Protocol I1F-MC-RHCF (a)

A 52-Week Multicenter, Randomized, Open-Label, Parallel-Group Study Evaluating the Efficacy and Safety of Ixekizumab versus Adalimumab in Patients with Psoriatic Arthritis Who Are Biologic Disease-Modifying Anti-Rheumatic Drug Naïve

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Ixekizumab (LY2439821)

Study I1F-MC-RHCF is a Phase 3b/4, multicenter, randomized, open-label, parallel-group study with blinded outcomes assessments evaluating the efficacy and safety of ixekizumab versus adalimumab in patients with psoriatic arthritis who are biologic disease-modifying anti-rheumatic drug naive during a 52-week treatment period.

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Protocol Electronically Signed and Approved by Lilly on 06 March 2017
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1. Synopsis

Title of Study:
A 52-Week Multicenter, Randomized, Open-Label, Parallel-Group Study Evaluating the Efficacy and Safety of Ixekizumab versus Adalimumab in Patients with Psoriatic Arthritis Who Are Biologic Disease-Modifying Anti-Rheumatic Drug Naive

Rationale:
The purpose of this trial is to compare the efficacy and safety of ixekizumab with adalimumab in patients with psoriatic arthritis (PsA) who are biologic disease-modifying anti-rheumatic drug (bDMARD) naive. Adalimumab, a widely used tumor necrosis factor inhibitor, was chosen as an active comparator because of its well-established efficacy and safety profile; treatment with adalimumab is a standard of care. As additional therapies become available, an important question is whether agents with different mechanisms of action have comparable clinical efficacy and safety. To date, no results of a direct comparator study in patients with PsA comparing 2 bDMARDs have been published. This type of study design is important for informing evidence-based treatment decisions with regards to a tumor necrosis factor inhibitor.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To assess whether ixekizumab is superior to adalimumab at Week 24 in the treatment of patients with active PsA as measured by American College of Rheumatology 50 (ACR50) and Psoriasis Area and Severity Index 100 (PASI 100)	• Proportion of patients simultaneously achieving ACR50 and PASI 100 at Week 24
Major Secondary Objectives: To assess whether ixekizumab is noninferior to adalimumab at Week 24 in the treatment of patients with active PsA as measured by ACR50 To assess whether ixekizumab is superior to adalimumab at Week 24 in the treatment of patients with active PsA as measured by PASI 100	• Proportion of patients achieving ACR50 in each treatment group at Week 24 • Proportion of patients achieving PASI 100 in each treatment group at Week 24
Other Secondary Objectives: To assess the effect of treatment with ixekizumab compared with adalimumab as measured by efficacy and quality of life outcomes	<u>PsA Endpoints</u> Time course of response to treatment over 52 weeks as measured by: • Proportion of patients achieving ACR20, ACR50, and ACR70 responses • Change from baseline in individual components of the American College of Rheumatology (ACR) Core Set - tender joint count, swollen joint count, patient's pain assessment, Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity,

Objectives	Endpoints
	C-reactive protein (CRP), and Health Assessment Questionnaire–Disability Index (HAQ-DI) score • Proportion of patients simultaneously achieving ACR50 and PASI 100 response • Change from baseline in the Disease Activity Score (28 diarthrodial joint count) based on C-reactive protein (DAS28-CRP) • Proportion of patients achieving Minimal Disease Activity (MDA) • Proportion of patients achieving Psoriatic Arthritis Response Criteria (PsARC) • Change from baseline in Modified Composite Psoriatic Disease Activity Index (CPDAI) score • Proportion of patients achieving low disease activity or remission according to the Modified Composite Psoriatic Disease Activity Index definition • Proportion of patients with HAQ-DI improvement ≥0.35 • Change from baseline in the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index score in patients with enthesitis at baseline (ie, baseline SPARCC Enthesitis Index score >0) • Change from baseline in the Leeds Enthesitis Index (LEI) score in patients with enthesitis at baseline (ie, baseline LEI score >0) • Proportion of patients with resolution in enthesitis in the subgroup of patients with enthesitis at baseline as measured by the SPARCC Enthesitis Index (ie, baseline SPARCC Enthesitis Index score >0) • Proportion of patients with resolution in enthesitis in the subgroup of patients with enthesitis at baseline as measured by the LEI (ie, baseline LEI score >0) • Change from baseline in the Leeds Dactylitis Index-Basic (LDI-B) score in patients with dactylitis at baseline (ie, baseline LDI-B score >0) • Proportion of patients with resolution in dactylitis in the subgroup of patients with dactylitis at baseline as measured by the LDI-B (ie, baseline LDI-B score >0) <u>Psoriasis/Nail Endpoints</u> Time course of response to treatment over 52 weeks as measured by: • Change from baseline in body surface area (BSA) • Proportion of patients who achieve the following PASI scores: PASI 75, PASI 90, or PASI 100 (defined as 75%, 90%, and 100% improvement from baseline in PASI criteria, respectively) • Proportion of patients achieving an absolute PASI score ≤1 or ≤2 or ≤3 • Change from baseline in the Nail Psoriasis Severity Index (NAPSI) Fingernails score in the subgroup of patients with fingernail involvement at baseline (ie, baseline NAPSI Fingernails score >0) <u>QoL Endpoints</u> Time course of response to treatment over 52 weeks as measured by: • Change from baseline in the Itch Numeric Rating Scale (NRS) score • Proportion of patients with Itch NRS score equal to 0 • Change from baseline in Fatigue Severity NRS score

Objectives	Endpoints

	• Change from baseline in Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)
	  o Physical Component Summary score
	  o Mental Component Summary score
	• Change from baseline in measures of health utility (European Quality of Life–5 Dimensions 5 Level health outcomes instrument [EQ-5D-5L])
	• Change from baseline in Dermatology Life Quality Index (DLQI) total score
	• Change from baseline in Treatment Satisfaction Questionnaire
	
	<u>Safety</u>
	• Change from baseline in Columbia–Suicide Severity Rating Scale (C-SSRS)

Summary of Study Design:

Study I1F-MC-RHCF is a Phase 3b/4, multicenter, randomized, open-label, parallel-group study with blinded outcomes assessments evaluating the efficacy and safety of ixekizumab versus adalimumab in patients with PsA who are bDMARD naive during a 52-week treatment period.

Treatment Groups and Duration:

<u>Ixekizumab: 80 mg subcutaneous (SC) injection</u>

A starting dose of ixekizumab 160 mg (two 80-mg SC injections) will be administered at randomization (Visit 2 [Week 0]) for all patients

- Patients with moderate-to-severe plaque psoriasis (Ps), defined as PASI ≥12, static Physician's Global Assessment (sPGA) ≥3, and BSA ≥10%, will receive ixekizumab 80 mg given as 1SC injection every 2 weeks (Q2W) from Week 2 to Week 12 and every 4 weeks (Q4W) thereafter
- Patients not meeting criteria for moderate-to-severe plaque Ps at randomization will receive ixekizumab 80 mg given as 1 SC injection Q4W starting at Week 4

<u>Adalimumab: 40 mg SC injection</u>

- Patients with moderate-to-severe plaque Ps, defined as PASI ≥12, sPGA ≥3, and BSA ≥10%, will receive a starting dose of adalimumab 80 mg (two 40-mg SC injections) administered at randomization (Visit 2 [Week 0]) followed by 40 mg given as 1 SC injection Q2W starting at Week 1
- Patients not meeting criteria for moderate-to-severe plaque Ps will receive a starting dose of adalimumab 40 mg given as 1 SC injection at randomization (Visit 2 [Week 0]) followed by 40 mg given as 1 SC injection Q2W starting at Week 2

The study will consist of 3 periods:

- Period 1: Screening Period (Visit 1) up to 28 days before randomization (Visit 2)
- Period 2: Open-Label Treatment Period (Visit 2 through Visit 11) from Week 0 to Week 52
- Period 3: Post-Treatment Follow-Up Period occurring from last treatment visit during Period 2 or Early Termination Visit (ETV) up to a minimum of 12 weeks after that visit

Number of Planned Patients:

- Enrolled/Randomized: 550 (275 ixekizumab; 275 adalimumab)

Statistical Analysis:

The total sample size for the study will be 550 patients randomized in a 1:1 ratio to ixekizumab or adalimumab (patients per treatment group) in Period 2.

A significance level of 0.05 is assumed for testing ixekizumab versus adalimumab.

Sample size was calculated assuming the proportion of patients simultaneously achieving ACR50 and PASI 100 as 13.6% and 31.3% in the adalimumab and ixekizumab treatment groups, respectively, as observed in the conventional synthetic disease-modifying anti-rheumatic drug (csDMARD)-experienced population from Study RHAP. According to the nQuery software, a total sample size of 550 patients (with 275 patients per treatment group) using a 2-sided Fisher's exact test at a 0.05 level of significance would yield approximately 99% power for testing ixekizumab versus adalimumab.

This sample size would yield 78% power for testing the noninferiority of ixekizumab to adalimumab at a one-sided 0.025 level of significance based on a noninferiority margin of –12% and using ACR50 response rates of 43.8% and 44.1% as observed for the ixekizumab and adalimumab treatment groups, respectively, in the csDMARD-experienced population from Study RHAP. For testing superiority of ixekizumab to adalimumab based on PASI 100 response rates of 46.9% and 23.7% as observed for ixekizumab and adalimumab in the csDMARD-experienced population from Study RHAP, this sample size would yield 99% power using a 2-sided Fisher's exact test at 0.05 level of significance.

2. Schedule of Activities

Study Schedule, Protocol I1F-MC-RHCF

	Screening Period 1	Treatment Phase: Study Drug Administration						
		Baseline	Open-Label Treatment Period 2[a]					
Visit No (V)	**V1**	**V2**	**V3[b]**	**V4**	**V5**	**V6**	**V7**	**V8**
Study Week (W)		**W0**	**W1**	**W4**	**W8**	**W12**	**W16**	**W24**
Study Days	**-28d**	**0d**	**7 ± 2d**	**28 ± 2d**	**56 ± 2d**	**84 ± 4d**	**112 ± 4d**	**168 ± 4d**
Informed consent	X							
Complete medical history	X							
Review preexisting conditions	X							
Age, sex	X							
Physical examination[c]	X							X
PsA classification criteria (CASPAR criteria)	X							
Inclusion/exclusion criteria	X	X						
Height		X						
Temperature		X						
Weight		X						
Sitting blood pressure and pulse	X	X[d]		X	X	X	X	X
Habits (tobacco, alcohol use)		X						
Concomitant medications	X	X	X	X	X	X	X	X
Review adverse events	X	X	X	X	X	X	X	X
Randomization		X						
Administer Study Drug		See Table RHCF.2.1[e]						
Dispense Study Drug and Study Drug Administration Log		X		X	X	X	X	X
Collect/Review/Enter Data from Study Drug Administration Log		X		X	X	X	X	X
Clinical Efficacy								
Patient-Rated Assessments								
Patient's Assessment of Pain VAS		X		X	X	X	X	X
Patient's Global Assessment of Disease Activity VAS		X		X	X	X	X	X
HAQ-DI		X		X	X	X	X	X
Itch NRS		X		X	X	X	X	X
SF-36		X		X		X	X	X

	Screen-ing Period 1	Treatment Phase: Study Drug Administration						
		Baseline	Open-Label Treatment Period 2[a]					
Visit No (V)	**V1**	**V2**	**V3[b]**	**V4**	**V5**	**V6**	**V7**	**V8**
Study Week (W)		**W0**	**W1**	**W4**	**W8**	**W12**	**W16**	**W24**
Study Days	**-28d**	**0d**	**7 ± 2d**	**28 ± 2d**	**56 ± 2d**	**84 ± 4d**	**112 ± 4d**	**168 ± 4d**
EQ-5D-5L		X		X		X	X	X
Fatigue Severity NRS		X		X		X	X	X
DLQI		X		X	X	X	X	X
Clinician-Rated or Administered Assessments								
TJC/SJC (68/66 joints)	X	X		X	X	X	X	X
Physician's Global Assessment of Disease Activity VAS		X		X	X	X	X	X
PASI		X		X	X	X	X	X
% Body Surface Area	X	X		X	X	X	X	X
Enthesitis Assessment (SPARCC and LEI)		X		X	X	X	X	X
LDI-B		X				X	X	X
sPGA		X						
NAPSI Fingernails		X				X	X	X
C-SSRS	X	X		X	X	X	X	X
Self-Harm Supplement Form and Self-Harm Follow-Up Form	X	X		X	X	X	X	X
Treatment Satisfaction Questionnaire						X		X
Laboratory Tests								
Administer TB test[f]	X							
Chest x-ray	X[g]							
ECG		X[h]						
FSH	X[i]							
HIV/HCV	X							
HBV Panel[j]	X							
HBV DNA[k]	X	X				X		X
Serum pregnancy test[l]	X							
Urine pregnancy test[m]		X				X		X
Serum chemistry	X	X[n]		X		X		X
Hematology	X	X		X		X		X
Urinalysis	X	X						X
RF	X							
hs-CRP		X		X	X	X	X	X

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	Treatment Phase: Study Drug Administration			
	Open-Label Treatment Period 2[a]			
Visit No (V)	**V9**	**V10**	**V11**	**ETV**
Study Week (W)	**W32**	**W40**	**W52**	
Study Days	**224 ± 4d**	**280 ± 4d**	**364 ± 4d**	
Physical examination[c]			X	X
Weight			X	X
Sitting blood pressure and pulse	X	X	X	X
Concomitant medications	X	X	X	X
Review adverse events	X	X	X	X
Administer Study Drug	See Table RHCF.2.1[e]			
Dispense Study Drug and Study Drug Administration Log	X	X		
Collect/Review/Enter Data from the Study Drug Administration Log	X	X	X	X
Clinical Efficacy				
Patient-Rated Assessments				
Patient's Assessment of Pain VAS	X	X	X	X
Patient's Global Assessment of Disease Activity VAS	X	X	X	X
HAQ-DI	X	X	X	X
Itch NRS	X	X	X	X
SF-36	X		X	X
EQ-5D-5L	X		X	X
Fatigue Severity NRS	X		X	X
DLQI	X	X	X	X
Clinician-Rated or Administered Assessments				
TJC/SJC (68/66 joints)	X	X	X	X
Physician's Global Assessment of Disease Activity VAS	X	X	X	X
PASI	X	X	X	X
% Body Surface Area	X	X	X	X
Enthesitis Assessment (SPARCC and LEI)	X	X	X	X
LDI-B	X	X	X	X
NAPSI Fingernails	X	X	X	X
C-SSRS	X	X	X	X
Self-Harm Supplement Form and Self-Harm Follow-Up Form	X	X	X	X
Treatment Satisfaction Questionnaire			X	X
Laboratory Tests				
HBV DNA[k]		X	X	X
Urine pregnancy test[m]	X	X	X	X
Serum chemistry		X	X	X
Hematology		X	X	X
Urinalysis				
hs-CRP	X	X	X	X

Study Schedule, Protocol I1F-MC-RHCF

	Post-Treatment Follow-Up Period 3[o]		
	Required Visits		As Needed
Visit No (V)	**V801**	**V802**	**V803**
Study Week (W)	**LTV + 4W**	**LTV + 12W**	**LTV + 24W**
Study Days	**+/- 14d**	**+/- 14d**	**+/- 14d**
Concomitant medications	X	X	X
Review adverse events	X	X	X
Clinician-Rated or Administered Assessments			
C-SSRS	X	X	X
Self-Harm Supplement Form and Self-Harm Follow-Up Form	X	X	X
Vital Signs/Laboratory Tests			
Sitting blood pressure and pulse	X	X	X
HBV Panel[j]		X	
HBV DNA[k]		X	
Serum chemistry	X	X	X
Hematology	X	X	X

Abbreviations: CASPAR = Classification for Psoriatic Arthritis; C-SSRS = Columbia–Suicide Severity Rating Scale; d = day; DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EQ-5D-5L = European Quality of Life–5 Dimensions 5 Level health outcomes instrument; ETV = Early Termination Visit; Fatigue Severity NRS = Fatigue Severity Numeric Rating Scale; FSH = follicle-stimulating hormone; HAQ-DI = Health Assessment Questionnaire–Disability Index; HBcAb = anti-hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hs-CRP = high sensitivity (assay) C-reactive protein; Itch NRS = Itch Numeric Rating Scale; LDI-B = Leeds Dactylitis Index-Basic; LEI = Leeds Enthesitis Index; LTV = last treatment visit during Period 2 or Early Termination Visit; NAPSI Fingernails = Nail Psoriasis Severity Index Fingernails; PASI = Psoriasis Area and Severity Index; PPD = purified protein derivative; PsA = psoriatic arthritis; RF = rheumatoid factor; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; SJC = swollen joint count; SPARCC = Spondyloarthritis Research Consortium of Canada; sPGA = static Physician Global Assessment of psoriasis; TB = tuberculosis; TJC = tender joint count; VAS = visual analog scale.

[a] If a patient discontinues the study drug early, the patient will complete the ETV and then enter the Post-Treatment Follow-Up Period of the protocol.

[b] Visit 3 will be a phone visit.

[c] One complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed at Visit 1 (screening). All remaining physical examinations throughout the study should include a symptom-directed physical evaluation as well as an examination of the heart, lungs, and abdomen and a visual examination of the skin.

[d] Sitting blood pressure and pulse rate must be measured before study drug dosing and 1 hour postdose at Visit 2 (Week 0).

[e] At randomization (Visit 2) for patients randomized to ixekizumab and for patients with moderate-to-severe plaque Ps symptoms randomized to adalimumab, the second injection of study drug will be administered by the patient or caregiver under site personnel supervision for injection training purposes. Thereafter, study drug will be administered by the patient or caregiver.

[f] In countries where the QuantiFERON®-TB Gold test or T-SPOT® is available, either test may be used instead of the purified PPD TB test. The QuantiFERON®-TB Gold test may be performed locally or centrally; the T-SPOT® must be performed locally. PPD tests must be read 48 to 72 hours after Visit 1. See Section 9.4.4.2 for TB testing details.

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[g] A chest x-ray (posterior-anterior view) will be taken at screening (Visit 1) and assessed locally, unless one has been obtained within the past 6 months and the x-ray or results are available for review.

[h] Obtain ECG within 1 week of Visit 2 (prior to the first dose); assessed locally.

[i] For female patients ≥40 and <60 years of age who have had a cessation of menses for at least 12 months, a follicle-stimulating hormone (FSH) test will be performed to confirm nonchildbearing potential (FSH ≥ 40 mIU/mL).

[j] All patients will be tested for HBV.

[k] Patients who meet criteria for HBV monitoring (see Section 9.4.5.4) will be identified by the central laboratory at baseline and monitored according to the study schedule.

[l] Only for females of childbearing potential.

[m] Only for females of childbearing potential. Additional urine pregnancy testing can be performed at the investigator's discretion or per applicable regulations/guidance.

[n] Visit 2 should be a fasting visit.

[o] Patients receiving study drug who discontinue at any time prior to the end of the study or who complete the study (Week 52) will enter the Post-Treatment Follow-Up Period occurring from last treatment visit or ETV up to a minimum of 12 weeks after that visit. Visit 803 will only occur if a patient's neutrophil counts have not returned to the criteria defined in Sections 5.1.3 and 8.1.1.

Table RHCF.2.1. Study Drug Administration Schedule

Visit	2	3			4				5				6				7								8
Weeks	**0[a]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Ixekizumab 80 mg Q2W/Q4W *Moderate-to-Severe Plaque Ps*[b]	X (160 mg)		X		X		X		X		X		X				X				X				X
Ixekizumab 80 mg Q4W[c]	X (160 mg)				X				X				X				X				X				X
Adalimumab 40 mg Q2W[d]	X (40 mg)		X		X		X		X		X		X		X		X		X		X		X		X
Adalimumab 40 mg Q2W *Moderate-to-Severe Plaque Ps*[e]	X (80 mg)	X		X		X		X		X		X		X		X		X		X		X		X	

Visit								9								10												11
Weeks	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**	**51**	**52**
Ixekizumab 80 mg Q2W/Q4W *Moderate-to-Severe Plaque Ps*[b]				X				X				X				X				X				X				
Ixekizumab 80 mg Q4W[c]				X				X				X				X				X				X				
Adalimumab 40 mg Q2W[d]		X		X		X		X		X		X		X		X		X		X		X		X		X		
Adalimumab 40 mg Q2W *Moderate-to-Severe Plaque Ps*[e]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	

Abbreviations: BSA = body surface area; PASI = Psoriasis Area and Severity Index; Ps = psoriasis; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; sPGA = static Physician Global Assessment of psoriasis.

[a] Starting dose.

Study Drug Administration Schedule

[b] Patients with moderate-to-severe plaque Ps, defined as PASI ≥12, sPGA ≥3, and BSA ≥10%, will receive ixekizumab 80 mg given as 1 SC injection Q2W from Week 2 to Week 12 and Q4W thereafter.

[c] Patients not meeting criteria for moderate-to-severe plaque Ps will receive ixekizumab 80 mg given as 1 SC injection Q4W starting at Week 4.

[d] Patients not meeting criteria for moderate-to-severe plaque Ps will receive a starting dose of adalimumab 40 mg given as 1 SC injection at randomization (Visit 2 [Week 0]) followed by 40 mg given as 1 SC injection Q2W starting at Week 2.

[e] Patients with moderate-to-severe plaque Ps, defined as PASI ≥12, sPGA ≥3, and BSA ≥10%, will receive a starting dose of adalimumab 80 mg (two 40-mg SC injections) administered at randomization (Visit 2 [Week 0]) followed by 40 mg given as 1 SC injection Q2W starting at Week 1.

3. Introduction

3.1. Study Rationale

During the last decade, the treatment of psoriatic arthritis (PsA) has significantly changed. Methotrexate (MTX) or other conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD) such as sulfasalazine or leflunomide are usually initiated as a first line of treatment. In patients with active PsA and an inadequate response or intolerance to a csDMARD, the use of a biologic DMARD (bDMARD) is recommended according to the European League Against Rheumatism (EULAR) and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) working group (Gossec et al. 2016; Coates et al. 2016).

Based on current treatment recommendations, a tumor necrosis factor (TNF) inhibitor is the usual first option for a bDMARD, mainly because of the long-term experience and the well-established efficacy and safety profile of these agents. Five TNF inhibitors have been approved and are available in major markets for the treatment of PsA to-date: etanercept, infliximab, adalimumab, golimumab, and certolizumab. In addition, biosimilars of infliximab, etanercept, and adalimumab (Amjevita package insert, 2016) have been recently approved for use in PsA. New bDMARDs targeting different mechanisms of action have also been approved for the treatment of PsA, with ustekinumab targeting the IL-12/IL-23 pathway, secukinumab and brodalumab targeting the IL-17 pathway, and apremilast, an oral molecule, inhibiting phosphodiesterase 4 (PDE 4). As additional therapies become available, an important question is whether bDMARDs with different mechanisms of action have comparable clinical efficacy and safety. Ixekizumab has been studied in patients with active PsA in a study that included adalimumab as an active control reference arm (Mease et al. 2017). Yet to date, no results of a direct comparator study in patients with PsA comparing 2 bDMARDs have been published. This type of study design is important for informing evidence-based treatment decisions with regard to a TNF inhibitor.

In this study, adalimumab has been chosen as the active comparator, as it is recognized as a standard of care for a bDMARD in the treatment of active PsA.

3.2. Background

PsA is an immune-mediated chronic inflammatory disorder commonly associated with psoriasis (Ps) that occurs in 0.04% to 1% of the general population but in 6% to 42% of patients with psoriasis. It is a progressive, destructive disease that results in deformities, impaired physical function, loss of QoL, and increased mortality (Kavanaugh et al 2016). PsA also has a considerable negative impact on multiple physical and emotional aspects of patients' lives (Gladman et al. 2005; Rosen et al. 2012). Patients with PsA have reported poorer health-related QoL compared to the general population and to Ps patients (Husted et al. 1997; Rosen et al. 2012) and suffer from a similar level of functional impairment to patients with rheumatoid arthritis (RA) (Husted et al. 2013).

The current standard of care for PsA includes nonsteroidal anti-inflammatory drugs; intra-articular and/or systemic glucocorticoids; conventional synthetic disease-modifying

anti-rheumatic drugs (csDMARDs) such as MTX, sulfasalazine (SSZ), leflunomide, and cyclosporine A; and biologic agents such as TNF inhibitors (Gossec et al. 2012; Smolen et al. 2014, Gossec et al. 2016). Although leflunomide has been shown to be effective in improving signs and symptoms of PsA as assessed by Psoriatic Arthritic Response Criteria (PsARC) and American College of Rheumatology 20 score (ACR20), there is only weak evidence that other csDMARDs are effective, though limited controlled clinical trial data are available (Gossec et al. 2012; Mease and Armstrong 2014, Gossec et al. 2016). In a recent randomized controlled trial of patients with PsA treated with MTX, no significant improvement was demonstrated in peripheral arthritis (Kaltwasser et al. 2004, Kingsley et al. 2012). Additionally, csDMARDs have not demonstrated efficacy in treating axial involvement, enthesitis, or dactylitis, though limited data are available (Gossec et al. 2012; Mease and Armstrong 2014). SSZ was effective for axial manifestations in an open-label trial, but not for enthesitis or dactylitis (Clegg et al. 1996; Dougados et al. 1995). Data on radiographic progression on MTX has not been conclusive and only analyzed in a small case-control study; for SSZ, radiographic progression was not prevented in a small case-control study of 20 SSZ-treated patients and 20 matched controls (Ash et al. 2012).

In patients with PsA, TNF inhibitors are effective in treating signs and symptoms, inhibiting or slowing structural progression (mainly bone degradation), and improving skin lesions (Kavanaugh et al. 2006; Mease et al. 2005; Mease et al. 2000; Mease et al. 2004; Kavanaugh et al. 2009; Antoni et al. 2005a; Antoni et al. 2005b). However, between 30% and 40% of patients with PsA have a partial response while others become resistant or intolerant to treatment and continue to accrue disability (Rudwaleit et al. 2010; Nash and Clegg 2005). In addition, infections, malignancies, blood dyscrasias, peripheral neuropathy, and central nervous system and spinal cord demyelination can present as major problems in some patients treated with these agents (Deepak et al. 2013; Ruderman 2012; Singh et al. 2011). Therefore, there is an unmet need for alternative effective medications with a different mechanism of action and an improved safety profile for patients with PsA.

Ixekizumab (LY2439821) is a humanized immunoglobulin G subclass 4 monoclonal antibody that neutralizes the cytokine IL-17A (also known as IL-17). Ixekizumab was developed by humanization and optimization of a mouse anti-human IL-17 antibody. It has a high affinity for and neutralizes the activity of both human and monkey IL-17. It has high specificity to IL-17A and has no cross-reactivity to other IL-17 family members (IL-17B-F). Ixekizumab blocks IL-17 binding to the IL-17 receptor (IL-17R).

A total of 7339 patients (5689 patients with psoriasis, 532 patients with RA, and 1118 patients with PsA) have been treated with at least 1 dose of ixekizumab. The efficacy of ixekizumab in patients with moderate-to-severe plaque psoriasis has been evaluated in 3 large, placebo-controlled, Phase 3 studies (Studies RHAZ, RHBA, and RHBC) involving a total of 2328 patients treated with ixekizumab and 791 patients treated with placebo. Ixekizumab was found to be superior to placebo in all 3 studies during both the induction and maintenance phases. In the 2 studies with etanercept as an active comparator during the induction phase, ixekizumab

was found to be superior to etanercept. Based on these results, ixekizumab has been approved for the treatment of moderate-to-severe psoriasis worldwide.

In patients with PsA, Study RHAP was designed to assess whether ixekizumab 80 mg every 2 weeks (Q2W) or 80 mg every 4 weeks (Q4W) was superior to placebo in the treatment of bDMARD-naive patients with active PsA. Significantly more patients treated with ixekizumab achieved an ACR20, ACR50, and ACR70 response compared with placebo-treated patients at Week 24 (all comparisons p≤.001; nonresponder imputation method):

- ACR20 response - IXEQ2W (62.1%), IXEQ4W (57.9%) versus placebo (30.2%)
- ACR50 response - IXEQ2W (46.6%), IXEQ4W (40.2%) versus placebo (15.1%).
- ACR70 response - IXEQ2W (34.0%), IXEQ4W (23.4%) versus placebo (5.7%).

Among patients with psoriasis at baseline affecting ≥3% body surface area (BSA), a significantly greater percentage of patients achieved PASI 75,PASI 90, and PASI 100 Week 24 (all comparisons (p<.001).

- PASI 75 - IXEQ2W (79.7%), IXEQ4W (71.2%) versus placebo (10.4%).
- PASI 90 - IXEQ2W (67.8%), IXEQ4W (56.2%) versus placebo (6.0%)
- PASI 100 - IXEQ2W (52.5%), IXEQ4W (42.5%) versus placebo (3.0%)

At Week 24, improvements from baseline in physical function, measured by Health Assessment Questionnaire-Disability Index (HAQ-DI), were significantly greater in patients receiving IXEQ4W (−0.44), IXEQ2W (−0.50) than in those receiving placebo (−0.18) (p≤.001). The improvement from baseline in Short Form (36 Items) Health Survey Physical Component Score was also significantly greater at Week 24 for patients receiving IXEQ4W (7.5) and IXEQ2W (8.2) compared with those receiving placebo (2.9) (p≤.01). For patients with dactylitis and LDI-B >0 at baseline, significantly greater improvements in mean LDI-B scores at Week 24 (post hoc analysis) were observed for the IXEQ4W and IXEQ2W groups compared with the placebo group (p≤.01) and complete resolution of dactylitis symptoms (LDI-B=0) at Week 24 (post hoc analysis) occurred at a greater rate in the IXEQ4W (80%) and IXEQ2W (77%) groups than in the placebo group (25%) (p≤.001). For patients with nail involvement at baseline, mean changes from baseline in the NAPSI score at Week 24 were significantly greater for the IXEQ4W (−14.0) and IXEQ2W (−15.5) groups than for the placebo group (−2.4) (p≤.001). Progression of structural damage, measured by changes from baseline in mTSS at Week 24, was significantly less in the IXEQ4W (0.17) and IXEQ2W (0.08) groups than in the placebo group (0.49) (p≤.01).

There was not a statistically significant difference between either ixekizumab group, compared with the placebo group, for the major secondary endpoints of change from baseline to Week 12 in Leeds Enthesitis Index (LEI) (Mease et al. 2017).

Significant therapeutic effects for the signs and symptoms of PsA, physical function, progression of structural damage, and skin manifestations of psoriasis were observed for many endpoints as early as 1 week after initiation of therapy. Effects were observed in the overall bDMARD-naive population and the subpopulation with csDMARD experience. The findings were clinically

significant and indicated that ixekizumab offers a potential therapeutic option for patients with active PsA who are bDMARD naive. Although adalimumab 40 mg Q2W was used as the active control for comparison with placebo, this study was not powered to compare ixekizumab with adalimumab. In addition, the Phase 3 clinical development program conducted in patients with active PsA includes 2 additional studies: Study RHBE in patients who are bDMARD experienced, and Study RHBF, a withdrawal study conducted in csDMARD-inadequate responder (IR) and bDMARD-naive patients.

Study I1F-MC-RHCF (RHCF) is a Phase 3b/4, multicenter, randomized, open-label, parallel-group study with blinded outcomes assessments evaluating the efficacy and safety of ixekizumab versus adalimumab in patients with PsA who are bDMARD naive during a 52-week treatment period. The primary objective of this study is to assess whether ixekizumab is superior to adalimumab as measured by the proportion of patients simultaneously achieving ACR50 and PASI 100 at Week 24. In addition, the effects of ixekizumab on extra-articular manifestations of PsA such as skin, fingernails, enthesitis, dactylitis, and the impact on QoL will be evaluated. This study also evaluates the long-term efficacy and safety of ixekizumab in PsA for up to 1 year.

3.3. Benefit/Risk Assessment

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

More detailed information about the known and expected benefits and risks of adalimumab may be found in the product labeling.

4. Objectives and Endpoints

Table RHCF.4.1 shows the objectives and endpoints of the study.

Table RHCF.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary To assess whether ixekizumab is superior to adalimumab at Week 24 in the treatment of patients with active PsA as measured by American College of Rheumatology 50 (ACR50) and Psoriasis Area and Severity Index 100 (PASI 100)	• Proportion of patients simultaneously achieving ACR50 and PASI 100 at Week 24
Major Secondary Objectives: To assess whether ixekizumab is noninferior to adalimumab at Week 24 in the treatment of patients with active PsA as measured by ACR50 To assess whether ixekizumab is superior to adalimumab at Week 24 in the treatment of patients with active PsA as measured by PASI 100	• Proportion of patients achieving ACR50 in each treatment group at Week 24 • Proportion of patients achieving PASI 100 in each treatment group at Week 24
Other Secondary Objectives: To assess the effect of treatment with ixekizumab compared with adalimumab as measured by efficacy and quality of life outcomes	PsA Endpoints Time course of response to treatment over 52 weeks as measured by: • Proportion of patients achieving ACR20, ACR50, and ACR70 responses • Change from baseline in individual components of the American College of Rheumatology (ACR) Core Set - tender joint count, swollen joint count, patient's pain assessment, Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, C-reactive protein (CRP), and Health Assessment Questionnaire–Disability Index (HAQ-DI) score • Proportion of patients simultaneously achieving ACR50 and PASI 100 response • Change from baseline in the Disease Activity Score (28 diarthrodial joint count) based on C-reactive protein (DAS28-CRP) • Proportion of patients achieving Minimal Disease Activity (MDA) • Proportion of patients achieving Psoriatic Arthritis Response Criteria (PsARC) • Change from baseline in Modified Composite Psoriatic Disease Activity Index (CPDAI) score • Proportion of patients achieving low disease activity or remission according to the Modified Composite Psoriatic Disease Activity Index definition • Proportion of patients with HAQ-DI improvement ≥0.35

Objectives	Endpoints

	• Change from baseline in the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index score in patients with enthesitis at baseline (ie, baseline SPARCC Enthesitis Index score >0)
	• Change from baseline in the Leeds Enthesitis Index (LEI) score in patients with enthesitis at baseline (ie, baseline LEI score >0)
	• Proportion of patients with resolution in enthesitis in the subgroup of patients with enthesitis at baseline as measured by the SPARCC Enthesitis Index (ie, baseline SPARCC Enthesitis Index score >0)
	• Proportion of patients with resolution in enthesitis in the subgroup of patients with enthesitis at baseline as measured by the LEI (ie, baseline LEI score >0)
	• Change from baseline in the Leeds Dactylitis Index-Basic (LDI-B) score in patients with dactylitis at baseline (ie, baseline LDI-B score >0)
	• Proportion of patients with resolution in dactylitis in the subgroup of patients with dactylitis at baseline as measured by the LDI-B (ie, baseline LDI-B score >0)
	
	<u>Psoriasis/Nail Endpoints</u>
	Time course of response to treatment over 52 weeks as measured by:
	• Change from baseline in body surface area (BSA)
	• Proportion of patients who achieve the following PASI scores: PASI 75, PASI 90, or PASI 100 (defined as 75%, 90%, and 100% improvement from baseline in PASI criteria, respectively)
	• Proportion of patients achieving an absolute PASI score ≤1 or ≤2 or ≤3
	• Change from baseline in the Nail Psoriasis Severity Index (NAPSI) Fingernails score in the subgroup of patients with fingernail involvement at baseline (ie, baseline NAPSI Fingernails score >0)
	
	<u>QoL Endpoints</u>
	Time course of response to treatment over 52 weeks as measured by:
	• Change from baseline in the Itch Numeric Rating Scale (NRS) score
	• Proportion of patients with Itch NRS score equal to 0
	• Change from baseline in Fatigue Severity NRS score
	• Change from baseline in Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)
	  o Physical Component Summary score
	  o Mental Component Summary score
	• Change from baseline in measures of health utility (European Quality of Life–5 Dimensions 5 Level health outcomes instrument [EQ-5D-5L])
	• Change from baseline in Dermatology Life Quality Index (DLQI) total score
	• Change from baseline in Treatment Satisfaction Questionnaire
	
	<u>Safety</u>
	• Change from baseline in Columbia–Suicide Severity Rating Scale (C-SSRS)

5. Study Design

5.1. Overall Design

Study RHCF is a Phase 3b/4, multicenter, randomized, open-label, parallel-group study with blinded outcomes assessments evaluating the efficacy and safety of ixekizumab versus adalimumab in patients with PsA who are bDMARD naive during a 52-week treatment period.

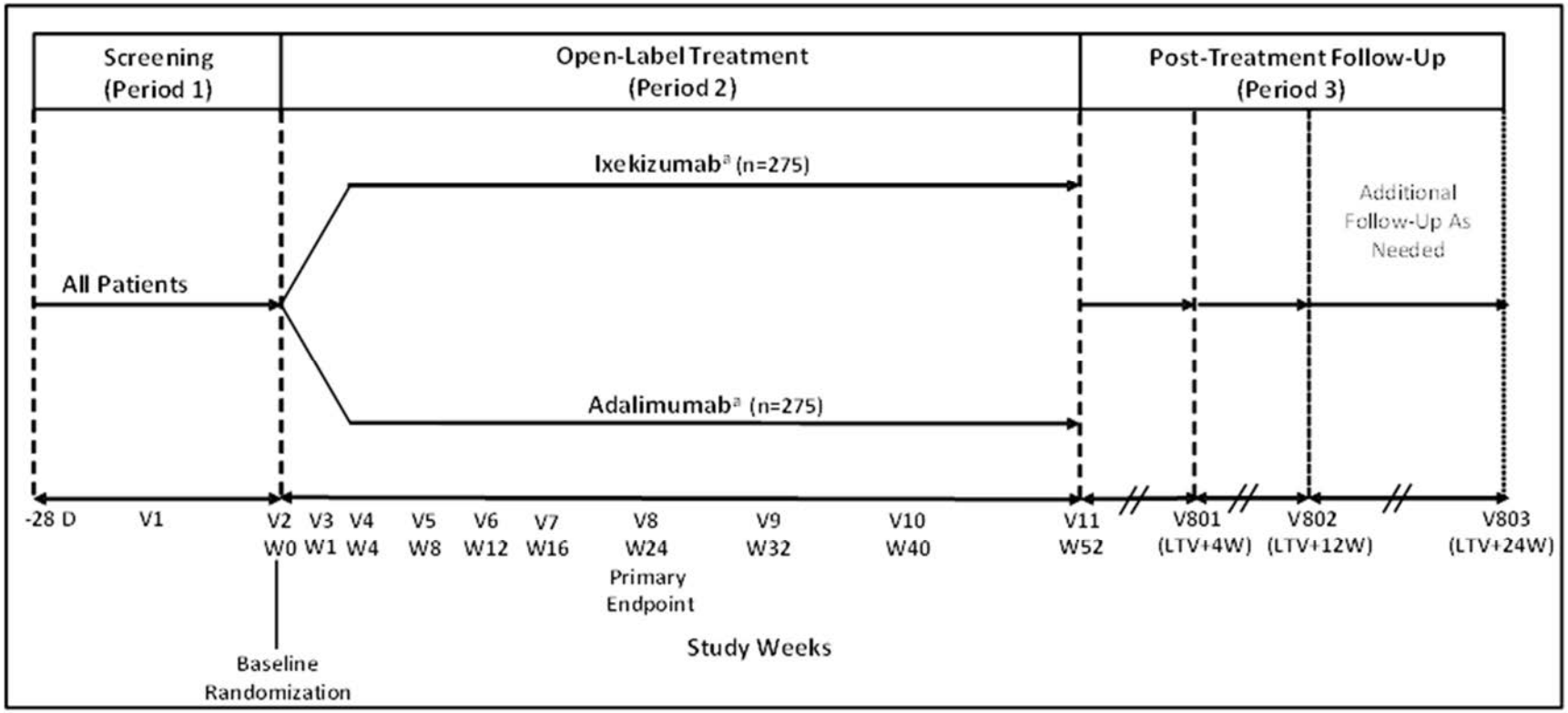
The study will consist of 3 periods:

- Period 1: Screening Period (Visit 1) up to 28 days before randomization (Visit 2)
- Period 2: Open-Label Treatment Period (Visit 2 through Visit 11) from Week 0 to Week 52
- Period 3: Post-Treatment Follow-Up Period occurring from last treatment visit during Period 2 or Early Termination Visit (ETV) up to a minimum of 12 weeks after that visit

All patients randomized to ixekizumab will receive a starting dose of 160 mg at randomization (Visit 2 [Week 0]). Patients with moderate-to-severe plaque Ps will receive ixekizumab 80 mg Q2W from Week 2 to Week 12 and Q4W thereafter. Patients not meeting criteria for moderate-to-severe plaque Ps at randomization will receive ixekizumab 80 mg Q4W starting at Week 4.

Patients randomized to adalimumab with moderate-to-severe plaque Ps will receive a starting dose of 80 mg at randomization (Visit 2 [Week 0]) followed by 40 mg Q2W starting at Week 1. Patients not meeting criteria for moderate-to-severe plaque Ps will receive a starting dose of 40 mg at randomization (Visit 2) followed by 40 mg Q2W starting at Week 2 (see Section 7.1 for details regarding treatments administered).

Figure RHCF.5.1 illustrates the study design.



Abbreviations: D = days; LTV = last treatment visit during Period 2 or Early Termination Visit; V = visit; W = week.
[a] See Section 7.1 for dosing details.

Figure RHCF.5.1. Illustration of study design for Clinical Protocol I1F-MC-RHCF.

All procedures to be conducted during the study, including timing and sequence (as necessary), are indicated in the Schedule of Activities (Section 2). Appendix 2 lists the specific laboratory tests that will be performed for this study.

Patients discontinuing from study treatment who have received at least 1 dose of investigational product will continue to the ETV before proceeding to the Post-Treatment Follow-Up Period (Period 3).

All treatment groups are described in Section 7, and administration of the investigational product is described in Section 7.1.

Excluded and restricted therapies are detailed in Section 7.7.

5.1.1. Screening Period (Period 1)

The duration of the Screening Period (Period 1) will be up to 28 days before randomization at (Visit 2) in the Open-Label Treatment Period (Period 2) to assess patient eligibility. The patient will sign the informed consent form (ICF) before any study assessments, examinations, or procedures are performed.

All inclusion and exclusion criteria are provided in Sections 6.1 and 6.2, respectively. Screening procedures (including complete medical history and demographics) will be performed according to the Schedule of Activities (Section 2). See Section 9.4.4.2 for details regarding required tuberculosis (TB) testing.

Investigators should review the vaccination status of their patients and follow the local guidelines for adult vaccination with nonlive vaccines intended to prevent infectious disease before therapy.

5.1.2. Open-Label Treatment Period (Period 2)

The Open-Label Treatment Period (Period 2) will occur from Week 0 (randomization; Visit 2) to Week 52 (Visit 11). See Section 7 and Table RHCF.7.1 for treatments administered during the Open-Label Treatment Period.

At Week 0 (randomization, Visit 2), routine safety assessments, laboratory tests, and clinical efficacy assessments (including height, weight, and temperature, as well as review of habits) will be performed on eligible patients according to the Schedule of Activities (Section 2). Patients will be randomized at a 1:1 ratio to either ixekizumab 80 mg or adalimumab 40 mg.

During the Open-Label Treatment Period, safety and efficacy parameters in participating patients will be evaluated according to the Schedule of Activities (Section 2).

Patients who permanently discontinue from study treatment for any reason during this period will continue to the ETV before entering the Post-Treatment Follow-Up Period (Period 3; Section 5.1.3).

5.1.3. Post-Treatment Follow-Up Period (Period 3)

All patients receiving at least 1 dose of investigational product will enter the Post-Treatment Follow-Up Period (Period 3), occurring from last treatment visit (LTV) during Period 2 or ETV up to a minimum of 12 weeks after that visit.

The required study visits should occur 4 weeks (Visit 801) and 12 weeks (Visit 802) after the last regularly scheduled visit in Period 2 (or the date of the patient's ETV), except for patients with a concurrent infection that requires systemic anti-infective therapy (described below).

If, at Visit 802, a patient's neutrophil count is ≥1500 cells/μL or greater than or equal to the patient's baseline neutrophil count, the patient's participation in the study will be considered complete unless the investigator determines additional follow-up may be necessary. An additional study visit (Visit 803) 12 weeks after Visit 802 may be required.

If, at the last scheduled visit or ETV, a patient's neutrophil count is <1500 cells/μL (<1.50 × 10^3/μL or <1.50 GI/L) and less than the patient's baseline neutrophil count, the following measures should be taken:

- Patients with concurrent infection: If there is a concurrent infection that requires systemic anti-infective therapy, the patient should receive appropriate medical care and a repeat test for neutrophil count should be performed at least Q4W (or sooner as appropriate) until resolution of infection. Upon resolution of infection, the neutrophil count should be monitored using the required study visits in the Post-Treatment Follow-Up Period (Period 3) design at Visits 801 (4 weeks after resolution of infection), 802 (8 weeks after Visit 801), 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 should be monitored using the required study visits in the Post-Treatment Follow-Up Period (Period 3) design, Visits 801 (4 weeks post ETV or last regularly scheduled visit), 802, and 803 (if necessary); additional visits may be required depending on the degree of neutropenia.
- For Visit 801 and subsequent visits, the following monitoring applies:
  - As long as a patient's neutrophil count is <1000 cells/μL (<1.00 × 10^3/μL or <1.00 GI/L) at any follow-up visit, the patient should return for additional visits at least Q4W (unscheduled visits may be required).
  - As long as a patient's neutrophil count is ≥1000 cells/μL and <1500 cells/μL (≥1.00 × 10^3/μL and <1.50 × 10^3/μL or ≥1.00 GI/L and <1.50 GI/L) at any follow-up visit, the patient should return for additional visit(s) at least every 4 to 8 weeks (unscheduled visits may be required).

- If at Visit 803 the patient's neutrophil count remains <1500 cells/μL (<1.50 × 10^3/μL or <1.50 GI/L) and less than the patient's baseline neutrophil count or if the investigator deems additional follow-up may be necessary, the investigator in consultation with Eli Lilly and Company (Lilly) or qualified designee will determine the appropriate management of the patient and the appropriate timing of additional contact(s) or visit(s).
- If at Visit 802 or Visit 803 the patient's neutrophil count is ≥1500 cells/μL (≥1.50 × 10^3/μL or ≥1.50 GI/L) or greater than or equal to the patient's baseline neutrophil count (whichever is lower), the patient's participation in the study will be considered complete unless the investigator deems additional follow-up necessary.

For patients who completed or discontinued study treatment and have entered the Post-Treatment Follow-Up Period (Period 3), PsA therapy with another agent is allowed, as determined appropriate by the investigator.

5.2. Number of Participants

Approximately 917 participants will be screened (assuming a 40% screen failure rate) to achieve randomization of 550 participants (275 per treatment group) and approximately 396 patients are expected to complete Week 52 (assuming 72% completion rate at Week 52).

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 randomized patient.

5.4. Scientific Rationale for Study Design

See Section 3.1 for scientific rationale for study design.

5.5. Justification for Dose

Protocol RHCF will include a starting dose of ixekizumab 160 mg for all patients randomized to ixekizumab followed by either ixekizumab 80 mg Q4W for patients not meeting criteria for moderate-to-severe plaque Ps or ixekizumab 80 mg Q2W (until Week 12) and then Q4W for patients with moderate-to-severe Ps.

Given the similar benefit/risk profile of the 2 dosing regimens studied in the pivotal Phase 3 studies, the dose justification for patients with PsA includes the following:

Dose Justification for Patients with PsA without Coexistent Moderate-to-Severe Plaque Psoriasis

Rationale: Studies RHAP and RHBE examined the effect of 2 dose regimens (80 mg Q2W and 80 mg Q4W) of ixekizumab compared to placebo in patients with active PsA. Overall, there were no clinically meaningful differences between the ixekizumab 80 mg Q2W and Q4W dosing regimens (Mease et al. 2017). The less-frequent ixekizumab regimen (Q4W) provided therapeutic benefit comparable to the more frequent regimen (Q2W) across a range of efficacy

endpoints up to Week 24 (Studies RHBE and RHAP) with efficacy sustained through Week 52 (Study RHAP) (Mease et al. 2016). While there were some numeric differences, the overall safety profiles were similar for the Q2W and Q4W dosing regimens. There were no unexpected findings in safety analyses, including within subgroups, across the 2 ixekizumab dosing regimens based on the previously recognized safety profile from the psoriasis clinical development program. The findings were confirmed with the exposure-response analyses of efficacy and safety.

Dose Justification for Patients with PsA with Coexistent Moderate-to-Severe Plaque Psoriasis

Rationale: Evidence from the pivotal Phase 3 trials for moderate-to-severe plaque psoriasis (Studies RHAZ, RHBA, and RHBC) demonstrated additional clinical benefit on skin measures for the ixekizumab 80 mg Q2W dosing regimen versus the Q4W dosing regimen at Week 12 (Gordon et al. 2016). In the pivotal Phase 3 studies for PsA, this additional clinical benefit was observed in patients with PsA who had higher levels of skin involvement (ie, BSA ≥10%) and those defined as having coexistent moderate-to-severe plaque psoriasis (Studies RHBE and RHAP). Given there were no meaningful differences in safety between these dosing regimens in patients defined as having coexistent moderate-to-severe plaque psoriasis, it is recommended that such patients use the dosing regimen approved for patients with moderate-to-severe plaque psoriasis.

Dose Justification for the 52-Week Study Duration

In addition, long-term efficacy and safety were evaluated for up to 52 weeks in Study RHAP. For patients who remained on ixekizumab after 24 weeks of treatment, durability of the therapeutic effects was observed for up to 52 weeks of treatment across relevant clinical domains of PsA, including the signs and symptoms of disease activity, as represented by ACR20/50/70 responses; physical function, as assessed by HAQ-DI; and skin manifestations of psoriasis, as assessed by PASI 75/90/100, indicating clinically meaningful responses. The overall efficacy findings when placed in the context of the safety results from the Extension Period for the ixekizumab dosing regimens of this global, multicenter study are consistent with a favorable benefit/risk profile for the long-term treatment with ixekizumab in patients with active PsA (Mease et al. 2016).

Lilly considers it appropriate to evaluate these 2 dose regimens in Study RHCF with regard to:

- The positive efficacy results (eg, primary endpoint achieved in the bDMARD naive patients) and the currently known safety profile from Study RHAP
- The overall consistency of the safety profile of ixekizumab across the patient populations studied thus far, including Ps, RA, and PsA
- The recommended dose regimen for the treatment of PsA and moderate-to-severe plaque psoriasis, respectively.

The evidence indicates a favorable benefit/risk profile that supports the conduct of the proposed PsA study, Study RHCF.

Adalimumab 40 mg subcutaneous (SC) Q2W was selected as the comparator because it is an approved therapy for the treatment of PsA and reflects the bDMARD treatment considered to be a standard of care. Adalimumab will be dosed according to its approved labelling. The subset of patients with PsA associated with moderate-to-severe plaque psoriasis will receive the dosing regimen approved for the treatment of moderate-to-severe plaque psoriasis.

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

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

Type of Patient and Disease Characteristics

Patients with a documented diagnosis of PsA for at least 6 months fulfilling the Classification for Psoriatic Arthritis (CASPAR) and the activity of disease as defined by the presence of at least 3 swollen joints (66 joints) and 3 tender joints (68 joints) in patients who are bDMARD naive. Patients must have active psoriatic skin lesions (plaque) of plaque psoriasis with a BSA of at least 3%.

Patient Characteristics

[1] Are male or female patients 18 years or older

[1a] Male patients agree to use a reliable method of birth control during the study.

[1b] Female patients:

Are women of childbearing potential who test negative for pregnancy and agree to use a reliable method of birth control or remain abstinent during the study and for at least 12 weeks after the last dose of investigational product, whichever is longer. Methods of contraception considered acceptable when used properly include oral contraceptives, contraceptive patch, injectable or implantable contraceptives, intrauterine device, vaginal ring, diaphragm with contraceptive gel, or condom with contraceptive foam.

OR

Are women of nonchildbearing potential, 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 FSH test confirming nonchildbearing potential (≥40 mIU/mL).

[2] Have a documented diagnosis of PsA for at least 6 months and currently meet the CASPAR classification criteria.

[3] Have active PsA defined as the presence of at least 3/68 tender and at least 3/66 swollen joints at Visit 1 (Screening) and Visit 2 (Week 0).

[4] Have active psoriatic skin lesions (plaque psoriasis) with a BSA ≥3% at Visit 1 (Screening) and Visit 2 (Week 0).

[50] Have had an inadequate response when treated with 1 or more csDMARDs.

Informed Consent

[5] Have given written informed consent approved by Lilly, or its designee, and Institutional Review Board/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 at screening:

[6] 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

[7] Have received any prior, or are currently receiving, treatment with any bDMARD therapy or small-molecule for PsA or for psoriasis, including investigational therapies (such as but not limited to TNF inhibitors, IL-1 receptor antagonists, IL-6 inhibitors, anti-IL-12/23p40 therapies, T cell or B cell targeted therapies, or Janus kinase inhibitors).

Exception: previous treatment of phosphodiesterase type 4 inhibitors will be permitted. Treatment with phosphodiesterase type 4 inhibitors must have been discontinued at least 8 weeks before randomization (Visit 2).

[8] Have previously completed or withdrawn from this study or any other study investigating ixekizumab or other IL-17 inhibitors, eg, anti-IL-17 or anti-IL-17 receptor (anti-IL-17R) monoclonal antibodies.

[9] Have a history of drug-induced Ps.

[10] Have used csDMARDs other than MTX, leflunomide, sulfasalazine, or cyclosporine in the 8 weeks prior to randomization (Visit 2).

Have discontinued MTX, sulfasalazine, or cyclosporine within 12 weeks prior to randomization.

If taking MTX, leflunomide, sulfasalazine, or cyclosporine, must have been treated for at least 12 weeks prior to randomization *and* on a stable dose for at least 8 weeks prior to randomization, as follows: oral or parenteral MTX = 10 to 25 mg/week, leflunomide = 20 mg/day, sulfasalazine = up to 3 g/day, or cyclosporine up to 5 mg/kg/day. The dose of these allowed concomitant medications must remain unchanged during the first 24 weeks of the Open-Label Treatment Period unless changes are required for safety issues. Local standard of care should be followed for concomitant administration of folic acid with MTX.

[11] Have discontinued leflunomide within 4 weeks prior to randomization or have received leflunomide from 4 to 12 weeks prior to randomization and have not undergone a drug elimination procedure.

[12] Use of oral corticosteroids at average daily doses of >10 mg/day of prednisone or its equivalent, or use of variable doses of any oral corticosteroids, within 4 weeks prior to randomization (Visit 2).

[13] Have received any parenteral glucocorticoid administered by intraarticular, intramuscular, or intravenous (IV) injection within 6 weeks prior to randomization, or for whom a parenteral injection of glucocorticosteroids is anticipated during the first 24 weeks of the Open-Label Treatment Period.

[14] Concomitant use of nonsteroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors, unless the patient is on a stable dose for at least 2 weeks prior to randomization (Visit 2).

[15] Use of any opiate analgesic at average daily doses of >30 mg/day of morphine or its equivalent or use of variable doses of any opiate analgesic within 6 weeks prior to randomization (Visit 2).

[16] Have received systemic nonbiologic Ps therapy other than csDMARDs or corticosteroids as indicated above (including, but not limited to oral psoralens and ultraviolet A light therapy oral retinoids, thioguanine, hydroxyurea, sirolimus, azathioprine, fumaric acid derivatives, or 1, 25 dihydroxy vitamin D3 and analogs) or phototherapy (including either oral and topical ultraviolet A, ultraviolet B or self-treatment with tanning beds or therapeutic sunbathing) within 4 weeks prior to randomization (Visit 2);

OR

Had topical Ps treatment within the previous 2 weeks prior to randomization (Visit 2).

Exceptions: weak potency (WHO Group 1 classification) topical steroids will be permitted.

[17] Patients with plaque Ps, who cannot avoid use of tanning booths for at least 4 weeks prior to randomization (Visit 2) and during the study.

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

[19] Have ever received efalizumab or natalizumab or other agents that target alpha-4-integrin.

[20] Had a live vaccination within 12 weeks prior to randomization (Visit 2), or intend to have a live vaccination during the course of the study, or within 12 weeks of completing treatment in this study, or have participated in a vaccine clinical study within 12 weeks prior to randomization. Investigators should review the vaccination status of their patients and follow the local guidelines for adult vaccination with nonlive vaccines intended to prevent infectious disease prior to therapy.

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

[21] Had a vaccination with Bacillus Calmette-Guérin (BCG) within 12 months prior to randomization (Visit 2), or intend to have this vaccination with BCG during the course of the study, or within 12 months of completing treatment in this study.

[22] Have a diagnosis of other inflammatory arthritic syndromes such as RA, ankylosing spondylitis, reactive arthritis, or enteropathic arthritis.

[23] Have active Crohn's disease or active ulcerative colitis (UC).

[24] Have fibromyalgia or other chronic pain condition that would confound evaluation of the patient.

[25] Have evidence of active vasculitis or uveitis.

[26] Have had surgical treatment of a joint within 8 weeks prior to randomization or will require such up to Week 24.

[27] Have had any major surgery within 8 weeks prior to randomization, or will require such during the study that in the opinion of the investigator and in consultation with Lilly or its designee would pose an unacceptable risk to the patient.

[28] Have diagnosis or history of malignant disease within the 5 years prior to randomization (Visit 2). Note: Patients with successfully treated basal-cell carcinoma (no more than 3), squamous-cell carcinoma of the skin (no more than 2) within the 5 years prior to randomization may participate in the study.

[29] Presence of significant uncontrolled cerebrocardiovascular events (for example, myocardial infarction [MI], unstable angina, unstable arterial hypertension, moderate-to-severe [NYHA class III/IV] heart failure, or cerebrovascular accident), respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic or neuropsychiatric disorders, or abnormal laboratory values, or illicit drug use (including cannabinoids, whether legalized or not) at screening that in the opinion of the investigator pose an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.

[30] Have a history of uncompensated heart failure, fluid overload, or MI, or evidence of new-onset ischemic heart disease or other serious cardiac disease, within 12 weeks prior to randomization (Visit 2).

[31] Presence of significant uncontrolled neuropsychiatric disorder; have recent history (within 30 days prior to screening visit (Visit 1) and any time between screening visit (Visit 1) and randomization (Visit 2) of a suicide attempt; 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 C-SSRS) or develops suicide-related behaviors as recorded on the C-SSRS at screening or randomization (Visit 2); or are clinically judged by the investigator to be at risk for suicide.

[32] Have presence or personal history or family history (first degree relative) of demyelinating disorder.

[33] Patients who have:

- in the past 12 weeks prior to randomization:
  - had a serious infection (for example, pneumonia, cellulitis)
  - have been hospitalized for an infection
  - have received IV antibiotics for an infection
- or in the past 24 weeks prior to randomization had a serious bone or joint infection,
- or have ever had
  - an infection of an artificial joint
  - an infection that occurs with increased incidence in an immunocompromised host (including, but not limited to, *Pneumocystis jirovecii* pneumonia, active histoplasmosis, or coccidioidomycosis); or have a known immunodeficiency.

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

[35] Have or had a herpes zoster or any other clinically apparent varicella-zoster virus infection within 12 weeks prior to randomization (Visit 2).

[36] Have evidence or suspicion of active or latent TB (refer to Section 9.4.4.2 for details on determining full TB exclusion criteria).

[37] Have any other active or recent infection other than mentioned above within 4 weeks of randomization (Visit 2) that, in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study.

Note: These patients may be rescreened one time ≥4 weeks after documented resolution of symptoms.

[38] Have a sitting systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg.

Note: Determined by 2 consecutive elevated readings. If an initial sitting blood pressure reading exceeds this limit, the blood pressure may be repeated once after the patient has rested sitting for ≥10 minutes. If the repeat value is less than the criterion limits, the second value may be accepted.

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

[40] Have evidence of or test positive for hepatitis B virus (HBV) by testing positive for: 1) HBV surface antigen (HBsAg+); OR 2) anti-hepatitis B core antibody (HBcAb+) and are HBV deoxyribonucleic acid (DNA) positive.

Note: Patients who are HBsAg-, and HBcAb+ and HBV DNA negative may be enrolled in the study. Patients who meet these criteria at screening will be identified by the central laboratory and monitored during the study as detailed in Section 9.4.5.4.

[41] Have evidence of or test positive for hepatitis C virus (HCV). A positive test for HCV is defined as: positive for hepatitis C antibody (anti-HCVAb) and positive via a confirmatory test for HCV (for example, HCV polymerase chain reaction).

[42] **Laboratory tests may not be repeated unless there is a technical error or clinical reason to believe a result may be erroneous.** Laboratory tests can be repeated a maximum of 1 time, and results must be received and reviewed prior to randomization (Visit 2). For eligibility, the most recent lab panel must not meet any of the following criteria:

[42a] Neutrophil count <1500 cells/µL

[42b] Lymphocyte count <800 cells/µL

[42c] Platelet count <100,000 cells/µL

[42d] Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal (ULN)

[42e] Total white blood cell count <3000 cells/µL

[42f] Hemoglobin <8.5 g/dL (85.0 g/L) for male patients and <8.0 g/dL (80 g/L) for female patients

[42g] Serum creatinine >2.0 mg/dL

[42h] Have clinical laboratory test results at screening that are outside the normal reference range for the population and are considered clinically significant, per investigator assessment.

[43] Have any condition or contraindication as addressed in the local labelling for adalimumab that would preclude the patient from participating in this protocol.

[44] Have any other condition that precludes the patient from following and completing the protocol, in the opinion of the investigator.

[45] Are women who are breastfeeding.

[46] Are study site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[47] Are Lilly employees or its designee or are employees of third-party organizations involved in the study.

[48] Are currently enrolled in, or discontinued from a clinical trial involving an investigational product or nonapproved use of a drug or device within the last 4 weeks or a period of at least 5 half-lives of the last administration of the drug, whichever is longer, or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

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

6.3. Lifestyle Restrictions

Patients should be instructed to inform the blood bank of their participation in this study and consult with the investigator before donating blood or blood products during participation in the study.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under the following circumstances: patients who test positive for latent TB at screening may be rescreened following appropriate treatment as described in Section 9.4.4.2. Additionally, patients who do not qualify at screening under Exclusion Criterion [37] may be rescreened once, 4 or more weeks after documented resolution of symptoms. When rescreening is performed, the individual must sign a new ICF and will be assigned a new study identification number.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of ixekizumab with adalimumab. Table RHCF.7.1 shows the treatment regimens.

Table RHCF.7.1. Treatment Regimens

Name of Drug	Starting Dose	Dosage	Frequency	Route of Administration
Ixekizumab	160 mg for all patients	80 mg	Q2W from Week 2 to Week 12 and Q4W thereafter for patients with moderate-to-severe plaque Ps --- Q4W starting at Week 4 for patients not meeting criteria for moderate-to-severe plaque Ps	SC injection
Adalimumab	80 mg for patients with moderate-to-severe plaque Ps --- 40 mg for patients not meeting criteria for moderate-to-severe plaque Ps	40 mg	Q2W starting at Week 1 for patients with moderate-to-severe plaque Ps --- Q2W starting at Week 2 for patients not meeting criteria for moderate-to-severe plaque Ps	SC injection

Abbreviations: Ps = psoriasis; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous.

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

- explaining the correct use of the investigational agent(s) to the patient/site personnel
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- at the end of the study returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law

7.1.1. Administration of Investigational Product

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

Training: At randomization (Visit 2), patients randomized to ixekizumab and patients with moderate-to-severe plaque Ps symptoms randomized to adalimumab will receive 2 injections. For training purposes, the proper procedures for administration of the initial injection will be performed by clinical staff. The second injection of study drug will be administered by the patient or caregiver under site personnel supervision. Thereafter, study drug should be administered by the patient or caregiver. If additional training is necessary, an injection may be administered by the patient or caregiver under the supervision of clinical staff.

Administration: If the patient is unable to administer the injection, a caregiver who will also be trained under supervision of site staff may administer the study drug. All subsequent injections will be administered by the patient or caregiver and should be administered unsupervised by the clinical staff (see Section 2). It is recommended that for these subsequent injections, the patient/caregiver administer the study drug outside the trial site, preferably at the patient's home. If the patient or caregiver is not able to administer the second injection of the starting dose or any dose throughout the study, study site personnel may administer that injection.

Refer to the appropriate directions for use provided by the sponsor for the study drug.

Study Drug Administration Logs will be dispensed to each patient as needed for recording pertinent data about each injection; details of the use of these logs are provided in Section 7.2.1.

Observation: Patients should remain under observation for at least 1 hour after dosing at randomization (Visit 2) to allow for observation for any AEs and collection of postinjection sitting BP and pulse measurements approximately 1 hour after administration of study drug (see Section 2).

7.1.2. Packaging and Labeling

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 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.

Adalimumab 40 mg will be supplied as single-dose, prefilled, disposable manual syringes with study-specific labels.

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

Patients who meet all Visit 1 and Visit 2 eligibility criteria for enrollment will be randomized at Visit 2 (Week 0) in a 1:1 ratio to open-label treatment with ixekizumab or adalimumab at Week 0 (Visit 2). Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign investigational product to each patient. Site personnel will confirm that they have located the correct investigational product by entering a confirmation number found on the investigational product into the IWRS. The randomization will be stratified by concomitant csDMARD use at baseline (Yes vs No) and moderate-to-severe plaque psoriasis involvement (Yes vs No).

7.2.1. Selection and Timing of Doses

Patients taking ixekizumab or adalimumab will receive the open-label study drug beginning on the day of Visit 2 (Week 0).

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

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

Patients will be instructed to contact their study site in the event of an injection problem. In addition, site personnel review all Study Drug Administration Logs at each visit to identify any product complaints, and they will complete a product complaint form for each operation failure reported on a Study Drug Administration Log (see Section 9.2.2 for additional instructions regarding complaint handling).

7.3. Blinding

This is an open-label study where treatment allocation is revealed after randomization. Specifically:

- A blinded assessor will complete the following assessments:
  - TJC/SJC
  - Psoriasis Area and Severity Index (PASI)
  - Percentage of BSA
  - Enthesitis
  - LDI-B
  - NAPSI Fingernails
  - sPGA

The blinded rater must not know the patient's treatment allocation and is not allowed to be otherwise involved in the study procedures.

The patients will be clearly instructed not to communicate with the blinded assessor except for communication required to conduct the blinded data assessment. During each procedure conducted by a blinded assessor, a third person from the study site (eg, a nurse) will be present to observe and document that blinding of the assessor is maintained. If a blinded assessor is unintentionally unblinded, he/she must be replaced as an assessor.

The availability of a blinded assessor is a prerequisite for study site selection.

7.4. Dosage Modification

Not applicable.

7.5. Preparation/Handling/Storage/Accountability

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

Investigational product will be stored refrigerated (2°C to 8°C; 36°F to 46°F) in its original carton to protect from light. Investigational product should not be frozen or shaken.

Sites will be required to monitor temperature of the on-site storage conditions of investigational products.

7.6. Treatment Compliance

Every attempt will be made to select patients who have the ability to understand and comply with study instructions. The investigator is responsible for discussing methods to ensure high treatment compliance with the patient before randomization.

Randomized patients will record the date and time of administration of investigational product in a Study Drug Administration Log throughout their participation in the study. The data from the Study Drug Administration Log must be transcribed into the eCRF by site personnel.

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 investigational product packaging, and/or direct questioning.

The patient should be instructed to retain all empty study drug packaging after using up the medication and to bring the empty packaging and any unused medication to the study site at each visit, so that the site staff can record the amount of medication used since the last visit. Deviation(s) from the prescribed dosage regimen should be documented.

If a patient is noncompliant with study procedures and/or study drug administration, the investigator should assess the patient to determine the reason for noncompliance and educate and/or manage the patient as appropriate to improve compliance. If, in consultation with Lilly or its designee, the noncompliance is deemed to be significant or if further noncompliance occurs, the patient should be discontinued from the study (see Section 10.3.2.4 Treatment Compliance).

In some circumstances, it may be necessary to temporarily interrupt treatment (see Section 8.1.2 and Section 9.4.5). Any necessary interruption of treatment should be considered when determining noncompliance.

7.7. Concomitant Therapy

All concomitant medication taken during the study must be recorded on the Concomitant Medication case report form (eCRF) at the study visits indicated in the Schedule of Activities (Section 2). Treatment with concomitant PsA therapies during the study will be permitted only as outlined in the inclusion and exclusion criteria (Sections 6.1 and 6.2, respectively) and as described below. Patients taking permitted PsA medications should be on stable doses at randomization (Visit 2) and through the first 24 weeks of the Open-Label Treatment Period, as specified below, unless changes are required for safety reasons. Table RHCF.7.2, Table RHCF.7.3, and Table RHCF.7.4 summarize concomitant medications that are and are not permitted and the conditions for use during the study for those which are permitted.

Table RHCF.7.2. Concomitant Medications Permitted/Not Permitted in the Open-Label Treatment Period from Week 0 to Week 24 for Treatment of PsA and Chronic Conditions

Drug Class	As Needed	Chronic Use	Conditions for Use
bDMARDs	N	N	Not allowed
PDE4 or JAK inhibitors	N	N	Not allowed
csDMARDs	N	Y	Stable dose allowed. Stable doses with no dose adjustments, changes, and/or introduction of a new csDMARD Allowed doses: • Oral or parenteral MTX; 10 to 25 mg/week • Leflunomide: up to 20 mg/day • Sulfasalazine: up to 3 g/day • Cyclosporine: up to 5 mg/kg/day
Live vaccines (including BCG)	N	N	Not allowed
Phototherapy	N	N	Not allowed

Drug Class	As Needed	Chronic Use	Conditions for Use
NSAIDs, COX-2 inhibitors	N	Y	Stable doses with no dose adjustments, changes, and/or introduction of a new NSAID. Allowed up to the maximum recommended doses for pain. Aspirin (doses not exceeding 350 mg/day) may be taken to manage cardiovascular risk.
Opiate analgesics	N	Y	Stable doses with no dose adjustments, changes, and/or introduction of a new opiate analgesic. May be used at average daily doses ≤30 mg/day of morphine or its equivalent
Nonopiod analgesics (paracetamol and acetaminophen)	Y	Y	Allowed up to the maximum recommended doses for pain. May be administered as needed basis during the study, but should be withheld within 24 hours of a visit. May be used at doses ≤1000 mg for premedication for allergic/hypersensitivity reactions from injections (see Section 7.8.3)
Topical steroids	Y	Y	Weak potency (WHO Group 1 classification only as needed, but not within 24 hours of PASI assessment
Oral corticosteroids	N	Y	Stable doses with no dose adjustments, changes, and/or introduction of a new oral corticosteroid Allowed doses: ≤ an average daily dose of 10 mg/day of prednisone or equivalent)
Intravascular and IM glucocorticoid	N	N	Not allowed
Intra-articular glucocorticoid	N	N	Not allowed
Inhaled steroids	Y	Y	As needed or regular use for asthma is permitted
Nasal corticosteroids	Y	Y	Use for allergies is permitted
Medicated shampoos Topical moisturizers/emollients and other nonprescription topical products Bath oils and oatmeal bath preparations	Y	Y	Shampoos that do not contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogs Topical moisturizers/emollients and other nonprescription topical products that do not contain, urea, >3% salicylic acid, alpha- or beta-hydroxyl acids, corticosteroids, or vitamin D3 analogs Allowed These topical therapies are not to be used within 12 hours prior to a study visit

Abbreviations: BCG = Bacillus Calmette-Guérin; bDMARD = biological disease-modifying anti-rheumatic drugs; COX-2 = cyclooxygenase-2; csDMARD = conventional synthetic disease-modifying anti-rheumatic drugs; IM = intramuscular; JAK = Janus kinase; MTX = methotrexate; N = No; NSAID = nonsteroidal anti-inflammatory drug; PASI = Psoriasis Area and Severity Index; PDE4 = phosphodiesterase type 4; Y = Yes; WHO = World Health Organization.

Table RHCF.7.3. Concomitant Medications Permitted/Not Permitted in the Open-Label Treatment Period from Week 24 to Week 52 for Treatment of PsA and Chronic Conditions

Drug Class	As Needed	Chronic Use	Conditions for Use
bDMARDs	N	N	Not allowed
PDE4 or JAK inhibitors	N	N	Not allowed
csDMARDs	N	Y	Allowed doses: • Oral or parenteral MTX; 10 to 25 mg/week • Leflunomide: up to 20 mg/day • Sulfasalazine: up to 3 g/day • Cyclosporine: up to 5 mg/kg/day
Live vaccines (including BCG)	N	N	Not allowed
Phototherapy	N	N	Not allowed
NSAIDs, COX-2 inhibitors	Y	Y	Allowed up to the maximum recommended doses for pain. Aspirin (doses not exceeding 350 mg/day) may be taken to manage cardiovascular risk.
Opiate analgesics	Y	Y	Allowed
Nonopiod analgesics (paracetamol and acetaminophen)	Y	Y	Allowed up to the maximum recommended doses for pain. May be administered as needed basis during the study, but should be withheld within 24 hours of a visit. May be used at doses ≤1000 mg for premedication for allergic/hypersensitivity reactions from injections (see Section 7.8.3)
Topical steroids	Y	Y	Allowed as needed, but not within 24 hours of PASI assessment
Oral corticosteroids	Y	Y	Allowed doses: ≤ an average daily dose of 10 mg/day of prednisone or equivalent)
Intravascular and IM glucocorticoid	N	N	Not allowed
Intra-articular glucocorticoid	N	N	Allowed on a limited basis: it is recommended that there be no more than 1 injection (one injection = one large joint or up to 5 small joints or one soft tissue)
Inhaled steroids	Y	Y	As needed or regular use for asthma is permitted
Nasal corticosteroids	Y	Y	Use for allergies is permitted

Drug Class	As Needed	Chronic Use	Conditions for Use
Medicated shampoos Topical moisturizers/emollients and other nonprescription topical products Bath oils and oatmeal bath preparations	Y	Y	Allowed Topical moisturizers/emollients and other nonprescription topical products that do not contain, urea, >3% salicylic acid, alpha- or beta-hydroxyl acids, corticosteroids, or vitamin D3 analogs Allowed These topical therapies are not to be used within 12 hours prior to a study visit

Abbreviations: BCG = Bacillus Calmette-Guérin; bDMARD = biological disease-modifying anti-rheumatic drugs; COX-2 = cyclooxygenase-2; csDMARD = conventional synthetic disease-modifying anti-rheumatic drugs; IM = intramuscular; JAK = Janus kinase; MTX = methotrexate; N = No; NSAID = nonsteroidal anti-inflammatory drug; PASI = Psoriasis Area and Severity Index; PDE4 = phosphodiesterase type 4; Y = Yes; WHO = World Health Organization.

Table RHCF.7.4. Allowed Concomitant Medications in the Post-Treatment Follow-Up Period (Period 3)

Drug Class	As Needed	Chronic Use	Conditions for Use
bDMARDs	Y	Y	Allowed Follow local guidance; at the discretion of investigator
PDE4 or JAK inhibitors	Y	Y	Allowed Follow local guidance; at the discretion of the investigator
csDMARDs	Y	Y	Allowed
Live vaccines (including BCG)	N	N	Not allowed
Phototherapy	Y	Y	Allowed
NSAIDs, COX-2 inhibitors	Y	Y	Allowed
Opiate analgesics	Y	Y	Allowed
Nonopiod analgesics (paracetamol and acetaminophen)	Y	Y	Allowed
Topical steroids	Y	Y	Allowed
Oral corticosteroids	Y	Y	Allowed
Intravascular and IM glucocorticoid	Y	Y	Allowed
Intra-articular glucocorticoid	Y	Y	Allowed
Inhaled steroids	Y	Y	As needed or regular use for asthma is permitted
Nasal corticosteroids	Y	Y	Use for allergies is permitted

Drug Class	As Needed	Chronic Use	Conditions for Use
Medicated shampoos Topical moisturizers/emollients and other nonprescription topical products Bath oils and oatmeal bath preparations	Y	Y	Allowed

Abbreviations: BCG = Bacillus Calmette-Guérin; bDMARDs = biological disease-modifying anti-rheumatic drugs; COX-2 = cyclooxygenase-2; csDMARD = conventional synthetic disease-modifying anti-rheumatic drugs; IM = intramuscular; JAK = Janus kinase; MTX = methotrexate; N = No; NSAID = nonsteroidal anti-inflammatory drug; PASI = Psoriasis Area and Severity Index; PDE4 = phosphodiesterase type 4; Y = Yes; WHO = World Health Organization.

To avoid any possible drug interactions for those patients randomized to adalimumab, please refer to the product labeling for adalimumab for further concomitant therapy restrictions.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem. If the need for concomitant medication arises, the investigator should base decisions on the patient and clinical factors.

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

7.8. Treatment after the End of the Study

7.8.1. Study Extensions

Not applicable.

7.8.2. Continued Access

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

7.8.3. 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 (eg, swelling of the lips and/or tongue)
- anaphylactic reaction

Sometimes these reactions can be life-threatening. Proteins may also cause redness, itching, swelling, or pain locally at the injection site. Therefore, all patients should be closely monitored for signs or symptoms that could result from such reactions, be educated on the signs or symptoms of these types of reactions, and be instructed to contact the study site immediately if any of the symptoms are experienced after an injection. If a patient experiences an acute allergic/hypersensitivity reaction after an injection of investigational product, he or she should be managed appropriately and given instruction to receive relevant supportive care.

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 and/or its designee. 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 (eg, injection-site erythema, injection-site pruritus). Patients who develop clinically significant systemic allergic/hypersensitivity reactions after administration of investigational product who do not respond to symptomatic medication or result in clinical sequelae should be discontinued from study treatment and not receive further doses of investigational product, with or without premedication (see Section 8). Medications considered appropriate for premedication include (but are not restricted to) acetaminophen/paracetamol up to 1000 mg and antihistamines (eg, oral diphenhydramine, 50 mg) given 30 to 60 minutes before investigational product injection. Patients may self-premedicate at home before administration of investigational product, as directed by the investigator. All such premedications will be recorded as concomitant therapy. Corticosteroids are not permitted as agents for premedication.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

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

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

In addition, patients will be discontinued from the investigational product in the following circumstances:

- Neutrophil (segmented) counts (see Section 9.4.5.3 for information on monitoring for neutropenia)
  - <500 cells/uL
  - ≥500 and <1000 cells/uL (based on 2 test results; the second test performed within 1 week from knowledge of the initial result).
  - ≥1000 and <1500 cells/uL (based on 3 test results) **and** an infection that is not fully resolved.
- Total white blood cell count <2000 cells/µL.
- Lymphocyte count <500 cells/µL.
- Platelet count <50,000 cells/µL.
- Changes in blood pressure defined as sitting systolic blood pressure at ≥160 mm Hg plus ≥20 mm Hg increase from baseline (Visit 2 [Week 0]), and/or diastolic blood pressure at ≥100 mm Hg plus ≥10 mm Hg increase from baseline, that do not respond following maximal allowed intervention (see Section 9.4.5.1 for information on monitoring hypertension).

- The patient experiences a severe AE, an SAE, or a clinically significant change in a laboratory value occurs 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.
- Clinically significant systemic hypersensitivity reaction after SC administration of investigational product that does not respond to symptomatic medication or results in clinical sequelae.
- The patient becomes pregnant.
- The patient develops a malignancy. **Note**: Patients may be allowed to continue if they develop no more than 2 nonmelanoma skin cancers over any 12-month period during the study.
- The patient develops symptoms suggestive of a lupus-like syndrome and is positive for antibodies against double-stranded DNA.
- If the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for the treatment of PsA or Ps, discontinuation from the study occurs prior to introduction of the new agent.
- 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.
- The patient 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 C-SSRS) or develops suicide-related behaviors as recorded on the C-SSRS. It is recommended that the subject be assessed by a psychiatrist or appropriately trained professional to assist in deciding whether the subject is to be discontinued from the study.
- The patient develops any condition or contraindication as addressed in the local labelling for adalimumab that would preclude the patient from continuing in this protocol.
- The investigator or attending physician decides that the patient should be withdrawn from the study.
- The patient requests to be withdrawn from the study.
- The investigator or Lilly 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).
- The patient becomes HBV DNA positive. The patient should be referred to a specialist physician.
- The patient is diagnosed with an active TB infection.

If in consultation with Lilly or its designee noncompliance is deemed to be significant or if further noncompliance occurs, the patient may be discontinued from the study (see Section 10.3.2.4 Treatment Compliance).

Any patient who permanently discontinues the study treatment for any reason will stop treatment and continue to the ETV prior to entering the Post-Treatment Follow-Up Period (Period 3).

8.1.2. Temporary Discontinuation from Study Treatment

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of abnormal laboratory values (see Section 8.1.1), AEs (see Section 9.2), hypertension (see Section 9.4.5.1) abnormal hepatic laboratory values (see Section 9.4.5.2), neutropenia (see Section 9.4.5.3), hepatitis B laboratory findings (see Section 9.4.5.4), or inflammatory bowel disease (IBD) events (see Section 9.2.1.1) that may have an unclear relationship to investigational product. See Section 9.4.4.2 for details regarding managing patients who test positive for TB at any time during the study.

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

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the sponsor CRP 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 CRP 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 good clinical practice (GCP)
- investigator decision
    - the investigator decides that the patient should be discontinued from the study
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- subject decision
    - the patient or the patient's designee requests to be withdrawn from the study

Any patient who discontinues the study for any reason will stop treatment and continue to the ETV prior to entering the Post-Treatment Follow-Up Period (Period 3).

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. Site personnel must, at a minimum, make 2 phone attempts and send a certified letter or its equivalent in that region.

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.

Appendix 4 lists the hepatic monitoring tests for treatment-emergent abnormality.

All study assessments except for the C-SSRS, Self-Harm, and Self-Harm Follow-Up will be completed electronically.

For all assessments, the same assessor should perform each assessment for a given patient during the study to minimize interobserver variation.

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessments

9.1.1.1. Combined Endpoint of American College of Rheumatology 50 Responder Index and Psoriasis Area and Severity Index 100

In order to be considered a responder to the primary efficacy measure at Week 24 in this study, a patient must simultaneously achieve both ACR50 and PASI 100 responses.

ACR50 response is an efficacy measure for which a patient must satisfy the following:

1) ≥50% improvement from baseline in TJC and
2) ≥50% improvement from baseline in SJC and
3) ≥50% improvement from baseline in at least 3 of the following 5 ACR Core Set criteria:
   a. Patient's Assessment of Pain Visual Analog Scale (VAS)
   b. PatGA VAS
   c. PGA VAS
   d. patient's assessment of physical function as measured by the HAQ-DI
   e. acute-phase reactant as measured by high sensitivity (assay) CRP (hs-CRP)

PASI 100 is described in Section 9.1.2.1. Patients achieving PASI 100 are defined as having an improvement of 100% in the PASI compared to baseline.

9.1.2. Secondary Efficacy Assessments

9.1.2.1. Psoriasis Area and Severity Index (PASI 75, PASI 90, PASI 100)

The PASI will be administered by a blinded assessor. The PASI is an accepted primary efficacy measurement for this phase of development of psoriasis treatments (EMA 2004). The PASI combines assessments of the extent of body-surface involvement in 4 anatomical regions (head, trunk, arms, and legs) and the severity of desquamation (scaling), erythema, and plaque induration/infiltration (thickness) in each region, yielding an overall score from 0 for no psoriasis up to 72 for the most severe disease (Fredriksson and Pettersson 1978). The PASI has been the most frequently used endpoint and measure of psoriasis severity in clinical trials (EMA 2004;

Menter et al. 2008). A clinically meaningful response is a PASI 75, which represents at least a 75% decrease (improvement) from the baseline PASI score. As minimum treatment response, the European and German guidelines mention a PASI 50 response. Higher levels of clearance (PASI 90), as well as complete resolution of psoriasis (PASI 100), have become additional endpoints because of the increasing recognition of the association of higher clearance with greater health-related QoL (Puig 2015).

Patients achieving PASI 75, 90, or 100 are defined as having an improvement of at least 75%, 90%, or 100%, respectively, in the PASI compared to baseline.

Absolute PASI scores of ≤1, ≤2, or ≤3 may be considered as treatment targets for the management of plaque psoriasis.

9.1.2.2. Percentage of Body Surface Area

The blinded assessor will evaluate the percentage involvement of psoriasis on each patient's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), in which 1% corresponds to the size of the patient's hand (including the palm, fingers, and thumb) (National Psoriasis Foundation [NPF] 2009).

9.1.2.3. American College of Rheumatology 20 Responder Index

ACR20 response is a secondary efficacy measure for which a patient must satisfy the following:

1) ≥20% improvement from baseline in tender joint count (TJC) and
2) ≥20% improvement from baseline in swollen joint count (SJC) and
3) ≥20% improvement from baseline in at least 3 of the following 5 ACR Core Set criteria:
   a. Patient's Assessment of Pain VAS
   b. PatGA VAS
   c. PGA VAS
   d. patient's assessment of physical function as measured by the HAQ-DI
   e. acute-phase reactant as measured by high sensitivity (assay) CRP (hs-CRP)

9.1.2.3.1. American College of Rheumatology Core Set

a. Tender Joint Count

TJC joint assessments will be performed by a blinded assessor.

For ACR measures, the number of tender and painful joints will be determined by examination of 68 joints (34 joints on each side of the patient's body). Any joints that require intra-articular injections during the study (according to Section 7.7) should be excluded from evaluation from the time of the injection to the conclusion of the study.

Joints will be assessed for tenderness by pressure and joint manipulation on physical examination. The patient will be asked for pain sensations on these manipulations and watched for spontaneous pain reactions. Any positive response on pressure, movement, or both will then be translated into a single tender-versus-nontender dichotomy.

Missing, replaced, ankylosed, or arthrodesed joints will be identified by the investigator at the Screening Visit and will be excluded from evaluation during the trial.

b. Swollen Joint Count

SJC joint assessments will be performed by a blinded assessor.

For ACR measures, the number of swollen joints will be determined by examination of 66 joints (33 joints on each side of the patient's body). Any joints that require intra-articular injections during the study (according to Section 7.7) should be excluded from evaluation from the time of the injection to the conclusion of the study.

Joints will be classified as either swollen or not swollen. Swelling is defined as palpable fluctuating synovitis of the joint. Swelling secondary to osteoarthritis will be assessed as not swollen, unless there is unmistakable fluctuation. Dactylitis should be counted as 1 swollen joint.

Missing, replaced, ankylosed, or arthrodesed joints will be identified by the investigator at the Screening Visit and will be excluded from evaluation during the trial.

c. Patient's Assessment of Pain Visual Analog Scale

The patient will be asked to assess his or her current level of joint pain by marking a vertical tick on a 100-mm horizontal VAS where the left end represents no joint pain and the right end represents worst possible joint pain. The Patient's Assessment of Pain VAS should be administered *prior to* the TJC and SJC examinations.

Results will be expressed in millimeters measured between the left end of the scale and the crossing point of the vertical line of the tick; *this procedure is applicable for all VAS used in the trial.*

d. Patient's Global Assessment of Disease Activity Visual Analog Scale

The patient's overall assessment of his or her PsA activity will be recorded using the 100-mm horizontal VAS. Patients will be asked, "Considering all the ways your PsA has affected you, how do you feel your PsA is today?" where the left end represents "very well" and the right end represents "very poor."

e. Physician's Global Assessment of Disease Activity Visual Analog Scale

The investigator, who must be a physician, will be asked to give an overall assessment of the severity of the patient's current PsA activity using a 100-mm horizontal VAS, where 0 represents no disease activity and 100 represents extremely active disease.

f. Patient's Assessment of Physical Function as Assessed by the Health Assessment Questionnaire-Disability Index

The HAQ-DI is a patient-reported standardized questionnaire that is commonly used in PsA to measure disease-associated disability (assessment of physical function). It consists of 24 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and other daily activities (Fries et al. 1980; Fries et al. 1982).

The disability section of the questionnaire scores the patient's self-perception on the degree of difficulty (0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to do), covering the 8 domains. The reported use of special aids or devices and/or the need for assistance of another person to perform these activities is also assessed. The scores for each of the functional domains will be averaged to calculate the functional disability index. An MCID is a clinically relevant change in a patient's status. The HAQ-DI MCID has been estimated to be about 0.35 for patients with PsA (Mease et al. 2011). Details of scoring and calculations are presented in the statistical analysis plan (SAP).

g. C-Reactive Protein

CRP will be the ACR Core Set 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 the patient's PsA.

9.1.2.4. American College of Rheumatology 50 and 70 Responder Index

ACR50 and ACR70 responses are secondary efficacy endpoints and are improvements of at least 50% and of at least 70%, respectively, in the multiple disease assessment ACR criteria. The ACR50 and ACR70 are calculated similarly to ACR20, as described in Section 9.1.2.3.

9.1.2.5. Individual Components of the American College of Rheumatology Core Set

The individual components of the ACR Core Set will be measured including TJC (68 joint count), SJC (66 joint count), Patient's Assessment of Pain VAS, PatGA VAS, PGA VAS, Patient's Assessment of Physical Function as measured by the HAQ-DI, and CRP (Section 9.1.2.3.1).

9.1.2.6. Psoriatic Arthritic Response Criteria

The PsARC is a composite criteria reported in terms of the percentage of patients achieving response according to the following criteria: PGA, PatGA, TJC, and SJC. Overall response is defined by improvement from the baseline assessment in 2 of the 4 criteria, 1 of which must be a joint count; there must not be worsening in any of the 4 criteria:

1. At least 30% reduction in TJC
2. At least 30% reduction in SJC
3. At least a 1 point reduction in physician's assessment
4. At least a 1 point reduction in patient's assessment

The PsARC response was modified in this study by using the PGA and the PatGA on a 100 mm VAS described in Section 9.1.2.3.1 instead of a 5-point Likert scale in the original criteria. The results from the 2 VAS measures were assessed as a difference from baseline (in mm), but criteria 3 and 4, above, were changed to "at least a 20 mm reduction" (Clegg 1996).

9.1.2.7. Minimal Disease Activity

The MDA score has been developed based on current expert opinion and uses a composite of 7 key outcome measures used in PsA to encompass all of the domains of the disease to measure

the overall state of a patient's disease (Coates et al. 2010a; Coates and Helliwell 2010b). The overall state of disease activity is deemed a useful target of treatment by both the patient and the physician, given current treatment possibilities and limitations. Preliminary validation work supports the use of the MDA criteria in both observational cohorts and in interventional trial cohorts. The PsA MDA criteria have evidence supporting their use within the OMERACT filter of truth, discrimination, and feasibility.

- MDA: Patients are classified as achieving MDA if they fulfill 5 of 7 outcome measures: TJC ≤1; SJC ≤1; psoriasis activity and severity index (PASI total score) ≤1 or BSA ≤3; patient pain VAS score of ≤15; patient global disease activity VAS score of ≤20; HAQ-DI score ≤0.5; and tender entheseal points ≤1.

9.1.2.8. Modified Composite Psoriatic Disease Activity Index

The Modified CPDAI is a validated instrument intended to assess composite psoriatic disease activity and response to therapy (Mumtaz et al. 2011). This instrument assesses individual domains involved as well as the global effect of disease in all dimensions by which each patient may be affected. Domains include peripheral arthritis as assessed by the number of tender and swollen joints and the HAQ-DI, skin as assessed by the PASI and the DLQI, enthesitis as assessed by the number of sites with enthesitis and the HAQ-DI, and dactylitis as assessed by the number of digits affected and the HAQ-DI. Scores range from 0 to 12, with a higher score indicating higher disease activity.

9.1.2.9. Leeds Enthesitis Index

If the patient has enthesitis, the LEI will be administered by a blinded assessor. The LEI has been developed specifically for use in PsA. It measures enthesitis at 6 sites (lateral epicondyle, left and right, medial femoral condyle, left and right, Achilles tendon insertion, left and right) (Healy and Helliwell 2008). Each site is assigned a score of 0 (absent) or 1 (present); the results from each site are then added to produce a total score (range 0 to 6).

9.1.2.10. Spondyloarthritis Research Consortium of Canada

If the patient has enthesitis, the SPARCC will be administered by a blinded assessor. The SPARCC enthesitis index evaluates tenderness in a total of 16 enthesitis sites: the greater trochanter (right/left [R/L]), quadriceps tendon insertion into the patella (R/L), patellar ligament insertion into the patella and tibial tuberosity (R/L), Achilles tendon insertion (R/L), plantar fascia insertion (R/L), medial and lateral epicondyles (R/L), and the supraspinatus insertion (R/L) (Mease 2011). Tenderness at each site is quantified on a dichotomous basis: 0 = nontender and 1 = tender. The results from each site are then added to produce a total score (range 0 to 16).

9.1.2.11. Leeds Dactylitis Index-Basic

If the patient has dactylitis, the LDI-B will be administered by a blinded assessor. The LDI-B has been developed to measure the severity of dactylitis. Once the presence of dactylitis is established in each digit, the ratio of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot is measured (Helliwell et al. 2005). Each dactylitic digit is defined by a minimum increase of 10% in circumference over the contra-lateral digit. If the

same digits on each hand or foot are thought to be involved, the clinician will refer to a table of normative values (provided to study sites) for a value which will be used to provide the comparison. If the ratio is >1.1, then subtract 1 from the calculated ratio and multiply it by 100 and the tenderness score of 0 (not tender) or 1 (tender). Otherwise, if the ratio of the circumference of the digit is ≤1.1, then the LDI-B score is set to 0. Tenderness is assessed in the area between the joints. The results of each digit are then added to produce a total score (Healy and Helliwell 2007).

9.1.2.12. Nail Psoriasis Severity Index Fingernails

If the patient has fingernail Ps, the NAPSI Fingernails will be administered by a blinded assessor. Site personnel should ensure that the patient makes their nails available for assessment during the study. The NAPSI Fingernails is a numeric, reproducible, objective tool for evaluation of nail Ps. This scale is used to evaluate the severity of nail bed Ps and nail matrix Ps by area of involvement in the nail unit. In this study, only fingernail involvement will be assessed. The fingernail is divided with imaginary horizontal and longitudinal lines into quadrants. Each fingernail is given a score for nail bed Ps (0 to 4) and nail matrix Ps (0 to 4) depending on the presence (1) or absence (0) of any of the features of nail Ps in each quadrant. The NAPSI Fingernails score of a nail is the sum of scores in nail bed and nail matrix from each quadrant (thus a maximum of 8). Each fingernail is evaluated, and the sum of all the nails is the total NAPSI Fingernails score. Thus, the sum of the scores from all fingernails is 0 to 80.

9.1.2.13. Disease Activity Score based on C-Reactive Protein

The DAS28-CRP is a measure of disease activity in 28 joints that consists of a composite numerical score utilizing the following variables: TJC, SJC, hs-CRP (measured in mg/L), and PatGA recorded by patients on a 0 to 100 mm VAS.

For DAS28-CRP, the 28 joints to be examined and assessed as tender or not tender for TJC and as swollen or not swollen for SJC (Section 9.1.2.3.1) are a subset of those assessed for the TJC and SJC, and include 14 joints on each side of the patient's body: the 2 shoulders, the 2 elbows, the 2 wrists, the 10 metacarpophalangeal joints, the 2 interphalangeal joints of the thumb, the 8 proximal interphalangeal joints, and the 2 knees (Smolen et al. 1995). The following equation will be used to calculate the DAS28 (Vander Cruyssen et al. 2005):

$$DAS\ 28\ -\ CRP\ = 0.56\left(\sqrt{TJC\ 28}\right)+ 0.28\left(\sqrt{SJC\ 28}\right)+ 0.36\left(\ln\left(CRP\ +1\right)\right)+ 0.014\ \left(VAS\ \right)+ 0.96$$

9.1.2.14. Static Physician Global Assessment

If the patient has plaque Ps, the static Physician Global Assessment of psoriasis (sPGA) will be administered by the blinded assessor. The sPGA is the assessor's determination of the patient's Ps lesions overall at a given time point. The sPGA is recommended as an endpoint to use to assess efficacy in the treatment of Ps (EMEA 2004). Overall lesions are categorized by descriptions for induration, erythema, and scaling. For the analysis of responses, the patient's Ps is assessed at a given time point on a 6 point scale in which 0 = cleared, 1 = minimal, 2 = mild, 3 = moderate; 4 = severe, 5 = very severe.

9.1.3. Appropriateness of Assessments

All of the clinical and safety assessments/measures included in the primary and major secondary objectives in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee 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 eCRF 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 eCRF.

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

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

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

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- 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 eCRF, 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 subjects once they have discontinued and/or completed the study (the patient summary eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

9.2.1.1. Adverse Events of Special Interest

The following adverse events of special interest will be evaluated in particular 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:

- cytopenias (leukopenia, neutropenia, and thrombocytopenia)
- liver function test changes/enzyme elevations (ALT, AST, bilirubin, and ALP)
- infections
- injection-site reactions
- allergic reactions/hypersensitivities
- cerebrocardiovascular events
- malignancies
- depression and suicide/self-injury
- inflammatory bowel disease (Crohn's disease and UC)
- interstitial lung disease (ILD)

Sites will provide details on some of these AEs as instructed on the eCRF. 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 Section 7.8.3).

Data on cerebrocardiovascular events will be collected and the events will be adjudicated by an external Clinical Events Committee (CEC) made up of a chairman, 2 cardiologists, and a neurologist.

- Cerebrocardiovascular events are defined as:
    - Death (Cardiovascular)
    - MI
    - Hospitalization for Unstable Angina
    - Hospitalization for Heart Failure
    - Serious Arrhythmia
    - Hospitalization for Hypertension
    - Resuscitated Sudden Death
    - Cardiogenic Shock due to MI
    - Coronary Revascularization Procedure
- Neurologic
    - Cerebrovascular Event: Transient Ischemic Attack or Stroke (Hemorrhagic, Ischemic and Undetermined)
- Peripheral Vascular Events
    - Peripheral Arterial Event
    - Peripheral Revascularization Procedure

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

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

9.2.1.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 Code of Federal Regulations 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies 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.

Complaints related to concomitant medications are reported directly to the manufacturers of those medications/devices in accordance with the package insert.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- Reviewing all Study Drug Administration Logs to identify any product complaints
- Recording a complete description of the product complaints reported and any associated AEs using the study-specific complaint forms provided for this purpose
- Faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

9.3. Treatment of Overdose

Refer to the ixekizumab IB and product labeling and the adalimumab product labeling.

9.4. Safety

9.4.1. Vital Signs

For each patient, vital signs measurements should be conducted according to the Schedule of Activities (Section 2).

Vital signs (sitting blood pressure and pulse rate) will be measured after the patient has been resting for a minimum of 10 minutes at times indicated in the study schedule (Section 2). At randomization (Visit 2), sitting blood pressure and pulse rate must be measured before administration of the investigational product and again approximately 1 hour after administration. Any clinically significant findings from vital signs measurements that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be

reported to Lilly or its designee as an AE via eCRF. Additional measurements of vital signs may be performed at the discretion of the investigator.

9.4.2. Laboratory Tests

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

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 eCRF.

9.4.3. Columbia Suicide Severity Rating Scale

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

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

9.4.4. Other Tests

9.4.4.1. Physical Examination

One complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed at Visit 1 (screening). This examination will determine whether the patient meets the criteria required to participate in the study and will also serve as a monitor for preexisting conditions and as a baseline for treatment-emergent AE (TEAE) assessment. All physical examinations throughout the study are indicated in the Schedule of Activities (Section 2) and should include a symptom-directed physical evaluation as well as an examination of the heart, lungs, and abdomen and a visual examination of the skin.

9.4.4.2. Chest X-Ray and Tuberculosis Testing

X-ray: At Visit 1, a posterior-anterior view chest x-ray will be obtained locally, unless the x-ray or results from a chest x-ray obtained within 6 months before randomization (Visit 2) are available. The chest x-ray or results will be reviewed by the investigator or designee to exclude patients with active TB infection.

TB testing: Patient history of TB test results should be assessed prior to screening (Visit 1).

Patients with no TB test results on file: Patients will be tested at screening (Section 2). A PPD skin test response of ≥5 mm induration, between approximately 48 and 72 hours after test application, regardless of BCG vaccination history, will be considered a positive result. In countries where the QuantiFERON-TB® Gold test or T-SPOT.TB test is available and in the judgment of the investigator preferred as an alternative to the PPD skin test for the evaluation of TB infection, it may be used instead of the PPD test and will be performed and read locally. If the QuantiFERON-TB® Gold test or the T-SPOT.TB test is indeterminate, 1 retest using the same TB test method is allowed. If the retest is indeterminate, then the patient is excluded from the study.

Patients with a positive TB test performed at screening but with no other evidence of active TB may be rescreened 1 time and may be enrolled without repeating the TB test based on the following requirements:

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

If rescreening occurs within 6 months of the date of the screening chest x-ray, there is no need for repeat of chest x-ray for considering enrollment.

Patients with negative TB test results on file: Patients with documentation of a negative test result within 3 months before randomization (Visit 2) should not be administered a TB test at Visit 1. Documentation of PPD test results must include a record of the size of the induration response; otherwise a retest at screening (Visit 1) will be required to determine patient eligibility.

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

9.4.5. Safety Monitoring

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

9.4.5.1. Hypertension

Patients who experience changes in sitting blood pressure defined as systolic blood pressure at ≥160 mm Hg plus ≥20 mm Hg increase from baseline (Week 0, Visit 2) and/or diastolic blood pressure at ≥100 mm Hg plus ≥10 mm Hg increase from baseline (Week 0, Visit 2) on

2 consecutive visits should 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 an anti-hypertensive agent (see Section 8.1.1 for criteria for patient discontinuation related to hypertension).

9.4.5.2. Hepatic Monitoring

If a study patient/subject experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient/subject safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests (see Appendix 4).

9.4.5.3. Neutropenia

Patients with neutrophil counts <1500 cells/μL should be managed for neutropenia as follows:

- <500 cells/μL, see Discontinuation Criteria (Section 8.1.1)
- ≥500 cells/μL and <1000 cells/μL, see Discontinuation Criteria (Section 8.1.1)
- ≥1000 cells/μL and <1500 cells/μL (based on 3 test results), and the patient has a concurrent infection that requires systemic anti-infective therapy (for example, antibiotic, antifungal agent, antiviral agent):
    - The dose of investigational product should be withheld, the patient should receive appropriate medical care, and a repeat test for neutrophil count should be performed within 4 weeks from knowledge of the initial report. If the repeat neutrophil count has returned to ≥1500 cells/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, investigational product should continue to be withheld and a repeat neutrophil count should again be performed within another 4 weeks. If, after 2 repeat tests, the neutrophil count still remains ≥1000 cells/μL and <1500 cells/μL, and:
        a. the infection has not fully resolved, the patient will be discontinued from the study.
        b. 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.
- ≥1000 cells/μL and <1500 cells/μL (based on 3 test results), and the patient has no concurrent infection that requires systemic anti-infective therapy (for example, antibiotic, antifungal agent, antiviral agent):

- Dosing may continue, and a repeat neutrophil count should 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 should be performed at 4- to 8-week intervals until the neutrophil count has returned to ≥1500 cells/μL. If the patient has 3 or more postbaseline neutrophil counts of ≥1000 cells/μL and <1500 cells/μL, no value of <1000 cells/μL, 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 should be managed as indicated above for patients with concurrent infection. Management of neutropenia during the Post-Treatment Follow-Up Period is described in Section 5.1.3.

9.4.5.4. Hepatitis B Monitoring

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

Any enrolled patient with a positive HBV DNA test result at any time must be discontinued from the study and should receive appropriate follow-up medical care, including consideration for antiviral therapy.

Study investigators should consult with a specialist physician in the care of patients with hepatitis (for example, infectious disease or hepatologist subspecialists) on whether to continue any immunosuppressant therapy including investigational product for a period of time while antiviral therapy is being initiated. Timing of withdrawal from investigational product should be based on recommendation of the consulting specialist physician in conjunction with the investigator and local or regional medical guidelines or standards of care.

Upon discontinuation from investigational product, the patient should be discontinued from the study. Any patient who discontinued the study for any reason will complete the ETV before entering the Post-Treatment Follow-Up Period (Period 3).

9.5. Pharmacokinetics

Not applicable.

9.6. Pharmacodynamics

Not applicable.

9.7. Genetics

Not applicable.

9.8. Biomarkers

Not applicable.

9.9. Health Outcome/Quality of Life Measures

9.9.1. Itch Numeric Rating Scale

The Itch NRS is a patient-administered, 11 point horizontal scale anchored at 0 and 10, with 0 representing "no itch" and 10 representing "worst itch imaginable." Overall severity of a patient's itching from Ps is indicated by selecting the number that best describes the worst level of itching in the past 24 hours.

9.9.2. Fatigue Severity Numeric Rating Scale Score

The Fatigue Severity NRS is a patient-administered single-item 11-point horizontal scale anchored at 0 and 10, with 0 representing "no fatigue" and 10 representing "as bad as you can imagine." Patients rate their fatigue (weariness, tiredness) by selecting the one number that describes their worst level of fatigue during the past 24 hours.

9.9.3. Medical Outcomes Study 36-Item Short Form Health Survey Physical Component Summary and Mental Component Summary Scores

The SF-36 is a 36-item, patient-completed 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, respectively. The summary scores range from 0 to 100, with higher scores indicating better levels of function and/or better health. Items are answered on Likert scales of varying lengths. The SF-36 acute version (Version 2) will be used, which has a 1 week recall period (SF-36 Health Survey Update page [WWW]).

9.9.4. European Quality of Life—5 Dimensions 5 Level [EQ-5D-5L])

The 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 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 selecting in the box associated with the most appropriate statement in each of the 5 dimensions. It should be noted that the numerals 1 to 5 have no arithmetic properties and should not be used as 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 (EuroQol Group [WWW]).

9.9.5. Dermatology Life Quality Index

The DLQI is a simple, patient-administered, 10 question, validated, quality-of-life questionnaire that covers 6 domains: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Response categories include "not at all," "a little," "a lot," and "very much," with corresponding scores of 0, 1, 2, and 3, respectively, and "not relevant" responses scored as "0." Totals range from 0 to 30 (less to more impairment).

9.9.6. Treatment Satisfaction Questionnaire

The Treatment Satisfaction Questionnaire is a clinician-administered questionnaire which provides an assessment of the patient's opinion of the effectiveness, safety, and overall satisfaction of the study medication. Patients will be asked to respond to questionnaire items using a 4-point Likert scale (from "very satisfied" to "very dissatisfied").

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 550 patients who meet all criteria for enrollment at Visits 1 and 2 will be randomized in a 1:1 ratio at Week 0 (Visit 2) in Period 2 to ixekizumab or adalimumab (275 patients per treatment group).

Sample size was calculated assuming the proportion of patients simultaneously achieving ACR50 and PASI 100 as 13.6% and 31.3% in the adalimumab and ixekizumab treatment groups, respectively, as observed in the csDMARD-experienced population from Study RHAP. According to the nQuery software, a total sample size of 550 (with 275 per treatment group) using a 2-sided Fisher's exact test at 0.05 level of significance would yield 99% power for testing ixekizumab versus adalimumab.

This sample size would yield 78% power for testing the noninferiority of ixekizumab to adalimumab at a one-sided 0.025 level of significance based on a noninferiority margin of –12% and using ACR50 response rates of 43.8% and 44.1% as observed for the ixekizumab and adalimumab treatment groups, respectively, in the csDMARD-experienced population from Study RHAP. For testing superiority of ixekizumab to adalimumab based on PASI 100 response rates of 46.9% and 23.7% as observed for ixekizumab and adalimumab in the csDMARD-experienced population from Study RHAP, this sample size would yield 99% power using a 2-sided Fisher's exact test at 0.05 level of significance.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Entered	All participants who sign informed consent
Randomized	Participants who met all entry criteria and were assigned a study treatment
Intent-to-treat (ITT)	The ITT population consists of all randomized patients. Even if the patients do not take the assigned treatment, do not receive the correct treatment, or otherwise do not follow the protocol, they will be analyzed according to the treatment group to which they were assigned. Unless otherwise specified, efficacy and health outcomes analyses for Period 2 will be conducted on the ITT population.
Safety	The safety population consists of all randomized patients who received at least 1 dose of study treatment in Period 2. Patients will be analyzed according to the treatment group to which they were assigned. Safety analyses for Period 2 will be conducted on this analysis set.
Post-treatment follow-up	The post-treatment follow-up population consists of all randomized patients who received at least 1 dose of study treatment during Period 2 and have entered the Post-Treatment Follow-Up Period. Patients will be analyzed according to the treatment group to which they were assigned in Period 2. Safety analyses for Period 3 (Post-Treatment Follow-Up Period) will be conducted on this analysis set.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

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

Any changes to the data analysis methods related to the primary and major secondary endpoints described in the protocol, and the justification for making the change, will be documented in the SAP and/or the clinical study report (CSR). Additional exploratory analyses of the data may be conducted as deemed appropriate.

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

10.3.1.1. General Considerations for Analyses during Period 2 (Open-Label Treatment Period)

Baseline will be defined as the last available value before the first injection of the study drug for both efficacy, health outcomes, and safety analyses. In most cases, this will be the measurement recorded at Week 0 (Visit 2).

Categorical data for baseline variables will be summarized as frequency counts and percentages. Continuous data for baseline variables will be summarized using the mean, standard deviation, minimum, maximum, median, and number of observations.

Comparisons of ixekizumab versus adalimumab will be performed for all outcome variables at all visits in Period 2; however, the primary time point of interest is Week 24.

Change from baseline at a particular visit will be calculated as the value at that visit minus the baseline value.

For outcome measures that are not collected at each post-baseline visit, data may exist at visits where the outcome measure was not scheduled to be collected, due to early discontinuation visits. In these situations, data from the early discontinuation visit that does not correspond to the planned collection schedule will be excluded from any mixed-effects models for repeated measures (MMRM) analysis. However, the data will still be used in other analyses, including shift analyses, change from baseline analyses using last observation carried forward (LOCF) imputation method, and other categorical analyses.

10.3.1.2. Missing Data Imputation

The methods for imputation of missing data to be used in this study are described below.

10.3.1.2.1. Nonresponder Imputation

Missing data for categorical efficacy and health outcome measures will be imputed using the nonresponder imputation (NRI) method. Patients will be considered nonresponders if they do not meet the clinical response criteria or have missing clinical response data at the time point of analysis. Randomized patients without at least one post-baseline observation will also be defined as nonresponders for the NRI analysis.

10.3.1.2.2. Last Observation Carried Forward

Missing data for continuous efficacy and health outcomes variables will be imputed using LOCF method. For patients discontinuing investigational product or having missing data at a visit, the last nonmissing post-baseline observation before discontinuation or before the visit with missing data will be carried forward to the corresponding time point. Randomized patients without at least one post-baseline observation will not be included in LOCF analyses.

In addition to NRI and LOCF, other imputation methods may be used as deemed appropriate.

10.3.1.3. Adjustment for Multiple Comparisons

A multiple testing strategy for the primary and major secondary endpoints will be implemented to control the family-wise type I error rate at a 2-sided α level of 0.05. The primary and major secondary endpoints will be sequentially tested in the following order to compare ixekizumab vs adalimumab, using the primary analysis method.

1. Test 1 for Primary Endpoint – Proportion of patients simultaneously achieving ACR50 and PASI 100 at Week 24: A superiority test of the primary endpoint will be performed at an overall 2-sided $\alpha = 0.05$ using the methods described in Section 10.3.3.1.1.
2. Test 2 for Major Secondary Endpoint #1 – Proportion of patients achieving ACR50 at Week 24: If the test for the primary endpoint is significant, then a noninferiority test for the major secondary endpoint #1 will be performed using the methods described in Section 10.3.3.3.
3. Test 3 for Major Secondary Endpoint #2 – Proportion of patients achieving PASI 100 at Week 24: If the test for major secondary endpoint #1 is significant, then a superiority test for major secondary endpoint #2 will be performed using the methods described in Section 10.3.3.1.1.

If a test in this sequence is not significant, all subsequent tests will be considered nonsignificant.

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

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

A detailed description of patient disposition will be provided at the end of the study. 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 and will include reasons for discontinuation. The reasons for discontinuation during Period 2 will be tested between treatment groups using Fisher's exact test.

10.3.2.2. Patient Characteristics

Baseline characteristics, clinical, and health outcome measurements will be summarized for the ITT population. Baseline characteristics will include sex, age, age category, weight, BMI, race, geographic region, baseline disease severity, duration of disease, previous nonbiologic systemic therapy, and previous biologic therapy. Baseline clinical measurements will include ACR component scores, PASI total score, DAS28-CRP, CRP, Modified CPDAI, HAQ-DI, Itch NRS score, NAPSI Fingernails, SPARCC Enthesitis Index, LEI, LDI-B, and other QoL scores.

Treatment group comparisons between ixekizumab and adalimumab will be conducted using Fisher's exact test for categorical data and an analysis of variance model with treatment as a factor for continuous data.

10.3.2.3. Concomitant Therapy

Previous and concomitant medications (including concomitant topical products such as emollients and other nonprescription topical products) will be summarized for patients who enter each treatment period and will be presented by World Health Organization Anatomic Therapeutic Class (WHOATC) Level 1 and generic name. Treatment group comparisons between ixekizumab and adalimumab 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 for patients who enter Period 2. A patient will be considered compliant overall to ixekizumab or adalimumab if he/she is missing no more than 20% of the expected doses, does not miss 2 consecutive doses, and does not double-dose (that is, take more injections at the same time point than specified in the protocol). Proportions of patients compliant by visit and overall will be compared between treatment groups during Period 2 using Fisher's exact test.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analysis Method

10.3.3.1.1. Categorical Variables

Unless specified otherwise, the primary analysis method for the categorical efficacy and health outcome variables will be using a logistic regression model with treatment, concomitant csDMARD use at baseline (Yes vs No), and moderate-to-severe plaque psoriasis involvement (Yes vs No) as factors and NRI method. Treatment group comparisons will be made at all visits up to Week 52 and odds ratios and their corresponding 95% confidence intervals (CIs) will be reported.

10.3.3.1.2. Continuous Variables

Unless specified otherwise, the primary analysis method for all continuous efficacy and health outcome variables will be using a MMRM analysis. The model will include treatment group, concomitant csDMARD use (Yes vs No) at baseline, moderate-to-severe plaque psoriasis involvement (Yes vs No), baseline value, visit, baseline-by-visit interaction, and treatment-by-visit interaction as fixed factors. The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III tests for the least squares means will be used for the statistical comparison; the 95% CI will also be reported. Treatment group comparisons at all visits up to Week 52 will be made.

10.3.3.2. Secondary Analysis Method

10.3.3.2.1. Categorical Variables

Secondary analyses for treatment comparisons on the categorical efficacy variables will be conducted using a Fisher's exact test.

10.3.3.2.2. Continuous Variables

Secondary analyses for treatment comparisons on continuous outcome variables will be performed using an analysis of covariance (ANCOVA) model and LOCF imputation method. The details of the analysis model will be presented in the SAP.

10.3.3.3. Methodology for Noninferiority Test

For assessing noninferiority of ixekizumab to adalimumab, missing data will be imputed using the NRI method. Noninferiority analysis will be performed on the ITT population using a prespecified fixed margin approach. There is no universally accepted value for what is considered to be a clinically unimportant difference between 2 treatments for a particular efficacy measure. We will consider the points from EMEA Committee for Medicinal Products for Human Use (CHMP) (CHMP 2005) and FDA guidance (2016) which state that an appropriate noninferiority margin should be based on both clinical and statistical grounds.

The null hypothesis will be rejected if the lower bound of the 2-sided 95% CI for the difference in proportions of responders on ixekizumab minus adalimumab is greater than the prespecified margin, meaning ixekizumab will be deemed noninferior to adalimumab. If the lower bound of the CI exceeds 0 (the corresponding p-value will also be produced), then ixekizumab will be deemed superior to adalimumab. The 95% CIs for the difference in proportions will be calculated using the simple asymptotic method, without continuity correction (that is, normal approximation to the binomial distribution).

Based on EMEA CHMP (CHMP 2005), FDA guidance (2016), and Weinblatt et al. (2013), a noninferiority margin of −12.0% for ACR50 between ixekizumab and adalimumab (ie, response rate of ixekizumab – response rate of adalimumab) is considered appropriate. This noninferiority margin represents an approximately 50% preservation of the adalimumab treatment effect (based on the difference between adalimumab and placebo) observed in a historical Phase 3 study for adalimumab 40 mg twice weekly compared with placebo (Mease et al 2005) and Study RHAP.

If it is deemed appropriate to perform noninferiority tests on endpoints other than ACR50, the details about selection of noninferiority margins for the other endpoints will be presented in the SAP.

10.3.4. Safety Analyses

Safety will be assessed by summarizing and analyzing AEs, laboratory analytes including neutrophil counts, vital signs, and concomitant medications. The duration of exposure will also be summarized.

The primary safety analyses will focus on comparisons of ixekizumab versus adalimumab in Period 2. Fisher's exact test will be used for all AEs and other categorical safety data. Continuous vital sign and laboratory values will be analyzed using ANCOVA method with

treatment and baseline value in the model. Other continuous safety variables will be analyzed by t-tests, unless otherwise stated.

Summaries of safety data collected during the Post-Treatment Follow-Up Period (Period 3) will be presented separately. Unless otherwise specified, the follow-up baseline is defined as the last nonmissing assessment on or prior to the Week 52 (Visit 11) or early discontinuation visit.

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

10.3.4.1. Adverse Events

AEs are classified based on the Medical Dictionary for Regulatory Activities (MedDRA). A TEAE is defined as an event that first occurred or worsened in severity after the first dose of study treatment and on or prior to the date of the last visit within the treatment period. Both the date/time of the event and the date/time of the dose (ie, injection) are considered when determining TEAEs. For each TEAE, the severity is recorded according to the patient's or physician's perceived severity of the event (mild, moderate, or severe). A follow-up emergent adverse event (FEAE) is defined as an event that first occurred or worsened in severity after the date of Week 52 (Visit 11) or the ETV. For events that are sex-specific, the denominator and computation of the percentage will only include subjects from the given sex.

An overall summary of AEs will be provided for Period 2, including the number and percentage of subjects who experienced TEAEs, TEAEs by maximum severity, death, SAEs, TEAEs related to study drug, discontinuations from treatment due to an AE, and treatment-emergent adverse events of special interest. TEAEs (all, by maximum severity, and TEAEs possibly related to study drug by the investigator), SAEs including deaths, and AEs that lead to treatment discontinuation will be summarized and analyzed by MedDRA system organ class (SOC) and preferred term.

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

Follow-Up emergent AEs, SAEs including deaths, and AEs that lead to study discontinuation will be summarized by MedDRA system organ class and preferred term for Period 3.

10.3.4.2. Clinical Laboratory Tests

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

- For categorical laboratory tests:
    - Treatment-emergent **abnormal** value = a change from normal at all baseline visits to abnormal at any time postbaseline.
- For continuous laboratory tests:

- Treatment-emergent **high** value = a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time postbaseline.
- Treatment-emergent **low** value = a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time postbaseline.

10.3.4.3. Vital Signs, Physical Findings, and Other Safety Evaluations

Vital signs will be analyzed as mean changes from baseline and as incidence of abnormal values and will be summarized for both predose and postdose at Week 0 (Week 2) and Week 52 (Visit 11), as applicable.

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

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

10.3.6. Other Analyses

10.3.6.1. Subgroup Analyses

Subgroup analysis will be conducted using the ITT population.

Subgroups to be evaluated will include concomitant csDMARD use at baseline (Yes vs No), concomitant MTX use at baseline (Yes vs No), sex (male vs female), age group (<65 vs ≥65). A detailed description of the subgroup variables will be provided in the SAP.

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

10.3.7. Interim Analyses

An interim database lock will occur, and the analysis will be performed at the time (that is, a cutoff date) when the last patient completes Visit 8 (Week 24), completes ETV, or discontinues from Period 2. This database lock will include all data collected by the cutoff date including data after Week 24 from the Open-Label Treatment Period (Period 2) and follow-up data from patients who have begun Post-Treatment Follow-Up Period (Period 3).

This interim database lock at Week 24 will be considered the primary database lock for this study because all primary and major secondary study objectives will be assessed at this time. Since the primary time point of interest is Week 24, efficacy and health outcomes data will be

reported up to Week 24 because of the lack of complete data for all patients beyond this visit. However, all safety data collected up to the cutoff date will be reported.

A final database lock will occur after all enrolled patients have completed or discontinued the Post-Treatment Follow-Up Period (Period 3). After the final database lock, all efficacy, health outcomes, and safety data collected until study completion will be reported.

There will be no data monitoring committee.

11. References

Amjevita [package insert]. Thousand Oaks, CA: Amgen Inc; 2016.

Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, Zhou B, Dooley LT, Kavanaugh A. IMPACT 2 Investigators. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis.* 2005a;64(8):1150–1157.

Antoni CE, Kavanaugh A, Kirkham B Tutuncu Z, Burmester GR, Schneider U, Furst DE, Molitor J, Keystone E, Gladman D, Manger B, Wassenberg S, Weier R, Wallace DJ, Weisman MH, Kalden JR, Smolen J. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). *Arthritis Rheum*. 2005b;52(4):1227-1236.

Ash Z, Gaujoux-Viala C, Gossec L, Hensor EM, FitzGerald O, Winthrop K, van der Heijde D, Emery P, Smolen JS, Marzo-Ortega H. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. *Ann Rheum Dis*. 2012;71(3):319-326.

[CHMP] Committee for Proprietary Medicinal Products for Human Use. Guideline on the Choice of the Noninferiority Margin. European Medicines Agency web site. EMEA/CPMP/EWP/2158/99. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003636.pdf. 27 July 2005. Accessed 27 Feb 2017.

Clegg DO, Reda DJ, Mejias E, Cannon GW, Weisman MH, Taylor T, Budiman-Mak E, Blackburn WD, Vassey FB, Mahowald ML, Cush JJ, Schumacher HR Jr, Silverman SL, Alepa FP, Luggen ME, Cohen MR, Makkena R, Haakenson CM, Ward RH, Manaster BJ, Anderson RJ, Ward JR, Henderson WG. Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. *Arthritis Rheum*. 1996;39(12):2013-2020.

Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann Rheum Dis*. 2010a;69(1):48-53.

Coates LC, Helliwell PS. Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. *Arthritis Care & Res*. 2010b;62(7):965-969.

Coates LC, Kavanaugh A, Mease PJ, Soriano ER, Laura Acosta-Felquer M, Armstrong AW, Bautista-Molano W, Boehncke WH, Campbell W, Cauli A, Espinoza LR, FitzGerald O, Gladman DD, Gottlieb A, Helliwell PS, Husni ME, Love TJ, Lubrano E, McHugh N, Nash P, Ogdie A, Orbai AM, Parkinson A, O'Sullivan D, Rosen CF, Schwartzman S, Siegel EL, Toloza S, Tuong W, Ritchlin CT. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. *Arthritis Rheumatol.* 2016;68(5):1060-1071.

Columbia University Medical Center. Columbia–Suicide Severity Rating Scale (C-SSRS) web site. Available at: http://www.cssrs.columbia.edu. Accessed 21 April 2011.

Deepak P, Stobaugh DJ, Ehrenpreis ED. Infectious complications of TNF-α inhibitor monotherapy versus combination therapy with immunomodulators in inflammatory bowel

disease: analysis of the Food and Drug Administration Adverse Event Reporting System. *J Gastrointestin Liver Dis.* 2013;22(3):269-276.

Dougados M, vam der Linden S, Leirisalo-Repo M, Huitfeldt B, Juhlin R, Veys E, Zeidler H, Kvien TK, Olivieri I, Dijkmans B, et al. Sulfasalazine in the treatment of spondylarthropathy. A randomized, multicenter, double-blind, placebo-controlled study. *Arthritis Rheum*. 1995;38(5):618-627.

The EuroQol Group. EQ-5D-5L user guide, version 2.0. October 2013. Available at: http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/UserGuide_EQ-5D-5L_v2.0_October_2013.pdf. Accessed 02 April 2015.

[EMA] European Medicines Agency. Committee for medicinal products for human use (CHMP). Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. November 2004. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003329.pdf. Accessed 17 March 2015.

[FDA] Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for industry, non-inferiority clinical trials to establish effectiveness. November 2016. Available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm202140.pdf. Accessed 02 March 2017.

Fredriksson T, Pettersson U. Severe psoriasis—oral therapy with a new retinoid. *Dermatologica*. 1978;157(4):238-244.

Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum*. 1980;23(2):137-145.

Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *J Rheumatol*. 1982;9(5):789-793.

Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis*. 2005;64(suppl 2):ii14-ii7.

Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger TL, Ohtsuki M, Reich K, Amato D, Ball SG, Braun DK, Cameron GS, Erickson J, Konrad RJ, Muram TM, Nickoloff BJ, Osuntokun OO, Secrest RJ, ZhaoF, Mallbris L, Leonardi CL, for the UNCOVER-1, UNCOVER-2, and UNCOVER-3 Study Groups. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med*. 2016;375:345-356.

Gossec L, Smolen JS, Gaujoux-Viala C, Ash Z, Marzo-Ortega H, van der Heijde D, FitzGerald O, Aletaha D, Balint P, Boumpas D, Braun J, Breedveld FC, Burmester G, Cañete JD, de Wit M, Dagfinrud H, de Vlam K, Dougados M, Helliwell P, Kavanaugh A, Kvien TK, Landewé R, Luger T, Maccarone M, McGonagle D, McHugh N, McInnes IB, Ritchlin C, Sieper J, Tak PP, Valesini G, Vencovsky J, Winthrop KL, Zink A, Emery P; European League Against Rheumatism. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann Rheum Dis.* 2012;71(1):4-12.

Gossec L, Smolen JS, Ramiro S, deWit M, Cutolo M, Dougados M, Emery P, Landewé R, Oliver S, Aletaha D, Betteridge N, Braun J, Burmester G, Cañete JD, Damjanov N, FitzGerald

O, Haglund E, Helliwell P, Kvien TK, Lories R, Luger T, Maccarone M, Marzo-Ortega H, McGonagle D, McInnes IB, Olivieri I, Pavelka K, Schett G, Sieper J, van den Bosch F, Veale DJ, Wollenhaupt J, Zink A, van der Heijde D. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis.* 2016;75(3):499-510.

Healy PJ, Helliwell PS. Measuring dactylitis in clinical trials: which is the best instrument to use? *J Rheumatol.* 2007;34:1302-1306.

Healy PJ, Helliwell PS. Measuring clinical enthesitis in psoriatic arthritis: assessment of existing measures and development of an instrument specific to psoriatic arthritis. *Arthritis Rheum.* 2008;59(5):686-691.

Helliwell PS, Firth J, Ibrahim GH, Melsom RD, Shah I, Turner DE. Development of an assessment tool for dactylitis in patients with psoriatic arthritis. *J Rheumatol.* 2005;32:1745-1750.

Husted JA, Gladman DD, Farewell VT, Long JA, Cook RJ. Validating the SF-36 health survey questionnaire in patients with psoriatic arthritis. *J Rheumatol*. 1997;24(3):511-517.

Husted JA, Thavaneswaran A, Chandran V, Gladman DD. Incremental effects of comorbidity on quality of life in patients with psoriatic arthritis. *J Rheumatol.* 2013;40(8):1349-1356.

Kaltwasser JP, Nash P, Gladman D, Rosen CF, Behrens F, Jones P, Wollenhaupt J, Falk FG, Mease P; Treatment of Psoriatic Arthritis Study Group. Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. *Arthritis Rheum*. 2004;50(6):1939–1950.

Kavanaugh A, Helliwell P, Ritchlin CT. Psoriatic arthritis and burden of disease: patient perspectives from the Population-Based Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) Survey. *Rheumatol Ther.* 2016;3(1):91-102.

Kavanaugh A, Antoni CE, Gladman D, Wassenberg S, Zhou B, Beutler A, Keenan G, Burmester G, Furst DE, Weisman MH, Kalden JR, Smolen J, van der Heijde D. The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year. *Ann Rheum Dis*. 2006;65(8):1038-1043.

Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, Papp K, Zrubek J, Mudivarthy S, Mack M, Visvanathan S, Beutler A. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four–week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum*. 2009;60(4):976–986.

Kingsley GH, Kowalczyk A, Taylor H, Ibrahim F, Packham JC, McHugh NJ, Mulherin DM, Kitas GD, Chakravarty K, Tom BD, O'Keeffe AG, Maddison PJ, Scott DL. A randomized placebo-controlled trial of MTX in PsA. *Rheumatology*. 2012;51(8):1368-1377.

Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Enteracept in the treatment of psoriatic arthritis and psoriasis: a randomized trial. *Lancet*. 2000;356(9227):385-390.

Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, Salonen D, Rubenstein J, Sharp JT, Tsuji W. Etanercept treatment of psoriatic arthritis safety, efficacy, and effect on disease progression. *Arthritis Rheum*. 2004;50(7):2264–2272.

Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, Sharp JT, Ory PA, Perdok RJ, Weinberg MA; Adalimumab Effectiveness in Psoriatic Arthritis Trial Study Group. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum*. 2005;52(10):3279–3289.

Mease PJ, Woolley JM, Bitman B, Wang BC, Globe DR, Singh A. Minimally important difference of Health Assessment Questionnaire in psoriatic arthritis: relating thresholds of improvement in functional ability to patient-rated importance and satisfaction. *J Rheumatol*. 2011;38(11):2461-2465.

Mease PJ. Measures of psoriatic arthritis: Tender and Swollen Joint Assessment, Psoriasis Area and Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI), Modified Nail Psoriasis Severity Index (mNAPSI), Mander/Newcastle Enthesitis Index (MEI), Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada (SPARCC), Maastricht Ankylosing Spondylitis Enthesis Score (MASES), Leeds Dactylitis Index (LDI), Patient Global for Psoriatic Arthritis, Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQOL), Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F), Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsAJAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI). *Arthritis Care Res*. 2011;63(S11):S64–S85.

Mease PJ, Armstrong AW. Managing patients with psoriatic disease: the diagnosis and Pharmacologic treatment of psoriatic arthritis in patients with psoriasis. *Drugs*. 2014;74(4);423-41.

Mease PJ, Okada M, Kishimoto M, Shuler CL, Carlier H, Lin CY, Mou J, Moriarty SR, Lee CH, Gladman DD. Efficacy and safety of ixekizumab in patients with active psoriatic arthritis: 52 week results from a phase 3 study (Spirit-P1). *Ann Rheum Dis.* 2016;75(suppl 2):96. Abstract OP0109.

Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, Lin CY, Braun DK, Lee CH, Gladman DD; SPIRIT-P1 Study Group. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis.* 2017;76(1):79-87.

Menter A, Gottlieb A, Feldman SR, VanVoorhees AS, Leonardi CL, Gordon KB, Lebwohl M, Koo JY, Elmets CA, Korman NJ, Beutner KR, Bhushan R. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2008;58(5):826-850.

Mumtaz A, **Gallagher P, Kirby B, Waxman R, Coates LC, Veale JD, Helliwell P, FitxGerald** O. Development of a preliminary composite disease activity index in psoriatic arthritis. *Ann Rheum Dis.* 2011;70(2):272-277.

Nash P, Clegg DO. Psoriatic arthritis therapy: NSAIDs and traditional DMARDs. *Ann Rheum Dis.* 2005;64(suppl 2):ii74-ii77.

[NPF] National Psoriasis Foundation. The psoriasis and psoriatic arthritis pocket guide. 2009. Available at: www.psoriasis.org/document.doc?id=354. Accessed 07 April 2015.

Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry.* 2007;164(7):1035-1043.

Puig L. PASI90 response: the new standard in therapeutic efficacy for psoriasis. *J Eur Acad Dermatol Venereol*. 2015;29(4):645-648.

Rosen CF, Mussani F, Chandran V, Eder L, Thavaneswaran A, Gladman DD. Patients with psoriatic arthritis have worse quality of life than those with psoriasis alone. *Rheumatology*. 2012;51(3):571-576.

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

Rudwaleit M, Van den Bosch F, Kron M, Kary S, Kupper H. Effectiveness and safety of adalimumab in patients with ankylosing spondylitis or psoriatic arthritis and history of anti-tumor necrosis factor therapy. *Arthritis Res Ther*. 2010;12(3):R117.

SF-36 Health Survey Update page. SF-36 web site. Available at: http://www.sf-36.org/tools/sf36.shtml. Accessed 12 June 2011.

Smolen JS, Braun J, Dougados M, Emery P, Fitzgerald O, Helliwell P, Kavanaugh A, Kvien TK, Landewé R, Luger T, Mease P, Olivieri I, Reveille J, Ritchlin C, Rudwaleit M, Schoels M, Sieper J, Wit Md, Baraliakos X, Betteridge N, Burgos-Vargas R, Collantes-Estevez E, Deodhar A, Elewaut D, Gossec L, Jongkees M, Maccarone M, Redlich K, van den Bosch F, Wei JC, Winthrop K, van der Heijde D. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. *Ann Rheum Dis*. 2014;73(1):6-16.

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

Smolen JS, Breedveld FC, Eberl G, Jones I, Leeming M, Wylie GL, Kirkpatrick J. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. *Arthritis Rheum.* 1995;38(1):38-43.

Vander Cruyssen B, Van Looy S, Wyns B, Westhovens R, Durez P, Van den Bosch F, Veys EM, Mielants H, De Clerck L, Peretz A, Malaise M, Verbruggen L, Vastesaeger N, Geldhof A, Boullart L, De Keyser F. DAS28 best reflects the physician's clinical judgment of response to infliximab therapy in rheumatoid arthritis patients: validation of the DAS28 score in patients under infliximab treatment. *Arthritis Res Ther.* 2005;7(5):R1063-R1071.

Weinblatt ME, Schiff M, Valente R, van der Heijde D, Citera G, Zhao C, Maldonado M, Fleischmann R. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. Arthritis Rheum. 2013;65(1):28-38.

12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ACR	American College of Rheumatology
ACR Core Set	Consists of 7 disease activity measurements: tender joint count, swollen joint count, patient's assessment of pain, Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, Patient's Assessment of Physical Function, and an acute-phase reactant value.
ACR Responder	**ACR20 Responder** A patient who has at least 20% improvement in both tender and swollen joint counts and at least 20% improvement in a minimum of 3 of the following 5 criteria: patient's assessment of arthritis pain, Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, Patient's Assessment of Physical Function (Health Assessment Questionnaire-Disability Index), and an acute-phase reactant value (CRP or ESR). **ACR50 Responder** A patient who has at least 50% improvement in both tender and swollen joint counts and at least 50% improvement in a minimum of 3 of the following 5 criteria: patient's assessment of arthritis pain, Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, Patient's Assessment of Physical Function (Health Assessment Questionnaire-Disability Index), and an acute-phase reactant value (CRP or ESR). **ACR70 Responder** A patient who has at least 70% improvement in both tender and swollen joint counts and at least 70% improvement in a minimum of 3 of the following 5 criteria: patient's assessment of arthritis pain, Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, Patient's Assessment of Physical Function (Health Assessment Questionnaire-Disability Index), and an acute-phase reactant value (CRP or ESR).
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.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures, good clinical practice (GCP), and the applicable regulatory requirement(s).
BCG	Bacillus Calmette-Guérin
bDMARD	Biologic disease-modifying anti-rheumatic drug (see also DMARD); examples of biologics include—but are not limited to—etanercept (Enbrel®), adalimumab (Humira®), and infliximab (Remicade®)

blinding	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). 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.
BSA	body surface area; measured in 1% increments with area of patient's hand including palm, fingers and thumb = 1%
CASPAR	Classification for Psoriatic Arthritis
CEC	Clinical Events Committee; responsible for adjudicating cerebrocardiovascular AEs to achieve consistency in reporting
CI	confidence interval
clinical research physician	Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
consent	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
CRP	C-reactive protein
CSR	clinical study report
C-SSRS	Columbia–Suicide Severity Rating Scale
DAS28-CRP	Disease Activity Score (28 diarthrodial joint count) based on C-reactive protein
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
eCRF	Case report form (electronic case report form). Sometimes referred to as clinical report form. A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
efficacy	Efficacy is the ability of a treatment to achieve a beneficial intended result.
end of study (trial)	End of study (trial) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active subject in the study.
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.
enthesitis	Inflammation of tendons and ligaments that can manifest as localized pain and tenderness.
EQ-5D-5L	European Quality of Life–5 Dimensions 5 Level

ERB	Ethical Review Board; a board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
ETV	Early Termination Visit
EU	European Union
FSH	follicle-stimulating hormone
GCP	good clinical practice
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBcAb+	positive for anti-hepatitis B core antibody
HBsAb+	positive for anti-hepatitis B surface antibody
HBsAg+	positive for hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIVAb	human immunodeficiency virus antibody
hs-CRP	high sensitivity (assay) C-reactive protein
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Conference on Harmonisation
IL	Interleukin (eg, IL-17; a proinflammatory cytokine produced by Th17 cells)
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
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.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
ITT	intention to treat; the principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
ERB	Ethical Review Board; a board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
IV	intravenous
IWRS	interactive web-response system
LDI-B	Leeds Dactylitis Index—Basic

legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical study.
LEI	Leeds Enthesitis Index
LOCF	last observation carried forward
MDA	Minimal Disease Activity
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMRM	mixed-effects model repeated measures
Modified CPDAI	Modified Composite Psoriatic Disease Activity Index
MTX	methotrexate
NAPSI Fingernails	Nail Psoriasis Severity Index Fingernails
NRI	nonresponder imputation
NRS	numeric rating scale
PASI	Psoriasis Area and Severity Index
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PPD	purified protein derivative
Ps	psoriasis
PsA	psoriatic arthritis
PsARC	Psoriatic Arthritic Response Criteria
QoL	quality of life
Q2W	every 2 weeks
Q4W	every 4 weeks
RA	rheumatoid arthritis
randomize	Refers to a method of treatment assignment. The point of randomization in this trial is the point at which treatment is assigned and the patient begins treatment; thus, patients who are randomized in the trial are those who have been assigned to a treatment.
registration	The act of assigning a registration number to the subject indicating that the registration center/sponsor/principal investigator or subinvestigator has verified that the subject meets the inclusion criteria and none of the exclusion criteria.
rescreen	To screen a patient who was previously declared a screen failure for the same study.
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	Medical Outcomes Study 36-Item Short Form Health Survey
SJC	swollen joint count
sPGA	static Physician Global Assessment of psoriasis
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBL	total bilirubin level
TEAE	Treatment-emergent adverse event; an untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, which and does not necessarily have to have a causal relationship with this treatment.
TJC	tender joint count
TNF	tumor necrosis factor
UC	ulcerative colitis

ULN	upper limit of normal
VAS	visual analog scale

Appendix 2. Clinical Laboratory Tests

Assays to be performed by the central laboratory unless otherwise noted.

Clinical Laboratory Tests

Hematology	**Clinical Chemistry**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Platelets	Alanine aminotransferase (ALT)
Absolute counts of:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Triglycerides
Lymphocytes	Total cholesterol
Monocytes	HDL/LDL cholesterol
Eosinophils	GGT
Basophils	Proteins (total)
	Blood urea nitrogen (BUN)
Other Tests	Creatinine
Human immunodeficiency virus antibody (HIV)	Uric acid
Hepatitis B Surface antigen (HBsAg)	Calcium
Anti-Hepatitis B Surface antibody (HBsAb)	Glucose, fasting at Visit 2 but nonfasting throughout
Anti-Hepatitis B Core antibody (HBcAb)	study, if clinically indicated
Anti-Hepatitis C antibody	Albumin
Purified Protein Derivative (PPD)[a]	Creatine Phosphokinase (CPK)
QuantiFERON®-TB Gold[a]	hs-CRP
T-SPOT.TB[a]	
HBV DNA	
HCV RNA	
Rheumatoid factor (RF)	
Urinalysis	**Pregnancy Test** (females only)
Specific gravity	Serum
pH	Urine[b]
Protein	FSH
Glucose	
Ketones	
Blood	
Urine leukocyte esterase	

Abbreviations: FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; HDL = high-density lipoprotein; HIVab = human immunodeficiency virus antibody; LDL = low-density lipoprotein; RBC = red blood cells; WBC = white blood cells.

a Test may be done by the physician, nurse, or at the local laboratory.

b Assay to be performed by study site or self-administered by patient. Additional urine pregnancy testing can be performed at the investigator's discretion. If required per local regulations, testing can occur at other intervals during the study treatment period and/or follow-up period.

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 or an appropriate local representative must give assurance that the ERB was properly constituted and convened as required by International Conference on Harmonisation (ICH) guidelines and other applicable laws and regulations.

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

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

- the current 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 will be assigned to a third party.

Appendix 3.1.4. Investigator Information

Physicians with a specialty in rheumatology 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 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 eCRFs, 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 eCRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

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

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

Appendix 3.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Electronic patient-reported outcome (ePRO) measures (for example, a rating scale) are entered into an ePRO instrument (tablet) at the time that the information is obtained. In these instances where there is no prior written or electronic source data at the site, the ePRO instrument record will serve as the source. In these instances where there are prior written source data that are subsequently entered into ePRO, the written record will serve as the source.

If ePRO records are stored at a third party site, study sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the ePRO instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Any data for which paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient will include a paper diary to collect a dosing schedule.

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 the Lilly, or its designee, clinical research physician.

Hepatic Monitoring Tests

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

Abbreviations: ALT = alanine aminotransferase; AST = aspartate 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-RHCF(a) Summary: A 52-Week Multicenter, Randomized, Open-Label, Parallel-Group Study Evaluating the Efficacy and Safety of Ixekizumab versus Adalimumab in Patients with Psoriatic Arthritis Who Are Biologic Disease-Modifying Anti-Rheumatic Drug Naive

Overview

Protocol I1F-MC-RHCF (A 52-Week Multicenter, Randomized, Open-Label, Parallel-Group Study Evaluating the Efficacy and Safety of Ixekizumab versus Adalimumab in Patients with Psoriatic Arthritis Who Are Biologic Disease-Modifying Anti-Rheumatic Drug Naive) has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table:

Amendment Summary for Protocol I1F-MC-RHCF Amendment (a)

Section # and Name	Description of Change	Brief Rationale
All protocol sections	Minor editorial changes.	Minor corrections made as needed.
1. Synopsis	Replaced "<" with "≤" for PASI score 1, 2, or 3 Updated Statistical Analysis section	Corrected symbols. Modified based on observations from the csDMARD-experienced population from Study RHAP.
2. Schedule of Activities	Footnote e: Removed that study drug will be administered by the patient or caregiver "at home". Footnote j: Added a missing letter "A" to the beginning of the sentence. Footnote m: Added that additional pregnancy could be performed at the investigator's discretion or per applicable regulations/guidance. Deleted reference to local regulations.	Removed "at home" to make the instruction less specific. Minor editorial correction. Updated language to allow for more frequent pregnancy testing for any reason.
Table RHCF.2.1 Study Drug Administration Schedule	Added "plaque" before Ps. Corrected footnote order.	Minor editorial corrections.
3.3 Benefit/Risk Assessment	Replaced "SPC" with "product labeling."	SPC is specific to EU; "product labeling" is more general.
4. Objectives and Endpoints	Replaced "<" with "≤" for PASI score 1, 2, or 3	Corrected symbols.
5.2 Number of Participants	Clarified wording.	Minor editorial change.
6.1. Inclusion Criteria	Added Inclusion Criterion 50: Have had an inadequate response when treated with 1 or more csDMARDs.	Patients must meet this additional inclusion criterion. Number 50 is the next number in the inclusion/exclusion list; however, this criterion was included in the inclusion criteria section.
6.2. Exclusion Criteria	Exclusion Criterion 10: Clarified that the dose of the allowed concomitant medications MTX, leflunomide, sulfasalazine, or cyclosporine must remain unchanged during the first 24 weeks only of the Open-Label Treatment Period. Deleted hydroxychloroquine. Exclusion Criterion 13: Clarified that patients anticipating needing a parenteral injection of glucocorticosteroids during the first 24 weeks only of the Open-Label Treatment Period are excluded. Exclusion Criterion 33: Clarified that patients who have had an infection of	Exclusion Criteria 10 and 13 apply to the first 24 weeks only of the 52-week Open-Label Treatment Period. Hydroxychloroquine was removed as a csDMARD. Minor editorial changes. Exclusion Criterion 33 was changed to exclude patients with infection of an artificial joint.

Section # and Name	Description of Change	Brief Rationale
	an artificial joint are excluded.	
7. Treatments	Added Section 7.1.1 Administration of Investigational Product. Packaging and Labeling was renumbered to Section 7.1.2.	Added to provide specific information regarding the administration of study drug. Minor editorial changes.
7.2. Method of Treatment Assignment	Clarified that the randomization will be stratified by "concomitant" csDMARD use "at baseline."	Stratification will occur by concomitant csDMARD use at baseline. Minor editorial changes.
7.3. Blinding	Added sPGA and Percentage of Body Surface Area to the list of blinded assessor rated assessment.	Previously missing from the list.
7.7. Concomitant Therapy	Added a sentence clarifying that PsA medications should remain at a stable dose for the first 24 weeks of Open-Label Treatment unless changes are required for safety reasons. Replace SPC with product labeling.	Added for consistency.
Table RHCF.7.2 Concomitant Medications Permitted/Not Permitted in the Open-Label Treatment Period from Week 0 to Week 24 for Treatment of PsA and Chronic Conditions Table RHCF.7.3 Concomitant Medications Permitted/Not Permitted in the Open-Label Treatment Period from Week 24 to Week 52 for Treatment of PsA and Chronic Conditions Table RHCF.7.4 Allowed Concomitant Medications in the Post-Treatment	Table RHCF.7.2: For opiate analgesics, added stable doses with no dose adjustments, changes, and/or introduction of new opiate analgesics as a condition for use. Table RHCF.7.2 and 7.3: Removed hydroxychloroquine. All 3 tables: Removed the abbreviation IV from the abbreviations lists and spelled out intravascular in each table.	Previously inconsistent compared to oral steroids and to the exclusion criteria. Hydroxychloroquine was removed as a csDMARD. The abbreviation IV is defined as intravenous. Minor formatting changes.

Section # and Name	Description of Change	Brief Rationale
Follow-Up Period (Period 3)		
8.1.1. Permanent Discontinuation from Study Treatment	Added an "X" to the final bullet in the list of permanent discontinuation for study treatment. "alkaline phosphatase >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)"	Corrected typo.
9.1.2.1. Psoriasis Area and Severity Index (PASI 75, PASI 90, PASI 100)	Replaced "<" with "≤" for PASI score 1, 2, or 3.	Corrected symbols.
9.1.2.3.1 American College of Rheumatology Core Set	Moved/added a sentence to the beginning of each assessment description stating that TJC and SJC assessments will be performed by a blinded assessor.	Minor editorial changes.
9.1.2.11. Leeds Dactylitis Index-Basic	Added the derivation for this assessment from the Statistical Analysis Plan (SAP) for Study I1F-MC-RHBE (RHBE).	The derivation was updated in this SAP.
9.1.2.14. Static Physician Global Assessment	Replaced physician with assessor for the determination of the patient's Ps lesions overall at a given time point.	Assessor is the appropriate role for this.
9.3. Treatment of Overdose	Replace SPC with product labeling.	SPC is specific to EU; "product labelling" is more general.
10.1. Sample Size Determination	Updated language.	Modified based on observations from the csDMARD-experienced population from Study RHAP.
10.3.1.1. General Considerations for Analyses during Period 2 (Open-Label Treatment Period)	Included a statement that the primary time point of interest is Week 24.	Clarification.
10.3.1.3. Adjustment for Multiple Comparisons	Modified number 3 to remove noninferiority.	The major secondary endpoint is superiority rather than noninferiority. Minor editorial changes.
10.3.2.2. Patient Characteristics	Removed CASPAR as a baseline clinical measurement.	Not collecting CASPAR scores at baseline; CASPAR is only an inclusion criterion.
10.3.3.1.1. Categorical Variables	Added "concomitant" csDMARD use at "baseline". Included that treatment group comparisons will be made at all visits up to	Clarified that the model will include concomitant csDMARD use at baseline.

Section # and Name	Description of Change	Brief Rationale
	Week 52 and odds ratios and their corresponding 95% confidence intervals (CIs) will be reported.	Added additional information to clarify that treatment group comparisons will be made at Week 52 and that odds ratios and their corresponding 95% CIs will be reported.
10.3.3.1.2. Continuous Variables	Added "concomitant" csDMARD use at "baseline".	Clarified that the model will include concomitant csDMARD use at baseline. Minor editorial changes.
10.3.3.3. Methodology for Noninferiority Test	Percent preservation of the adalimumab treatment effect was modified from 60% to 50%.	Correction.
10.3.6.1. Subgroup Analysis	Added that subgroups to be evaluated will include "concomitant" csDMARD use and MTX use "at baseline".	Clarified. Minor editorial changes.
10.3.7 Interim Analysis	Added "(Period 2)" after Open-Label Treatment Period. Added a statement that since Week 24 is the primary time point of interest efficacy and health outcomes data will be reported up to Week 24 because of the lack of complete data for all patients beyond this visit. However, all safety data collected up to the cutoff date will be reported. Added a statement that after the final database lock, all efficacy, health outcomes, and safety data collected until study completion will be reported.	Minor editorial change. Clarified.
Appendix 1. Abbreviations and Definitions	Removed SPC.	SPC is no longer used in the protocol.
Appendix 2. Clinical Laboratory Tests	Deleted one instance of "cholesterol" from the table as it was included twice.	Repetitive.

Revised Protocol Sections

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

Note: The numbering system used for inclusion and exclusion criteria provides a unique number for each criterion and allows for efficiency in data collection. In case an amendment to the protocol adds a criterion, that criterion will receive the next available number, regardless of whether it is an inclusion or exclusion criterion. In this amendment, the additional inclusion criterion is numbered 50, but remains in the inclusion criteria section.

1. Synopsis

Objective(s)/Endpoints:

Psoriasis/Nail Endpoints

Time course of response to treatment over 52 weeks as measured by:

- Change from baseline in body surface area (BSA)
- Proportion of patients who achieve the following PASI scores: PASI 75, PASI 90, or PASI 100 (defined as 75%, 90%, and 100% improvement from baseline in PASI criteria, respectively)
- Proportion of patients achieving an absolute PASI score ~~<~~ ≤1 or ~~<~~ ≤2 or ~~<~~ ≤3
- Change from baseline in the Nail Psoriasis Severity Index (NAPSI) Fingernails score in the subgroup of patients with fingernail involvement at baseline (ie, baseline NAPSI Fingernails score >0)

Statistical Analysis:

A significance level of 0.05 is assumed for testing ~~each dosing regimen of~~ ixekizumab versus adalimumab.

Sample size was calculated assuming the proportion of patients simultaneously achieving ACR50 and PASI 100 as ~~13.2~~ 13.6% and ~~28.8~~ 31.3% in the adalimumab and ixekizumab treatment groups, respectively, as observed in the conventional synthetic disease-modifying anti-rheumatic drug (csDMARD)-experienced population from Study RHAP. According to the nQuery software, a total sample size of 550 patients (with 275 patients per treatment group) using a 2-sided Fisher's exact test at a 0.05 level of significance would yield approximately 99% power for testing ixekizumab versus adalimumab.

This sample size would yield ~~79~~ 78% power for testing the noninferiority of ixekizumab to adalimumab at a one-sided 0.025 level of significance based on a noninferiority margin of –12% and using ACR50 response rates of ~~42.5~~ 43.8% and 44.1% as observed for ~~in~~ the ixekizumab and adalimumab treatment groups, respectively, in the csDMARD-experienced population from Study RHAP~~, respectively~~. For testing superiority of ixekizumab to adalimumab based on PASI 100 response rates of ~~42.5~~ 46.9% and ~~23.5~~ 23.7% as observed for ixekizumab and adalimumab in the csDMARD-experienced population from Study RHAP, this sample size would yield 99% power using a 2-sided Fisher's exact test at 0.05 level of significance.

2. Schedule of Activities

Table footnotes:

[e] At randomization (Visit 2) for patients randomized to ixekizumab and for patients with moderate-to-severe plaque Ps symptoms randomized to adalimumab, the second injection of study drug will be administered by the patient or caregiver under site personnel supervision for injection training purposes. Thereafter, study drug will be administered by the patient or caregiver ~~at home~~.

[j] All patients will be tested for HBV.

[m] Only for females of childbearing potential. Additional urine pregnancy testing can be performed at the investigator's discretion or per applicable regulations/guidance. ~~If required per local regulations, testing can occur at other intervals during the study treatment period and/or follow-up period.~~

Table RHCF.2.1. Study Drug Administration Schedule

Visit	2	3			4				5				6				7								8
Weeks	0[a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Ixekizumab 80 mg Q2W/Q4W *Moderate-to-Severe Plaque Ps*[b]	X (160 mg)		X		X		X		X		X		X				X				X				X
Ixekizumab 80 mg Q4W[c]	X (160 mg)				X				X				X				X				X				X
Adalimumab 40 mg Q2W[d]	X (40 mg)		X		X		X		X		X		X		X		X		X		X		X		X
Adalimumab 40 mg Q2W *Moderate-to-Severe Plaque Ps*[e]	X (80 mg)	X		X		X		X		X		X		X		X		X		X		X		X	

Visit								9								10												11
Weeks	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52
Ixekizumab 80 mg Q2W/Q4W *Moderate-to-Severe Plaque Ps*[b]				X				X				X				X				X				X				
Ixekizumab 80 mg Q4W[c]				X				X				X				X				X				X				
Adalimumab 40 mg Q2W[d]		X		X		X		X		X		X		X		X		X		X		X		X		X		
Adalimumab 40 mg Q2W *Moderate-to-Severe Plaque Ps*[e]	X		X		X		X		X		X		X		X		X		X		X		X		X		

Abbreviations: BSA = body surface area; PASI = Psoriasis Area and Severity Index; Ps = psoriasis; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; sPGA = static Physician Global Assessment of psoriasis.

[a] Starting dose.

Study Drug Administration Schedule

[b] Patients with moderate-to-severe plaque Ps, defined as PASI ≥12, sPGA ≥3, and BSA ≥10%, will receive ixekizumab 80 mg given as 1 SC injection Q2W from Week 2 to Week 12 and Q4W thereafter.

[c] Patients not meeting criteria for moderate-to-severe plaque Ps will receive ixekizumab 80 mg given as 1 SC injection Q4W starting at Week 4.

[d~~e~~] Patients not meeting criteria for moderate-to-severe plaque Ps will receive a starting dose of adalimumab 40 mg given as 1 SC injection at randomization (Visit 2 [Week 0]) followed by 40 mg given as 1 SC injection Q2W starting at Week 2.

[e~~d~~] Patients with moderate-to-severe plaque Ps, defined as PASI ≥12, sPGA ≥3, and BSA ≥10%, will receive a starting dose of adalimumab 80 mg (two 40-mg SC injections) administered at randomization (Visit 2 [Week 0]) followed by 40 mg given as 1 SC injection Q2W starting at Week 1.

~~[d] Patients with moderate-to-severe plaque Ps, defined as PASI ≥12, sPGA ≥3, and BSA ≥10%, will receive a starting dose of adalimumab 80 mg (two 40-mg SC injections) administered at randomization (Visit 2 [Week 0]) followed by 40 mg given as 1 SC injection Q2W starting at Week 1.~~

~~[e] Patients not meeting criteria for moderate-to-severe plaque Ps will receive a starting dose of adalimumab 40 mg given as 1 SC injection at randomization (Visit 2 [Week 0]) followed by 40 mg given as 1 SC injection Q2W starting at Week 2.~~

3.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of ixekizumab are to be found in the Investigator's Brochure (IB) and the product labeling ~~Summary of Product Characteristics (SPC)~~.

More detailed information about the known and expected benefits and risks of adalimumab may be found in the ~~SPC~~ product labeling.

4. Objectives and Endpoints

Table RHCF.4.1.

Psoriasis/Nail Endpoints

Time course of response to treatment over 52 weeks as measured by:

- Change from baseline in body surface area (BSA)
- Proportion of patients who achieve the following PASI scores: PASI 75, PASI 90, or PASI 100 (defined as 75%, 90%, and 100% improvement from baseline in PASI criteria, respectively)
- Proportion of patients achieving an absolute PASI score ~~<~~ ≤1 or ~~<~~ ≤2 or ~~<~~ ≤3
- Change from baseline in the Nail Psoriasis Severity Index (NAPSI) Fingernails score in the subgroup of patients with fingernail involvement at baseline (ie, baseline NAPSI Fingernails score >0)

5.2. Number of Participants

Approximately 917 participants will be screened (assuming a 40% screen failure rate) to achieve randomization of 550 participants (275 per treatment group) and approximately 396 patients are expected to complete Week 52 ~~have approximately 396 participants evaluable~~ (assuming 72% completion rate at Week 52)~~ at the completion of the study~~.

6.1. Inclusion Criteria

Patient Characteristics

…

[4] Have active psoriatic skin lesions (plaque psoriasis) with a BSA ≥3% at Visit 1 (Screening) and Visit 2 (Week 0).

[50] Have had an inadequate response when treated with 1 or more csDMARDs.

6.2. Exclusion Criteria

…

[10] Have used csDMARDs other than MTX, leflunomide, sulfasalazine, or cyclosporine ~~or hydroxychloroquine~~ in the 8 weeks prior to randomization (Visit 2).

Have discontinued MTX, sulfasalazine, ~~hydroxychloroquine,~~ or cyclosporine within 12 weeks prior to randomization.

If taking MTX, leflunomide, sulfasalazine, or cyclosporine, must have been treated for at least 12 weeks prior to randomization *and* on a stable dose for at least 8 weeks prior to randomization, as follows: oral or parenteral MTX = 10 to 25 mg/week, leflunomide = 20 mg/day, sulfasalazine = up to 3 g/day, ~~hydroxychloroquine = up to 400 mg/day,~~ or cyclosporine up to 5 mg/kg/day. The dose of these allowed concomitant medications must remain unchanged during the first 24 weeks of the Open-Label Treatment Period unless changes are required for safety issues. Local standard of care should be followed for concomitant administration of folic acid with MTX.

…

[13] Have received any parenteral glucocorticoid administered by intraarticular, intramuscular, or intravenous (IV) injection within 6 weeks prior to randomization, or for whom a parenteral injection of glucocorticosteroids is anticipated during the first 24 weeks of the Open-Label Treatment Period.

…

[33] Patients who have:

- in the past 12 weeks prior to randomization:
  - had a serious infection (for example, pneumonia, cellulitis)
  - have been hospitalized for an infection
  - have received IV antibiotics for an infection
- or in the past 24 weeks prior to randomization had a serious bone or joint infection,
- or have ever had
  - an infection of an artificial joint
  - an infection that occurs with increased incidence in an immunocompromised host (including, but not limited to, *Pneumocystis jirovecii* pneumonia, active histoplasmosis, or coccidioidomycosis); or have a known immunodeficiency.

7.1.1. Administration of Investigational Product

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

Training: At randomization (Visit 2), patients randomized to ixekizumab and patients with moderate-to-severe plaque Ps symptoms randomized to adalimumab will receive 2 injections. For training purposes, the proper procedures for administration of the initial injection will be performed by clinical staff. The second injection of study drug will be administered by the patient or caregiver under site personnel supervision. Thereafter, study drug should be

administered by the patient or caregiver. If additional training is necessary, an injection may be administered by the patient or caregiver under the supervision of clinical staff.

Administration: If the patient is unable to administer the injection, a caregiver who will also be trained under supervision of site staff may administer the study drug. All subsequent injections will be administered by the patient or caregiver and should be administered unsupervised by the clinical staff (see Section 2). It is recommended that for these subsequent injections, the patient/caregiver administer the study drug outside the trial site, preferably at the patient's home. If the patient or caregiver is not able to administer the second injection of the starting dose or any dose throughout the study, study site personnel may administer that injection.

Refer to the appropriate directions for use provided by the sponsor for the study drug.

Study Drug Administration Logs will be dispensed to each patient as needed for recording pertinent data about each injection; details of the use of these logs are provided in Section 7.2.1.

Observation: Patients should remain under observation for at least 1 hour after dosing at randomization (Visit 2) to allow for observation for any AEs and collection of postinjection sitting BP and pulse measurements approximately 1 hour after administration of study drug (see Section 2).

~~7.1.1.~~ 7.1.2. Packaging and Labeling

7.2. Method of Treatment Assignment

Patients who meet all Visit 1 and Visit 2 eligibility criteria for enrollment will be randomized at Visit 2 (Week 0) in a 1:1 ratio to open-label treatment with ixekizumab or adalimumab at Week 0 (Visit 2). Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign investigational product to each patient. Site personnel will confirm that they have located the correct investigational product by entering a confirmation number found on the investigational product into the IWRS. The randomization will be stratified by concomitant csDMARD use at baseline (Yes~~,~~ vs No) and moderate-to-severe plaque psoriasis involvement (Yes~~,~~ vs No) ~~severity of plaque psoriasis moderate-to-severe (Yes, No)~~.

7.3. Blinding

This is an open-label study where treatment allocation is revealed after randomization. Specifically:

- A blinded assessor will complete the following assessments:
  - TJC/SJC
  - Psoriasis Area and Severity Index (PASI)
  - Percentage of BSA
  - Enthesitis
  - LDI-B
  - NAPSI Fingernails
  - sPGA

7.7. Concomitant Therapy

All concomitant medication taken during the study must be recorded on the Concomitant Medication case report form (eCRF) at the study visits indicated in the Schedule of Activities (Section 2). Treatment with concomitant PsA therapies during the study will be permitted only as outlined in the inclusion and exclusion criteria (Sections 6.1 and 6.2, respectively) and as described below. Patients taking permitted PsA medications should be on stable doses at randomization (Visit 2) and through the first 24 weeks of the Open-Label Treatment Period, as specified below, unless changes are required for safety reasons. Table RHCF.7.2, Table RHCF.7.3, and Table RHCF.7.4 summarize concomitant medications that are and are not permitted and the conditions for use during the study for those which are permitted.

Table RHCF.7.2. Concomitant Medications Permitted/Not Permitted in the Open-Label Treatment Period from Week 0 to Week 24 for Treatment of PsA and Chronic Conditions

Drug Class	As Needed	Chronic Use	Conditions for Use
…			
csDMARDs	N	Y	Stable dose allowed. Stable doses with no dose adjustments, changes, and/or introduction of a new csDMARD Allowed doses: • Oral or parenteral MTX; 10 to 25 mg/week • Leflunomide: up to 20 mg/day • Sulfasalazine: up to 3 g/day • ~~Hydroxychloroquine: up to 400 mg/day~~ • Cyclosporine: up to 5 mg/kg/day
…			
Opiate analgesics	N	Y	Stable doses with no dose adjustments, changes, and/or introduction of a new opiate analgesic. May be used at average daily doses ≤30 mg/day of morphine or its equivalent
…			
Intravascular~~V~~ and IM glucocorticoid	N	N	Not allowed
…			

Abbreviations: BCG = Bacillus Calmette-Guérin; bDMARD = biological disease-modifying anti-rheumatic drugs; COX-2 = cyclooxygenase-2; csDMARD = conventional synthetic disease-modifying anti-rheumatic drugs; IM = intramuscular; ~~IV = intravascular;~~ JAK = Janus kinase; MTX = methotrexate; N = No; NSAID = nonsteroidal anti-inflammatory drug; PASI = Psoriasis Area and Severity Index; PDE4 = phosphodiesterase type 4; Y = Yes; WHO = World Health Organization.

Table RHCF.7.3. Concomitant Medications Permitted/Not Permitted in the Open-Label Treatment Period from Week 24 to Week 52 for Treatment of PsA and Chronic Conditions

Drug Class	As Needed	Chronic Use	Conditions for Use
…			
csDMARDs	N	Y	Allowed doses: • Oral or parenteral MTX; 10 to 25 mg/week • Leflunomide: up to 20 mg/day • Sulfasalazine: up to 3 g/day • ~~Hydroxychloroquine: up to 400 mg/day~~ • Cyclosporine: up to 5 mg/kg/day
…			
Intravascular~~V~~ and IM glucocorticoid	N	N	Not allowed
…			

Abbreviations: BCG = Bacillus Calmette-Guérin; bDMARD = biological disease-modifying anti-rheumatic drugs; COX-2 = cyclooxygenase-2; csDMARD = conventional synthetic disease-modifying anti-rheumatic drugs; IM = intramuscular; ~~IV = intravascular;~~ JAK = Janus kinase; MTX = methotrexate; N = No; NSAID = nonsteroidal anti-inflammatory drug; PASI = Psoriasis Area and Severity Index; PDE4 = phosphodiesterase type 4; Y = Yes; WHO = World Health Organization.

Table RHCF.7.4. Allowed Concomitant Medications in the Post-Treatment Follow-Up Period (Period 3)

Drug Class	As Needed	Chronic Use	Conditions for Use
…			
Intravascular~~V~~ and IM glucocorticoid	Y	Y	Allowed
…			

Abbreviations: BCG = Bacillus Calmette-Guérin; bDMARDs = biological disease-modifying anti-rheumatic drugs; COX-2 = cyclooxygenase-2; csDMARD = conventional synthetic disease-modifying anti-rheumatic drugs; IM = intramuscular; ~~IV = intravascular;~~ JAK = Janus kinase; MTX = methotrexate; N = No; NSAID = nonsteroidal anti-inflammatory drug; PASI = Psoriasis Area and Severity Index; PDE4 = phosphodiesterase type 4; Y = Yes; WHO = World Health Organization.

To avoid any possible drug interactions for those patients randomized to adalimumab, please refer to the ~~SPC~~ product labeling for adalimumab for further concomitant therapy restrictions.

8.1.1. Permanent Discontinuation from Study Treatment

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

…

- alkaline phosphatase >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

9.1.2.1. Psoriasis Area and Severity Index (PASI 75, PASI 90, PASI 100)

…

Absolute PASI scores of ~~<~~ ≤1, ~~<~~ ≤2, or ~~<~~ ≤3 may be considered as treatment targets for the management of plaque psoriasis.

9.1.2.3.1. American College of Rheumatology Core Set

a. Tender Joint Count

TJC joint assessments will be performed by a blinded assessor.

…

b. Swollen Joint Count

SJC joint assessments will be performed by a blinded assessor.

…

Missing, replaced, ankylosed, or arthrodesed joints will be identified by the investigator at the Screening Visit and will be excluded from evaluation during the trial.

~~TJC/SJC joint assessments will be performed by a blinded assessor.~~

9.1.2.11. Leeds Dactylitis Index-Basic

If the patient has dactylitis, the LDI-B will be administered by a blinded assessor. The LDI-B has been developed to measure the severity of dactylitis. Once the presence of dactylitis is established in each digit, the ratio of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot is measured (Helliwell et al. 2005). Each dactylitic digit is defined by a minimum increase of 10% in circumference over the contra-lateral digit. If the same digits on each hand or foot are thought to be involved, the clinician will refer to a table of normative values (provided to study sites) for a value which will be used to provide the comparison. ~~The calculated ratio is then multiplied by a tenderness score of 0 (not tender) or 1 (tender).~~ If the ratio is >1.1, then subtract 1 from the calculated ratio and multiply it by 100 and the tenderness score of 0 (not tender) or 1 (tender). Otherwise, if the ratio of the circumference of the digit is ≤1.1, then the LDI-B score is set to 0. Tenderness is assessed in the area between the joints. The results of each digit are then added to produce a total score (Healy and Helliwell 2007).

9.1.2.14. Static Physician Global Assessment

If the patient has plaque Ps, the static Physician Global Assessment of psoriasis (sPGA) will be administered by the blinded assessor. The sPGA is the assessor's ~~physician's~~ determination of the patient's Ps lesions overall at a given time point. The sPGA is recommended as an endpoint to use to assess efficacy in the treatment of Ps (EMEA 2004). Overall lesions are categorized by descriptions for induration, erythema, and scaling. For the analysis of responses, the patient's Ps is assessed at a given time point on a 6 point scale in which 0 = cleared, 1 = minimal, 2 = mild, 3 = moderate; 4 = severe, 5 = very severe.

9.3. Treatment of Overdose

Refer to the ixekizumab IB and product labeling ~~SPC~~ and the adalimumab product labeling ~~SPC~~.

10.1. Sample Size Determination

Sample size was calculated assuming the proportion of patients simultaneously achieving ACR50 and PASI 100 as ~~13.2~~ 13.6% and ~~28.8~~ 31.3% in the adalimumab and ixekizumab treatment groups, respectively, as observed in the csDMARD-experienced population from Study RHAP. According to the nQuery software, a total sample size of 550 (with 275 per treatment group) using a 2-sided Fisher's exact test at 0.05 level of significance would yield 99% power for testing ixekizumab versus~~s~~ adalimumab.

This sample size would yield ~~79~~ 78% power for testing the noninferiority of ixekizumab to adalimumab at a one-sided 0.02~~5~~ level of significance based on a noninferiority margin of –12% and using ACR50 response rates of ~~42.5~~ 43.8% and 44.1% as observed for the ixekizumab and adalimumab treatment groups, respectively, in the csDMARD-experienced population from Study RHAP ~~in the ixekizumab and adalimumab treatment groups, respectively~~. For testing superiority of ixekizumab to adalimumab based on PASI 100 response rates of ~~42.5~~ 46.9% and ~~23.5~~ 23.7% as observed for ixekizumab and adalimumab in the csDMARD-experienced population from Study RHAP, this sample size would yield 99% power using a 2-sided Fisher's exact test at 0.05 level of significance.

10.3.1.1. General Considerations for Analyses during Period 2 (Open-Label Treatment Period)

…

Comparisons of ixekizumab versus adalimumab will be performed for all outcome variables at all visits in Period 2; however, the primary time point of interest is Week 24.

10.3.1.3. Adjustment for Multiple Comparisons

…

3. Test 3 for Major Secondary Endpoint #2 – Proportion of patients achieving PASI 100 at Week 24: If the test for major secondary endpoint #1 is significant, then a superiority ~~noninferiority~~ test for major secondary endpoint #2 will be performed~~, followed by a test for superiority. The noninferiority test will be performed using the methods described in Section 10.3.3.3, and the superiority test will be performed~~ using the methods described in Section 10.3.3.1.1.

10.3.2.2. Patient Characteristics

Baseline characteristics, clinical, and health outcome measurements will be summarized for the ITT population. Baseline characteristics will include sex, age, age category, weight, BMI, race, geographic region, baseline disease severity, duration of disease, previous nonbiologic systemic therapy, and previous biologic therapy. Baseline clinical measurements will include ~~CASPER,~~ ACR component scores, PASI total score, DAS28-CRP, CRP, Modified CPDAI, HAQ-DI, Itch NRS score, NAPSI Fingernails, SPARCC Enthesitis Index, LEI, LDI-B, and other QoL scores.

10.3.3.1.1. Categorical Variables

Unless specified otherwise, the primary analysis method for the categorical efficacy and health outcome variables will be using a logistic regression model with treatment, concomitant csDMARD use at baseline (Yes vs No) ~~(yes or no)~~, and ~~severity of plaque psoriasis~~ moderate-to-severe plaque psoriasis involvement (Yes vs No) ~~(yes or no)~~ as factors and NRI method. Treatment group comparisons will be made at all visits up to Week 52 and odds ratios and their corresponding 95% confidence intervals (CIs) will be reported.

10.3.3.1.2. Continuous Variables

Unless specified otherwise, the primary analysis method for all continuous efficacy and health outcome variables will be using a MMRM analysis. The model will include treatment group, concomitant csDMARD use (Yes vs No) at baseline, moderate-to-severe plaque psoriasis involvement (Yes vs No) ~~severity of plaque psoriasis~~, baseline value, visit, baseline-by-visit interaction, and treatment-by-visit interaction as fixed factors. The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III tests for the least squares means will be used for the statistical comparison; the 95% ~~confidence interval (~~CI~~)~~ will also be reported. Treatment group comparisons at all visits up to Week 52 will be ~~tested~~ made.

10.3.3.3. Methodology for Noninferiority Test

…

Based on EMEA CHMP (CHMP 2005), FDA guidance (2016), and Weinblatt et al. (2013), a noninferiority margin of −12.0% for ACR50 between ixekizumab and adalimumab (ie, response rate of ixekizumab – response rate of adalimumab) is considered appropriate. This noninferiority margin represents an approximately ~~60~~ 50% preservation of the adalimumab treatment effect

(based on the difference between adalimumab and placebo) observed in a historical Phase 3 study for adalimumab 40 mg twice weekly compared with placebo (Mease et al 2005) and Study RHAP.

10.3.6.1. Subgroup Analyses

…

Subgroups to be evaluated will include concomitant csDMARD use at baseline (Yes vs No), concomitant MTX use at baseline (Yes ~~or~~ vs No), sex (male vs female), age group (<65 vs ≥65). A detailed description of the subgroup variables will be provided in the SAP.

10.3.7. Interim Analyses

An interim database lock will occur, and the analysis will be performed at the time (that is, a cutoff date) when the last patient completes Visit 8 (Week 24), completes ETV, or discontinues from Period 2. This database lock will include all data collected by the cutoff date including data after Week 24 from the Open-Label Treatment Period (Period 2) and follow-up data from patients who have begun Post-Treatment Follow-Up Period (Period 3).

This interim database lock at Week 24 will be considered the primary database lock for this study because all primary and major secondary study objectives will be assessed at this time. Since the primary time point of interest is Week 24, efficacy and health outcomes data will be reported up to Week 24 because of the lack of complete data for all patients beyond this visit. However, all safety data collected up to the cutoff date will be reported.

A final database lock will occur after all enrolled patients have completed or discontinued the Post-Treatment Follow-Up Period (Period 3). After the final database lock, all efficacy, health outcomes, and safety data collected until study completion will be reported.

Appendix 2. Clinical Laboratory Tests

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Other Tests	Creatinine
Human immunodeficiency virus antibody (HIV)	Uric acid
Hepatitis B Surface antigen (HBsAg)	Calcium
Anti-Hepatitis B Surface antibody (HBsAb)	Glucose, fasting at Visit 2 but nonfasting throughout
Anti-Hepatitis B Core antibody (HBcAb)	study, if clinically indicated
Anti-Hepatitis C antibody	Albumin
Purified Protein Derivative (PPD)[a]	~~Cholesterol~~
QuantiFERON®-TB Gold[a]	Creatine Phosphokinase (CPK)
T-SPOT.TB[a]	hs-CRP
HBV DNA	
HCV RNA	
Rheumatoid factor (RF)	

Appendix 1. Abbreviations and Definitions

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Term	Definition
~~**SPC**~~	~~Summary of Product Characteristics~~

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