Protocol: I1F-MC-RHBY (a)

A Multicenter, Long-Term Extension Study of 104 Weeks, Including a Double-Blind, Placebo-Controlled 40-Week Randomized Withdrawal-Retreatment Period, to Evaluate the Maintenance of Treatment Effect of Ixekizumab (LY2439821) in Patients With Axial Spondyloarthritis

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Ixekizumab (LY2439821)

Study I1F-MC-RHBY (RHBY) is a Phase 3, multicenter, long-term extension study of 104 weeks in patients with axial spondyloarthritis that includes a double-blind, placebo-controlled, randomized withdrawal–retreatment period. The study duration will be up to 2 years for ixekizumab administration, and up to 2 years and 6 months for study participation over 4 periods.

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Protocol Electronically Signed and Approved by Lilly: 26 August 2016
Amendment (a) Electronically Signed and Approved by Lilly on approval date provided below.

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1. Synopsis

Title of Study:

A Multicenter, Long-Term Extension Study of 104 Weeks, Including a Double-Blind, Placebo-Controlled 40-Week Randomized Withdrawal–Retreatment Period, to Evaluate the Maintenance of Treatment Effect of Ixekizumab (LY2439821) in Patients with Axial Spondyloarthritis

Rationale:

In the context of long-term treatment, it is important to understand the long-term efficacy and safety of ixekizumab treatment in patients with axial spondyloarthritis (axSpA). The current 2-year study will, together with the preceding 1-year originating studies I1F-MC-RHBV (RHBV), I1F-MC-RHBW (RHBW), and I1F-MC-RHBX (RHBX), provide efficacy and safety data of ixekizumab after long-term treatment for patients with axSpA, including both radiographic axSpA (rad-axSpA) and nonradiographic axSpA (nonrad-axSpA) patients, and biological disease modifying antirheumatic drug (bDMARD)-naive as well as tumor necrosis factor (TNF)-experienced patients. Therefore, data generated from the current study will provide further information on the long-term efficacy and safety profile of ixekizumab.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary	
• 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 who do not experience a flare during Period 2

Objectives	Endpoints
Major Secondary	
• To compare the combined ixekizumab treatment group to historical control for 2-year radiographic progression in spine in patients with active radiographic axSpA (rad axSpA)	• Change in modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) score
• To evaluate in patients having achieved a state of sustained remission whether the ixekizumab 80 mg every 2 weeks (Q2W) treatment group or ixekizumab 80 mg every 4 weeks (Q4W) treatment group is superior to placebo in maintaining response after randomized withdrawal	• The proportion of patients in the randomized withdrawal population who do not experience a flare during Period 2
• 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 after randomized withdrawal	• Time to flare for patients in the randomized withdrawal population during Period 2

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

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

Objectives	Endpoints
	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 • Proportion of patients with change in mSASSS score <2 from baseline of originating study to Week 56 in RHBY • Proportion of patients with no new syndesmophyte formation from baseline of originating study to Week 56 in RHBY • Change from baseline in the following health outcomes measures o Fatigue NRS score o QIDS SR16 o SF-36 (both physical and mental component scores) o ASAS-HI o EQ-5D-5L o WPAI-SpA o JSEQ
• To evaluate the development of anti-ixekizumab antibodies and its impact on the efficacy of ixekizumab	• Efficacy response rates listed below at Week 64 and Week 104 by treatment-emergent anti-drug antibody (TE-ADA) status and by neutralizing anti-drug antibody (NAb) status: o Proportion of patients achieving ASAS40 o Proportion of patients achieving ASAS20 o Proportion of patients achieving ASDAS inactive disease

Summary of Study Design:

Study I1F-MC-RHBY (RHBY) is a Phase 3, multicenter, long-term extension study that provides patients who have completed any of the originating studies (RHBV, RHBW, and RHBX) an opportunity to continue ixekizumab (LY2439821) treatment for up to 2 additional years. Study RHBY includes 4 study periods:

- Lead-In [Period 1]: 24 weeks (Week 0 to Week 24)
- Extension Period including Double-Blind, Placebo-Controlled, Randomized Withdrawal–Retreatment [Period 2]: 40 weeks (Week 24 to Week 64)
- Long-Term Extension Period [Period 3]: 40 weeks (Week 64 to Week 104)
- Post-Treatment Follow-Up [Period 4]: at least 12 weeks and up to 24 weeks after the date of the patient's early termination visit (ETV) or last regularly scheduled visit

Treatment Arms and Duration:

The study duration will be up to 2 years for ixekizumab administration (80 mg Q2W or 80 mg Q4W), and up to 2 years and 6 months for study participation over 4 periods:

- During the Lead-In Period (Period 1; 24 weeks), patients will receive active treatment in the form of ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W (open label or blinded depending on the previous originating study).
- During the Extension Period, including blinded, randomized withdrawal–retreatment (Period 2; 40 weeks):
  (Group A): Patients who do **not** meet entry criteria for participation in the randomized withdrawal–retreatment period will continue to receive uninterrupted ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W.
  (Group B): For patients having achieved a state of sustained remission who do meet the criteria for participation in the 40-week double-blind placebo-controlled randomized withdrawal–retreatment period
    - Patients in the ixekizumab 80 mg Q2W treatment group will be re-randomized to either ixekizumab 80 mg Q2W or placebo. Patients who experience a flare will receive ixekizumab 80 mg Q2W.
    - Patients in the ixekizumab 80 mg Q4W treatment group will be re-randomized to either ixekizumab 80 mg Q4W or placebo. Patients who experience a flare will receive ixekizumab 80 mg Q4W.
- During the Long-Term Extension Period (Period 3; 40 weeks),
    - (Group A): Patients in Group A will continue their assigned treatment regimen uninterrupted. 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 and meets criteria for retreatment, 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 the Long-Term Extension Period, 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.
- 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).

Number of Patients:

It is estimated that approximately 750 patients will enter the long-term extension study (RHBY) after completion of studies RHBV, RHBW, or RHBX and that 30% of these patients (i.e., approximately 200 patients) will meet the criteria to enter the double-blind randomized withdrawal–retreatment period. Approximately 100 patients who achieved a state of sustained remission on ixekizumab Q2W will be randomized to ixekizumab 80 mg Q2W or

placebo, and approximately 100 patients who achieved a state of sustained remission on ixekizumab Q4W will be randomized to ixekizumab 80 mg Q4W or placebo. Study RHBY will include patients who have completed one of the originating studies (RHBV, RHBW, and RHBX), and will include rad-axSpA and nonrad-axSpA patients, as well as bDMARD-naive and TNF-experienced patients.

Statistical Analysis:

Approximately 100 patients who achieved a state of sustained remission on ixekizumab 80 mg Q4W will be randomized in a 2:1 ratio to ixekizumab 80 mg Q4W or placebo, and approximately 100 patients who achieved a state of sustained remission on ixekizumab 80 mg Q2W will be randomized in a 2:1 ratio to ixekizumab 80 mg Q2W or placebo in the double-blind randomized withdrawal–retreatment period. This total sample size of 200 will provide over 99% power to detect a difference in the proportion of patients who do not experience a flare between the combined ixekizumab treatment group (including Q2W and Q4W) and placebo using a 2-sided Fisher's exact test at the 0.05 level, assuming the flare rates are 10% for ixekizumab and 70% for placebo.

During Period 2, the primary analysis (the proportion of patients in the combined ixekizumab treatment group who do not experience a flare during Period 2 compared with placebo) will be based on the Randomized Withdrawal ITT Population. 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 regions, and originating study in the model. The odds ratio and 95% confidence intervals (CIs) will be reported; treatment difference and 95% CIs will also be reported. Secondary analysis will be conducted using a Fisher's exact test.

For the primary analysis, missing data will be imputed using the nonresponder imputation (NRI) method. Patients will be considered a nonresponder (having a flare) 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.

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 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.

The Kaplan-Meier product limit method will be used to estimate the survival curves for time-to-flare for the patients who are randomized to the randomized withdrawal–retreatment period. Treatment comparisons will be performed using the stratified log-rank test with treatment, geographic region, and originating study in the model.

The analysis for all continuous efficacy and health outcome variables will be made using analysis of covariance (ANCOVA) with treatment, baseline value, geographic region, and originating study in the model. Missing data will be imputed using modified baseline observation carried forward (mBOCF). Type III sums of squares for the least-squares (LS) means will be used for the statistical comparison; the 95% CI will also be reported.

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

For patients who are randomized and subsequently experience a flare in Period 2, efficacy, health outcomes, and safety data collected between time of flare and the end of Period 2 will be summarized for ixekizumab 80 mg Q2W or ixekizumab Q4W without inferential statistics.

2. Schedule of Activities

Schedule of Activities, Protocol I1F-MC-RHBY

	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	
Informed consent	X																			
Physical examination[d]	X												X						X	
Vital signs (BP and pulse)[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight[f]	X	X	X		X		X		X		X		X		X	X	X	X	X	X
Habits[g]	X												X						X	
Inclusion/ exclusion criteria[h]	X																			
Randomization[i]					X[i]															
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NSAID use	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pre-existing conditions and medical history[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Eye symptom assessment[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Enter ASDAS[l]			X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]		
Dispense IP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
IP compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense SDAL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

	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

	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

	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	
Urinalysis	X				X						X					X			X	X
[redacted] CCI																				
Immunogenicity testing[v,w]	X				X						X				X		X		X	X
PK sampling[v,x]	X				X						X				X		X		X	X

	Post-Treatment Follow-Up for Patients Discontinuing Treatment (Period 4)[y]		
	Required Follow-Up Visits		As-Needed Follow-Up Visits
Visit No	V801	V802	V803 and Onwards
Study Week	LV + 4W	LV + 12W	LV + 24 W
Study Day	±14d	±14d	±14d
Concomitant medications	X	X	X
Vital signs (BP and pulse)[e]	X	X	X
Weight[f]	X	X	X
Preexisting conditions and medical history[j]	X	X	X
Adverse events	X	X	X
C-SSRS	X	X	X
Self-Harm Supplement Form[o]	X	X	X
QIDS-SR16	X	X	X
HBV DNA[q]	X	X	
Serum chemistry	X	X	X
Hematology	X	X	X
CCI			
Immunogenicity testing[v,w]		X	
PK sampling[v,x]		X	

Abbreviations: ASAS-HI = Assessment of Spondyloarthritis International Society–Health Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index ; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; BP = blood pressure; CRP = high sensitivity C-reactive protein; C-SSRS = Columbia-Suicide Severity Rating Scale; d = days; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eCRF = electronic case report form; ePRO = electronic patient-reported outcome; EQ-5D-5L = European Quality of Life-5 Dimensions 5-Level; ETV = early termination visit; HBV = hepatitis B virus; INR = international normalized ratio; IP = investigational product; IWRS = interactive web-response system; JSEQ = Jenkins Sleep Evaluation Questionnaire; LV= last visit; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drug; 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; SIJ = sacroiliac joints; SJC = swollen joint count; SPARCC = Spondyloarthritis Research Consortium of Canada; TB = tuberculosis; TJC = tender joint count; V = study visit; W = study week; WPAI-SpA = Work Productivity Activity Impairment Questionnaire-Spondyloarthritis.

[a] For most patients, the final visit of the originating study (RHBV, RHBW, or RHBX) will coincide with Visit 1 (Week 0) of Study RHBY. In these cases, any assessments/procedures (including laboratory tests) conducted during the patient's final visit in the originating study should not be repeated for Visit 1 (Week 0) of Study RHBY. In cases where entry into Study RHBY is delayed beyond Week 52 of the originating study, assessments/procedures (including laboratory tests) indicated for Visit 1 (Week 0) of Study RHBY that are not conducted during the last visit (Visit 801 or Visit 802) of the originating study will be performed as indicated in the Schedule of Activities.

[b] For most patients, the final visit of the originating study (RHBV, RHBW, or RHBX) will coincide with Visit 1 (Week 0) of Study RHBY. However, in particular circumstances, the duration between the final visit of the originating study and Visit 1 (Week 0) of Study RHBY may be extended after consultation with the sponsor. Therefore, there is no specified visit window for Visit 1 (Week 0) of Study RHBY.

[c] Patients will be assigned to Group A or Group B at Visit 5/Visit 505 (Week 24).

[d] A complete physical examination (excluding pelvic, rectal examination) will be performed at baseline. 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.

[e] 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.

[f] Weight is only captured on eCRF at Visit 1 (Week 0), Visit 10/Visit 515 (Week 64), Visit 14/Visit 519 (Week 104), or ETV. Body weight collected at other visits is used only for calculation of creatinine clearance.

[g] Habits include recording of caffeine, alcohol, and tobacco consumption.

[h] If patients are not eligible to enter Study RHBY at Week 52 in the originating study (e.g., due to unresolved safety concerns), then entry into Study RHBY may be delayed beyond Week 52 of the originating study. See Section 6.1.

[i] Patients who have achieved a state of sustained remission (Group B) will participate in randomized withdrawal–retreatment and will be randomized to their treatment assignment at Week 24. See Section 5.1.

[j] Evaluation includes both historical events as well as preexisting conditions which are assessed after baseline to determine any treatment-emergent worsening of preexisting conditions. Adverse events that initiated in the originating study (RHBV, RHBW, or RHBX) and are ongoing by the time the patient completes participation in the originating study will be considered as preexisting conditions in Study RHBY.

[k] Patients need to be asked about presence of eye symptoms; if eye symptoms are present then an eye examination is required. See Section 9.4.5.

[l] Sites will enter into IWRS the partial ASDAS score provided by the EPX™ website and the central laboratory CRP value from this visit, as soon as available. **After Visit 5/Visit 505**, the partial ASDAS score and CRP value will be entered into IWRS only for patients participating in the randomized withdrawal–retreatment (Group B). Once a patient experiences a flare (see Section 5.1), the partial ASDAS score and CRP value are no longer entered into IWRS.

[m] An MRI of the spine plus SIJ will be performed at Week 24 (±10 days) for patients participating in randomized withdrawal–retreatment (Group B). If the MRI was not completed within the protocol-defined window, please contact Lilly medical for additional guidance. See Section 7.7 for additional guidance regarding concomitant therapy for patients undergoing an MRI.

[n] Cervical and lumbar spine only. An x-ray is only needed for patients initially enrolled in Studies RHBV or RHBW. If the patient's ETV occurs prior to Visit 9/Visit 513 (Week 56), then an x-ray will need to be performed at the ETV. If the patient's ETV occurs after Visit 9/Visit 513 (Week 56), an x-ray will only be required at ETV if an x-ray was not collected at Week 56.

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

[p] TB testing required only based on clinical assessment of TB risk (symptoms/signs/known or suspected TB exposure), as determined by the principal investigator, and according to local regulations and/or local standard of care (Section 9.4.6).

[q] HBV DNA monitoring will be performed as indicated in the Schedule of Activities for patients positive for hepatitis B core antibody at the screening visit of the originating study (RHBV, RHBW, or RHBX) and who required HBV DNA monitoring during the originating study (RHBV, RHBW, or RHBX). If the result of the HBV DNA testing is positive, the patient is to be discontinued from the study and is to receive appropriate follow-up medical care (refer to Section 9.4.10.2 for further information regarding the timing of discontinuation).

[r] Only for females of childbearing potential. Urine pregnancy test will be collected and read/analyzed locally. Patients will undergo urine pregnancy testing during designated scheduled visits. Additional urine pregnancy testing can be performed at the investigator's discretion. 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. Patients determined to be pregnant will be discontinued from treatment and will no longer be administered investigational product.

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

[t] Where collection is allowed by local regulations. All samples (urine, serum, plasma, RNA, and whole blood) will be collected at the designated scheduled visits.

CCI

[v] 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.

[w] Immunogenicity samples are to be collected before investigational product injection.

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

[y] 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). 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-Treatment Follow-Up (Period 4). 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 9.4.10.1.

3. Introduction

3.1. Study Rationale

The clinical development plan to evaluate the efficacy and safety of ixekizumab in patients with axial spondyloarthritis (axSpA) includes three Phase 3 studies (I1F-MC-RHBV [RHBV], I1F-MC-RHBW [RHBW], and I1F-MC-RHBX [RHBX]; hereafter referred to as the originating studies). The current study (I1F-MC-RHBY [RHBY]) is an extension study and offers patients who have completed any of these originating studies an opportunity to continue ixekizumab (LY2439821) treatment for up to 2 additional years.

Ixekizumab is a humanized immunoglobulin G subclass 4 (IgG4) high-affinity monoclonal antibody (MAb) that selectively targets the cytokine interleukin-17A (IL-17A, also known as IL-17). Ixekizumab treatment is administered by subcutaneous (SC) injections. The demonstration of increased IL-17 producing Th17 lymphocyte numbers and serum IL-17 levels in radiographic axSpA (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). Compelling scientific information exists to date suggesting an important role of the IL-23/IL-17 pathway in the pathogenesis of axSpA (Baeten et al. 2010; Maksymowych 2010; Baraliakos et al. 2011; Reveille 2011; Baeten et al. 2013, 2014; Yeremenko et al. 2014).

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 with axSpA who have failed nonsteroidal anti-inflammatory drugs (NSAIDs), and for patients with axSpA 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.

Axial spondyloarthritis requires long-term and often life-long treatment and data from withdrawal studies with tumor necrosis factor alpha inhibitors (TNF inhibitors) have shown that in most patients with axSpA, treatment needs to be maintained long-term in order to maintain response (Baraliakos et al. 2005, 2007; Brandt et al. 2003, 2005). In patients with early disease, the likelihood of maintaining response after treatment withdrawal may be somewhat higher (Haibel et al. 2008; Barkham et al. 2009; Haibel et al. 2010; and Sieper et al. 2014).

Inhibition of IL-17A represents a newer therapeutic class for the treatment of axSpA. Accordingly, there is clinical utility in understanding whether an alternative mechanism-of-action other than inhibition of TNF may offer durability in maintaining an achieved response following the withdrawal of treatment. During the double-blind, placebo-controlled, randomized withdrawal–retreatment period, the current study (RHBY) will evaluate what happens with patients who achieved sustained remission on ixekizumab treatment when they are discontinued from treatment, as well as how long it takes for these patients to relapse. In addition, the study will evaluate the effect of ixekizumab on structure progression in the spine approximately 2 years post-baseline of the originating Phase 3 study.

3.2. Background

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

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

According to several national and international referral programs (Rudwaleit and Sieper 2012; Poddubnyy et al. 2012), the proportion of nonrad-axSpA patients among all axSpA patients ranges from 40% to 60%.

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 -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.

Axial spondyloarthritis affects up to 1.4% of the adult population worldwide (Braun and Sieper 2007; Reveille et al. 2012; Strand et al. 2013). Current standard of care for rad-axSpA includes regular exercise, physical therapy, NSAIDs, and TNF inhibitors (Braun et al. 2011; Ward et al. 2015). In addition, recently completed registration studies of secukinumab (an IL-17A

antagonist like ixekizumab) have also demonstrated efficacy in patients with rad-axSpA (Baeten et al. 2015; Braun et al. 2015). For patients with nonrad-axSpA, the current standard of care includes regular exercise, physical therapy, and NSAIDs. TNF inhibitors have also demonstrated efficacy in nonrad-axSpA; however, although they are approved in some geographies, 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) including methotrexate (MTX) or systemic corticosteroids (Braun and Sieper 2009; Haibel and Specker 2009).

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

3.3. Benefit/Risk Assessment

The 2 ixekizumab treatment regimens in Study RHBY (ixekizumab 80 mg every 2 weeks [Q2W] and ixekizumab 80 mg every 4 weeks [Q4W]) have also been tested in pivotal Phase 3 studies in patients with psoriasis (Ps) and psoriatic arthritis (PsA), and demonstrated efficacy with favorable benefit-risk profile in patients with Ps (Griffiths et al. 2015) and in patients with PsA (Gottlieb et al. 2015; Mease et al. 2015). Other therapies (most TNF inhibitors and secukinumab) have demonstrated efficacy with common dose regimens across various rheumatological conditions (RA, PsA, axSpA) (Humira® package insert, 2016 [WWW]; Enbrel® package insert, 2015 [WWW]; Simponi® package insert, 2016 [WWW]; Cimzia® package insert 2016, [WWW]; Cosentyx® package insert 2016, [WWW]; Sanford and McKeage 2015). The collective data from ixekizumab and secukinumab on efficacy of IL-17A inhibition across various indications support a reasonable expectation of efficacy for ixekizumab in patients with rad-axSpA, both short and long-term. As up to 40% of the patients do not get appropriate benefit

from TNF inhibitors and TNF inhibitors have failed to demonstrate significant effect on structural progression, there is a need for additional alternative therapies.

Eli Lilly and company (Lilly) has considerable experience with ixekizumab across indications, and more than 4950 patients (4209 Ps patients, 532 RA patients, and 209 PsA patients) have been treated with at least 1 dose of ixekizumab. Across 3 disease states (RA, PsA, and Ps), no notable safety concerns have been observed with the currently proposed dose regimens that would preclude the study of ixekizumab for the treatment of patients with axSpA. Events identified as important potential risks for ixekizumab include serious infections, serious hypersensitivity, and IBD. 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 Investigator's Brochure (IB). The protocol for Study RHBY includes appropriate inclusion/exclusion criteria to minimize enrolling patients with greater safety risks, as well as criteria to discontinue those patients who develop potentially increased safety risks during the study. Regular review of blinded safety data and risk mitigation actions by Lilly or its designee are intended to assist in identification and reduction of potential risks associated with ixekizumab administration. In addition, patients participating in Study RHBY will already have successfully completed one of the originating 1-year axSpA studies.

The current benefit/risk profile of ixekizumab therefore supports further research of ixekizumab in axSpA.

4. Objectives and Endpoints

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

Table RHBY.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• 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 who do not experience a flare during Period 2

Objectives and Endpoints

Objectives	Endpoints
Major Secondary	
• To compare the combined ixekizumab treatment group to historical control for 2-year radiographic progression in spine in patients with active radiographic axSpA (rad-axSpA)	• Change in modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS score)
• To evaluate in patients having achieved a state of sustained remission whether the ixekizumab 80 mg every 2 weeks (Q2W) treatment group or ixekizumab 80 mg every 4 weeks (Q4W) treatment group is superior to placebo in maintaining response after randomized withdrawal	• The proportion of patients in the randomized withdrawal population who do not experience a flare during Period 2
• 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 after randomized withdrawal	• Time to flare for patients in the randomized withdrawal population during Period 2
• 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 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

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

Objectives	Endpoints
	• Proportion of patients with change in mSASSS score <2 from baseline of originating study to Week 56 in RHBY • Proportion of patients with no new syndesmophyte formation from baseline of originating study to Week 56 in RHBY • Change from baseline in the following health outcomes measures: o Fatigue NRS score o QIDS SR16 o SF-36 (both physical and mental component scores) o ASAS-HI o EQ-5D-5L o WPAI-SpA o JSEQ
• To evaluate the development of anti-ixekizumab antibodies and its impact on the efficacy of ixekizumab	• Efficacy response rates listed below at Weeks 64 and 104 by treatment-emergent anti-drug antibody (TE-ADA) status and by neutralizing anti-drug antibody (NAb) status: o Proportion of patients achieving ASAS40 o Proportion of patients achieving ASAS20 o Proportion of patients achieving ASDAS inactive disease
[redacted]	

5. Study Design

5.1. Overall Design

Study I1F-MC-RHBY (RHBY) is a Phase 3, multicenter, long-term extension study that includes a double-blind, placebo-controlled, randomized withdrawal–retreatment period. The study duration will be up to 2 years for ixekizumab administration, and up to 2 years and 6 months for study participation over 4 study periods:

- Lead-In [**Period 1**]: 24 weeks (Week 0 to Week 24)
- Extension Period including Double-Blind, Placebo-Controlled, Randomized Withdrawal–Retreatment [**Period 2**]: 40 weeks (Week 24 to Week 64)
- Long-Term Extension Period [**Period 3**]: 40 weeks (Week 64 to Week 104)
- Post-Treatment Follow-Up [**Period 4**]: at least 12 weeks and up to 24 weeks after the date of the patient's early termination visit [ETV] or last regularly scheduled visit).

Patients who completed an originating study (RHBV, RHBW, or RHBX) through Week 52 may be eligible for enrollment into Study RHBY provided they fulfill study entry criteria for Study RHBY (see Section 6).

Study RHBY will evaluate the sustainability of clinical benefits, safety, and tolerability of ixekizumab treatment as well as the impact of ixekizumab on structural progression in patients with axSpA. In addition, maintenance of response after treatment withdrawal will be evaluated in those patients having achieved a state of sustained remission, defined as one of the following:

- Ankylosing Spondylitis Disease Activity Score (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.

Figure RHBY.1 illustrates the study design. During the 24-Week Lead-In Period [Period 1]), all patients will receive active treatment in the form of ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W.

[Group A]: Patients who DO NOT meet entry criteria for participation in the 40-week double-blind, placebo-controlled, randomized withdrawal–retreatment period will continue to receive the ixekizumab dose regimen that they were receiving at Week 24 during Periods 2 and 3.

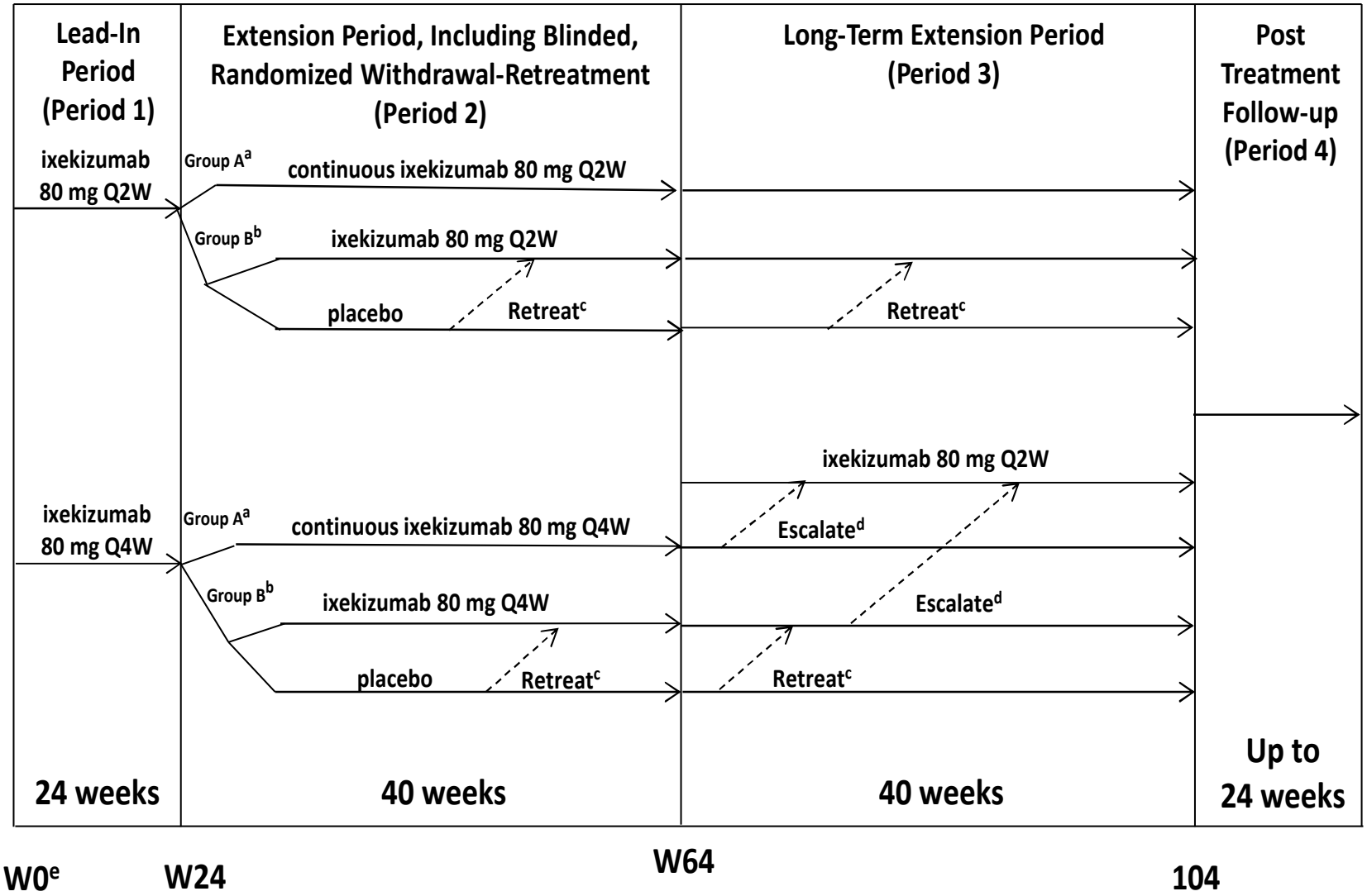
[Group B]: For patients who DO meet entry criteria for participation in the 40-week double-blind, placebo-controlled, randomized withdrawal–retreatment period (i.e., patients having achieved a state of sustained remission),

- 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.


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

Abbreviations: Q2W = once every 2 weeks; Q4W = once every 4 weeks; W = week.

[a] Patients in Group A will continue to receive the same ixekizumab dose regimen that they were receiving during Period 1.

[b] Only patients having achieved a state of sustained remission (Group B) are eligible for participation in the randomized withdrawal–retreatment period.

[c] Patients who experience a flare will be retreated with the ixekizumab treatment regimen that they were receiving prior to withdrawal.

[d] As of Week 64, patients receiving ixekizumab 80 mg Q4W during Period 3 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. However, for patients in Group B, 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.

[e] For patients who were receiving ixekizumab in the originating study, the dose in the 24-week Lead-In Period (Period 1) will be based on the current dosing in the originating study. For patients in Study RHBX who were on placebo, patients will receive ixekizumab 80 mg Q4W.

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

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.

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%.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

In the context of long-term treatment, it is important to understand the long-term efficacy and safety of ixekizumab treatment in patients with axSpA. The current 2-year study will, together with the preceding 1-year studies RHBV, RHBW, and RHBX, provide descriptive data about efficacy and safety of ixekizumab after long-term treatment, up to 3 years (including the 1-year duration of the originating study), for patients with axSpA, including both rad-axSpA and nonrad-axSpA patients, and biological disease modifying antirheumatic drug (bDMARD)-naive as well as TNF inhibitor-experienced patients. Therefore, data generated from the current study will help to provide further information on the long-term efficacy and safety profile of ixekizumab.

As axSpA is a chronic condition that may require long-term treatment, there is increasing interest in evaluating the need for long-term uninterrupted treatment compared to temporary treatment withdrawal after achieving clinical response, followed by retreatment if there is loss of clinical response (i.e., flare). Data from withdrawal studies with TNF inhibitors have shown that in most patients with axSpA, treatment needs to be maintained long-term in order to maintain response (Baraliakos et al. 2005, 2007; Brandt et al. 2003, 2005). In patients with early axSpA, the likelihood of success of this approach may be somewhat higher (Haibel et al. 2008; Barkham et al. 2009; Haibel et al. 2010; Sieper et al. 2014). The potential of ixekizumab (with a mechanism of action [MOA] different from TNF inhibitors) to maintain response after treatment withdrawal will be evaluated in the current study during a double blind placebo-controlled randomized withdrawal period (Period 2).

To increase the likelihood of successful withdrawal without immediate relapse, only patients having achieved a state of sustained remission will participate in the randomized withdrawal–retreatment period. It is anticipated that approximately 30% of the 750 patients will meet the entry criteria for randomized withdrawal (Sieper et al. 2015). These patients will be re-randomized in blinded fashion to either continue their current regimen or receive placebo. Patients randomized to placebo may still receive treatment in the form of the allowed concomitant medications as described in the concomitant therapy section (Section 7.7).

The monthly visit schedule for patients participating in the randomized withdrawal–retreatment period (Group B) allows these patients to be followed closely and ixekizumab treatment to be resumed upon signs of relapse.

The length of the randomized withdrawal period is 40 weeks and considered sufficiently long based on previous randomized withdrawal studies of TNF inhibitors in RA and axSpA (Haibel et al. 2008; Barkham et al. 2009; Haibel et al. 2010; Sieper et al. 2014; Smolen et al. 2014). It is anticipated that the majority of patients who no longer receive active treatment will relapse within that time frame.

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.

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.

(Note: Where required by regulation, a highly effective method of birth control is required. A highly effective method of birth control is defined as one that results in a low failure rate [that is, <1% per year] when used consistently and correctly, such as male sterilization, oral contraceptives, contraceptive patch, injectable or implantable contraceptives, intrauterine device, or vaginal ring).

OR

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

  Women who have had surgical sterilization (hysterectomy, 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).

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

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria:

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

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

[6.] Had investigational product permanently discontinued during a previous ixekizumab study.

[7.] Had temporary investigational product interruption at any time during or at the final study visit of the originating ixekizumab study (RHBV, RHBW, or RHBX) **and**, in the opinion of the investigator, restarting ixekizumab poses an unacceptable risk for the patient's participation in the study.

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

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

6.3. Lifestyle Restrictions

Study participants should be instructed not to donate blood or blood products during the study.

6.4. Screen Failures

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

7. Treatments

7.1. Treatments Administered

During the Lead-In Period (Period 1; Week 0 to Week 24), patients will receive active treatment in the form of ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W (open-label or blinded depending on the previous originating study; Table RHBY.2).

During the Extension Period, including blinded, randomized withdrawal–retreatment (Period 2; Week 24 to Week 64), patients who do not meet entry criteria for participation in the randomized withdrawal–retreatment period (Group A) will continue to receive uninterrupted ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W (Table RHBY.2).

For patients having achieved a state of sustained remission who do meet the criteria for participation in the 40-week double-blind, placebo-controlled, randomized withdrawal–retreatment period (Group B)

- Patients in the ixekizumab 80 mg Q2W treatment group will be re-randomized to either ixekizumab 80 mg Q2W or placebo. Patients who experience a flare (see Section 5.1) will receive ixekizumab 80 mg Q2W.
- Patients in the ixekizumab 80 mg Q4W treatment group will be re-randomized to either ixekizumab 80 mg Q4W or placebo. Patients who experience a flare (see Section 5.1) will receive ixekizumab 80 mg Q4W.

During the Long-Term Extension Period (Period 3; Week 64 to Week 104), patients in Group A will continue their assigned treatment regimen. 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 (see Section 7.4).

During the Long-Term Extension Period, 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 and meets criteria for retreatment (see Section 5.1), 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. As of Week 64 and during the Long-Term Extension Period, 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 with the ixekizumab treatment regimen received during Period 1 (ixekizumab 80 mg Q4W) for at least 12 weeks (see Section 7.4).

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 they have 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 7.1.1 and 7.1.2.

Table RHBY.2. Summary of Treatment Regimens Study RHBY

Originating Study	Treatment at End of Originating Study	Treatment During RHBY Period 1	Treatment During RHBY Period 2 and Period 3
RHBV or RHBW	ixekizumab 80 mg Q2W	ixekizumab 80 mg Q2W (*open-label*) [Dose: 1 ixekizumab 80-mg Q2W injection (beginning at Week 0)]	**Group A:** *open-label* ixekizumab 80 mg Q2W [Dose: 1 ixekizumab 80-mg Q2W injection (beginning at Week 24)]
			Group B: *blinded*[a,d] ixekizumab 80 mg Q2W (*blinded)* [Dose: 1 ixekizumab 80-mg Q2W injection (beginning at Week 24)] or placebo (*blinded*) [Dose: 1 placebo for ixekizumab injection Q2W (beginning at Week 24)]
	ixekizumab 80 mg Q4W	ixekizumab 80 mg Q4W (*open-label*) [Dose: 1 ixekizumab 80-mg Q4W injection (beginning at Week 0)]	**Group A:** *open-label*[c] ixekizumab 80 mg Q4W [Dose: 1 ixekizumab 80-mg Q4W injection (beginning at Week 24)]
			Group B: *blinded*[b,d] ixekizumab 80 mg Q4W (*blinded)* [Dose: 1 ixekizumab 80-mg Q4W injection (beginning at Week 24)] or placebo (*blinded*) [Dose: 1 placebo for ixekizumab injection Q4W (beginning at Week 24)]

Originating Study	Treatment at End of Originating Study	Treatment During RHBY Period 1	Treatment During RHBY Period 2 and Period 3
RHBX	rescued to ixekizumab 80 mg Q2W	ixekizumab 80 mg Q2W (*open-label*) [Dose: 1 ixekizumab 80-mg Q2W injection (beginning at Week 0)]	**Group A:** *open-label* ixekizumab 80 mg Q2W [Dose: 1 ixekizumab 80-mg Q2W injection (beginning at Week 24)]
			Group B: *blinded*[a,d] ixekizumab 80 mg Q2W (*blinded)* [Dose: 1 ixekizumab 80-mg Q2W injection (beginning at Week 24)] or placebo (*blinded*) [Dose: 1 placebo for ixekizumab injection Q2W (beginning at Week 24)]
	ixekizumab 80 mg Q2W (*blinded*)	ixekizumab 80 mg Q2W (*blinded*)[e] [Dose: 1 ixekizumab 80-mg Q2W injection (beginning at Week 0)]	**Group A:** *blinded*[e] ixekizumab 80 mg Q2W [Dose: 1 ixekizumab 80-mg Q2W injection (beginning at Week 24)]
			Group B: *blinded*[a,d,e] ixekizumab 80 mg Q2W (*blinded)* [Dose: 1 ixekizumab 80-mg Q2W injection (beginning at Week 24)] or placebo (*blinded*) [Dose: 1 placebo for ixekizumab injection Q2W (beginning at Week 24)]

Originating Study	Treatment at End of Originating Study	Treatment During RHBY Period 1	Treatment During RHBY Period 2 and Period 3
	ixekizumab 80 mg Q4W (*blinded*)	ixekizumab 80 mg Q4W (*blinded*)[e] [Dose: 1 ixekizumab 80-mg Q4W injection (beginning at Week 0); and 1 placebo for ixekizumab injection Q4W (beginning at Week 2)]	**Group A:** *blinded*[c,e] ixekizumab 80 mg Q4W [Dose: 1 ixekizumab 80-mg Q4W injection (beginning at Week 24); and 1 placebo for ixekizumab injection Q4W (beginning at Week 26)]
			Group B: *blinded*[b,d,e] ixekizumab 80 mg Q4W (*blinded)* [Dose: 1 ixekizumab 80-mg Q4W injection (beginning at Week 24); and 1 placebo for ixekizumab injection Q4W (beginning at Week 26)] or placebo (*blinded*) [Dose: 1 placebo for ixekizumab injection Q2W (beginning at Week 24)]
	placebo (*blinded*)	ixekizumab 80 mg Q4W (*blinded*)[e] [Dose: 1 ixekizumab 80-mg Q4W injection (beginning at Week 0); and 1 placebo for ixekizumab injection Q4W (beginning at Week 2)]	**Group A:** *blinded*[c,e] ixekizumab 80 mg Q4W [Dose: 1 ixekizumab 80-mg Q4W injection (beginning at Week 24); and 1 placebo for ixekizumab injection Q4W (beginning at Week 26)]
			Group B: *blinded*[b,d,e] ixekizumab 80 mg Q4W (*blinded)* [Dose: 1 ixekizumab 80-mg Q4W injection (beginning at Week 24); and 1 placebo for ixekizumab injection Q4W (beginning at Week 26)] or placebo (*blinded*) [Dose: 1 placebo for ixekizumab injection Q2W (beginning at Week 24)]

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

[a] Patients who experience a flare and meet the criteria for retreatment during Period 2 or Period 3 will receive ixekizumab 80 mg Q2W.

[b] Patients who experience a flare and meet the criteria for retreatment during Period 2 or Period 3 will receive ixekizumab 80 mg Q4W. As of Week 64, patients in Group B may have their dose escalated to ixekizumab 80 mg Q2W only after the patient was retreated upon flare with ixekizumab 80 mg Q4W for at least 12 weeks (Section 7.4).

[c] As of Week 64, patients in Group A receiving ixekizumab 80 mg Q4W may have their dose escalated to ixekizumab 80 mg Q2W (Section 7.4). Dose escalation may begin at the next scheduled visit or at an unscheduled visit prior to the next scheduled visit.

[d] All patients in Group B will remain on blinded study drug from Week 24 until the completion of the study or time of flare (Section 7.3).

[e] For patients entering Study RHBY from Study RHBX who were receiving blinded treatment at the end of the originating study, patients will continue to receive blinded treatment in Study RHBY until the 52-week datalock for Study RHBX is achieved.

7.1.1. Administration of Investigational Product

Administration: Injections will be self-administered SC by the patient or caregiver. It is recommended that these injections be administered away from the investigational site. If the patient or caregiver is not able to administer 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 the 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 7.2.1.

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

7.1.2. Special Treatment Considerations

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 (e.g., 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 will be drawn as soon as possible for immunogenicity and PK testing (Section 9.4.9).

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 (e.g., 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 8.1.1). Medications considered appropriate for premedication include, but are not restricted to, acetaminophen/paracetamol up to 1000 mg and antihistamines (e.g., oral diphenhydramine 50 mg) given after all efficacy assessments have been completed for a given visit. 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.

7.1.3. 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.

7.2. Method of Treatment Assignment

During the 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 who were previously in Study RHBX, treatment during the Lead-In Period will be assigned as follows:

- Patients who were rescued to open-label 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.

During the Extension Period (Period 2), patients in Group A who do not meet entry criteria for randomized withdrawal–retreatment will continue to receive the same ixekizumab dose regimen

that they were receiving during the Lead-In Period (ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W).

During the Extension Period (Period 2), patients in Group B, who have achieved a state of sustained remission, and meet the criteria for randomized withdrawal–retreatment (see Section 5.1), will be assigned to treatment groups as follows by a computer-generated random sequence using an interactive web-response system (IWRS).

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

During the Extension Period, the IWRS will be used to assign double-blind investigational product to each patient in Group B. 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.

7.2.1. Selection and Timing of Doses

Investigational product is to be administered at approximately the same time each day, as much as possible. For injections not administered on the scheduled day of the week from Week 0 to Week 104, 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 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 9.2.3 for additional instructions regarding complaint handling).

7.3. Blinding

Patients, study site personnel, and study team in Study RHBY will remain blinded to the initial treatment assigned in the originating study (RHBV, RHBW, or RHBX) until the time of datalock for the respective originating study (i.e., Week 16 datalock for Studies RHBV and RHBW, and Week 52 datalock for Study RHBX).

During the Lead-In Period (Period 1), all patients from studies RHBV and RHBW will receive treatment with either ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W in open-label fashion. For patients from Study RHBX, patients who were rescued to open-label treatment with

ixekizumab 80 mg Q2W will continue to receive open-label treatment with ixekizumab 80 mg Q2W during the Lead-In Period. All other patients from Study RHBX will continue on blinded treatment in the extension Study RHBY until Week 52 datalock has occurred for Study RHBX.

During the Extension Period (Period 2), including blinded, randomized withdrawal–retreatment, patients who do not meet entry criteria for participation in the randomized withdrawal–retreatment period (Group A) will continue to receive ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W. Patients having achieved a state of sustained remission and do meet the criteria outlined in Section 5.1 (Group B) will participate in the double-blind, placebo-controlled, randomized withdrawal–retreatment period. During the randomized withdrawal–retreatment period, patients in Group B, study site personnel, and study team will be blinded to study treatment randomization. Patients participating in the randomized withdrawal–retreatment period will continue to receive blinded treatment until the completion of the study or time of flare. Upon flare, patients will be retreated with the ixekizumab treatment regimen assigned in Period 1 in an open-label fashion. Patients who experience a flare and were originally from Study RHBX will not receive open-label treatment until the Week 52 datalock has occurred for Study RHBX.

During the Long-Term Extension Period (Period 3), patients from Group A will continue to receive ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W. Patients from Group B will continue the same treatment they were receiving at the end of Period 2 (ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, or placebo) in blinded fashion until the completion of the study or time of flare. Upon flare, patients will be retreated with the ixekizumab treatment regimen assigned in Period 1 in an open-label fashion. As of Week 64, patients initially treated with ixekizumab 80 mg Q4W during Period 1 may have their dose escalated to ixekizumab 80 mg Q2W, in an open-label fashion, only after the patient has experienced a flare and been subsequently retreated with ixekizumab 80 mg Q4W for at least 12 weeks.

Patients who experience a flare and were originally from Study RHBX will not receive open-label treatment until the Week 52 datalock has occurred for Study RHBX.

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 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 unless this could delay emergency treatment of the patient. If the patient's treatment assignment is unblinded, Lilly must be notified immediately.

7.4. Dosage Modification

As described in Section 5.1, if a patient who has achieved a state of sustained remission (Group B) during the randomized withdrawal–retreatment period experiences a flare and meets the criteria for retreatment, the patient will be retreated with the ixekizumab treatment regimen that he or she was receiving prior to withdrawal (ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W). During Period 2, retreatment will begin at the next scheduled visit. During Period 3, given the longer interval between visits, retreatment may begin at the next scheduled visit or at an unscheduled visit prior to the next scheduled visit.

As of Week 64, patients in Group A receiving ixekizumab 80 mg Q4W may have their dose escalated to ixekizumab 80 mg Q2W in Period 3 if the investigator determines that the patient may benefit from an increase in frequency of dosing to achieve adequate disease control. Dose escalation may begin at the next scheduled visit or at an unscheduled visit prior to the next scheduled visit.

As of Week 64, patients in Group B (Table RHBY.3):

- who are receiving placebo will remain on placebo, and will be monitored per the Schedule of Activities (Section 2) for eligibility (i.e., flare) to be retreated with the ixekizumab treatment regimen they were receiving prior to withdrawal (ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W).
- who are receiving ixekizumab 80 mg Q4W may have their dose escalated to ixekizumab 80 mg Q2W in Period 3 if the investigator determines that the patient may benefit from an increase in 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.
- who are receiving ixekizumab 80 mg Q2W will remain on this dose until completion of the study or early discontinuation.

Table RHBY.3. Dosage Modification for Group B during Period 2 and Period 3

Period 1 (Open-Label)	Period 2 (Blinded)	Period 3 (Blinded)	If Flare during Period 2 or 3, Retreat (Open-Label)	12 Weeks after Retreat, Escalate (Period 3) (Open-Label)
ixekizumab 80 mg Q2W	ixekizumab 80 mg Q2W	ixekizumab 80 mg Q2W	ixekizumab 80 mg Q2W	N/A
	placebo	placebo	ixekizumab 80 mg Q2W	N/A
ixekizumab 80 mg Q4W	ixekizumab 80 mg Q4W	ixekizumab 80 mg Q4W	ixekizumab 80 mg Q4W	ixekizumab 80 mg Q2W
	placebo	placebo	ixekizumab 80 mg Q4W	ixekizumab 80 mg Q2W

Abbreviations: N/A = not applicable; Q2W = every 2 weeks; Q4W = every 4 weeks.

Note: Patients from Group B who experience a flare and meet criteria for retreatment during Period 2 or Period 3 will be retreated with the ixekizumab treatment regimen received during Period 1 in an open-label fashion. As of Week 64, patients initially treated with ixekizumab 80 mg Q4W during Period 1 may have their dose escalated to ixekizumab 80 mg Q2W, in an open-label fashion, only after the patient has experienced a flare and been subsequently retreated with ixekizumab 80 mg Q4W for at least 12 weeks. Patients who experience a flare and were originally from Study RHBX will not receive open-label treatment until the Week 52 datalock has occurred for Study RHBX.

In addition, Section 9.4.10.1 describes instances where drug may be withheld.

Other than these exceptions, investigational product dose modifications are not permitted.

7.5. Preparation/Handling/Storage/Accountability

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.

7.6. 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 10.3.2.4.

7.7. Concomitant Therapy

All concomitant medication taken during the study must be recorded in the eCRF. Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem. Patients will maintain their usual medication regimen for other concomitant diseases throughout the study unless specifically excluded in the protocol.

During the randomized withdrawal–retreatment phase of Period 2, patients in Group B are requested to not have any changes to concomitant medications during the 40-week observation

period except for the defined retreatment medication or changes needing to be made for an AE or for safety reasons.

Patients undergoing an MRI at Week 24 (see Schedule of Activities, Section 2) may receive premedication of ≤30 mg of morphine or equivalent or other NSAIDs/cyclooxygenase-2 inhibitors, on the day of the MRI, for significant pain as judged by the investigator. Patients with claustrophobia may receive premedication with benzodiazepine; the investigator should assess for potential interactions with other concomitant medication(s), such as opiates.

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.

Conventional DMARDs and/or other therapies such as, but not limited to, gold salts, cyclosporine, azathioprine, dapsone, 6 mercaptopurine, mycophenolate mofetil, or any other immunosuppressive agents are prohibited (see Table RHBY.4 for additional information regarding methotrexate). 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) are also prohibited.

Additional information regarding concomitant treatment with NSAIDs and analgesics, conventional DMARDs, and corticosteroids is provided in Table RHBY.4.

Table RHBY.4. Concomitant Treatment with NSAIDs and Analgesics, Conventional DMARDs, and Corticosteroids Study RHBY

	Period 1	Period 2	Period 3
NSAIDs and Analgesics	NSAIDs, including COX-2 inhibitors, will be allowed up to the maximum recommended doses for pain. Patients are to be on stable dose during Period 1. Introduction of a new NSAID or dose adjustment to an existing NSAID is not permitted, unless required for safety reasons. Short-acting analgesics with no anti-inflammatory action (such as paracetamol) are permitted and may be administered ad hoc as needed and are to be withheld within the 24-hour period prior to any assessment. Aspirin (dose not exceeding 350 mg/day) may be taken to manage cardiovascular risk. Opiate analgesic use is allowed but not to exceed >30 mg/day of morphine or its equivalent. Patients are to be on stable dose during Period 1. 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.	**Group A**: Alterations of NSAIDs, including COX-2 inhibitors (dose change, introduction, or withdrawal) are allowed. Doses are recommended to be stable in the 2 weeks prior to an arthritis assessment. Short-acting analgesics with no anti-inflammatory action (such as paracetamol) are permitted and may be administered ad hoc as needed but are to be withheld within the 24-hour period prior to any assessment. Aspirin (dose not exceeding 350 mg/day) may be taken to manage cardiovascular risk. Opiate analgesic use is allowed but not to exceed >30 mg/day of morphine or its equivalent. **Group B** (participating in randomized withdrawal): Same as Period 1 until they flare. Once they flare, same as patients in Group A during Period 2.	**Group A**: Alterations of NSAIDs, including COX-2 inhibitors (dose change, introduction, or withdrawal) are allowed. Doses are recommended to be stable in the 2 weeks prior to an arthritis assessment. Short-acting analgesics with no anti-inflammatory action (such as paracetamol) are permitted and may be administered ad hoc as needed but are to be withheld within the 24-hour period prior to any assessment. Aspirin (dose not exceeding 350 mg/day) may be taken to manage cardiovascular risk. Opiate analgesic use is allowed but not to exceed >30 mg/day of morphine or its equivalent. **Group B** (participating in randomized withdrawal): Same as Period 1 until they flare. Once they flare, same as patients in Group A during Period 3.

	Period 1	Period 2	Period 3
Conventional DMARDs	Methotrexate (oral or parenteral up to 25 mg/week), sulfasalazine (up to 3 g/day), or hydroxychloroquine (up to 400 mg/day) is allowed. During Period 1, alteration of cDMARD dose or route, and/or introduction of a new cDMARD are not permitted, unless required for safety reasons. Conventional DMARDs can only be used as single agents and not in combination with other cDMARDs. Any changes must be recorded in the eCRF. If, at any time, the investigator believes that side effects or laboratory abnormalities may be attributable to the cDMARD, the cDMARD dose is to be lowered or the medication stopped. (Note: For all study periods, the maximum allowed doses are 25 mg/week MTX, 400 mg/day hydroxychloroquine and 3 g/day sulfasalazine. Local standards of care are to be followed for concomitant administration of folic or folinic acid if MTX is taken, and for administration of other cDMARDs.)	**Group A**: Methotrexate (oral or parenteral up to 25 mg/week), sulfasalazine (up to 3 g/day), or hydroxychloroquine (up to 400 mg/day) may be allowed, and adjustment of allowed cDMARDs (e.g., dose change, introduction, withdrawal of cDMARDs or replacement of a current cDMARD with the introduction of a new cDMARD) is permitted. Not more than 1 adjustment of cDMARDs at 1 time within 12 weeks is recommended. Conventional DMARDs can only be used as single agents and not in combination with other cDMARDs. Any changes must be recorded in the eCRF. If, at any time, the investigator believes that side effects or laboratory abnormalities may be attributable to the cDMARD, the cDMARD dose is to be lowered or the medication stopped. (Note: For all study periods, the maximum allowed doses are 25 mg/week MTX, 400 mg/day hydroxychloroquine and 3 g/day sulfasalazine. Local standards of care are to be followed for concomitant administration of folic or folinic acid if MTX is taken, and for administration of other cDMARDs.) **Group B** (participating in randomized withdrawal): Same as Period 1 until they flare. Once they flare, same as patients in Group A during Period 2.	**Group A**: Methotrexate (oral or parenteral up to 25 mg/week), sulfasalazine (up to 3 g/day), or hydroxychloroquine (up to 400 mg/day) may be allowed, and adjustment of allowed cDMARDs (e.g., dose change, introduction, withdrawal of cDMARDs or replacement of a current cDMARD with the introduction of a new cDMARD) is permitted. Not more than 1 adjustment of cDMARDs at 1 time within 12 weeks is recommended. Conventional DMARDs can only be used as single agents and not in combination with other cDMARDs. Any changes must be recorded in the eCRF. If, at any time, the investigator believes that side effects or laboratory abnormalities may be attributable to the cDMARD, the cDMARD dose is to be lowered or the medication stopped. (Note: For all study periods, the maximum allowed doses are 25 mg/week MTX, 400 mg/day hydroxychloroquine and 3 g/day sulfasalazine. Local standards of care are to be followed for concomitant administration of folic or folinic acid if MTX is taken, and for administration of other cDMARDs.) **Group B** (participating in randomized withdrawal): Same as Period 1 until they flare. Once they flare, same as patients in Group A during Period 3.

	Period 1	Period 2	Period 3
Corticosteroids	*Oral corticosteroids:* If on oral corticosteroids, the dose must not exceed 10 mg/day of prednisone or its equivalent at any time during the study. During Period 1, treatment alterations in oral corticosteroid dose are strongly discouraged. *Parenteral corticosteroids (intravenous, intramuscular):* Treatment with intravenous or intramuscular corticosteroids is not permitted. *Parenteral corticosteroids (intra-articular):* Intra-articular injection of corticosteroid may be allowed on a limited basis: It is recommended that there be no more than 1 injection within any 1 year period. 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.	**Group A**: *Oral corticosteroids:* 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 the study. *Parenteral corticosteroids (intravenous, intramuscular, intra-articular):* Treatment with parenteral corticosteroids is not recommended. 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. **Group B** (participating in randomized withdrawal): Same as Period 1 until they flare. Once they flare, same as patients in Group A during Period 2.	**Group A**: *Oral corticosteroids:* 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 the study. *Parenteral corticosteroids (intravenous, intramuscular, intra-articular):* Treatment with parenteral corticosteroids is not recommended. 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. **Group B** (participating in randomized withdrawal): Same as Period 1 until they flare. Once they flare, same as patients in Group A during Period 3.

Abbreviations: cDMARD = conventional disease modifying antirheumatic drug; COX-2 = cyclooxygenase-2; eCRF = electronic case report form; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; SJC = swollen joint count; TJC = tender joint count.

Other Concomitant Medications:

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.

If the need for concomitant medication arises, the investigator is to base decisions on the patient and on clinical factors. Any additional medication, whether prescription or over-the-counter, used at baseline and/or during the course of the study, must be documented with the start and stop dates in the eCRF. Additional systemic drugs are to be avoided during the study, unless required to treat an AE. Other medications may be allowed, if approved by the sponsor or its designee.

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

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

7.8. Treatment after the End of the Study

7.8.1. Continued Access

Investigational product will not be made available to patients after conclusion of this study.

8. Discontinuation Criteria

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

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

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

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

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8x upper limit of normal (ULN)
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3x ULN and total bilirubin level >2xULN or prothrombin time >1.5xULN
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase >2.5xULN and total bilirubin >2xULN
- alkaline phosphatase >2.5xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

[2] Other Laboratory tests:

- neutrophil (segmented) counts (see safety monitoring for neutropenia in Section 9.4.10.1):
  - <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 9.4.10.1)
  - AND - a concurrent infection

- total white blood count (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)

Note: Laboratory test(s) that may result in discontinuation based on a single result may be repeated 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.

[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 AEs, Section 9.2.

[4] Any positive TB test that indicates TB test conversion since prior testing (based on patient medical history), AND the patient does not receive appropriate treatment for latent TB; or there is evidence of active TB infection at any time.

[5] Clinically significant systemic hypersensitivity reaction following SC administration of investigational product that does not respond to symptomatic medication or results in clinical sequelae.

[6] The patient becomes pregnant.

[7] 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.

[8] 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.

[9] It is recommended that the patient is assessed by a psychiatrist or appropriately trained professional to assist in deciding whether the patient 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 Quick Inventory of Depressive Symptomatology-self report (16 items) (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 suicidal behaviors as recorded on the C-SSRS.

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

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

[12] Lilly or its designee stops the patient's participation in the study or Lilly stops the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).

[13] The patient becomes hepatitis B virus (HBV) deoxyribonucleic acid (DNA) positive. The patient is to be referred to a specialist physician. Discussion of the timing of discontinuation from study treatment and from the study is provided in Section 9.4.10.2.

8.1.2. Temporary Discontinuation from Study Treatment

Section 9.4.10.1 describes instances where drug may be withheld.

8.1.3. Discontinuation of Inadvertently Enrolled Patients

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

8.2. 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 (Section 2).

8.3. Lost to Follow-Up

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

9. Study Assessments and Procedures

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

Appendix 2 lists the laboratory tests that will be performed for this study.

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

9.1. Efficacy Assessments

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

9.1.1. Primary Efficacy Assessments

As described in Section 10.3.3.1, the primary efficacy endpoint is the proportion of patients in the randomized withdrawal population who do not experience a flare (a flare is defined as ASDAS ≥2.1 at 2 consecutive visits, or ASDAS >3.5 at any visit during Period 2). The ASDAS is a composite index to assess disease activity in axSpA (Machado et al. 2011a, 2011b; Zochling 2011). The parameters used for the ASDAS (with high sensitivity C-reactive protein [CRP] as acute phase reactant) are the following:

1) Total back pain (BASDAI question 2)
2) Patient global assessment (Section 9.1.2.4)
3) Peripheral pain/swelling (BASDAI question 3)
4) Duration of morning stiffness (BASDAI question 6)
5) CRP in mg/L

The $ASDAS_{crp}$ is calculated with the following equation: 0.121 × 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.)

9.1.2. Secondary Efficacy Assessments

9.1.2.1. Ankylosing Spondylitis Disease Activity Score

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
- ASDAS >3.5 defines very high disease activity

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)

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

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.

9.1.2.12. 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), c 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.

9.1.2.13. Peripheral Arthritis

9.1.2.13.1. 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 7.7) 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, randomized withdrawal–retreatment period (Period 2), it is recommended that the same assessor performs the tender joint count (TJC) for a given patient. Missing, replaced, ankylosed, or arthrodesed joints will be identified by the investigator and will be excluded from evaluation during the study.

The TJC data will be collected electronically.

9.1.2.13.2. 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 7.7) 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, randomized withdrawal–retreatment period (Period 2), it is

recommended that the same assessor performs the swollen joint count (SJC) for a given patient. Missing, replaced, ankylosed, or arthrodesed joints will be identified by the investigator and will be excluded from evaluation during the study.

The SJC data will be collected electronically.

9.1.2.14. Laboratory Tests Used for Efficacy Measures and Disease Diagnosis

9.1.2.14.1. High Sensitivity C-Reactive Protein

High sensitivity C-reactive protein 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.

9.1.2.15. Health Outcomes Measures

9.1.2.15.1. 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 or designee in the study's CRF. These data will be collected to support economic evaluations of treatment.

9.1.2.15.2. Fatigue Severity Numeric Rating Scale

The fatigue severity NRS is a patient-reported 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.

9.1.2.15.3. Medical Outcomes Study 36-Item Short-Form Health Survey

The Short Form 36 (SF-36) is a 36-item patient-reported 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).

9.1.2.15.4. Assessment of Spondyloarthritis International Society Health Index

The ASAS–Health Index (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.

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).

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.

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).

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.

9.4.7. 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 (Section 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 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]).

9.4.8. 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 Treatment of Adolescent Suicide Attempters trial group for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events. Patients will be assessed according to the Schedule of Activities (Section 2).

The Self-Harm Supplement Form is a one-question form 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.

9.4.9. Immunogenicity

For each patient, an immunogenicity sample will be collected according to the Schedule of Activities (Section 2). If necessary, samples may also be tested for ixekizumab drug concentrations to facilitate the interpretation of the immunogenicity data.
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.

9.4.10. Safety Monitoring

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

If a study patient experiences elevated ALT ≥3x ULN, alkaline phosphatase ≥2x ULN, or elevated total bilirubin ≥2x ULN, 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.

9.4.10.1. Neutropenia

9.4.10.1.1. During Treatment

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 8.1)
- ≥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 8.1)
- ≥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 (e.g., 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 (e.g., 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.

9.4.10.1.2. Early Termination Visit

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-Treatment Follow-Up Period (Period 4) 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.
- *Patients without Concurrent Infection:* If there is no concurrent infection that requires systemic anti-infective therapy, the neutrophil count is to be monitored using the required study visits in the Post-Treatment Follow-Up Period (Period 4), 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.

9.4.10.1.3. Post-Treatment Follow-Up

At Visit 801 and subsequent visits, the following monitoring applies:

- As long as a patient's neutrophil count is <1000 cells/μL (<1.00x10^3/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 (≥1.00x10^3/μL and <1.50x10^3/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 (≥1.50x10^3/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 (<1.50x10^3/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).

9.4.10.2. Hepatitis B Monitoring

Hepatitis B virus DNA monitoring will be performed as indicated in the Schedule of Activities (Section 2) for patients positive for hepatitis B core antibody at the screening visit of the originating study (RHBV, RHBW, or RHBX) and who required HBV DNA monitoring during the originating study (RHBV, RHBW, or RHBX).

If the result of any 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 (e.g., 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.

9.4.10.3. Hypertension

Patients who experience changes in BP (systolic BP at ≥160 mm Hg plus ≥20 mm Hg increase from baseline [Week 0; Visit 1]; 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.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2) for immunogenicity samples, blood samples of approximately 4 mL each will also be collected and may be used to determine the serum concentrations of ixekizumab. These blood samples may be used to aid in interpretation of the immunogenicity data. 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.

9.6. Pharmacodynamics

Refer to Section 10.3.5.

9.7.1. 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 (Section 2). Immunogenicity will be assessed using a validated assay designed to detect anti-drug antibodies 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.

9.8. Health Economics

Refer to Section 9.1.2.15.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 100 patients who achieved a state of sustained remission on ixekizumab Q4W will be randomized in a 2:1 ratio to ixekizumab 80 mg Q4W or placebo, and approximately 100 patients who achieved a state of sustained remission on ixekizumab Q2W will be randomized in a 2:1 ratio to ixekizumab 80 mg Q2W or placebo in the double-blind randomized withdrawal–retreatment period. This 200 total sample size will provide over 99% power to detect a difference in the proportion of patients who do not experience a flare between ixekizumab treatment (including both Q2W and Q4W) and placebo using a 2-sided Fisher's exact test at the 0.05 level, assuming the flare rates are 10% for ixekizumab and 70% for placebo. It is estimated that approximately 30% of total enrolled patients (i.e., approximately 200 patients) will meet the criteria to enter the double-blind randomized withdrawal–retreatment period.

If less than the anticipated number of patients meet the criteria to enter the double-blind randomized withdrawal–retreatment period (e.g., 20%), the total number of patients (approximately 150) would still provide over 95% power to detect a difference between ixekizumab treatment and placebo in the proportion of patients who do not experience a flare.

10.2. Populations for Analyses

For purposes of analysis, the following major patient populations are defined (Table RHBY.5).

Table RHBY.5. Major Patient Populations for Study RHBY

Population	Description
Lead-In Period Safety Population	All patients who receive at least 1 dose of ixekizumab in Period 1.
Randomized Withdrawal Intent-to-Treat (ITT) Population	All patients who are randomized in Period 2 (Group B), even if the patient does not receive the correct treatment or does not follow the protocol. Patients will be analyzed according to the treatment which they were assigned.
Randomized Withdrawal Safety Population	All patients in Group B who receive at least 1 dose of study treatment after Period 2 randomization. Patients will be analyzed according to the treatment to which they were assigned.
Ixekizumab Structure Population	All patients who (i) are from either RHBV or RHBW study; (ii) have been treated with ixekizumab for at least 18 months; and (iii) have mSASSS data at both Week 0 in the originating study and Week 56 in RHBY.
Long-Term Ixekizumab Treatment Efficacy Population	All patients who are randomized to ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W at Week 0 of the originating studies and consistently received ixekizumab in RHBY.
Flare Population	All patients in Group B who experience a flare after randomization at Week 24 and who receive ixekizumab retreatment after flare in Period 2 and Periods 2 and 3 combined (exploratory analyses).
Follow-Up Period Population	All patients who receive at least 1 dose of study treatment at any time during Study RHBY and enter the Post-Treatment Follow-Up Period (Period 4). Patients will be analyzed according to the treatment they were taking before entering Period 4.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

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

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. Additional exploratory analyses of the data will be conducted as deemed appropriate. Complete details of the planned analyses will be documented in the statistical analysis plan (SAP).

10.3.1.1. General Considerations for Analyses during the Combined Periods 1, 2, and 3

Combined Periods 1, 2, and 3 start at the first injection of ixekizumab 80 Q2W or ixekizumab 80 mg Q4W in Study RHBY and ends on the date of Week 104 (Group A: Visit 14/Group B: Visit 519) or at early termination visit (ETV) prior to Week 104.

10.3.1.1.1. Lead-In Period Safety Population

Safety data collected in Combined Periods 1, 2 and 3 will be summarized for the Lead-In Period Safety Population by combined ixekizumab treatment group and each of the ixekizumab dose groups without inferential statistics.

10.3.1.1.2. Long-Term Ixekizumab Treatment Efficacy Population

The long-term treatment effect in both categorical and continuous variables will be summarized by treatment group at each scheduled visit including Week 24, Week 64, and Week 104, and will also be summarized graphically using the response rate for categorical variables and mean for continuous variables by group at each scheduled visit in the Combined Periods 1, 2, and 3.

10.3.1.2. General Considerations for Analyses during Period 2 (Extension Period, Including Blinded, Randomized Withdrawal–Retreatment)

10.3.1.2.1. Randomized Withdrawal ITT Population

For patients who are randomized in Period 2, comparisons between combined ixekizumab treatments versus placebo, as well as each ixekizumab dose treatment to placebo, will be performed for all analyses in Study Period 2. For efficacy, and health outcomes, baseline is defined as the last available value before the first dose of study treatment in Period 2 from the originating study and in most cases will be the value recorded at Week 0 (from the originating study). For safety analysis, baseline is defined as the last available value before the first dose at the start of Period 2 in Study RHBY.

Endpoint for Study Period 2 is defined as the last visit in Period 2 (Week 64; Group A: Visit 10/Group B: Visit 515). Change from baseline will be calculated as the visit value of interest minus the baseline value.

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 regions, and originating study in the model. The odds ratio and 95% confidence intervals (CIs) will be reported; treatment difference and 95% CIs will also be reported. Secondary analysis will be conducted using a Fisher's exact test.

The Kaplan-Meier product limit method will be used to estimate the survival curves for time-to-flare for the patients who are randomized to the randomized withdrawal–retreatment period. Treatment comparisons will be performed using the stratified log-rank test with treatment, geographic region, and originating study in the model.

The analysis for all continuous efficacy and health outcome variables, change from baseline to endpoint analysis, will be made using analysis of covariance (ANCOVA) with treatment, baseline value, geographic region, and originating study in the model. Missing data will be imputed using modified baseline observation carried forward (mBOCF). Type III sums of squares for the least-squares (LS) means will be used for the statistical comparison; the 95% CI will also be reported.

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

For patients who are randomized and subsequently experience a flare in Period 2, efficacy, health outcomes, and safety data collected between time of flare and the end of Period 2 will be summarized for ixekizumab 80 mg Q2W or ixekizumab Q4W without inferential statistics.

10.3.1.2.2. Flare Population

For the Flare Population, Period 2 starts at the time of first injection of the retreatment of ixekizumab 80 mg Q2W or 80 mg Q4W following the flare and ends on the date of Week 64 prior to injection of study treatment (Visit 515) or the ETV before the date of Week 64.

Summary statistics will be provided based on the Flare Population within 16 weeks after the ixekizumab retreatment for patients who have 16 weeks of post-retreatment follow-up. No inferential statistics will be provided. The Kaplan–Meier estimates of the proportion of patients who first regain response on the variables of interest will be carried out at each post-retreatment interval (4 weeks, 8 weeks, etc.) up to 40 weeks. If a patient has not regained response or discontinues the study by Week 64, the patient will be censored at the date of their last visit during Period 2.

10.3.1.3. General Considerations for Analyses at Week 56 for the 2-Year Radiographic Progression in Spine Assessments

Assessment of 2-year radiographic progression in the spine from baseline in Studies RHBV and RHBW to Week 56 (Group A: Visit 9/Group B: Visit 513) in Study RHBY will be evaluated by

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

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.

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

10.3.2.3. Concomitant Therapy

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

10.3.2.4. Treatment Compliance

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

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

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary analysis, the proportion of patients in the combined ixekizumab treatment group who do not experience a flare during Period 2 compared with placebo, will be based on the Randomized Withdrawal ITT Population.

Treatment comparison between combined ixekizumab treatment group and placebo in the proportion of patients who do not experience a flare during Period 2 will be analyzed using the logistic regression model defined in Section 10.3.1.2. Missing data will be imputed using the NRI method described in Section 10.3.1.5.1.

10.3.3.2. Major Secondary Analyses

The major secondary analysis for the time to flare will be based on the Randomized Withdrawal ITT Population. Time to flare will be calculated in weeks as follows:

$$\frac{\text{Date of flare} - \text{Date of First Dose in Period 2} + 1}{7}$$

The date of flare is the time point when the patient qualifies for retreatment. If the date of the first dose is missing, the date of randomization will be used. Patients who complete Period 2 without a flare will be censored at the date of completion (i.e., the date of the last scheduled visit in the period). Patients without a date of completion or discontinuation for Period 2 and who did not experience a flare will be censored at the latest nonmissing date out of the following dates: date of last dose and date of last attended visit in Period 2 (scheduled or unscheduled).

Treatment comparisons between ixekizumab and placebo in time to flare for the Randomized Withdrawal ITT Population will be analyzed using a stratified log-rank test with treatment, geographic region, and originating study in the model. The Kaplan-Meier product limit method

will be used to estimate the survival curves for time to flare. Time to flare will also be summarized graphically by treatment group using Kaplan-Meier techniques.

Treatment comparisons in the proportion of patients who do not experience a flare at Week 64 (Group A: Visit 10/Group B: Visit 515) will be analyzed using the logistic regression model defined in Section 10.3.1.2. Missing data will be imputed using NRI method described in Section 10.3.1.5.1.

The 2-year radiographic progression reflected by change from baseline of originating studies RHBV and RHBW to Week 56 of Study RHBY (Group A: Visit 9/Group B: Visit 513) will be measured by mSASSS score and summarized by treatment. The comparison of the ixekizumab treatment group to the historical control will be analyzed by ANCOVA, with baseline score as covariate. The historical control will be defined in the SAP. Within-treatment changes from baseline along with 95% CI will be assessed by a paired t-test using the LS means.

10.3.3.3. Other Secondary Efficacy Analyses

There will be no adjustment for multiple comparisons. Analyses will be conducted for the other secondary objectives defined in Section 4.

The secondary efficacy and health outcomes analysis for Period 2 will be based on the Randomized Withdrawal ITT Population or the Flare Population. Additional efficacy and health outcome analysis for combined Periods 1, 2, and 3 analyses will be based on the Long-Term Ixekizumab Treatment Efficacy Population.

10.3.3.3.1. Combined Periods 1, 2, and 3

The long-term treatment effect in both categorical and continuous variables will be summarized by treatment group at each scheduled visit including Week 24, Week 64, and Week 104. Missing data will be imputed using mNRI for categorical efficacy variables, described in Section 10.3.1.5.2, and mBOCF and multiple imputation for continuous efficacy variables, described in Sections 10.3.1.5.3 and 10.3.1.5.4, respectively.

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

The other secondary analysis during Period 2 will be based on the Randomized Withdrawal ITT and Flare Populations.

For the Randomized Withdrawal ITT Population, all categorical efficacy variables and treatment group comparisons will be analyzed at each visit using the logistic regression model described in Section 10.3.1.2.1. Missing data will be imputed using the NRI method described in Section 10.3.1.5.1. All continuous efficacy variables and treatment group comparisons will be analyzed at each visit using the ANCOVA models as described in Section 10.3.1.2.1 when appropriate. For the ANCOVA analysis, missing data will be imputed by the mBOCF as described in Section 10.3.1.5.3.

For the Flare Population who were retreated with ixekizumab following the flare, the following summaries will be provided:

- The proportion of patients who regain sustained remission criteria within 16 weeks after ixekizumab retreatment will be summarized by the original re-randomization treatment group.
- The proportion of patients with ASAS20 as well as the proportion of patients with ASAS40 within 16 weeks after ixekizumab retreatment will be summarized by the original re-randomization treatment group.

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10.3.4. Safety Analyses

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

Primary safety analyses will be based on the Randomized Withdrawal Safety Population in Period 2.

For combined Periods 1, 2, and 3, safety data will be summarized for the Lead-In Period Safety Population.

For Period 2, safety data will be summarized for the Randomized Withdrawal Safety Population. Treatment group comparisons will be performed on categorical safety data using Fisher's exact test as described in Section 10.3.1.2.1; continuous safety data will be analyzed by an ANCOVA model.

For Period 4 safety data will be summarized according to the treatment patients were on prior to entering Period 4.

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

Further details will be described in the SAP.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Blood samples for determination of ixekizumab concentrations will be collected and may be analyzed using graphical methods to aid in interpretation of the immunogenicity data.

Additional exploratory analyses of the data may be conducted if deemed appropriate.

10.3.6. Other Analyses

10.3.6.1. Health Outcomes

There will be no adjustment for multiple comparisons. Analyses will be conducted for the other secondary health outcomes objectives as defined in Section 4.

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.

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.

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12. Appendices

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
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BCG	Bacillus Calmette- Guérin
bDMARD	biological disease modifying antirheumatic drug
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. 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.

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

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

Term	Definition
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
NSAID	nonsteroidal anti-inflammatory drug
PK/PD	pharmacokinetics/pharmacodynamics
PPD	Purified protein derivative
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
Ps	psoriasis
PsA	psoriatic arthritis
PT	prothrombin time
Q2W	every 2weeks
Q4W	every 4 weeks
QIDS-SR 16	Quick Inventory of Depressive Symptomatology-Self-Report 16
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 joint

Term	Definition
SJC	swollen joint count
SpA	Spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SUSARs	suspected unexpected serious adverse reactions
TB	tuberculosis
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
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. Clinical Laboratory Tests

Clinical Laboratory Tests to Be Performed by Sponsor-Designated Laboratory

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[b]
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	
HBV DNA[f]	Follicle-stimulating hormone (FSH)[e]
High sensitivity C-reactive protein (CRP)	Ixekizumab serum concentration (pharmacokinetic)
Urine pregnancy test[d] (assayed by clinical study site)	Partial thromboplastin time (PTT)
TB test (e.g., PPD, QuantiFERON®-TB Gold, T-SPOT®)[g]	Prothrombin time/international normalized ratio
	Exploratory storage samples (serum, urine, plasma, and RNA)
	Immunogenicity testing (anti-ixekizumab Ab)

Abbreviations: Ab = antibody; DNA = deoxyribonucleic acid; HBV = hepatitis B virus; PPD = purified protein derivative; RNA = messenger ribonucleic acid; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; TB = tuberculosis.

[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.

[d] Urine pregnancy test performed locally for women of childbearing potential.

[e] For female patients ≥40 and <60 years of age who cease menstruation for at least 12 months during study participation, an FSH test may be performed to confirm nonchildbearing potential (FSH ≥40 mIU/mL). FSH test

will be performed centrally.

[f] HBV DNA monitoring will be performed as indicated in the Schedule of Activities for patients positive for hepatitis B core antibody at the screening visit of the originating study (RHBV, RHBW, or RHBX) and who required HBV DNA monitoring during the originating study (RHBV, RHBW, or RHBX). If the result of the HBV DNA testing is positive, the patient is to be discontinued from the study and is to receive appropriate follow-up medical care (refer to Section 9.4.10.2 for further information regarding the timing of discontinuation).

[g] See Section 9.4.6: In countries where the QuantiFERON®-TB Gold test or T-SPOT® test is available, it may be used instead of the PPD TB test. The QuantiFERON®-TB Gold test and the T-SPOT® test will be performed locally.

Appendix 3. Study Governance Considerations

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

Appendix 3.1.1. Informed Consent

The investigator is responsible for ensuring:

- that the patient understands the 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 informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

Appendix 3.1.2. Ethical Review

The investigator must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

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

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

- the current Investigator Brochure (IB) and updates during the course of the study
- informed consent form
- relevant curricula vitae

Appendix 3.1.3. 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.

Appendix 3.1.4. 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.

Appendix 3.1.5. 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.

Appendix 3.1.6. Final Report Signature

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

The 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.

Appendix 3.2. Data Quality Assurance

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

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

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

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

Appendix 3.2.1. Data Capture System

An electronic data capture system 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.

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

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

Appendix 3.3.2. Discontinuation of the Study

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

Appendix 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 Lilly medical.

Hepatic Monitoring Tests

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

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

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

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

Appendix 5. Protocol Amendment I1F-MC-RHBY(a) Summary: A Multicenter, Long-Term Extension Study of 104 Weeks, Including a Double-Blind, Placebo-Controlled 40-Week Randomized Withdrawal-Retreatment Period, to Evaluate the Maintenance of Treatment Effect of Ixekizumab (LY2439821) in Patients with Axial Spondyloarthritis

Overview

Protocol I1F-MC-RHBY, A Multicenter, Long-Term Extension Study of 104 Weeks, Including a Double-Blind, Placebo-Controlled 40-Week Randomized Withdrawal–Retreatment Period, to Evaluate the Maintenance of Treatment Effect of Ixekizumab (LY2439821) in Patients with Axial Spondyloarthritis, has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

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

- In the original protocol, patients participating in the randomized withdrawal–retreatment period (Group B) were unblinded to study treatment once the Week 64 datalock had been completed. In Protocol RHBY Amendment (a), patients in Group B will be blinded until the completion of the study or time of flare. Changing the time of unblinding for patients in Group B will help to eliminate bias from participants and retain patients who are on placebo; therefore, it will facilitate the assessment of the proportion of patients who experience a flare after Week 64. Revisions were made to Section 7.3 (Blinding), Section 10.3.7 (Interim Analyses), and Table RHBY.2.
- Section 10 (Statistical Considerations) was revised, as follows:
    - The Ixekizumab Structure Population definition was added to Table RHBY.5 to align with the structure objective.
    - To assess the long-term efficacy of ixekizumab treatment, an analysis of Combined Periods 1, 2, and 3 was added. Therefore, the Long-Term Ixekizumab Treatment Efficacy Population was defined in Table RHBY.5. The analysis methods were updated to include the handling of missing data (i.e., mNRI and MI). Due to the inclusion of the assessment of Combined Periods 1, 2, and 3, it was determined that the analysis of Period 1 only and Combined Periods 2 and 3 was longer needed.
    - The last observation carried forward method for handling missing data was removed; other methods for missing data are included and considered more appropriate for the analysis.
- The remainder of the changes to the protocol were added to improve clarity.
    - The following changes were made to the Section 2 (Schedule of Activities [SOA]):

- Assessment of Linear BASMI, Chest expansion, Occiput–to-wall distance, Enthesitis, and TJC/SJC was added to the ETV so that the structure data can be interpreted in the context of other functional outcomes.
- Minor additions to Footnotes "h," "i," "k," and "p" were made for consistency with the main body of the protocol.
- It was clarified that AEs initiating in the originating study and are ongoing by the time the patient completes in the originating study will be considered as preexisting conditions in Study RHBY.
- How and for whom to "Enter ASDAS" was clarified.
- The collection window for the MRI at Visit 505 was clarified. Additional guidance regarding concomitant therapy for patients undergoing an MRI is provided in Section 7.7 (Concomitant Therapy).
- The x-ray requirement at ETV was clarified. In addition, the amendment noted that x-rays are required only for patients initially enrolled in Studies RHBV or RHBW; this change was made to Section 2 (SOA), Section 5.4 (Scientific Rationale for Study Design), and Section 9.1.2.2.1 (Radiographic Imaging of the Spine).
- Footnote "o" was added to Self-Harm Supplement Form on Page 3 of the SOA. The footnote was excluded in error.
- It was noted that HBV DNA monitoring is only indicated for patients positive for hepatitis B core antibody at the screening visit of the originating study and who required HBV DNA monitoring during the originating study; this clarification was also made in Section 9.4.10.2 (Hepatitis B Monitoring) and Appendix 2 (Clinical Laboratory Tests). Additionally, Discontinuation Criterion [13] was clarified to discuss the timing of discontinuation for those patients who were HBV DNA positive.

- The Objectives and Endpoints (Section 4) were revised for clarity. There were no changes (additions and/or deletions) to the objectives and endpoints. Sections 1 (Synopsis) and 9.1.1 (Primary Efficacy Assessments) were also updated to reflect these revisions.
- In Section 5.1 (Overall Design), the definition of sustained remission was fully defined for further clarity and to reduce misinterpretation.
- In Section 5.1 (Overall Design), the definition of a flare was clarified to include Period 2 and/or Period 3.
- Patients in Group B who experience a flare after Week 64 may have their dose escalated to ixekizumab 80 mg Q2W. Throughout the amendment, additional clarity is provided on the requirements for the dose escalation (Sections 1 [Synopsis], 5.1 [Overall Design], 7.1 [Treatments Administered], and 7.4 [Dosage Modification]).

- Minor additions and deletions were made to Sections 5.2 [Number of Participants], 5.4 [Scientific Rationale for Study Design], 7.2 [Method of Treatment Assignment], and 7.7 [Concomitant Therapy] to improve clarity and reduce redundancy.
- Inclusion Criterion [2] and Exclusion Criteria [4] and [7] were revised for clarity.
- Section 6.4 (Screen Failures) was updated to provide more clarity.
- Table RHBY.3 was added to explain dosage modification for patients in Group B who flare during Period 2 and/or Period 3.
- The concomitant treatment with NSAIDs and analgesics, cDMARDs, and corticosteroids for patients in Group B during Period 3 were clarified (Table RHBY.4).
- In Section 9.1.1 (Primary Efficacy Assessments), typographical errors in the $ASDAS_{crp}$ formula were corrected.
- Additional detail to provide clarity was included in Section 9.4.6 (Tuberculosis Testing). The type of TB test was clarified in Appendix 2 (Clinical Laboratory Tests).

- The footnotes in Figure RHBY.1 and Table RHBY.2 were modified accordingly with the changes made in this protocol amendment.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

Section 1. Synopsis

Objective(s)/Endpoints:

Objectives	Endpoints
Primary • 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 ~~the randomized withdrawal-retreatment period~~Period 2	• The proportion of patients in the randomized withdrawal population who do not experience a flare during ~~the randomized withdrawal-retreatment period~~Period 2

Objectives	Endpoints
Major Secondary	
• To compare the combined ixekizumab treatment group to historical control for 2-year radiographic progression in spine in patients with active radiographic axSpA (rad axSpA)	• Change in modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) score
• To evaluate in patients having achieved a state of sustained remission whether the ixekizumab 80 mg every 2 weeks (Q2W) treatment group or ixekizumab 80 mg every 4 weeks (Q4W) treatment group is superior to placebo in maintaining response after randomized withdrawal	• The proportion of patients in the randomized withdrawal population who do not experience a flare during ~~the randomized withdrawal-retreatment period~~Period 2
• 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 after ~~treatment~~randomized withdrawal	• Time to flare for patients in the randomized withdrawal population during ~~the randomized withdrawal-retreatment period~~Period 2
• 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 ~~treatment~~randomized withdrawal	• Time to flare for patients in the randomized withdrawal population during ~~the randomized withdrawal-retreatment period~~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 ~~the randomized withdrawal retreatment period~~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 ~~the randomized withdrawal treatment period~~Period 2 • Change from baseline ~~of originating study~~ in the individual components of the ASAS criteria • Change from baseline ~~of originating study~~ in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) • Proportion of patients with Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI50) response • Change from baseline ~~of originating study~~ in ASDAS • Change from baseline ~~of originating study~~ in the measure of high sensitivity C-reactive protein (CRP) • Change from baseline ~~of originating study~~ in Bath Ankylosing Spondylitis Functional Index (BASFI) • Change from baseline ~~of originating study~~ 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 ~~of originating study~~ 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 ~~of originating study~~ in

Objectives	Endpoints
	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 ~~in the randomized withdrawal treatment period~~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 ~~whether~~ the long-term treatment effect of 80 mg ixekizumab Q2W and 80 mg ixekizumab Q4W ~~is maintained~~ through Week 104	• The proportion of patients with ASAS20, ASAS40, ASAS 5/6, ASAS partial remission, clinically important improvement ~~(change of ASDAS ≥1.1 units)~~, major improvement ~~(change of ASDAS ≥2.0 units)~~, and inactive disease ~~(ASDAS <1.3)~~ • Change from baseline ~~of originating study~~ in the individual components of the ASAS criteria • Change from baseline ~~of originating study~~ in BASDAI • Proportion of patients with BASDAI50 response • Change from baseline ~~of originating study~~ in ASDAS • Change from baseline ~~of originating study~~ in

Objectives	Endpoints
	the measure of CRP • Change from baseline ~~of originating study~~ in BASFI • Change from baseline ~~of originating study~~ 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 ~~of originating study~~ 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 • Proportion of patients with change in mSASSS score <2 from baseline of originating study to Week 56 in RHBY • Proportion of patients with no new syndesmophyte formation from baseline of originating study to Week 56 in RHBY • Change from baseline ~~of originating study~~ in the following health outcomes measures o Fatigue NRS score o QIDS SR16 o SF-36 (both physical and mental component scores) o ASAS-HI o EQ-5D-5L o WPAI-SpA o JSEQ
• To evaluate the development of anti-ixekizumab antibodies and its impact on the efficacy of ixekizumab	• Efficacy response rates listed below at Weeks ~~56~~64 and 104 by treatment-emergent anti-drug antibody (TE-ADA) status and by neutralizing anti-drug antibody (NAb) status: o Proportion of patients achieving ASAS40 o Proportion of patients achieving ASAS20 o Proportion of patients achieving ASDAS inactive disease

Treatment Arms and Duration:

- During the Long-Term Extension Period (Period 3; 40 weeks),
    - (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 and meets criteria for retreatment, 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 the Long-Term Extension Period, 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.

Statistical Analysis:

The analysis for all continuous efficacy and health outcome variables will be made using analysis of covariance (ANCOVA) with treatment, baseline value, geographic region, and originating study in the model. Missing data will be imputed using ~~last observation carried forward (LOCF) or~~ modified baseline observation carried forward (mBOCF). Type III sums of squares for the least-squares (LS) means will be used for the statistical comparison; the 95% CI will also be reported.

Section 2. Schedule of Activities

Schedule of Activities, Protocol I1F-MC-RHBY (changes/additions)

Page 1

	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]					V**505**[c]	V**506**	V**507**	V**508**	V**509**	V**510**	V**511**	V**512**	V**513**	V**514**	V**515**	V**516**	V**517**	V**518**	V**519**	
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	
Enter ASDAS[l]			X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]		

Schedule of Activities, Protocol I1F-MC-RHBY (changes/additions)

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	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]					V**505**[c]	V**506**	V**507**	V**508**	V**509**	V**510**	V**511**	V**512**	V**513**	V**514**	V**515**	V**516**	V**517**	V**518**	V**519**	
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	
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

Schedule of Activities, Protocol I1F-MC-RHBY (changes/additions)

Page 3

	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]					V**505**[c]	V**506**	V**507**	V**508**	V**509**	V**510**	V**511**	V**512**	V**513**	V**514**	V**515**	V**516**	V**517**	V**518**	V**519**	
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	
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

Schedule of Activities, Protocol I1F-MC-RHBY (changes/additions)

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	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	
Urinalysis	X				X						X					X			X	X

[redacted]

Abbreviations: ASDAS = Ankylosing Spondylitis Disease Activity Score; BASMI = Bath Ankylosing Spondylitis Metrology Index; CRP = high sensitivity C-reactive protein; d = days; DNA = deoxyribonucleic acid; ETV = early termination visit; HBV = hepatitis B virus; IWRS = interactive web-response system; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MRI = magnetic resonance imaging; RNA = ribonucleic acid; SIJ = sacroiliac joints; SJC = swollen joint count; SPARCC = Spondyloarthritis Research Consortium of Canada; TJC = tender joint count; V = study visit; W = study week.

[a] For most patients, the final visit of the originating study (RHBV, RHBW, or RHBX) will coincide with Visit 1 (Week 0) of Study RHBY. In these cases, any assessments/procedures (including laboratory tests) conducted during the patient's final visit in the originating study should not be repeated for Visit 1 (Week 0) of Study RHBY. In cases where entry into Study RHBY is delayed beyond Week 52 of the originating study, assessments/procedures (including laboratory tests) indicated for Visit 1 (Week 0) of Study RHBY that are not conducted during the last visit (Visit 801 or Visit 802) of the originating study will be performed as indicated in the Schedule of Activities.

[b] For most patients, the final visit of the originating study (RHBV, RHBW, or RHBX) will coincide with Visit 1 (Week 0) of Study RHBY. However, in particular circumstances, the duration between the final visit of the originating study and Visit 1 (Week 0) of Study RHBY may be extended after consultation with the sponsor. Therefore, there is no specified visit window for Visit 1 (Week 0) of Study RHBY.

[c] Patients will be assigned to Group A or Group B at Visit 5/Visit 505 (Week 24).

h If patients are not eligible to enter Study RHBY at Week 52 in the originating study (e.g., due to unresolved safety concerns), then entry into Study RHBY may be delayed beyond Week 52 of the originating study. See Section 6.1.

i Patients who have achieved a state of sustained remission (Group B) will participate in randomized withdrawal–retreatment and will be randomized to their treatment assignment at Week 24. See Section 5.1.

j Evaluation includes both historical events as well as preexisting conditions which are assessed after baseline to determine any treatment-emergent worsening of preexisting conditions. AEs that initiated in the originating study (RHBV, RHBW, or RHBX) and are ongoing by the time the patient completes participation in the originating study will be considered as preexisting conditions in Study RHBY.

k Patients need to be asked about presence of eye symptoms; if eye symptoms are present then an eye examination is required. See Section 9.4.5.

l Sites will enter into IWRS the partial ASDAS score provided by the ~~SITEpro tablet~~EPX™ website and the central laboratory CRP value ~~from the central laboratory results~~ from this visit, as soon as available ~~into IWRS as appropriate~~. **After Visit 5/Visit 505**, the partial ASDAS score and CRP value will be entered into IWRS only for patients participating in the randomized withdrawal–retreatment (Group B). Once a patient experiences a flare (see Section 5.1), the partial ASDAS score and CRP value is no longer entered into IWRS.

m An MRI of the spine plus SIJ will be performed at Week 24 (±10 days) for patients participating in randomized withdrawal–retreatment (Group B). If the MRI was not completed within the protocol-defined window, please contact Lilly medical for additional guidance. See Section 7.7 for additional guidance regarding concomitant therapy for patients undergoing an MRI.

n Cervical and lumbar spine only. An x-ray is only needed for patients initially enrolled in Studies RHBV or RHBW. If the patient's ETV occurs prior to Visit 9/Visit 513 (Week 56), then an x-ray will need to be performed at the ETV. If the patient's ETV occurs after Visit 9/Visit 513 (Week 56), an x-ray will only be required at ETV if an x-ray was not collected at Week 56.

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

p TB testing required only based on clinical assessment of TB risk (symptoms/signs/known or suspected TB exposure), as determined by the principal investigator, and according to local regulations and/or local standard of care (Section 9.4.6).

q HBV DNA monitoring will be performed as indicated in the Schedule of Activities for patients positive for hepatitis B core antibody at the screening visit of the originating study (RHBV, RHBW, or RHBX) and who required HBV DNA monitoring during the originating study (RHBV, RHBW, or RHBX). If the result of the HBV DNA testing is positive, the patient is to be discontinued from the study and is to receive appropriate follow-up medical care (refer to Section 9.4.10.2 for further information regarding the timing of discontinuation).

t Where collection is allowed by local regulations. All samples (urine, serum, plasma, RNA, and whole blood) will be collected at the designated scheduled visits.

Section 4. Objectives and Endpoints

Table RHBY.1. Objectives and Endpoints

Objectives	Endpoints
Primary • 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 ~~the randomized withdrawal-retreatment period~~Period 2	• The proportion of patients in the randomized withdrawal population who do not experience a flare during ~~the randomized withdrawal-retreatment period~~Period 2

Objectives and Endpoints

Objectives	Endpoints
Major Secondary	
• To compare the combined ixekizumab treatment group to historical control for 2-year radiographic progression in spine in patients with active radiographic axSpA (rad-axSpA)	• Change in modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS score)
• To evaluate in patients having achieved a state of sustained remission whether the ixekizumab 80 mg every 2 weeks (Q2W) treatment group or ixekizumab 80 mg every 4 weeks (Q4W) treatment group is superior to placebo in maintaining response after randomized withdrawal	• The proportion of patients in the randomized withdrawal population who do not experience a flare during ~~the randomized withdrawal-retreatment~~Period 2
• 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 after ~~treatment~~randomized withdrawal	• Time to flare for patients in the randomized withdrawal population during ~~the randomized withdrawal-retreatment period~~Period 2
• 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 ~~treatment~~randomized withdrawal	• Time to flare for patients in the randomized withdrawal population during ~~the randomized withdrawal-retreatment period~~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 ~~the randomized withdrawal-retreatment period~~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 ~~the randomized withdrawal-retreatment period~~Period 2 • Change from baseline ~~of originating study~~ in the individual components of the ASAS criteria • Change from baseline ~~of originating study~~ in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) • Proportion of patients with Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI50) response • Change from baseline ~~of originating study~~ in (ASDAS) • Change from baseline ~~of originating study~~ in the measure of high sensitivity C-reactive protein (CRP) • Change from baseline ~~of originating study~~ in Bath Ankylosing Spondylitis Functional Index (BASFI) • Change from baseline ~~of originating study~~ 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 ~~of originating study~~ 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 ~~of originating study~~ in the following health outcomes measures:

Objectives	Endpoints
	○ Fatigue numeric rating scale (NRS) score ○ Quick Inventory of Depressive Symptomatology Self-Report-16 (QIDS-SR16) ○ SF-36 (both physical and mental component scores) ○ Assessments of Spondyloarthritis international Society Health Index (ASAS-HI) ○ European Quality of Life - 5 Dimensions 5 Level (EQ-5D-5L) ○ Work Productivity Activity Impairment-Spondyloarthritis (WPAI-SpA) ○ Jenkins Sleep Evaluation Questionnaire (JSEQ)
• To assess the efficacy of retreatment with ixekizumab following a flare ~~in the randomized withdrawal retreatment period~~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 ~~whether~~ the long-term treatment effect of 80 mg ixekizumab Q2W and 80 mg ixekizumab Q4W ~~is maintained~~ through Week 104	• The proportion of patients with ASAS20, ASAS40, ASAS 5/6, ASAS partial remission, clinically important improvement ~~(change of ASDAS ≥1.1 units)~~, major improvement ~~(change of ASDAS ≥2.0 units)~~, and inactive disease ~~(ASDAS <1.3)~~ • Change from baseline ~~of originating study~~ in the individual components of the ASAS criteria • Change from baseline ~~of originating study~~ in BASDAI • Proportion of patients with BASDAI50 response • Change from baseline ~~of originating study~~ in ASDAS • Change from baseline ~~of originating study~~ in the measure of CRP • Change from baseline ~~of originating study~~ in

Objectives	Endpoints
	BASFI • Change from baseline ~~of originating study~~ 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 ~~of originating study~~ 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 • Proportion of patients with change in mSASSS score <2 from baseline of originating study to Week 56 in RHBY • Proportion of patients with no new syndesmophyte formation from baseline of originating study to Week 56 in RHBY • Change from baseline ~~of originating study~~ in the following health outcomes measures: o Fatigue NRS score o QIDS SR16 o SF-36 (both physical and mental component scores) o ASAS-HI o EQ-5D-5L o WPAI-SpA o JSEQ
• To evaluate the development of anti-ixekizumab antibodies and its impact on the efficacy of ixekizumab	• Efficacy response rates listed below at Weeks ~~56~~64 and 104 by treatment-emergent anti-drug antibody (TE-ADA) status and by neutralizing anti-drug antibody (NAb) status: o Proportion of patients achieving ASAS40 o Proportion of patients achieving ASAS20 o Proportion of patients achieving ASDAS inactive disease
CCI	

Section 5.1. Overall Design

Study RHBY will evaluate the sustainability of clinical benefits, safety, and tolerability of ixekizumab treatment as well as the impact of ixekizumab on structural progression in patients with axSpA. In addition, maintenance of response after treatment withdrawal will be evaluated in those patients having achieved a state of sustained remission, defined as one of the following:

- Ankylosing Spondylitis Disease Activity Score (ASDAS) <1.3 at Weeks 16 and 20~~.~~,

OR

- ASDAS <1.3 at Week 16~~ or Week 20,~~ and ASDAS <2.1 ~~at the other visit.~~Week 20,

OR

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

Abbreviations: Q2W = once every 2 weeks; Q4W = once every 4 weeks; W = week.

a Patients in Group A will continue to receive the same ixekizumab dose regimen that they were receiving ~~at Week 24 during Periods 2 and 3~~during Period 1.

b Only patients having achieved a state of sustained remission (Group B) are eligible for participation in the randomized withdrawal–retreatment period.

c Patients who experience a flare will be retreated with the ixekizumab treatment regimen that they were receiving prior to withdrawal.

d ~~After the 64-week database lock for Study RHBY~~As of Week 64, patients receiving ixekizumab 80 mg Q4W during Period 3 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. However, for patients in Group B, 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.

e For patients who were receiving ixekizumab in the originating study, the dose in the 24-week Lead-In Period (Period 1) will be based on the current dosing in the originating study. For patients in Study RHBX who were on placebo, patients will receive ixekizumab 80 mg Q4W.

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

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

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

- ASDAS <1.3 at Weeks 16 and 20~~.~~,

OR

- ASDAS <1.3 at Week 16~~ or Week 20,~~ and ASDAS <2.1 at ~~the other visit.~~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.

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 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. ~~A flare is defined as follows:~~

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

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 received during Period 1 (ixekizumab 80 mg Q4W) for at least 12 weeks.

Section 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%.

Section 5.4. Scientific Rationale for Study Design

The length of the randomized withdrawal period is ~~10 months~~40 weeks and considered sufficiently long based on previous randomized withdrawal studies of TNF inhibitors in RA and axSpA (Haibel et al. 2008; Barkham et al. 2009; Haibel et al. 2010; Sieper et al. 2014; Smolen et al. 2014). It is anticipated that the majority of patients who no longer receive active treatment will relapse within that time frame.

~~Patients who do not meet entry criteria for randomized withdrawal by Week 24 (anticipated to be approximately 70% of the 750 patients) will continue to receive their active treatment regimen during the remainder of the study (Group A). Patients receiving ixekizumab 80mg 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. Patients who have their dose escalated will continue on ixekizumab 80 mg Q2W for the remainder of Period 3.~~

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.

Section 6.1. Inclusion Criteria

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

- If ~~a~~the patient is male, the patient~~, the patient~~ must agree~~s~~ 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~~the patient is female ~~patient, patient is~~and is a woman of childbearing potential who tests negative for pregnancy, the patient must ~~and~~ agree~~s~~ 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, ~~condoms with spermicide, male sterilization,~~ oral contraceptives, contraceptive patch, injectable or implantable contraceptives, intrauterine device, vaginal ring, or diaphragm with contraceptive gel.

Section 6.2. Exclusion Criteria

[4.] Have significant uncontrolled cerebro-cardiovascular (e.g., myocardial infarction [MI], unstable angina, unstable arterial hypertension, severe heart failure, or cerebrovascular accident), respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neuropsychiatric disorders, or abnormal laboratory values that developed during ~~a previous ixekizumab study~~the originating ixekizumab study (RHBV, RHBW, or RHBX) that, in the opinion of the investigator, pose an unacceptable risk to the patient if investigational product continues to be administered.

[7.] Had temporary investigational product interruption at any time during or at the final study visit of ~~a previous ixekizumab study~~the originating ixekizumab study (RHBV, RHBW, or RHBX) **and**, in the opinion of the investigator, restarting ixekizumab poses an unacceptable risk for the patient's participation in the study.

Section 6.4. Screen Failures

~~Not applicable.~~Individuals who do not meet the criteria for participation in this study (screen failure) will not be rescreened.

Section 7.1. Treatments Administered

During the Long-Term Extension Period, 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 and meets criteria for retreatment (see Section 5.1), 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~~As of Week 64 and during the Long-Term Extension Period, patients in Group B receiving ixekizumab 80 mg Q4W may also have their dose escalated to ixekizumab 80 mg Q2W ~~after the 64-week database lock for Study RHBY~~, 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 (see Section 7.4).

Table RHBY.2. Summary of Treatment Regimens Study RHBY

Originating Study	Treatment at End of Originating Study	Treatment During RHBY Period 1	Treatment During RHBY Period 2 and Period 3
RHBV or RHBW	ixekizumab 80 mg Q2W	ixekizumab 80 mg Q2W (*open-label*) [Dose: 1 ixekizumab 80-mg Q2W injection (beginning at Week 0)]	**Group A:** *open-label* ixekizumab 80 mg Q2W [Dose: 1 ixekizumab 80-mg Q2W injection (beginning at Week 24)]
			Group B: *blinded*[f,a,d] ixekizumab 80 mg Q2W (*blinded*)[e] [Dose: 1 ixekizumab 80-mg Q2W injection (beginning at Week 24)] or placebo (*blinded*)[a] [Dose: 1 placebo for ixekizumab injection Q2W (beginning at Week 24)]
	ixekizumab 80 mg Q4W	ixekizumab 80 mg Q4W (*open-label*) [Dose: 1 ixekizumab 80-mg Q4W injection (beginning at Week 0)]	**Group A:** *open-label*[d,c] ixekizumab 80 mg Q4W [Dose: 1 ixekizumab 80-mg Q4W injection (beginning at Week 24)]
			Group B: *blinded*[f,b,d] ixekizumab 80 mg Q4W (*blinded*)[e] [Dose: 1 ixekizumab 80-mg Q4W injection (beginning at Week 24)] or placebo (*blinded*)[b] [Dose: 1 placebo for ixekizumab injection Q4W (beginning at Week 24)]

Originating Study	Treatment at End of Originating Study	Treatment During RHBY Period 1	Treatment During RHBY Period 2 and Period 3
RHBX	rescued to ixekizumab 80 mg Q2W	ixekizumab 80 mg Q2W (*open-label*) [Dose: 1 ixekizumab 80-mg Q2W injection (beginning at Week 0)]	**Group A:** *open-label* ixekizumab 80 mg Q2W [Dose: 1 ixekizumab 80-mg Q2W injection (beginning at Week 24)]
			Group B: *blinded*[f,a,d] ixekizumab 80 mg Q2W (*blinded)*[e] [Dose: 1 ixekizumab 80-mg Q2W injection (beginning at Week 24)] or placebo (*blinded*)[a] [Dose: 1 placebo for ixekizumab injection Q2W (beginning at Week 24)]
	ixekizumab 80 mg Q2W (*blinded*)	ixekizumab 80 mg Q2W (*blinded*)[g,e] [Dose: 1 ixekizumab 80-mg Q2W injection (beginning at Week 0)]	**Group A:** *blinded*[g,e] ixekizumab 80 mg Q2W [Dose: 1 ixekizumab 80-mg Q2W injection (beginning at Week 24)]
			Group B: *blinded*[f, g,a,d,e] ixekizumab 80 mg Q2W (*blinded)*[e] [Dose: 1 ixekizumab 80-mg Q2W injection (beginning at Week 24)] or placebo (*blinded*)[a] [Dose: 1 placebo for ixekizumab injection Q2W (beginning at Week 24)]

Originating Study	Treatment at End of Originating Study	Treatment During RHBY Period 1	Treatment During RHBY Period 2 and Period 3
	ixekizumab 80 mg Q4W (*blinded*)	ixekizumab 80 mg Q4W (*blinded*)~~g~~[e] [Dose: 1 ixekizumab 80-mg Q4W injection (beginning at Week 0); and 1 placebo for ixekizumab injection Q4W (beginning at Week 2)]	**Group A:** *blinded*~~d, g~~[c,e] ixekizumab 80 mg Q4W [Dose: 1 ixekizumab 80-mg Q4W injection (beginning at Week 24); and 1 placebo for ixekizumab injection Q4W (beginning at Week 26)]
			Group B: *blinded*~~f, g~~[b,d,e] ixekizumab 80 mg Q4W (*blinded)*[e] [Dose: 1 ixekizumab 80-mg Q4W injection (beginning at Week 24); and 1 placebo for ixekizumab injection Q4W (beginning at Week 26)] or placebo (*blinded*)~~b~~ [Dose: 1 placebo for ixekizumab injection Q2W (beginning at Week 24)]
	placebo (*blinded*)	ixekizumab 80 mg Q4W (*blinded*)~~g~~[e] [Dose: 1 ixekizumab 80-mg Q4W injection (beginning at Week 0); and 1 placebo for ixekizumab injection Q4W (beginning at Week 2)]	**Group A:** *blinded*~~d, g~~[c,e] ixekizumab 80 mg Q4W [Dose: 1 ixekizumab 80-mg Q4W injection (beginning at Week 24); and 1 placebo for ixekizumab injection Q4W (beginning at Week 26)]
			Group B: *blinded*~~f, g~~[b,d,e] ixekizumab 80 mg Q4W (*blinded)*[e] [Dose: 1 ixekizumab 80-mg Q4W injection (beginning at Week 24); and 1 placebo for ixekizumab injection Q4W (beginning at Week 26)] or placebo (*blinded*)~~b~~ [Dose: 1 placebo for ixekizumab injection Q2W (beginning at Week 24)]

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

[a] Patients who experience a flare and meet the criteria for retreatment during Period 2 or Period 3 will receive ixekizumab 80 mg Q2W.

[b] Patients who experience a flare and meet the criteria for retreatment during Period 2 or Period 3 will receive ixekizumab 80 mg Q4W. As of Week 64, patients in Group B may have their dose escalated to ixekizumab 80 mg Q2W only after the patient was retreated upon flare with ixekizumab 80 mg Q4W for at least 12 weeks (Section 7.4).

~~[c] Patients who experience a flare and meet the criteria for retreatment will remain on their assigned dosing regimen of ixekizumab 80 mg Q2W.~~

~~[d]~~[c] ~~After 64 weeks of treatment~~As of Week 64, patients in Group A receiving ixekizumab 80 mg Q4W may have their dose escalated to ixekizumab 80 mg Q2W ~~in Period 3 if the investigator determines that the patient may benefit from an increase in frequency of dosing to achieve adequate disease control~~ (Section 7.4). Dose escalation may begin at the next scheduled visit or at an unscheduled visit prior to the next scheduled visit.

~~[e] After the 64-week datalock for Study RHBY, patients in Group B receiving ixekizumab 80 mg Q4W may have their dose escalated to ixekizumab 80 mg Q2W in Period 3 if the investigator determines that the patient may benefit from an increase in frequency of dosing to achieve adequate disease control (Section 7.4).~~

~~[f]~~[d] All patients in Group B will remain on blinded study drug from Week 24 until the ~~64-week datalock for Study RHBY has been completed~~completion of the study or time of flare (Section 7.3). ~~See Section 7.3.~~

~~[g]~~[e] For patients entering Study RHBY from Study RHBX who were receiving blinded treatment at the end of the originating study, patients will continue to receive blinded treatment in Study RHBY until the 52-week datalock for Study RHBX is achieved.

Section 7.2. Method of Treatment Assignment

~~The~~During the Extension Period, the IWRS will be used to assign double-blind investigational product to each patient in Group B. 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.

~~During the Long-Term Extension Period (Period 3), patients will continue the same treatment that they were receiving at the end of Period 2.~~

Section 7.3. Blinding

During the Extension Period (Period 2), including blinded, randomized withdrawal–retreatment, patients who do not meet entry criteria for participation in the randomized withdrawal–retreatment period (Group A) will continue to receive ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W. Patients having achieved a state of sustained remission and do meet the criteria outlined in Section 5.1 (Group B) will participate in the double-blind, placebo-controlled, randomized withdrawal–retreatment period. During the randomized withdrawal–retreatment period, patients in Group B, study site personnel, and study team will be blinded to study treatment randomization. Patients participating in the randomized withdrawal–retreatment period will continue to receive blinded treatment until ~~Week 64 datalock for Study RHBY has been completed~~the completion of the study or time of flare. Upon flare, patients will be retreated with the ixekizumab treatment regimen assigned in Period 1 in an open-label fashion. Patients who experience a flare and were originally from Study RHBX will not receive open-label treatment until the Week 52 datalock has occurred for Study RHBX.

During the Long-Term Extension Period (Period 3), patients from Group A will continue to receive ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W. Patients from Group B will continue the same treatment they were receiving at the end of Period 2 (ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, or placebo) in blinded fashion until the ~~Week 64 datalock for the randomized withdrawal-retreatment period for Study RHBY has been completed~~completion of the study or time of flare. Upon flare, patients will be retreated with the ixekizumab treatment regimen assigned in Period 1 in an open-label fashion. As of Week 64, patients initially treated with ixekizumab 80 mg Q4W during Period 1 may have their dose escalated to ixekizumab 80 mg Q2W, in an open-label fashion, only after the patient has experienced a flare and been subsequently retreated with ixekizumab 80 mg Q4W for at least 12 weeks.~~Patients may receive open-label treatment thereafter.~~

Patients who experience a flare and were originally from Study RHBX will not receive open-label treatment until the Week 52 datalock has occurred for Study RHBX.

~~During the Long-Term Extension Period (Period 3), patients from Group A will continue to receive ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W. Patients from Group B will continue the same treatment they were receiving at the end of Period 2 (ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, or placebo) in blinded fashion until Week 64 datalock for the~~

~~randomized withdrawal-retreatment period for Study RHBY has been completed. Patients may receive open-label treatment thereafter.~~

Section 7.4. Dosage Modification

~~After 64 weeks of treatment~~As of Week 64, patients in Group A receiving ixekizumab 80 mg Q4W may have their dose escalated to ixekizumab 80 mg Q2W in Period 3 if the investigator determines that the patient may benefit from an increase in frequency of dosing to achieve adequate disease control. Dose escalation may begin at the next scheduled visit or at an unscheduled visit prior to the next scheduled visit.

~~After the 64-week datalock for Study RHBY~~As of Week 64, patients in Group B (Table RHBY.3):

- who are receiving placebo will remain on placebo, and will be monitored per the Schedule of Activities (Section 2) for eligibility (i.e., flare) to be retreated with the ixekizumab treatment regimen they were receiving prior to withdrawal (ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W). ~~After a minimum of 12 weeks on ixekizumab 80 mg Q4W, dosing may be escalated to 80 mg Q2W if the investigator determines that the patient may benefit from an increase in dosing to achieve adequate disease control.~~
- who are receiving ixekizumab 80 mg Q4W may have their dose escalated to ixekizumab 80 mg Q2W in Period 3 if the investigator determines that the patient may benefit from an increase in 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.
- who are receiving ixekizumab 80 mg Q2W will remain on this dose until completion of the study or early discontinuation.

Table RHBY.3. Dosage Modification for Group B during Period 2 and Period 3

Period 1 (Open-Label)	Period 2 (Blinded)	Period 3 (Blinded)	If Flare during Period 2 or 3, Retreat (Open-Label)	12 Weeks after Retreat, Escalate (Period 3) (Open-Label)
ixekizumab 80 mg Q2W	ixekizumab 80 mg Q2W	ixekizumab 80 mg Q2W	ixekizumab 80 mg Q2W	N/A
	placebo	placebo	ixekizumab 80 mg Q2W	N/A
ixekizumab 80 mg Q4W	ixekizumab 80 mg Q4W	ixekizumab 80 mg Q4W	ixekizumab 80 mg Q4W	ixekizumab 80 mg Q2W
	placebo	placebo	ixekizumab 80 mg Q4W	ixekizumab 80 mg Q2W

Abbreviations: N/A = not applicable; Q2W = every 2 weeks; Q4W = every 4 weeks.

Note: Patients from Group B who experience a flare and meet criteria for retreatment during Period 2 or Period 3 will be retreated with the ixekizumab treatment regimen received during Period 1 in an open-label fashion. As of Week 64, patients initially treated with ixekizumab 80 mg Q4W during Period 1 may have their dose escalated to ixekizumab 80 mg Q2W, in an open-label fashion, only after the patient has experienced a flare and been subsequently retreated with ixekizumab 80 mg Q4W for at least 12 weeks. Patients who experience a flare and were originally from Study RHBX will not receive open-label treatment until the Week 52 datalock has occurred for Study RHBX.

Section 7.7. Concomitant Therapy

~~Patients participating in~~During the randomized withdrawal–retreatment ~~period~~ phase of Period 2, patients in Group B are requested to not have any changes to concomitant medications during the 40-week observation period except for the defined retreatment medication or changes needing to be made for an AE or for safety reasons.

Patients undergoing an MRI at Week 24 (see Schedule of Activities, Section 2) may receive premedication of ≤30 mg of morphine or equivalent or other NSAIDs/cyclooxygenase-2 inhibitors, on the day of the MRI, for significant pain as judged by the investigator. Patients with claustrophobia may receive premedication with benzodiazepine; the investigator should assess for potential interactions with other concomitant medication(s), such as opiates.

Table RHBY.4. Concomitant Treatment with NSAIDs and Analgesics, Conventional DMARDs, and Corticosteroids Study RHBY

	Period 1	Period 2	Period 3
NSAIDs and Analgesics	NSAIDs, including COX-2 inhibitors, will be allowed up to the maximum recommended doses for pain. Patients are to be on stable dose during Period 1. Introduction of a new NSAID or dose adjustment to an existing NSAID is not permitted, unless required for safety reasons. Short-acting analgesics with no anti-inflammatory action (such as paracetamol) are permitted and may be administered ad hoc as needed and are to be withheld within the 24-hour period prior to any assessment. Aspirin (dose not exceeding 350 mg/day) may be taken to manage cardiovascular risk. Opiate analgesic use is allowed but not to exceed >30 mg/day of morphine or its equivalent. Patients are to be on stable dose during Period 1. 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.	**Group A**: Alterations of NSAIDs, including COX-2 inhibitors (dose change, introduction, or withdrawal) are allowed. Doses are recommended to be stable in the 2 weeks prior to an arthritis assessment. Short-acting analgesics with no anti-inflammatory action (such as paracetamol) are permitted and may be administered ad hoc as needed but are to be withheld within the 24-hour period prior to any assessment. Aspirin (dose not exceeding 350 mg/day) may be taken to manage cardiovascular risk. Opiate analgesic use is allowed but not to exceed >30 mg/day of morphine or its equivalent. **Group B** (participating in randomized withdrawal): Same as Period 1 until they flare. Once they flare, same as patients in Group A during Period 2.	**Group A ~~and Group B~~**: Alterations of NSAIDs, including COX-2 inhibitors (dose change, introduction, or withdrawal) are allowed. Doses are recommended to be stable in the 2 weeks prior to an arthritis assessment. Short-acting analgesics with no anti-inflammatory action (such as paracetamol) are permitted and may be administered ad hoc as needed but are to be withheld within the 24-hour period prior to any assessment. Aspirin (dose not exceeding 350 mg/day) may be taken to manage cardiovascular risk. Opiate analgesic use is allowed but not to exceed >30 mg/day of morphine or its equivalent. **Group B** (participating in randomized withdrawal): Same as Period 1 until they flare. Once they flare, same as patients in Group A during Period 3.

	Period 1	Period 2	Period 3
Conventional DMARDs	Methotrexate (oral or parenteral up to 25 mg/week), sulfasalazine (up to 3 g/day), or hydroxychloroquine (up to 400 mg/day) is allowed. During Period 1, alteration of cDMARD dose or route, and/or introduction of a new cDMARD are not permitted, unless required for safety reasons. Conventional DMARDs can only be used as single agents and not in combination with other cDMARDs. Any changes must be recorded in the eCRF. If, at any time, the investigator believes that side effects or laboratory abnormalities may be attributable to the cDMARD, the cDMARD dose is to be lowered or the medication stopped. (Note: For all study periods, the maximum allowed doses are 25 mg/week MTX, 400 mg/day hydroxychloroquine and 3 g/day sulfasalazine. Local standards of care are to be followed for concomitant administration of folic or folinic acid if MTX is taken, and for administration of other cDMARDs.)	**Group A**: Methotrexate (oral or parenteral up to 25 mg/week), sulfasalazine (up to 3 g/day), or hydroxychloroquine (up to 400 mg/day) may be allowed, and adjustment of allowed cDMARDs (e.g., dose change, introduction, withdrawal of cDMARDs or replacement of a current cDMARD with the introduction of a new cDMARD) is permitted. Not more than 1 adjustment of cDMARDs at 1 time within 12 weeks is recommended. Conventional DMARDs can only be used as single agents and not in combination with other cDMARDs. Any changes must be recorded in the eCRF. If, at any time, the investigator believes that side effects or laboratory abnormalities may be attributable to the cDMARD, the cDMARD dose is to be lowered or the medication stopped. (Note: For all study periods, the maximum allowed doses are 25 mg/week MTX, 400 mg/day hydroxychloroquine and 3 g/day sulfasalazine. Local standards of care are to be followed for concomitant administration of folic or folinic acid if MTX is taken, and for administration of other cDMARDs.) **Group B** (participating in randomized withdrawal): Same as Period 1 until they flare. Once they flare, same as patients in Group A during Period 2.	**Group A ~~and Group B~~**: Methotrexate (oral or parenteral up to 25 mg/week), sulfasalazine (up to 3 g/day), or hydroxychloroquine (up to 400 mg/day) may be allowed, and adjustment of allowed cDMARDs (e.g., dose change, introduction, withdrawal of cDMARDs or replacement of a current cDMARD with the introduction of a new cDMARD) is permitted. Not more than 1 adjustment of cDMARDs at 1 time within 12 weeks is recommended. Conventional DMARDs can only be used as single agents and not in combination with other cDMARDs. Any changes must be recorded in the eCRF. If, at any time, the investigator believes that side effects or laboratory abnormalities may be attributable to the cDMARD, the cDMARD dose is to be lowered or the medication stopped. (Note: For all study periods, the maximum allowed doses are 25 mg/week MTX, 400 mg/day hydroxychloroquine and 3 g/day sulfasalazine. Local standards of care are to be followed for concomitant administration of folic or folinic acid if MTX is taken, and for administration of other cDMARDs.) **Group B** (participating in randomized withdrawal): Same as Period 1 until they flare. Once they flare, same as patients in Group A during Period 3.

	Period 1	Period 2	Period 3
Corticosteroids	*Oral corticosteroids:* If on oral corticosteroids, the dose must not exceed 10 mg/day of prednisone or its equivalent at any time during the study. During Period 1, treatment alterations in oral corticosteroid dose are strongly discouraged. *Parenteral corticosteroids (intravenous, intramuscular):* Treatment with intravenous or intramuscular corticosteroids is not permitted. *Parenteral corticosteroids (intra-articular):* Intra-articular injection of corticosteroid may be allowed on a limited basis: It is recommended that there be no more than 1 injection within any 1 year period. 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.	**Group A**: *Oral corticosteroids:* 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 the study. *Parenteral corticosteroids (intravenous, intramuscular, intra-articular):* Treatment with parenteral corticosteroids is not recommended. 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. **Group B** (participating in randomized withdrawal): Same as Period 1 until they flare. Once they flare, same as patients in Group A during Period 2.	**Group A ~~and Group B~~**: *Oral corticosteroids:* 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 the study. *Parenteral corticosteroids (intravenous, intramuscular, intra-articular):* Treatment with parenteral corticosteroids is not recommended. 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. **Group B** (participating in randomized withdrawal): Same as Period 1 until they flare. Once they flare, same as patients in Group A during Period 3.

Abbreviations: cDMARD = conventional disease modifying antirheumatic drug; COX-2 = cyclooxygenase-2; eCRF = electronic case report form; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; SJC = swollen joint count; TJC = tender joint count.

Section 8.1.1. Permanent Discontinuation from Study Treatment

[13] The patient becomes hepatitis B virus (HBV) deoxyribonucleic acid (DNA) positive. The patient is to be referred to a specialist physician. Discussion of the timing of discontinuation from study treatment and from the study is provided in Section 9.4.10.2.

Section 9.1.1. Primary Efficacy Assessments

As described in Section 10.3.3.1, the primary efficacy endpoint is the proportion of patients in the randomized withdrawal population who do not experience a flare (a flare is defined as ASDAS ≥2.1 at 2 consecutive visits, or ASDAS >3.5 at any visit during Period 2). The ASDAS is a composite index to assess disease activity in axSpA (Machado et al. 2011a, 2011b; Zochling 2011). The parameters used for the ASDAS (with high sensitivity C-reactive protein [CRP] as acute phase reactant) are the following:

1) Total back pain (BASDAI question 2)
2) Patient global assessment (Section 9.1.2.4)
3) Peripheral pain/swelling (BASDAI question 3)
4) Duration of morning stiffness (BASDAI question 6)
5) CRP in mg/L

The $ASDAS_{crp}$ is calculated with the following equation: 0.121~~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). (Note: CRP is in mg/liter, the range of other variables is from 0 to 10; Ln represents the natural logarithm.)

Section 9.1.2.2.1. Radiographic Imaging of the Spine

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).

Section 9.4.6. Tuberculosis Testing

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.

Section 9.4.10.2. Hepatitis B Monitoring

Hepatitis B virus DNA monitoring will be performed as indicated in the Schedule of Activities (Section 2) for patients positive for hepatitis B core antibody at the screening visit of the originating study (RHBV, RHBW, or RHBX) and who required HBV DNA monitoring during the originating study (RHBV, RHBW, or RHBX).

Table RHBY.5. Major Patient Populations for Study RHBY

Population	Description
Lead-In Period Safety Population	All patients who receive at least 1 dose of ixekizumab in Period 1.
Randomized Withdrawal Intent-to-Treat (ITT) Population	All patients who are randomized in Period 2 (Group B), even if the patient does not receive the correct treatment or does not follow the protocol. Patients will be analyzed according to the treatment which they were assigned.
Randomized Withdrawal Safety Population	All patients in Group B who receive at least 1 dose of study treatment after Period 2 randomization. Patients will be analyzed according to the treatment to which they were assigned.
~~Nonrandomized population~~	~~All patients in Group A who were not randomized in Period 2 and receive at least 1 dose of ixekizumab in Period 2.~~
Ixekizumab Structure Population	All patients who i) are from either RHBV or RHBW study; ii) have been treated with ixekizumab for at least 18 months; and iii) have mSASSS data at both Week 0 in the originating study and Week 56 in RHBY.
Long-Term Ixekizumab Treatment Efficacy Population	All patients who are randomized to ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W at Week 0 of the originating studies and consistently received ixekizumab in RHBY.
Flare Population	All patients in Group B who experience a flare after ~~Period 2~~ randomization at Week 24 and who receive ~~at least 1 dose of ixekizumab in Period 2~~ixekizumab retreatment after flare in Period 2 and Periods 2 and 3 combined (exploratory analyses).

Population	Description
Follow-Up Period Population	All patients who receive at least 1 dose of study treatment at any time during Study RHBY and enter the Post-Treatment Follow-Up Period (Period 4). Patients will be analyzed according to the treatment they were taking before entering Period 4.

Section 10.3.1.1. General Consideration for Analyses during ~~Period 1 (Lead-in)~~the Combined Periods 1, 2, and 3

~~Unless otherwise specified, baseline will be defined as the last available value before the first injection of originating studies for efficacy analyses. For safety analysis, baseline is defined as the last available value before the first dose of study treatment in RHBY.~~

~~Endpoint for Period 1 is defined as the last visit in Period 1 (Week 24; Group A: Visit 5/Group B: Visit 505). Change from baseline will be calculated as the visit value of interest minus the baseline value.Efficacy, health outcome, and safety data collected in Period 1 will be summarized for each ixekizumab dose regimen without inferential statistics.~~

Combined Periods 1, 2, and 3 start at the first injection of ixekizumab 80 Q2W or ixekizumab 80 mg Q4W in Study RHBY and ends on the date of Week 104 (Group A: Visit 14/Group B: Visit 519) or at early termination visit (ETV) prior to Week 104.

Section 10.3.1.1.1. Lead-In Period Safety Population

Safety data collected in Combined Periods 1, 2 and 3 will be summarized for the Lead-In Period Safety Population by combined ixekizumab treatment group and each of the ixekizumab dose groups without inferential statistics.

Section 10.3.1.1.2. Long-Term Ixekizumab Treatment Efficacy Population

The long-term treatment effect in both categorical and continuous variables will be summarized by treatment group at each scheduled visit including Week 24, Week 64, and Week 104, and will also be summarized graphically using the response rate for categorical variables and mean for continuous variables by group at each scheduled visit in the Combined Periods 1, 2, and 3.

Section 10.3.1.2. General Consideration for Analyses during Period 2 (Extension Period, Including Blinded, Randomized Withdrawal–Retreatment)

10.3.1.2.1 Randomized Withdrawal ITT Population

The analysis for all continuous efficacy and health outcome variables, change from baseline to endpoint analysis, will be made using analysis of covariance (ANCOVA) with treatment, baseline value, geographic region, and originating study in the model. Missing data will be imputed using ~~last observation carried forward (LOCF) or~~ modified baseline observation carried forward (mBOCF). Type III sums of squares for the least-squares (LS) means will be used for the statistical comparison; the 95% CI will also be reported.

10.3.1.2.2 Flare Population

For the Flare Population, Period 2 starts at the time of first injection of the retreatment of ixekizumab 80 Q2W or 80 mg Q4W following the flare and ends on the date of Week 64 prior to injection of study treatment (Visit 515) or the ETV before the date of Week 64.

Summary statistics will be provided based on the Flare Population within 16 weeks after the ixekizumab retreatment for patients who have 16 weeks of post-retreatment follow-up. No inferential statistics will be provided. The Kaplan–Meier estimates of the proportion of patients who first regain response on the variables of interest will be carried out at each post-retreatment interval (4 weeks, 8 weeks, and etc.) up to 40 weeks. If a patient has not regained response or discontinues the study by Week 64, the patient will be censored at the date of their last visit during Period 2.

Section 10.3.1.3. General Consideration for Analyses ~~during Period 3 (Long-Term Extension)~~at Week 56 for the 2-Year Radiographic Progression in Spine Assessments

~~Unless otherwise specified, Period 3 starts at the first injection of study treatment at Week 64 (Group A: Visit 10/Group B: Visit 515) and ends on the date of Week 104 (Group A: Visit 14/Group B: Visit 519) or the ETV (between Weeks 64 and 104).~~

~~For the efficacy and health outcomes analysis, baseline is defined as the last available value before the start of treatment in Period 1 from originating study and, in most cases, will be the value recorded at Week 0 (from the originating study).~~

~~For the safety analysis, baseline is defined as last available value before first dose at the start of the Long-Term Extension Period (Week 64; Group A: Visit 10/Group B: Visit 515).~~

~~All efficacy and safety data collected will be summarized without inferential statistics.~~

Assessment of 2-year radiographic progression in the spine from baseline in Studies RHBV and RHBW to Week 56 (Group A: Visit 9/Group B: Visit 513) in Study RHBY will be evaluated by 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 non-progressors 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.

~~**Section 10.3.1.4. General Considerations for Analyses during Period 2 and 3 Combined**~~

~~For patients who are participating in randomized withdrawal-retreatment in Period 2, efficacy, health outcomes, and safety data collected in Periods 2 and 3 combined will be summarized for ixekizumab 80 mg Q2W or ixekizumab Q4W without inferential statistics.~~

~~For efficacy, and health outcomes, baseline is defined as the last available value before the first dose of study medication in Period 2 from originating study and in most cases will be the value recorded at Week 0 (from the originating study).~~

~~For safety analysis, baseline is defined as the last available value before the first dose at the start of Period 2 in RHBY.~~

~~For patients who are not participating in randomized withdrawal-retreatment in Period 2, efficacy, health outcomes, and safety data collected in Periods 2 and 3 combined will be summarized for ixekizumab 80 mg Q2W or ixekizumab Q4W without inferential statistics.~~

Section 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.

~~**Section 10.3.1.5.4. Last Observation Carried Forward**~~

~~An LOCF analysis will be performed on selective continuous efficacy and health outcomes variables. 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.~~

~~Randomized patients without at least 1 postbaseline observation will not be included for evaluation.~~

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 non-monotone missing data using Markov chain Monte Carlo method with the simple imputation model, followed by a sequential regression imputation with the baseline score.

Section 10.3.2.2. Patient Characteristics

Patient characteristics and baseline clinical measures will be summarized ~~for each treatment period~~. 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.

Section 10.3.2.3. Concomitant Therapy

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

Section 10.3.2.4. Treatment Compliance

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

Section 10.3.3.2. Major Secondary Analyses

The 2-year radiographic progression reflected by change from baseline of originating studies RHBV and RHBW to Week 56 of Study RHBY (Group A: Visit 9/Group B: Visit 513) will be measured by mSASSS score and summarized by treatment. The comparison of the ixekizumab treatment group to the historical control will be analyzed by ANCOVA, with baseline score as covariate. The historical control will be defined in the SAP. ~~The historical control aims to include both the Outcome in AS International Study (OASIS cohort; van der Heijde et al. 2005) and the German SpA Inception Cohort (GESPIC; Reveille et al. 2012).~~ Within-treatment changes from baseline along with 95% CI will be assessed by a paired t-test using the LS means.

Section 10.3.3.3. Other Secondary Efficacy Analyses

The secondary efficacy and health outcomes analysis for Period 2 will be based on the Randomized Withdrawal ITT Population or the Flare Population. Additional efficacy and health outcome analysis for combined ~~Period 2 and Period 3~~Periods 1, 2, and 3 analyses will be based on the ~~nonrandomized population~~ Long-Term Ixekizumab Treatment Efficacy Population.

~~Section 10.3.3.3.1. Period 1 (Initial Lead-in treatment period)~~

~~The proportion of patients who achieve sustained remission during the initial lead-in treatment period will be summarized.~~

Combined Periods 1, 2, and 3

The long-term treatment effect in both categorical and continuous variables will be summarized by treatment group at each scheduled visit including Week 24, Week 64, and Week 104. Missing data will be imputed using mNRI for categorical efficacy variables, described in Section 10.3.1.5.2, and mBOCF and multiple imputation for continuous efficacy variables, described in Sections 10.3.1.5.3 and 10.3.1.5.4, respectively.

Section 10.3.3.3.2. Period 2 (Extension Period, Including Blinded, Randomized Withdrawal–Retreatment)

For the Randomized Withdrawal ITT Population, all categorical efficacy variables and treatment group comparisons will be analyzed at each visit using the logistic regression model described in Section 10.3.1.2.1. Missing data will be imputed using the NRI method described in Section 10.3.1.5.1. All continuous efficacy variables and treatment group comparisons will be analyzed at each visit using the ANCOVA models as described in Section 10.3.1.2.1 when appropriate. For the ANCOVA analysis, missing data will be imputed by the mBOCF ~~and LOCF methods~~ as described in Section 10.3.1.5.3 ~~and Section 10.3.1.6.3, respectively~~.

~~Section 10.3.3.3.3. Period 2 and 3 Combined~~

~~Data collected in these study periods for the nonrandomized population will be summarized. The within-treatment group comparisons will be conducted as appropriate.~~

Section 10.3.4. Safety Analyses

For ~~Period 1~~combined Periods 1, 2, and 3, safety data will be summarized for the Lead-In Period Safety Population.

~~For Period 3, the safety data will be summarized for the randomized withdrawal-retreatment safety population and no treatment group comparisons will be performed.~~

~~For Periods 2 and 3 combined, the safety data will be summarized for the nonrandomized population and no treatment group comparisons will be performed.~~

Section 10.3.6.1. Health Outcomes

~~**Period 3 (Long-Term Extended Treatment Period):**~~

~~Data collected in Period 3 will be summarized for the randomized withdrawal ITT population. The within-treatment group comparisons may be conducted as appropriate.~~

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

~~Period 2 and 3~~ Combined Periods 1, 2, and 3:

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

Section 10.3.7. Interim Analysis

The study will have approximately 1 interim database lock and 1 final database lock. The interim database lock ~~and the unblinding~~ 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 final database lock and the analysis will occur when all patients have completed or discontinued the study.~~ 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.

Section 11. References

~~van der Heijde D, Landewé R, van der Linden S. How should treatment effect on spinal radiographic progression in patients with ankylosing spondylitis be measured? *Arthritis Rheum*. 2005;52(7):1979-1985.~~

Appendix 1. Abbreviations and Definitions

Term	Definition
~~**LOCF**~~	~~last observation carried forward~~
mNRI	modified nonresponder imputation

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests to Be Performed by Sponsor-Designated Laboratory

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[b]
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	
HBV DNA[f]	Follicle-stimulating hormone (FSH)[e]
High sensitivity C-reactive protein (CRP)	Ixekizumab serum concentration (pharmacokinetic)
Urine pregnancy test[d] (assayed by clinical study site)	Partial thromboplastin time (PTT)
TB test (e.g., PPD, QuantiFERON®-TB Gold, T-SPOT®)[g]	Prothrombin time/international normalized ratio
	Exploratory storage samples (serum, urine, plasma, and RNA)
	Immunogenicity testing (anti-ixekizumab Ab)

Abbreviations: Ab = antibody; DNA = deoxyribonucleic acid; HBV = hepatitis B virus; PPD = ~~Purified~~purified protein derivative; RNA = messenger ribonucleic acid; ~~RBC = red blood cells;~~ SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; TB = tuberculosis~~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.

d Urine pregnancy test performed locally for women of childbearing potential.

e For female patients ≥40 and <60 years of age who cease menstruation for at least 12 months during study participation, an FSH test may be performed to confirm nonchildbearing potential (FSH ≥40 mIU/mL). FSH test will be performed centrally.

f HBV DNA monitoring will be performed as indicated in the Schedule of Activities for patients positive for hepatitis B core antibody at the screening visit of the originating study (RHBV, RHBW, or RHBX) and who required HBV DNA monitoring during the originating study (RHBV, RHBW, or RHBX). If the result of the HBV DNA testing is positive, the patient is to be discontinued from the study and is to receive appropriate follow-up medical care (refer to Section 9.4.10.2 for further information regarding the timing of discontinuation).

g See Section 9.4.6. In countries where the QuantiFERON®-TB Gold test or T-SPOT® test is available, it may be used instead of the PPD TB test. The QuantiFERON®-TB Gold test and the T-SPOT® test will be performed locally.

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