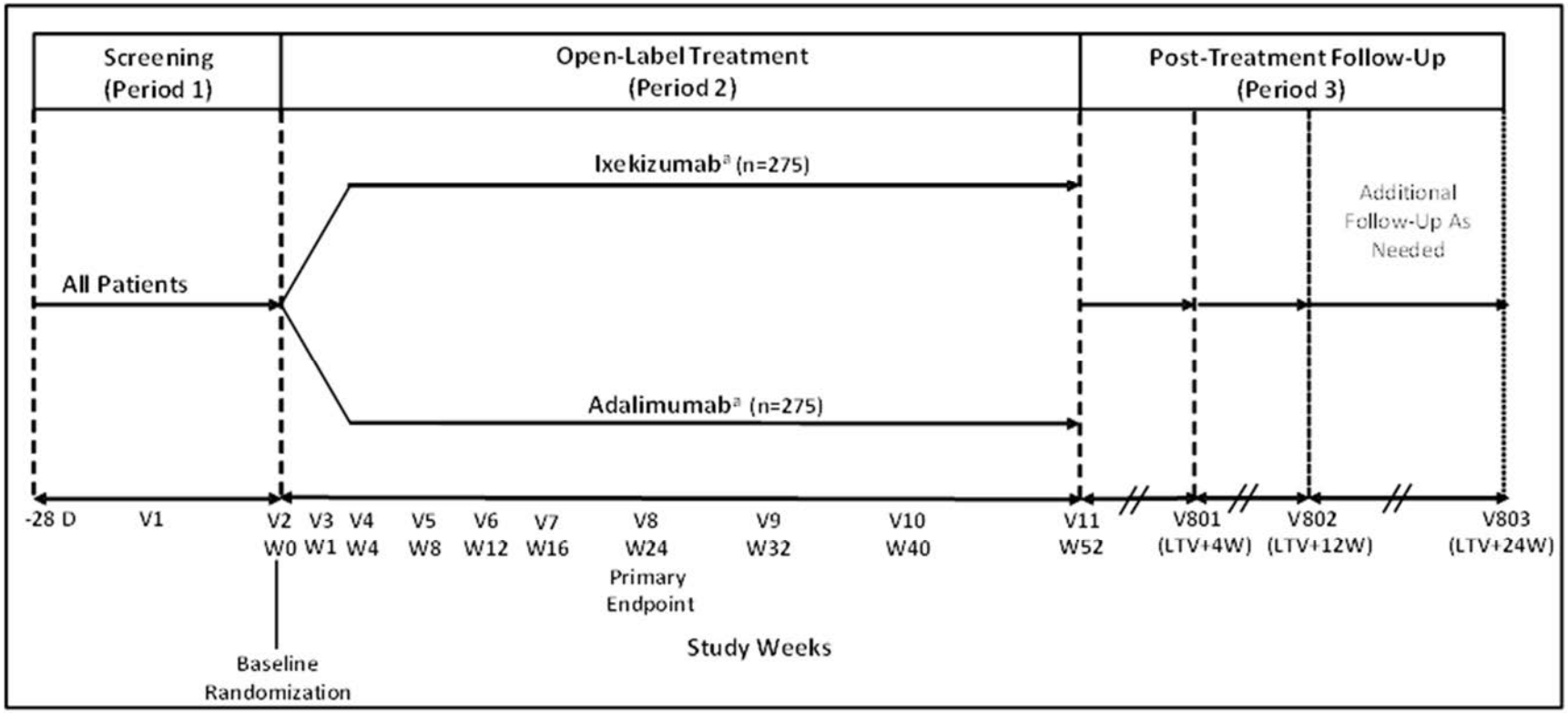
Objectives	Endpoints
	C-reactive protein (CRP), and Health Assessment Questionnaire–Disability Index (HAQ-DI) score • Proportion of patients simultaneously achieving ACR50 and PASI 100 response • Change from baseline in the Disease Activity Score (28 diarthrodial joint count) based on C-reactive protein (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

	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

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)



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.

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.

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.

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.

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.

- 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.

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

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.

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).

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

Study Schedule, Protocol I1F-MC-RHCF

	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

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.

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.

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).

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

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.

11. References

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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

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

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).