity with respect to safety will include comparison of patients who experience treatment-emergent adverse event (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.

10.3.7. Interim Analyses

The study will have approximately 1 interim database lock and 1 final database lock. The interim database lock will occur and the analysis will be performed at the time when all patients have completed through Week 64 or have discontinued at or prior to Week 64. At this time, study team members will become unblinded; however, investigators, patients, and site personnel will remain blinded to study treatment until final database lock. The interim database lock will include all data collected by the cutoff date, including the data from the Long-Term Extended Treatment Period (Period 3), and follow-up data from patients that have begun the Post-Treatment Follow-Up Period (Period 4). The analyses from the Week 64 database lock will be treated as a primary analysis because all primary and major secondary study objectives will be assessed at this time. The final database lock, unblinding, and analysis will occur when all patients have completed or discontinued the study.

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

Unblinding details are specified in the blinding/unblinding plan.

Patients who DO meet entry criteria for participation in the 40-week double-blind, placebo-controlled, randomized withdrawal–retreatment period (i.e., patients having achieved a state of sustained remission) are referred to as Group B and will be re-randomized at Week 24 as follows:

- Patients in the ixekizumab 80 mg Q2W treatment group will be re-randomized 2:1 at Week 24 to either ixekizumab 80 mg Q2W or placebo. Patients who experience a flare will return to treatment with ixekizumab 80 mg Q2W.
- Patients in the ixekizumab 80 mg Q4W treatment group will be re-randomized 2:1 at Week 24 to either ixekizumab 80 mg Q4W or placebo. Patients who experience a flare will return to treatment with ixekizumab 80 mg Q4W.

A flare is defined as follows:

- ASDAS ≥2.1 at 2 consecutive visits, or ASDAS >3.5 at any visit during Period 2 and/or Period 3.

Long-Term Extension Period (Period 3):

Group A: All patients will continue to receive uninterrupted ixekizumab therapy. During Period 3, patients in Group A receiving ixekizumab 80 mg Q4W may have their dose escalated to ixekizumab 80 mg Q2W if the investigator determines that the patient may benefit from an increase in frequency of dosing to achieve adequate disease control.

Group B: Patients in Group B will continue the same treatment that they were receiving at the end of Period 2. However, if a patient experiences a flare, the patient will be retreated with the ixekizumab treatment regimen (ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W) that he or she was receiving prior to withdrawal to evaluate whether the patient can regain his or her original response.

During Period 3, patients in Group B receiving ixekizumab 80 mg Q4W may also have their dose escalated to ixekizumab 80 mg Q2W if the investigator determines that the patient may benefit from an increase in frequency of dosing to achieve adequate disease control. Escalation to ixekizumab 80 mg Q2W may occur only after the patient has been retreated upon flare with the ixekizumab treatment regimen received during Period 1 (ixekizumab 80 mg Q4W) for at least 12 weeks.

Post-Treatment Follow-Up (Period 4): All patients receiving at least 1 dose of investigational product will enter the Post-Treatment Follow-Up (Period 4) for a minimum of 12 weeks and up to 24 weeks after their last regularly scheduled visit (or the date of their ETV).

5.2. Number of Participants

It is estimated that approximately 750 patients will enter the long-term extension study (RHBY) after completion of studies RHBV, RHBW, or RHBX. This sample size is estimated based on the 1-year retention rates from ixekizumab Ps studies and from 1 secukinumab rad-axSpA study (Baeten et al. 2015), which had a retention rate of approximately 85%.

Term	Definition
IBD	Inflammatory bowel disease (e.g., Crohn's disease and Ulcerative Colitis)
ICF	informed consent form
ICFD	International Classification of Functioning Disability and Health
ICH	International Council for 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
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 (i.e., 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
LS	least-squares
MAb	monoclonal antibody
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
mBOCF	modified baseline observation carried forward
MI	myocardial infarction
MOA	mechanism of action
mNRI	modified nonresponder imputation