

Protocol I1F-MC-RHBQ

A Multicenter, Randomized, Double-Blind Study Comparing the Efficacy and Safety of Ixekizumab Versus
Placebo in Patients with Moderate-to-Severe Genital Psoriasis

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ixekizumab (LY2439821)

Study I1F-MC-RHBQ is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study examining the efficacy and safety of ixekizumab 80 mg Q2W (subcutaneous [SC]) as compared to placebo SC in patients with moderate-to-severe genital psoriasis, during a double-blind, 12-week Blinded Treatment Period followed by a 40-week Open-Label Treatment Period.

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1. Protocol Synopsis

Title of Study:

A Multicenter, Randomized, Double-Blind Study Comparing the Efficacy and Safety of Ixekizumab Versus Placebo in Patients with Moderate-to-Severe Genital Psoriasis

Rationale:

Approximately 29% to 63% of patients with chronic plaque psoriasis are impacted by psoriatic lesions in the genital area at some point during the course of the disease (Fouéré et al. 2005; Meeuwis et al. 2010, 2011a; Ryan et al. 2015). When compared to psoriasis patients without genital involvement, quality of life was found to be significantly worse in patients with genital lesions (Meeuwis et al. 2011b; Ryan et al. 2015). Itch and sexual impairment have been reported as key bothersome issues for patients with genital psoriasis (Meeuwis et al. 2015; Ryan et al. 2015). Despite the significant impact on quality of life and sexual health, genital psoriasis is neither frequently discussed by patients (AAD Work Group et al. 2011; Meeuwis et al. 2012; Andreassi and Bilenchi 2014) nor routinely questioned or examined by health care professionals (Farber and Nall 1992; AAD Work Group et al. 2011).

Although genital psoriasis appears to be pathophysiologically identical to plaque psoriasis in other skin regions, the skin in this area is highly sensitive and at increased risk of adverse reactions to topical treatments (CDA 2009 [WWW]; Meeuwis et al. 2011a; Guglielmetti et al. 2012). Specifically, available topical agents may not offer the optimal or even appropriate level of clinical improvement or tolerability, especially for patients with moderate-to-severe genital psoriasis.

Currently, there are limited data from clinical trials, particularly well-controlled therapeutic interventional studies, which measure the efficacy of treatments for genital psoriasis. To date, the only published treatment studies of genital psoriasis include open-label studies of topical treatments (Jemec and Baadsgaard 1993; Rallis et al. 2005; Martín Ezquerro et al. 2006; Bissonnette et al. 2008), a recent open-label study of a stepwise treatment algorithm (Meeuwis et al. 2015), and scattered case reports. Based on the Phase 3 psoriasis clinical trial outcomes, ixekizumab therapy in patients with moderate-to-severe genital psoriasis could address an unmet patient need and a clinical research gap identified by the dermatology community and the American Academy of Dermatology Psoriasis Guidelines of Care Working Group (Ryan et al. 2014).

Objective(s)/Endpoints:

Objectives	Endpoints
<p>Primary: To assess whether 80 mg ixekizumab every 2 weeks (Q2W) is superior to placebo at Week 12 in the treatment of patients with moderate-to-severe genital psoriasis as measured by static Physician Global Assessment (sPGA) of Genitalia (0,1)</p>	<p>The proportion of patients achieving sPGA of Genitalia (0,1) at Week 12</p>

Objectives	Endpoints
<p>Major Secondary: To assess whether 80 mg ixekizumab Q2W is superior to placebo at Week 12 in the treatment of patients with moderate-to-severe genital psoriasis as measured by change in itch, utilizing a modified genital psoriasis itch Numeric Rating Scale (NRS) item within the Genital Psoriasis Symptom Scale (GPSS)</p>	<ul style="list-style-type: none"> • Mean change from baseline in the genital psoriasis itch NRS item within the GPSS at Week 12

Summary of Study Design:

Study I1F-MC-RHBQ is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study examining the efficacy and safety of ixekizumab 80 mg Q2W dosing as compared to placebo for 12 weeks, followed by a 40-week Open-Label Treatment Period with 80 mg every 4 weeks (Q4W) dosing (with an option to step-up to 80 mg Q2W dosing) in patients with moderate-to-severe genital psoriasis.

Treatment Arms and Duration:

There are 2 treatment groups in the Blinded Treatment Period, and patients will be randomized at Week 0 to 1 of the groups. The 2 groups are: ixekizumab 80 mg Q2W subcutaneous (SC) dosing and placebo Q2W SC dosing. There is 1 treatment group in the Open-Label Treatment Period: ixekizumab 80 mg SC Q4W dosing with an option to step-up to Q2W dosing starting at Week 24 through Week 40. The study duration will be up to 1 year for ixekizumab administration, and up to 1 year and 4 months for study participation over 4 periods (Screening Period: 7 to 30 days; Blinded Treatment Period: 12 weeks; Open-Label Treatment Period: 40 weeks; Post-Treatment Follow-Up: at least 12 weeks after the date of the patient's early termination visit [ETV] or last regularly scheduled visit).

Number of Patients:

146 randomized

Statistical Analysis:

For the Blinded Treatment Period, analyses of efficacy and health outcomes will be conducted on the intent-to-treat (ITT) population, and safety analyses will be conducted on the safety population.

The primary analysis method for treatment comparisons of categorical efficacy and health outcome variables will be a logistic regression analysis with treatment and body surface area (BSA) category as factors, using the nonresponder imputation (NRI) method.

The primary analyses for the continuous efficacy and health outcome variables will be performed using mixed-effects model for repeated measures (MMRM) analysis. The model will include treatment, baseline BSA category, baseline value, visit, treatment-by-visit interaction, and baseline-by-visit interaction as fixed factors.

A sequential multiple testing procedure for the primary and the major secondary endpoint will be implemented to control the family-wise type I error rate at a 2-sided α level of 0.05.

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

Consistency of results among the 2 subpopulations determined by baseline BSA category ($<10\%$ versus $\geq 10\%$ baseline BSA involvement) will be assessed by performing additional subgroup analyses on the primary endpoint. The baseline BSA category by treatment interaction will be tested at the significance level of 0.10. Treatment group differences will be evaluated within each baseline BSA category using Fisher's exact test, regardless of whether the interaction is statistically significant.

2. Introduction

2.1. Background

Chronic plaque psoriasis is a common, lifelong, and life-shortening chronic inflammatory skin disease with an estimated prevalence in populations of approximately 3% which manifests as prototypic red, thick, and scaly plaques (Greaves and Weinstein 1995). Psoriasis has been shown to have a significant impact on the overall health of patients with considerable effects on social functioning and quality of life.

Approximately 29% to 63% of patients with chronic plaque psoriasis are impacted by psoriatic lesions in the genital area at some point during the course of the disease (Fouéré et al. 2005; Meeuwis et al. 2010, 2011a; Ryan et al. 2015). Due to moisture and maceration, genital psoriasis can sometimes lack the characteristic scale present at other body sites (Buechner 2002; Weichert 2004). Both penile and vulvar psoriatic lesions generally appear as symmetrical, bright red thin plaques with a well-defined edge (Buechner 2002; Welsh et al. 2003; ISSVD 2014 [WWW]; Meeuwis et al. 2015). Painful fissures and erosions can also be a problematic clinical feature of genital psoriasis (Barchino-Ortiz et al. 2012; Guglielmetti et al. 2012; Meeuwis et al. 2015), and severe pruritus may lead to scratching with significant excoriations and lichenification (Weichert 2004; Guglielmetti et al. 2012).

When compared to psoriasis patients without genital involvement, quality of life was found to be significantly worse in patients with genital lesions (Meeuwis et al. 2011b, Ryan et al. 2015). Overall Dermatology Life Quality Index (DLQI) score, all domain scores, and DLQI Question 9 (skin caused sexual difficulties) were significantly worse for those psoriasis patients with current genital involvement compared to those without genital lesions. Itch and sexual impairment have been reported as key bothersome issues for patients with genital psoriasis (Meeuwis et al. 2015; Ryan et al. 2015).

Despite the significant impact on quality of life and sexual health, genital psoriasis is often not discussed by patients (AAD Work Group et al. 2011; Meeuwis et al. 2012; Andreassi and Bilenchi 2014), and health care professionals do not routinely question or examine patients for its presence in clinical practice (Farber and Nall 1992; AAD Work Group et al. 2011). While patients with genital psoriasis often do not discuss their symptoms with health care providers, many patients report actively treating their genital lesions (Meeuwis et al. 2012). Therefore, this may indicate a risk of self-treatment in the genital area using medications that were originally prescribed for treatment of other body locations. Inappropriate self-treatment has the potential to result in less than optimal or over-treatment (for example, with potent corticosteroids) and significant adverse reactions. Although genital psoriasis appears to be pathophysiologically identical to plaque psoriasis in other skin regions, the skin in this area is highly sensitive and at increased risk of adverse reactions to topical treatments (CDA 2009 [WWW]; Meeuwis et al. 2011a; Guglielmetti et al. 2012). Moreover, currently available topical agents may not offer an optimal or even appropriate level of clinical improvement or tolerability, especially for patients with moderate-to-severe genital psoriasis. Weaker potency corticosteroids often have limited efficacy for use in maintenance treatment (Welsh et al. 2003), and the use of higher potency

corticosteroids is limited due to the development of skin atrophy and striae (Linden and Weinstein 1999). Irritation is commonly reported with vitamin D analogs (Scott et al. 2001; Mason et al. 2013), and they may not be tolerated in the genital region (CDA 2009 [WWW]). Topical calcineurin inhibitors such as pimecrolimus and tacrolimus may improve genital psoriasis but can cause irritancy or a burning sensation, are not helpful in many patients (Menter et al. 2009; Meeuwis et al. 2011[a]), and are not indicated for the treatment of psoriasis. Beyond such topical therapies, there is rather limited evidence for viable therapeutic options to adequately manage genital psoriasis. For instance, psoralen and ultraviolet A (PUVA) and narrowband ultraviolet B (UVB) are not advised for use in the genital region due to potential carcinogenic adverse effects (Stern et al. 1990; Stern et al. 1994; Stern et al. 2002).

Currently, there are limited data from clinical trials, particularly well-controlled therapeutic interventional studies, which measure the efficacy of treatments for genital psoriasis. To date, the only published treatment studies of genital psoriasis include open-label studies of topical treatments (Jemec and Baadsgaard 1993; Rallis et al. 2005; Martín Ezquerro et al. 2006; Bissonnette et al. 2008), a recent open-label study of a stepwise treatment algorithm (Meeuwis et al. 2015), and scattered case reports.

2.2. Study Rationale

Ixekizumab (LY2439821) is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody designed and engineered to selectively inhibit interleukin-17A (IL-17A). It binds with high affinity (<3 pM) and specificity to IL-17A, a proinflammatory cytokine. Neutralization of IL-17A by ixekizumab has been shown to reduce excess keratinocyte proliferation and activation (Krueger et al. 2012). Ixekizumab does not bind to ligands IL-17B, IL-17C, IL-17D, IL-17E, or IL-17F.

Phase 3 clinical trials of ixekizumab therapy were completed in patients with moderate-to-severe plaque psoriasis with percentage of body surface area (BSA) $\geq 10\%$. Ixekizumab was highly efficacious in these trials as evidenced by over 80% of patients achieving at least a 75% reduction in their Psoriasis Area and Severity Index (PASI) from baseline (PASI 75) and over one-third having complete resolution of psoriatic plaques (PASI 100) by Week 12 using a dosing regimen of 80 mg every 2 weeks following a 160-mg starting dose (Griffiths et al. 2015). In addition, patients with moderate-to-severe plaque psoriasis who were treated with ixekizumab in these studies reported significant improvements as early as Week 2 in sexual difficulties compared to placebo as measured by Question 9 of the DLQI. Thus, it is likely that ixekizumab is effective in the genital region in patients with a baseline BSA $\geq 10\%$ and may lead to improvement in sexual function in these patients. The most significant unmet medical need is in patients with BSA $< 10\%$ who have moderate-to-severe genital psoriasis and limited treatment options because of the limitations of topical and phototherapy treatments for genital psoriasis described in Section 2.1.

Based on the Phase 3 psoriasis clinical trial outcomes, ixekizumab therapy in patients with moderate-to-severe genital psoriasis could address an unmet patient need and a clinical research gap identified by the dermatology community and the American Academy of Dermatology Psoriasis

Guidelines of Care Working Group (Ryan et al. 2014). One subcutaneous (SC) ixekizumab regimen will be explored: a 160-mg starting dose followed by 80 mg every 2 weeks (Q2W) for 12 weeks, and then 80 mg every 4 weeks (Q4W) with the opportunity to step up to Q2W (Section 6.1). The efficacy and safety profile of this ixekizumab dosing regimen was established in previous Phase 3 clinical studies of patients with moderate-to-severe plaque psoriasis.

3. Objectives and Endpoints

Table RHBQ.3.1 shows the objectives and endpoints of the study.

Table RHBQ.3.1. Objectives and Endpoints

Objectives	Endpoints
<p>Primary Objective</p> <ul style="list-style-type: none"> To assess whether 80 mg ixekizumab Q2W is superior to placebo at Week 12 in the treatment of patients with moderate-to-severe genital psoriasis as measured by sPGA of Genitalia (0,1) 	<p>Primary Endpoint</p> <ul style="list-style-type: none"> The proportion of patients achieving sPGA of Genitalia (0,1) at Week 12
<p>Major Secondary Objective</p> <ul style="list-style-type: none"> To assess whether 80 mg ixekizumab Q2W is superior to placebo at Week 12 in the treatment of patients with moderate-to-severe genital psoriasis as measured by change in itch, utilizing a modified genital psoriasis itch NRS item within the GPSS 	<p>Major Secondary Endpoint</p> <ul style="list-style-type: none"> Mean change from baseline in the genital psoriasis itch NRS item within the GPSS at Week 12
<p>Other Secondary Objectives</p> <ul style="list-style-type: none"> To assess whether 80 mg ixekizumab Q2W is superior to placebo at Week 12 in the treatment of patients with moderate-to-severe genital psoriasis as measured by change in impact of genital psoriasis on sexual activity, utilizing the GPSIS, Sexual Activity Avoidance Subscale To assess whether 80 mg ixekizumab Q2W is superior to placebo at Week 12 in the treatment of patients with moderate-to-severe genital psoriasis as measured by change in frequency of sexual activity due to genital psoriasis, utilizing the SFQ item 2 To assess whether 80 mg ixekizumab Q2W is superior to placebo at Week 12 in the treatment of patients with moderate-to-severe genital psoriasis as measured by change in mGPASI To assess whether 80 mg ixekizumab Q2W is superior to placebo at Week 12 in the treatment of patients with moderate-to-severe genital psoriasis as measured by overall sPGA (0,1) To assess whether 80 mg ixekizumab Q2W is superior to placebo at Week 12 in the treatment of patients with moderate to severe genital psoriasis as measured by the following health outcomes measures: <ul style="list-style-type: none"> PatGA-Genital 	<p>Other Secondary Endpoints</p> <ul style="list-style-type: none"> The proportion of patients with at least a 2-point improvement from baseline to Week 12 in the GPSIS, Sexual Activity Avoidance Subscale The proportion of patients with at least a 2-point improvement from baseline to Week 12 in the SFQ item 2 Mean change from baseline in mGPASI at Week 12 The proportion of patients achieving overall sPGA (0,1) at Week 12 The proportion of patients with at least a 2-point improvement from baseline to Week 12 in PatGA-Genital

Objectives	Endpoints
<ul style="list-style-type: none"> ○ DLQI <ul style="list-style-type: none"> ▪ Total score ▪ Item 9 ▪ DLQI (0,1) and DLQI 0 ○ SF-36 ○ GPSS <ul style="list-style-type: none"> ▪ Total score ▪ Individual items other than itch • Evaluate the incidence of anti-ixekizumab antibodies and its relationship to patient efficacy of ixekizumab at Week 12 • Time course of response to treatment as measured by sPGA of Genitalia (0,1) • Time course of response to treatment as measured by mGPASI 	<ul style="list-style-type: none"> • Mean change from baseline in DLQI total score and Item 9 score at Week 12 • The proportions of patients achieving DLQI (0,1) or DLQI 0, respectively • Mean change from baseline on the SF-36 PCS and MCS at Week 12 • Mean change from baseline to Week 12 in <ul style="list-style-type: none"> ▪ GPSS total score and ▪ individual items (other than itch) • The proportion of patients achieving sPGA of Genitalia (0,1) at Week 12 by TE-ADA status and by NAb status • The proportion of patients who achieve sPGA of Genitalia (0,1) over time through Week 52 • Mean change in mGPASI over time through Week 52
<p>Exploratory Objectives</p> <ul style="list-style-type: none"> • To assess whether 80 mg ixekizumab Q2W is superior to placebo at Week 12 in the treatment of genital psoriasis patients with baseline BSA $\geq 10\%$ as measured by overall PASI • To assess whether 80 mg ixekizumab Q2W is superior to placebo at Week 12 in genital psoriasis patients with baseline BSA $\geq 10\%$ as measured by overall PASI 75/90/100 • To assess whether 80 mg ixekizumab Q2W is superior to placebo at Week 12 in patients with moderate-to-severe genital psoriasis as measured by: <ul style="list-style-type: none"> ○ sPGA of Genitalia (0) ○ overall sPGA (0) • To explore whether there is any impact of Fitzpatrick Skin Type on improvement measured by sPGA of Genitalia (0,1) response at Week 12 • To assess whether 80 mg ixekizumab Q2W is superior to placebo at Week 12 in the treatment of patients with moderate to severe genital psoriasis as measured by: <ul style="list-style-type: none"> ○ GPSIS, Impact of Sexual Activity on Genital Psoriasis Symptoms Subscale for patients who reported being sexually active at baseline (score of “0” on GPSIS Question 1) ○ SFQ item 1 	<p>Exploratory Endpoints</p> <ul style="list-style-type: none"> • Mean change from baseline in overall PASI at Week 12 • The proportion of patients achieving overall PASI 75/90/100 at Week 12 • The proportion of patients achieving <ul style="list-style-type: none"> ○ sPGA of Genitalia (0) at Week 12 ○ overall sPGA (0) at Week 12 • Association between Fitzpatrick Skin Type (reported at baseline) and sPGA of Genitalia (0,1) response at Week 12 • The proportion of patients with at least a 2-point improvement from baseline to Week 12 in the GPSIS, Impact of Sexual Activity on Genital Psoriasis Symptoms Subscale for patients who reported a score of “0” on GPSIS Question 1 at baseline. • The proportion of patients at each level of SFQ item 1

Objectives	Endpoints
<ul style="list-style-type: none"> ○ CAPP Genital subindex ○ Touch Avoidance NRS • To explore the impact of ixekizumab versus placebo at Week 12 on the change in presence or absence of fissure, ulcer, and/or erosion in the genital area and its association with measures of quality of life • To explore the impact of ixekizumab versus placebo at Week 12 on the change in presence or absence of psoriasis in perianal/gluteal cleft area (as indicated by the investigator in the case report form) and its association with measures of quality of life • To explore the impact of ixekizumab versus placebo at Week 12 on the change in presence or absence of psoriasis on the face and its association with measures of quality of life • To explore long-term impact of ixekizumab on symptoms and quality of life through Week 52 • To assess the psychometric properties (including reliability, validity, and responsiveness) of the GPSS, GPSIS, SFQ, and sPGA of Genitalia • To measure ixekizumab exposure and assess the relationship between exposure and efficacy, and exposure and immunogenicity • To explore biomarkers that are predictive of response to ixekizumab treatment that may be contained in DNA, RNA, serum, or plasma samples 	<ul style="list-style-type: none"> • Mean change from baseline in the total CAPP Genital subindex score • Mean change from baseline in the Touch Avoidance NRS • The proportion of patients with presence or absence of genital fissure, ulcer, and/or erosion and the association of absence/presence with measures of quality of life (SF-36 MCS, DLQI, GPSIS Subscales, and SFQ items) in the subgroup of patients with fissure, ulcer, and/or erosion • The proportion of patients with presence or absence of perianal/gluteal cleft psoriasis and the association of absence/presence with measures of quality of life (SF-36 MCS, DLQI, GPSIS Subscales, and SFQ items) in the subgroup of patients with psoriasis located in perianal area • The proportion of patients with presence or absence of facial psoriasis and the association of absence/presence with measures of quality of life (SF-36 MCS, DLQI, and SFQ items) in the subgroup of patients with psoriasis located on the face • The change over time through Week 52 in DLQI, SF-36 MCS, GPSS items, GPSIS Subscales, and SFQ items • Test-retest reliability, construct validity, and responsiveness will be assessed by ICCs, Pearson correlation/Spearman rank-based correlation coefficient, and correlations of calculated changes in scores, respectively, or as deemed appropriate • Serum trough concentrations of ixekizumab • Model parameters for the exposure-response relationship between ixekizumab serum trough concentrations and efficacy endpoints • Ixekizumab serum trough concentrations associated with ADA titer subgroups • Association between biomarker and ixekizumab response

Abbreviations: ADA = anti-drug antibodies; BSA = body surface area; CAPP = Comprehensive Assessment of the Psoriasis Patient; DLQI = Dermatology Life Quality Index; DLQI (0,1) = DLQI total score of 0 and 1; DNA = deoxyribonucleic acid; GPSIS = Genital Psoriasis Sexual Impact Scale; GPSS = Genital Psoriasis Symptom Scale; ICC = intraclass correlation coefficients; MCS = mental component summary; mGPASI = modified Genital PASI; NAb = neutralizing anti-drug antibody; NRS = Numeric Rating Scale; PASI = Psoriasis Area and Severity Index; PASI 75/90/100 = 75/90/100% improvement from baseline in the PASI; PatGA-Genital = Patient's Global Assessment of Genital Psoriasis; PCS = physical component summary; Q2W = every 2 weeks; SF-36 = Short-Form (36) Health Survey; SFQ = Sexual Frequency Questionnaire; RNA = ribonucleic acid; sPGA of Genitalia = static Physician Global Assessment of Genitalia; TE-ADA = treatment-emergent anti-drug antibody.

4. Study Design

4.1. Overview of Study Design

Study I1F-MC-RHBQ (RHBQ) is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study examining the efficacy and safety of ixekizumab as compared to placebo in patients with moderate-to-severe genital psoriasis. The study consists of 4 periods:

- **Period 1: Screening Period** (Visit 1 and Visit 1A) will assess patient eligibility and start e-diary data collection, occurring approximately 7 to 30 days prior to Period 2 (baseline; Week 0; Visit 2).
- **Period 2: Blinded Treatment Period** will occur from Week 0 (Visit 2) up to Week 12 (Visit 7). Patients will be randomized to ixekizumab or placebo in a 1:1 ratio. Two injections of ixekizumab 80 mg SC (total dose of 160 mg) or 2 injections of placebo SC, respectively, will be given at Week 0 (Visit 2). From Week 2 through Week 10 patients will receive ixekizumab 80 mg Q2W SC or placebo Q2W SC (Section 6.1).
- **Period 3: Open-Label Treatment Period** will occur from Week 12 (Visit 7) up to Week 52 (Visit 12). At Week 12 (Visit 7) 1 injection of ixekizumab 80 mg SC and 1 injection of placebo SC (total dose of ixekizumab 80 mg) will be given to patients who were randomized to ixekizumab in Period 2; and 2 injections of ixekizumab 80 mg SC (total dose of ixekizumab 160 mg) will be given to patients who were randomized to placebo in Period 2. During the remainder of Period 3, patients will receive ixekizumab 80 mg Q4W dosing with an option to step-up to Q2W dosing starting at Week 24 through Week 40 (at Visit 9 [Week 24], Visit 10 [Week 28], or Visit 11 [Week 40]) (Section 6.1). This open-label period will allow evaluation of long-term efficacy and safety of ixekizumab through 1 year (52 weeks).
- **Period 4: Post-Treatment Follow-Up** (Visit 801 through Visit 803) is for safety monitoring after treatment discontinuation for any patient receiving at least 1 dose of investigational product. Once patients complete study treatment or discontinue study treatment early, patients will complete the Post-Treatment Follow-Up (Period 4). This period occurs from the last treatment period visit or early termination visit (ETV) up to a minimum of 12 weeks following that visit.

Figure RHBQ.4.1 illustrates the study design, and all treatment groups and administration of the investigational product are described in Section 6.1. The study drug administration log (SDAL) is described in Section 6.2.1.

All procedures to be conducted during the study, including timing of all procedures, are indicated in the Schedule of Activities (Appendix 2). Selected study procedures should be performed prior to administration of the investigational product, as applicable. Appendix 3 lists the specific laboratory tests that will be performed for this study. Patients discontinuing from the study who have received at least 1 dose of investigational product will continue to the ETV prior to proceeding to the Post-Treatment Follow-Up Period (Period 4). For the management of patient

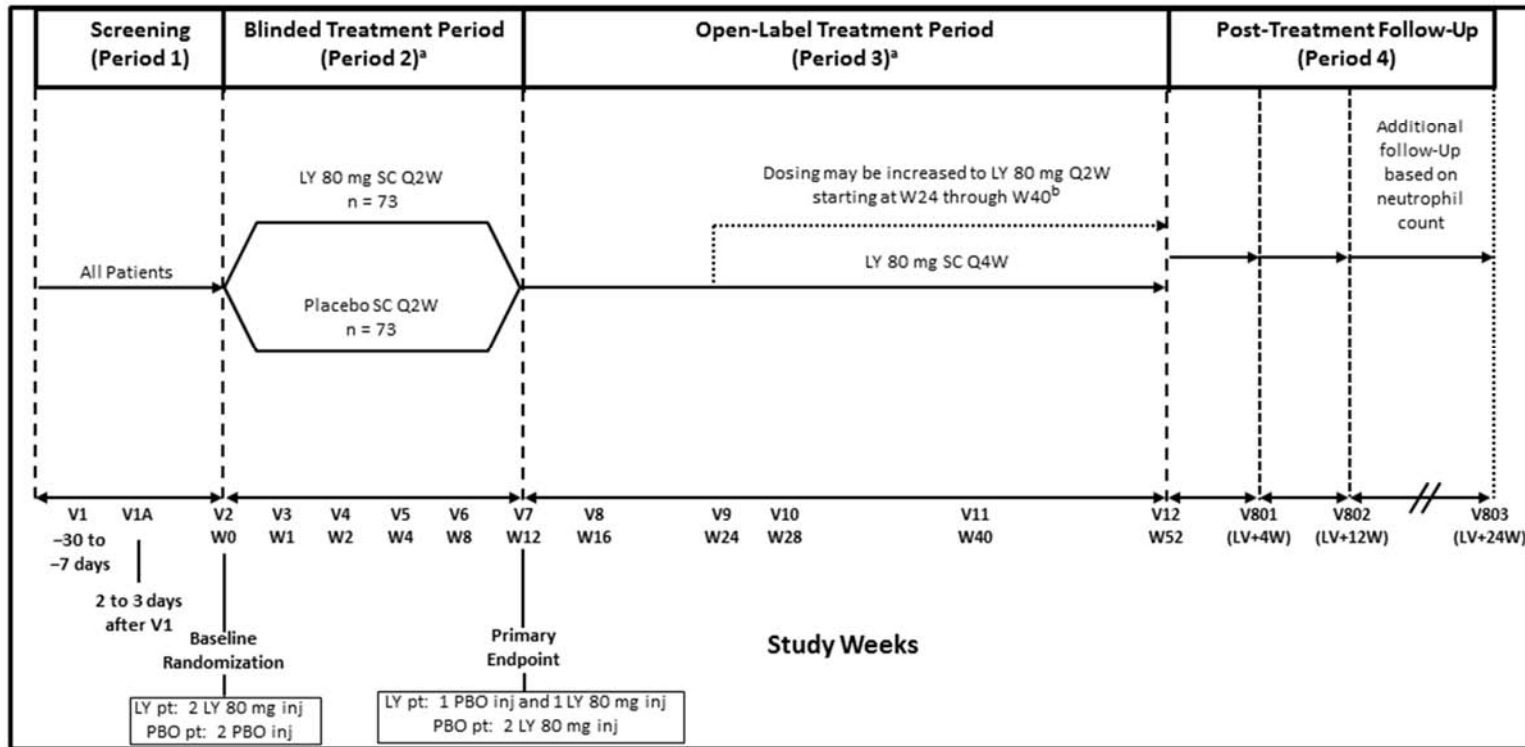
safety, all patients should be monitored through the Post-Treatment Follow-Up Period at least as frequently as indicated on the Schedule of Activities ([Appendix 2](#)).

Excluded and restricted therapies are detailed in Section [6.8](#).

Pharmacokinetic (PK) sampling is detailed in Section [8.5](#).

Section [9.9](#) outlines the information regarding the interim analyses including the primary database lock at Week 12.

[Figure RHBQ.4.1](#) illustrates the study design.



Abbreviations: inj = injection; LV = date of last visit; LY = LY2439821(ixekizumab); n = number of patients; pt = patient; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; V = visit; W = study week.

a Patients who discontinue the study for any reason and who have received at least 1 dose of investigational product will continue to Early Termination Visit before entering the Post-Treatment Follow-Up Period.

b All patients who increase dosing from 80 mg Q4W to 80 mg Q2W will remain on Q2W until completion of the study (W52 or early discontinuation) (Section 6.1).

Figure RHBQ.4.1. Illustration of study design for Clinical Protocol I1F-MC-RHBQ.

4.2. End of Trial Definition

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

4.3. Scientific Rationale for Study Design

Study RHBQ includes a blinded treatment period (Period 2) and an open-label treatment period (Period 3) to determine the efficacy and safety of ixekizumab. During the 12-week blinded treatment period, ixekizumab Q2W is compared to placebo Q2W, while during the 40-week open-label treatment period, patients are treated with ixekizumab Q4W. These period durations were chosen based on Phase 3 pivotal clinical studies in moderate-to-severe plaque psoriasis. The 12-week blinded treatment period will allow for the assessment of the response of moderate-to-severe genital psoriasis to treatment with ixekizumab while limiting exposure to placebo treatment.

The efficacy of ixekizumab will be primarily assessed at Week 12, using the static Physician Global Assessment (sPGA) of Genitalia. In addition, efficacy at Week 12 will be assessed using outcome measures such as the modified Genital PASI (mGPASI) as well as the e-diary to assess symptoms and impact of genital psoriasis using the Genital Psoriasis Symptom Scale (GPSS), Genital Psoriasis Sexual Impact Scale (GPSIS), and Sexual Frequency Questionnaire (SFQ).

All patients will begin ixekizumab 80 mg Q4W at Week 12 to assess the efficacy and safety of ixekizumab treatment over the total 52-week period. During the Open-Label Treatment Period (Period 3), patients may ‘step-up’ in dosing frequency from ixekizumab 80 mg Q4W to Q2W in order to achieve or maintain a sufficient level of efficacy (Section [6.1](#)).

4.4. Justification for Dose

The ixekizumab dosing regimen of ixekizumab 80 mg Q2W for 12 weeks (starting dose 160 mg) and ixekizumab 80 mg Q4W for 40 weeks was chosen based on results from the pivotal Phase 3 studies which provided safety and efficacy data for Q2W/Q4W dosing and Q4W/Q4W dosing following an initial dose of 160 mg. These studies did not evaluate Q2W dosing beyond 12 weeks; however, continuous Q2W dosing is being evaluated in an ongoing study, I1F-MC-RHBP.

As no treatment to date has been demonstrated to be effective and safe for the treatment of moderate-to-severe genital psoriasis in a controlled trial, placebo will be included as the comparator.

Study RHBQ is designed to assess the efficacy and safety profile of the Q2W regimen in the first 12 weeks (Blinded Treatment Period, Period 2) in patients with genital psoriasis. In addition, the study will collect long-term safety data for patients taking Q4W in the Open-Label Treatment Period (Period 3), as well as for those initially taking Q4W who increase dose frequency to Q2W of ixekizumab during the Open-Label Treatment Period (Period 3) if they do not achieve or maintain satisfactory disease control (Section [6.1](#)).

4.5. Benefit/Risk Assessment

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

5. Study Population

The study population will include patients with moderate-to-severe genital psoriasis who have given written informed consent approved by Eli Lilly and Company (Lilly), or its designee, and the ethical review board (ERB)/institutional review board (IRB) governing the site.

Study investigator(s) will review patient records and screening test results from Visit 1, Visit 1A (as applicable for purified protein derivative [PPD] read), and Visit 2 to determine if the patient meets all inclusion and exclusion criteria to qualify for participation in the study as noted in Section 5.1 and Section 5.2, respectively. All screening activities must be completed and reviewed before the patient is randomized. Individuals who do not meet study entry criteria (screen failure) may be rescreened as described in Section 5.3.

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

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

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria prior to randomization as indicated below:

Type of Patient and Disease Characteristics

- [1] Present with chronic plaque psoriasis based on a diagnosis of chronic plaque psoriasis for at least 6 months before baseline (Week 0; Visit 2), as determined by the investigator
- [2] Are candidates for phototherapy and/or systemic therapy
- [3] Have an overall sPGA ≥ 3 at screening (Visit 1) and at baseline (Week 0, Visit 2)
- [4] Have sPGA of Genitalia ≥ 3 at screening (Visit 1) and at baseline (Week 0, Visit 2)
- [5] Have BSA involvement of $\geq 1\%$ at screening (Visit 1) and at baseline (Week 0, Visit 2)

(Note: Approximately 60% of patients will be required to have BSA involvement $\geq 10\%$ and approximately 40% of patients will be allowed to have BSA involvement of 1 to $<10\%$. Enrollment will be closely monitored, and enrollment in this lower BSA subpopulation will be stopped if a maximum of 40% is reached.)
- [6] Have confirmation of plaque psoriasis in a nongenital area at screening (Visit 1) and baseline (Week 0, Visit 2)

- [7] Have failed to respond to, or are intolerant of, at least 1 topical therapy (corticosteroids, calcineurin inhibitors and/or vitamin D analogs) used for treatment of psoriasis affecting the genital area

Patient Characteristics

- [8] Are male or female patients of 18 years or older
- [9] Must agree to use reliable method of birth control:
- If a male patient, agree to use a reliable method of birth control during the study and for at least 12 weeks following the last dose of investigational product. Examples of reliable methods include abstinence, vasectomy, and male condom with spermicide.

OR

- If a female patient of childbearing potential, must test negative for pregnancy and agree to use a reliable method of birth control during the study and for at least 12 weeks following the last dose of investigational product. Methods of contraception considered acceptable include abstinence, oral contraceptives, contraceptive patch, intrauterine device, vaginal ring, diaphragm with contraceptive gel, or condom with contraceptive gel.

OR

- For nonchildbearing potential female patients, patients must be:

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

OR

Women who are ≥ 60 years of age

OR

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

Informed Consent

- [10] Are able and have given written informed consent approved by Lilly, or its designee, and the IRB/ ERB governing the site

5.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria prior to randomization as indicated below:

Medical Conditions

- [11] Have predominant pattern of pustular, erythrodermic, and/or guttate forms of psoriasis
- [12] Have pustules or vesicles in the genital area
- [13] Have a history of drug-induced psoriasis

Prior/Concomitant Therapy

- [14] Have received systemic nonbiologic psoriasis therapy or phototherapy within 4 weeks of baseline (Week 0, Visit 2), or have had topical psoriasis treatment within 2 weeks of baseline (Week 0, Visit 2) as specified in [Table RHBQ.6.2](#)

Exceptions (see [Table RHBQ.6.2](#)):

- mild corticosteroids will be permitted for use limited to the face and/or axilla
- [15] Cannot avoid excessive sun exposure or use of tanning booths for at least 4 weeks prior to baseline (Week 0, Visit 2) and during the study, per investigator assessment
- [16] Concurrent or recent use of any biologic agent within the following periods prior to baseline (Week 0, Visit 2): etanercept <28 days; infliximab or adalimumab <60 days; golimumab <90 days; ustekinumab <8 months; rituximab <12 months; or any other biologic agent <5 half-lives
- [17] Have ever received natalizumab or other agents that target alpha-4 integrin
- [18] Have ever received treatment with IL-17 antagonists such as ixekizumab, secukinumab, or brodalumab

Vaccinations

- [19] Had a live vaccination within 12 weeks prior to baseline (Week 0, Visit 2), intend to have a live vaccination during the course of the study or within 12 weeks of completing treatment in this study, or have participated in a vaccine clinical study within 12 weeks prior to baseline. 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.)

- [20] Had a vaccination with Bacillus Calmette-Guérin (BCG) within 12 months prior to baseline (Week 0, Visit 2) or intend to have vaccination with BCG during the course of the study or within 12 months of completing treatment in this study

Medical Status and Medical History

- [21] Have a known allergy or hypersensitivity to any biologic therapy that would, in the opinion of the investigator, pose an unacceptable risk to the patient if participating in this study
- [22] Have current or a history of lymphoproliferative disease or signs or symptoms of lymphoproliferative disease within 5 years prior to baseline (Week 0; Visit 2); or have active or history of malignant disease within 5 years prior to baseline (Week 0; Visit 2)
- (Note: Patients with history of malignancy with no evidence of recurrence or active disease within the 5 years prior to baseline may participate in the study.)
- [23] Had any major surgery within 8 weeks prior to baseline (Week 0, Visit 2) or will require such during the study that, in the opinion of the investigator in consultation with Lilly or its designee, would pose an unacceptable risk to the patient
- [24] Presence of significant uncontrolled respiratory, hepatic, renal, gastrointestinal (including Crohn's disease or ulcerative colitis), endocrine, hematologic (including a history of bleeding disorder), neurologic, or neuropsychiatric disorders that would, 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
- [25] Presence of significant uncontrolled cerebrocardiovascular (for example, myocardial infarction [MI], unstable angina, unstable arterial hypertension, moderate to severe [New York Heart Association (NYHA) class III/IV] heart failure, or cerebrovascular accident [CVA]) that would, 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
- [26] Have electrocardiogram (ECG) abnormalities that are considered clinically significant and would pose an unacceptable risk to the patient if participating in the study, in the opinion of the investigator
- [27] Have uncontrolled arterial hypertension characterized by a systolic blood pressure (BP) >160 mm Hg or diastolic BP >100 mm Hg at screening (Visit 1) or at baseline randomization (Week 0, Visit 2)
- (Note: If an initial BP reading exceeds this limit, the BP 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.)
- [28] Have had fluid overload, MI, or new onset ischemic heart disease (for example, unstable angina), uncompensated heart failure, or in the opinion of the investigator other serious cardiac disease within 12 weeks prior to baseline (Week 0; Visit 2)

- [29] Recent history of a suicide attempt (≤ 30 days), have a score of 3 on Item 12 (Thoughts of Death or Suicide) of the Quick Inventory of Depressive Symptomatology–Self Report (16 items) (QIDS-SR16) at screening (Visit 1) or baseline (Week 0; Visit 2), or are clinically judged by the investigator to be at risk for suicide
- [30] Have evidence or suspicion of active or latent tuberculosis (TB) (refer to Section 8.4.5 for details on determining full TB exclusion criteria)
- [31] Are positive for human immunodeficiency virus serology (HIV; positive for human immunodeficiency virus antibody [HIVAb])
- [32] Have evidence of or test positive for hepatitis B virus (HBV) by testing: 1) positive for hepatitis B surface antigen (HBsAg+) OR 2) positive for anti-hepatitis B core antibody (HBcAb+) and are HBV DNA positive
(Note: Patients who are HBcAb+ and HBV DNA negative may be enrolled in the study. Patients who meet these criteria at screening will be identified by the central laboratory and monitored during the study as detailed in Section 8.4.8.2.)
- [33] Have evidence of or test positive for hepatitis C virus (HCV). A positive test for HCV is defined as: 1) positive for hepatitis C antibody (anti-HCVAb) and 2) positive via a confirmatory test for HCV (for example, HCV polymerase chain reaction).
- [34] Have a body temperature $\geq 38^{\circ}\text{C}$ (100.5°F) at baseline (Week 0; Visit 2); these patients may be rescreened (1 time) ≥ 4 weeks after documented resolution of elevated temperature. Body temperature will be determined via tympanic or oral methods.

Infections

- [35] Had a serious infection (for example, pneumonia, cellulitis), have been hospitalized, or have received intravenous (IV) antibiotics for an infection within 12 weeks prior to baseline (Week 0, Visit 2); or had a serious bone or joint infection within 24 weeks prior to baseline; or have ever had an infection of an artificial joint; or are immunocompromised to an extent such that participation in the study would pose an unacceptable risk to the patient
- [36] Have or had an infection typical of an immunocompromised host and/or that occurs with increased incidence in an immunocompromised host (including, but not limited to, *Pneumocystis jirovecii* pneumonia, histoplasmosis, or coccidioidomycosis) or have a known immunodeficiency
- [37] Have or had a herpes zoster or any other clinically apparent varicella-zoster virus infection within 12 weeks of baseline (Week 0, Visit 2)

- [38] Have any other active or recent infection within 4 weeks of baseline (Week 0, Visit 2) that, in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study; these patients may be rescreened (1 time) ≥ 4 weeks after documented resolution of symptoms
- [39] Have, or currently receiving treatment for, active candidiasis or tinea in the genital area. Patients with active candidiasis or tinea in the genital area may be treated and rescreened (1 time) ≥ 4 weeks after documented resolution of symptoms.

(Note: Investigator may clinically assess for active infection as needed using potassium hydroxide [KOH] preparation tests or other methodology per local procedures.)

Prior/Concurrent Clinical Trial Experience

- [40] 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
- [41] Have previously completed or withdrawn from this study or participated in any other study with ixekizumab, or have participated in any study investigating other IL-17 antagonists
- [42] Are currently enrolled in, have participated, or discontinued from a clinical trial involving an investigational product or nonapproved use of a drug or device within the last 30 days or a period of at least 5 half-lives of the last administration of the drug, whichever is longer, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study (eg, observational study requiring blood draws, biopsies, and/or other interventional monitoring procedures)

Diagnostics Assessments

Laboratory tests should not be repeated unless there is a technical error or clinical reasons to believe a result may be erroneous (except for exclusion criteria [46]).

- [43] At screening, have a neutrophil count < 1500 cells/ μL ($< 1.50 \times 10^3/\mu\text{L}$ or < 1.50 GI/L)
- [44] At screening, have a lymphocyte count < 800 cells/ μL ($< 0.80 \times 10^3/\mu\text{L}$ or < 0.80 GI/L)
- [45] At screening, have a platelet count $< 100,000$ cells/ μL ($< 100 \times 10^3/\mu\text{L}$ or < 100 GI/L)
- [46] At screening, have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 times the upper limit of normal (ULN)

(Note: The AST and ALT may be repeated once within a week if the initial response exceeds this limit, and the repeat value may be accepted if it meets this criterion.)

- [47] At screening, have a total white blood cell (WBC) count <3000 cells/ μ L (<3.00x10³/ μ L or <3.00 GI/L)
- [48] At screening, have hemoglobin <8.5 g/dL (85.0 g/L) for male patients and <8.0 g/dL (80 g/L) for female patients
- [49] Have other clinical laboratory test results at screening that are outside the normal reference range for the population and are considered clinically significant, per investigator assessment

Other Exclusions

- [50] Have donated more than 1 unit (approximately 450 mL) of blood within the last 4 weeks prior to screening (Visit 1) or intend to donate blood during the course of the study. These patients may be rescreened (1 time) to allow the required 4-week minimum time since donation of more than 1 unit of blood.
- [51] Are women who are lactating or breast feeding
- [52] Have any other condition that precludes the patient from following and completing the protocol, in the opinion of the investigator
- [53] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
- [54] Are Lilly employees or its designee or are employees of third-party organizations (TPOs) involved in the study
- [55] Are unwilling or unable to comply with the use of a data collection device to directly record data from the subject

5.3. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened in the following circumstances: Patients who test positive for latent TB at screening may be rescreened following appropriate treatment as described in Section 8.4.5; patients who do not qualify at screening under exclusion criteria [34], [38], or [39] may be rescreened once, 4 or more weeks after documented resolution of symptoms. Patients who do not qualify at screening under exclusion criterion [50] may be rescreened once to allow the required 4-week minimum time since donation of more than 1 unit of blood. When rescreening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number. Additionally, all screening procedures must be conducted to ensure all eligibility criteria are met.

5.4. Lifestyle and/or Dietary Requirements

See inclusion criterion [9] in Section 5.1 for birth control requirements.

6. Treatment

6.1. Treatments Administered

The Blinded Treatment Period (Period 2) involves a comparison of ixekizumab 80 mg Q2W (starting dose of 160 mg) and placebo Q2W. All doses are administered via SC injection.

All patients assigned to ixekizumab 80 mg Q2W regimen will receive a starting dose of 160 mg ixekizumab as 2 SC injections. The placebo group will receive 2 SC injections of placebo at this visit as well, to maintain the blind.

For training purposes, the starting dose of 160 mg (two 80-mg SC injections) will be administered at the clinic at Week 0 (Visit 2). The first injection will be administered by clinical staff, and the second injection will be administered by the patient or the patient's caregiver while under supervision of clinical staff. Subsequent injections of investigational product will be administered by the patient or the patient's caregiver unsupervised by the clinical staff, regardless of whether there is a study visit scheduled except at Visit 7 (Week 12). At Visit 7 (Week 12), the 2 injections will be administered by the patient or the patient's caregiver supervised by the clinical staff to allow for vital sign monitoring (Section 8.4.2). It is recommended that all subsequent injections be administered outside the trial site, preferably at the patient's home.

A dose of investigational product will consist of 1 SC injection of ixekizumab or placebo. Possible injection sites include the abdomen (upper left, upper right, lower left, or lower right quadrant [with the umbilicus being the center]), left or right thigh, and left or right upper arm. If the upper arm is utilized as the injection site, the injection must be administered by a caregiver. The injection site should not be in a psoriatic lesion. On days when multiple injections will be administered, the injection sites should be in different areas (note the abdomen has 4 possible injection areas).

At Week 12, during the Open-Label Treatment Period (Period 3), all patients will be reassigned to ixekizumab 80 mg Q4W. Patients originally assigned to placebo will receive a blinded ixekizumab starting dose of 160 mg as 2 SC injections. To maintain blinding, patients originally assigned to ixekizumab 80 mg Q2W will receive a blinded ixekizumab 80-mg dose and a placebo dose at Week 12. Dosing may be increased in the Open-Label Treatment Period (Period 3) to ixekizumab 80 mg Q2W, starting at Week 24 through Week 40 (at Visit 9 [Week 24], Visit 10 [Week 28], or Visit 11 [Week 40]), if the patient is eligible to receive additional investigational product (that is, if it is determined by the patient and the investigator that the patient needs additional ixekizumab in order to achieve or maintain satisfactory disease control). All patients who increase dosing to 80 mg Q2W will remain on this dose until completion of the treatment period or early discontinuation. [Table RHBQ.6.1](#) shows the treatment regimens. If patients remain on ixekizumab 80 mg Q4W, their last dose will occur at Week 48. If patients step up to ixekizumab 80 mg Q2W, their last dose will occur at Week 50.

Treatment received during the Blinded Treatment Period (Period 2) will remain blinded to investigators, study site personnel, and patients until all patients have completed Week 52

(Visit 12) or have discontinued from the study (moved into Post-Treatment Follow-Up [Period 4]).

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

- explaining the correct use of the investigational product to the patient/patient caregiver
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing, collection, and administration
- returning all unused medication to Lilly or its designee at the end of the study

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

Further instructions and special considerations for the administration of the investigational product are provided in Sections [6.2.1](#) and [6.6.1](#).

Table RHBQ.6.1. Treatment Regimens

Randomized Treatment Arm	Dose Week 0 (Day 1)	Dose Week 2 to Week 10	Dose Week 12	Dose Week 16 to Week 50 ^a
	Blinded Dosing			Open-Label Dosing
Ixekizumab 80 mg	2 ixekizumab 80-mg injections	1 ixekizumab 80-mg injection Q2W	1 ixekizumab 80-mg injection 1 placebo injection	1 ixekizumab 80-mg injection Q4W with Q2W step-up as needed ^b
Placebo	2 placebo injections	1 placebo injection Q2W	2 ixekizumab 80-mg injections	1 ixekizumab 80-mg injection Q4W with Q2W step-up as needed ^b

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

- ^a If patients remain on ixekizumab 80 mg Q4W, their last dose will occur at Week 48. If patients step up to ixekizumab 80 mg Q2W, their last dose will occur at Week 50 (Section 6.1).
- ^b Dosing may be increased to ixekizumab 80 mg Q2W starting at Week 24 through Week 40 (at Visit 9 [Week 24], Visit 10 [Week 28], or Visit 11 [Week 40]). Once a step-up from Q4W to Q2W occurs, the dose is maintained at Q2W for the remainder of the treatment period (Section 6.1).

6.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to blinded treatment at Visit 2 (Week 0) in a 1:1 ratio to ixekizumab 80 mg Q2W or placebo. 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 double-blind investigational product to each patient. Site personnel will confirm that they have located the correct assigned investigational product package by entering a confirmation number found on the package into the IWRS.

To achieve between-group comparability for BSA, the randomization will be stratified by BSA (1% to <10% versus $\geq 10\%$).

6.2.1. Selection and Timing of Doses

Patients are randomized to dosing regimens and will receive their assigned investigational product as outlined in Section 6.2 and Section 6.1, respectively.

Investigational product should be administered at approximately the same time of day each time, as much as possible. For injections that are missed and not administered on the scheduled day of the week, the missed dose should be administered within 5 days of the originally scheduled day. Dates of subsequent study visits should not be modified according to the delay of the injection of the missed scheduled dose.

Throughout their participation in the study, randomized patients and/or site personnel will record information in a Study Drug Administration Log, including the date, time, and anatomical location of administration of investigational product (for treatment compliance), syringe number, who administered the investigational product, and the reason if investigational product was not fully administered.

6.3. Blinding

This is a double-blind study. To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All actions resulting in an unblinding event are recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study treatment. All patients should continue to be followed for safety (Period 4). In cases where there are ethical reasons to have the patient remain on study treatment, the investigator must obtain specific approval from a Lilly clinical research physician (CRP) for the patient to continue study treatment.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first

consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly CRP prior to unblinding a patient's treatment assignment. If a patient's treatment assignment is unblinded, Lilly must be notified immediately by telephone, email, or fax. Including this unblinding information in the SAE report is not sufficient for notification purposes.

6.4. Packaging and Labelling

The investigational products will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practices (cGMP).

Clinical trial materials will be labeled according to the country's regulatory requirements. All investigational products will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

Ixekizumab and placebo to match (excipients only) will be supplied as an injectable solution in 1-mL, single-dose, prefilled, disposable manual syringes with study specific labels. Each syringe of ixekizumab is designed to deliver ixekizumab 80 mg. The syringes (and contents) containing either ixekizumab or placebo will be visibly indistinguishable from each other. Syringes will be supplied in cartons; each carton will contain the appropriate quantity of syringes specific to the planned dispensing schedule of the investigational product.

6.5. Preparation/Handling/Storage

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

The investigational product should be stored at 2°C to 8°C (36°F to 46°F) in its original carton to protect from light. Investigational product should not be frozen. Sites will be required to monitor temperature of the on-site storage conditions of the investigational product.

6.6. Dose Modification

Dose adjustments are not permitted for the Q2W dosing regimen during the Blinded Treatment Period (Period 2). During the Open-Label Treatment Period (Period 3), patients will receive continuous Q4W dosing from Week 12 through Week 20. Patients may step-up the Q4W dosing regimen to Q2W starting at Week 24 through Week 40 as outlined in Section 6.1. Once a step-up to Q2W occurs, the dose is maintained at Q2W for the remainder of the Open-Label Treatment Period (Period 3).

6.6.1. Special Treatment Considerations

Patients will be screened for eligibility in the study as described in Section 5.1 and Section 5.2 and will be informed of the study-specific restrictions and requirements of the study. Patients who are not willing to comply with the study restrictions and requirements of the study will not be eligible for enrollment.

Patients should be instructed not to donate blood or blood products during participation in the study.

All biological agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include, but are not limited to:

- skin rash
- pruritus (itching)
- urticaria (hives)
- angioedema (for example, swelling of the lips and/or tongue)
- anaphylactic reaction

Sometimes, these reactions can be life-threatening. Proteins may also cause redness, itching, swelling, or pain locally at the injection site. Therefore, all patients should be closely monitored for signs or symptoms that could result from such reactions, educated on the signs or symptoms of these types of reactions, and instructed to contact the study site immediately if any of the symptoms are experienced following an injection. If a patient experiences an acute allergic/hypersensitivity reaction after an injection of investigational product, he or she should be managed appropriately and given instruction to receive relevant supportive care. Additionally, for an event judged by the investigator to be a potential systemic allergic/hypersensitivity reaction, a blood sample should be drawn as soon as possible. These samples may be tested for anti-drug antibodies (ADAs), other laboratory tests needed to elucidate the cause of the allergic/hypersensitivity reaction, and/or ixekizumab serum concentration. These results will not be provided to the investigator for patient care decisions but are intended to assist the sponsor in accurately characterizing the reaction.

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 (for example, injection-site erythema, injection-site pruritus). Patients who develop clinically significant systemic allergic/hypersensitivity reactions following administration of investigational product and who do not respond to symptomatic medication or who experience clinical sequelae (for example, hospitalization) should be discontinued from study treatment and should not receive further doses of investigational product, with or without premedication (see Section 7.1). Medications considered appropriate for premedication include but are not restricted to acetaminophen/paracetamol up to 1000 mg and antihistamines (for example, oral diphenhydramine, 50 mg), given 30 to 60 minutes prior to investigational product injection. Patients may self-premedicate at home prior to administration of investigational product, as directed by the investigator. All such premedications will be recorded as concomitant therapy. Corticosteroids are not permitted as agents for premedication.

6.7. Treatment Compliance

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

Patient compliance with the investigational product (Section 9.4.4) will be assessed at each study visit during the Blinded Treatment and Open-Label Treatment Periods (Periods 2 and 3) by review of the SDAL (Section 6.2.1), return of empty investigational product packaging, and/or direct questioning. Deviation(s) from the prescribed dosage regimen should be documented.

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 7.1.3).

6.8. 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 (Appendix 2). Treatment with concomitant psoriasis therapies during the study will be permitted only as outlined in the exclusion criteria (Sections 5.2) and as described in the table below. Patients taking permitted medications should be on stable doses at the baseline visit (Week 0, Visit 2) as specified in Section 5.2. Table RHBQ.6.2 summarizes concomitant medications that are or are not permitted for use during the study and related comments and conditions for use.

Table RHBQ.6.2. Concomitant Medication Permitted/Not Permitted in the Study

Drug Class	Use During Study	Comments/Conditions
SYSTEMIC THERAPIES		
Biologic agent other than investigational product as part of this protocol	<u>Not permitted</u>	<p><u>Minimum required time since last biologic agent dose prior to baseline (Week 0, Visit 2):</u></p> <ul style="list-style-type: none"> • etanercept – at least 28 days • infliximab, adalimumab – at least 60 days • golimumab- at least 90 days • ustekinumab – at least 8 months • rituximab– at least 12 months • any other biologic agent – at least 5 half-lives <p>IL-17 antagonists, other than investigational product as part of this protocol:</p> <ul style="list-style-type: none"> • Must never have received, or participated in any study investigating, IL-17 antagonists • <u>Examples include:</u> ixekizumab, secukinumab, brodalumab
Natalizumab , or other agents targeting α 4 integrin	<u>Not permitted</u>	<ul style="list-style-type: none"> • Must have never received
Systemic nonbiologic psoriasis therapy	<u>Not permitted</u>	<ul style="list-style-type: none"> • Must not have received within 4 weeks prior to baseline (Week 0, Visit 2) • <u>Examples include:</u> oral PUVA light therapy, cyclosporine, corticosteroids, MTX, apremilast, tofacitinib, oral retinoids, mycophenolate mofetil, thioguanine, hydroxyurea, sirolimus, azathioprine, fumaric acid derivatives, 1, 25 dihydroxy vitamin D3 and analogs
PHOTOTHERAPY		
Phototherapy	<u>Not permitted</u>	<ul style="list-style-type: none"> • Must not have received within 4 weeks prior to baseline (Week 0, Visit 2) • <u>Examples include:</u> either oral and topical PUVA light therapy, UVB, self-treatment with tanning beds or therapeutic sunbathing

Drug Class	Use During Study	Comments/Conditions
TOPICAL THERAPIES		
Bath oils and oatmeal bath preparations	<u>Permitted with conditions</u>	<ul style="list-style-type: none"> Not to be used within 12 hours prior to a study visit
Shampoos <u>NOT</u> containing salicylic acid, corticosteroids, coal tar, or vitamin D analogs	<u>Permitted with conditions</u>	<ul style="list-style-type: none"> Not to be used within 12 hours prior to a study visit
Shampoos and Scalp Treatments containing salicylic acid, corticosteroids, coal tar, or vitamin D analogs	<u>Not permitted</u>	<ul style="list-style-type: none"> Must not be used within 2 weeks prior to baseline (Week 0, Visit 2).
Topical moisturizers/emollients and other nonprescription topical products <u>NOT</u> containing urea, salicylic acid, alpha- or beta-hydroxyl acids, corticosteroids, or vitamin D analogs	<u>Permitted with conditions</u>	<ul style="list-style-type: none"> Not to be used within 12 hours prior to a study visit
Topical moisturizers/emollients and other nonprescription topical products containing urea, salicylic acid, alpha- or beta-hydroxyl acids, corticosteroids, or vitamin D analogs	<u>Not permitted</u>	<ul style="list-style-type: none"> Must not be used within 2 weeks prior to baseline (Week 0, Visit 2).
Topical corticosteroids, more potent than mild	<u>Not permitted</u>	<ul style="list-style-type: none"> Must not be used within 2 weeks prior to baseline (Week 0, Visit 2).

Drug Class	Use During Study	Comments/Conditions
Topical corticosteroids, low to mild potency	<u>Permitted with conditions</u>	<ul style="list-style-type: none"> • Must not be used within 2 weeks prior to baseline (Week 0, Visit 2). • <u>Study Periods 1 and 2</u>: Not permitted for use except to face and/or axilla. If used for face and/or axilla, may not be used within approximately 24 hours prior to study visits requiring sPGA and PASI measures • <u>Study Periods 3 and 4</u>: Permitted for use, as needed, after Week 12 assessments are complete but not for the genital area. May not be used within approximately 24 hours prior to study visits requiring sPGA and PASI measures. • <u>Examples include</u>: desonide, hydrocortisone
Other prescription topical products	<u>Not permitted</u>	<ul style="list-style-type: none"> • Must not be used within 2 weeks prior to baseline (Week 0, Visit 2) • <u>Examples include</u>: calcineurin inhibitors, anthralin, vitamin D analogs, and retinoids
VACCINES		
Vaccine, Bacillus Calmette-Guérin (BCG)	<u>Not permitted</u>	<ul style="list-style-type: none"> • Must not have received within 12 months prior to baseline (Week 0, Visit 2) • Should not receive within 12 months of completed treatment in this study
Vaccines, live	<u>Not permitted</u>	<ul style="list-style-type: none"> • Must not have received within 12 weeks prior to baseline (Week 0, Visit 2) • Should not receive within 12 weeks of completed treatment in this study
Vaccines, nonlive seasonal and/or emergency	<u>Permitted with conditions</u>	<ul style="list-style-type: none"> • Killed/inactive or subunit vaccines are expected to be safe; however, their efficacy with concomitant ixekizumab treatment is unknown
OTHER		
NSAIDs, aspirin, or acetaminophen/paracetamol	<u>Permitted</u>	<ul style="list-style-type: none"> • Allowed as needed

Abbreviations: IL = interleukin; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; PASI = Psoriasis Area and Severity Index; PUVA = psoralen and ultraviolet A; sPGA = static Physician Global Assessment; UVB = ultraviolet B.

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 for an AE or for appropriate medical management (including the limited use of therapeutic agents which, if used under treatment regimens other than for treating an AE or for appropriate medical management, might be considered psoriasis therapies), the investigator should base decisions on the patient and clinical factors. Any additional medication, whether prescription or over-the-counter, used at baseline (Week 0, Visit 2) and/or during the course of the study must be documented with the start and stop dates on the Concomitant Medications eCRF.

Patients will maintain their usual medication regimen for other concomitant diseases throughout the study unless those medications are specifically excluded in the protocol. Patients taking concomitant medications should be on stable doses at the time of baseline (Week 0, Visit 2) and should remain at a stable dose throughout the study, unless changes need to be made for an AE or for appropriate medical management. Other medications may be allowed if approved by the sponsor or its designee.

6.9. Treatment after Study Completion

6.9.1. Continued Access

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

7. Discontinuation Criteria

7.1. Discontinuation from Study Treatment

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

For any patient discontinuing from study treatment, the investigational product will be withheld, and the patient will complete the ETV and the Post-Treatment Follow-Up Period (Period 4), as shown in the Schedule of Activities ([Appendix 2](#)).

Missing data may compromise the integrity of the study. Complete information from each patient is critical to achieving the fullest understanding of the potential benefits and risks of ixekizumab. All efforts should be made to keep patients in the study, to attend scheduled visits and procedures, and to take investigational product as medically appropriate.

Patients who meet any of the criteria described in Section 7.1.1 will be discontinued from the study treatment.

7.1.1. *Permanent Discontinuation from Study Treatment*

Patients will permanently discontinue from study treatment in the following situations:

- [1] Discontinuation of the investigational product for abnormal liver tests should be considered by the investigator when a patient meets 1 of the following conditions after consultation with the Lilly designated medical monitor:
- ALT or AST >8X ULN
 - ALT or AST >5X ULN for more than 2 weeks
 - ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or prothrombin time >1.5X ULN
 - ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5% of total leukocytes)
 - ALP >2.5X ULN and TBL >2X ULN
 - ALP >2.5 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:

- [2] Laboratory results:
- Neutrophil (segmented) counts (see safety monitoring for neutropenia in Section 8.4.8.1);
 - <500 cells/ μ L (<0.50x10³/ μ L or <0.50 GI/L)

- ≥ 500 and < 1000 cells/ μL ($\geq 0.50 \times 10^3/\mu\text{L}$ and $< 1.00 \times 10^3/\mu\text{L}$ or ≥ 0.50 GI/L and < 1.00 GI/L) (based on 2 test results; the second test performed within 1 week from knowledge of the initial result)
 - ≥ 1000 and < 1500 cells/ μL ($\geq 1.00 \times 10^3/\mu\text{L}$ and $< 1.50 \times 10^3/\mu\text{L}$ or ≥ 1.00 GI/L and < 1.50 GI/L) (based on 3 test results as specified in Section 8.4.8.1)
 - AND - a concurrent infection
 - Total WBC count < 2000 cells/ μL ($< 2.00 \times 10^3/\mu\text{L}$ or < 2.00 GI/L)
 - Lymphocyte count < 500 cells/ μL ($< 0.50 \times 10^3/\mu\text{L}$ or < 0.50 GI/L)
 - Platelet count $< 50,000$ cells/ μL ($< 50 \times 10^3/\mu\text{L}$ or < 50 GI/L)
- [3] Changes in BP (systolic BP at ≥ 160 mm Hg plus ≥ 20 mm Hg increase from baseline [Week 0; Visit 2]; and/or diastolic BP at ≥ 100 mm Hg plus ≥ 10 mm Hg increase from baseline) that do not respond following intervention (Section 8.4.8.3)
- [4] 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. Refer to Adverse Events, Section 8.2.
- [5] Clinically significant systemic hypersensitivity reaction following SC administration of investigational product that does not respond to symptomatic medication or results in clinical sequelae
- [6] The patient becomes pregnant. Patients will undergo urine pregnancy self-testing at home on a monthly basis during periods between scheduled visits until Week 52. During these intervisit periods, the site must call the patient each month to obtain her pregnancy test results. Additional urine pregnancy testing can be performed at the investigator's discretion. Patients that are determined to be pregnant will be discontinued from treatment and will no longer be administered investigational product.
- [7] The patient develops a malignancy.
(Note: Patients may be allowed to continue if they develop no more than 2 nonmelanoma skin cancers during the study.)
- [8] Any patient who has a change in disease phenotype at any time (for example, a change to pustular psoriasis)
- [9] If the patient requires long-term treatment with a therapeutic regimen that has been demonstrated to be effective for the treatment of psoriasis
- [10] 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

- [11] The patient scores a 3 for Item 12 (Thoughts of Death or Suicide) on the QIDS-SR16 at any time in the study. The patient should be evaluated on-site for risk of suicide and/or referred to a mental health provider for assessment.
- [12] The investigator or attending physician decides that the patient should be withdrawn from study treatment.
- [13] The patient requests to be withdrawn from study treatment.
- [14] The investigator or Lilly stops the patient's participation in the study.
- [15] The patient becomes HBV DNA positive. The patient should be referred to a specialist physician. Discussion of the timing of discontinuation from the study and study treatment is provided in Section 8.4.8.2.

If a patient is noncompliant with study procedures and/or investigational product 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 (Section 6.7).

Patients who discontinue the investigational product early will have an ETV and end-of-therapy procedures performed as shown in the Schedule of Activities (Appendix 2) and will continue into the Post Treatment Follow-up Period.

7.1.2. Discontinuation of Inadvertently Enrolled Patients

The criteria for enrollment must be followed explicitly. If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the sponsor CRP and the investigator to determine if the patient may continue in the study treatment. 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.

7.1.3. Permanent Discontinuation from the Study

Some possible reasons that may lead to permanent discontinuation include:

- 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)
- Subject Decision
 - the patient requests to be withdrawn from the study

7.1.4. Patients Lost to Follow-Up

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

8. Study Assessments and Procedures

[Appendix 2](#) lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing). [Appendix 3](#) lists the laboratory tests that will be performed for this study.

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

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessments

8.1.1.1. Static Physician Global Assessment of Genitalia

The sPGA of Genitalia is the clinician's determination of the patient's psoriasis lesions' overall severity in the genital area (labia majora, labia minora, and perineum in females; penis, scrotum, and perineum in males) at a given time point. Overall, lesions are categorized by descriptions for elevation, erythema, and scaling. It is not necessary that all 3 criteria be fulfilled. The sPGA of Genitalia score is based on a combination of erythema and the secondary features (plaque elevation and/or scale). Since erythema is the most robust finding, it should be the dominant feature influencing the sPGA of Genitalia rating in the majority of cases. For the analysis of responses, the patient's psoriasis is assessed as clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).

8.1.2. Secondary Efficacy Assessments

8.1.2.1. Clinician Reported Assessments

8.1.2.1.1. Modified Genital Psoriasis Area and Severity Index

The mGPASI was adapted from the standard PASI by Bissonnette et al. (2008) and Ryan et al. (2015) for use in male and female genital psoriasis patients. The measure is the clinician's determination of the patient's psoriasis severity in the genital region (labia majora, labia minora, and perineum in females; penis, scrotum, and perineum in males) at a given time point yielding an overall score of 0 for no psoriasis to 72 for the most severe disease. The scoring index incorporates the degree of erythema, induration, and scaling of the genital plaques as well as erosion, fissure, and/or ulcer as a product of the genital area involved. Severity is rated for each characteristic on a 0 to 4 scale (0 for no involvement up to 4 for severe involvement including erosion, fissure, and/or ulcer). The area of involvement for the entire genital area, excluding the inguinal area, is graded on a 0 to 6 scale (0 for no involvement; up to 6 for 90% to 100% involvement).

8.1.2.1.2. (Overall) static Physician Global Assessment

The sPGA is the physician's determination of the patient's psoriasis lesions overall at a given time point. The sPGA is recommended as an endpoint to assess efficacy in the treatment of psoriasis (EMA 2004). Overall, lesions are categorized by descriptions for induration, erythema, and scaling. For the analysis of responses, the patient's psoriasis is assessed as clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).

8.1.2.2. Patient Reported Assessments

The patient-reported questionnaires will be administered according to the Schedule of Activities ([Appendix 2](#)) in countries where the questionnaires have been translated into the native language of the region and linguistically validated.

8.1.2.2.1. Genital Psoriasis Symptoms Scale

The GPSS is a patient-administered assessment of 8 symptoms: itch, pain, discomfort, stinging, burning, redness, scaling, and cracking. Respondents are asked to answer the questions based on their psoriasis symptoms in the genital area. Genital area is defined as the labia majora (outer lip), labia minora (inner lip), and perineum (area between vagina and anus) for females; penis, scrotum, and perineum (area between the penis and anus) for males.

Numeric rating scales (NRS) are used to assess the self-reported overall severity of each of the 8 symptoms individually in the genital area on an 11-point horizontal scale anchored at 0 (no) and 10 (worst imaginable). The overall severity for each individual symptom from patient's genital psoriasis is indicated by selecting the number from 0 to 10 that best describes the worst level of each symptom in the genital area in the past 24 hours. An e-diary will be used to collect these patient rated assessments during the first 12 weeks; thereafter, patients will answer these questions only at scheduled study visits using the same recall period as used for the e-diary. The GPSS can be completed within 1 minute by patients. It will be completed before the patient's clinical examination; before the patient receives any text or test results; and before the patient's health, health data, or emotions are discussed. The instructions for completion are embedded within the GPSS questionnaire for patients to read before responding to the items. The symptom severity scores, ranging from 0 to 10, are the values of the selected numbers indicated by the patient on the instrument's horizontal scale. Each of the 8 individual items will receive a score of 0 to 10 and will be reported as item scores for itch, pain, discomfort, stinging, burning, redness, scaling, and cracking. In addition, a total score ranging from 0 (no genital psoriasis symptoms) to 80 (worst imaginable genital psoriasis symptoms) will be reported.

8.1.2.2.2. Genital Psoriasis Sexual Impact Scale

The GPSIS is a patient reported outcome measure to evaluate the impact of genital psoriasis symptoms on sexual activity. Respondents are asked to answer the questions based on their psoriasis symptoms in the genital area. Genital area is defined as the labia majora (outer lip), labia minora (inner lip), and perineum (area between vagina and anus) for females; penis, scrotum, and perineum (area between the penis and anus) for males. The definition of sexual activity is not limited to intercourse and includes activities such as masturbation. The instructions for completion are embedded within the GPSIS questionnaire for patients to read before responding to the items.

The GPSIS consists of 3 items that include 2 subscales on avoidance of sexual activity (Sexual Activity Avoidance Subscale) as well as the worsening of genital psoriasis symptoms during or following sexual activity (Impact of Sexual Activity on Genital Psoriasis Symptoms Subscale).

The Sexual Activity Avoidance Subscale includes items 1 and 2. Item 1 asks whether the patient has been sexually active in the past week. If a patient selects “no due to reasons other than my genital psoriasis,” they do not answer any additional questions on the scale and do not receive a score on the Sexual Activity Avoidance Subscale. If a patient responds “no due to my genital psoriasis” on GPSIS item 1, this receives a score of “5” (equivalent to always avoid sexual activity due to genital psoriasis on item 2) on the Sexual Activity Avoidance Subscale. For patients who are sexually active, a response of never, rarely, sometimes, and often on item 2 receive a score of 1, 2, 3, and 4, respectively, on the Sexual Activity Avoidance Subscale. The Sexual Activity Avoidance Subscale ranges from 1 (never) to 5 (always) avoid sexual activity.

The Impact of Sexual Activity on Genital Psoriasis Symptoms Subscale score includes only the score for GPSIS item 3. Those patients who report as being sexually active on the GPSIS item 1 are given the opportunity to respond to item 3. Item 3 asks the patient to select a response of very low or not at all (1) to very high (5) to reflect the level (degree) of worsening of genital psoriasis symptoms following sexual activity.

No total score is calculated for the GPSIS.

During the first 12 weeks, patients will use an e-diary, using a recall period of 1 week, and the response for each item uses a Likert scale. Thereafter, study participants will answer these questions only at scheduled study visits using the same 1-week recall period as used for the e-diary.

8.1.2.2.3. Sexual Frequency Questionnaire

The SFQ is a patient reported outcome measure to evaluate the impact of genital psoriasis symptoms on sexual frequency. It consists of 2 items that assess the impact of genital psoriasis symptoms on the frequency of sexual activity. Respondents are asked to answer the questions based on their psoriasis symptoms in the genital area. Genital area is defined as the labia majora (outer lip), labia minora (inner lip), and perineum (area between vagina and anus) for females; penis, scrotum, and perineum (area between the penis and anus) for males. The definition of sexual activity is not limited to intercourse and includes activities such as masturbation.

Item 1 asks how many times the patient engaged in sexual activity in the past week with response options of none/zero (2), once (1), and two or more (0).

Item 2 assesses how often genital psoriasis symptoms limited the frequency of sexual activity with response options ranging from 0 (never) to 4 (always).

The individual item scores of the SFQ are reported separately. No total score is calculated for the SFQ.

The instructions for completion are embedded within the SFQ questionnaire for patients to read before responding to the items. During the first 12 weeks, patients will use an e-diary, using a

recall period of 1 week, and the response for each item uses a Likert scale. Thereafter, study participants will answer these questions only at scheduled study visits using the same 1-week recall period as used for the e-diary.

8.1.2.2.4. Patient's Global Assessment of Genital Psoriasis

The Patient's Global Assessment of Genital Psoriasis (PatGA-Genital) is a patient-administered, single-item scale on which patients are asked to rank, by circling a number on a 0 to 5 NRS, the severity of their genital psoriasis "today" from 0 (clear), no genital psoriasis; to 5 (severe).

8.1.2.2.5. 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). A DLQI total score of 0 to 1 is considered as having no effect on a patient's HRQoL, and a 5-point change from baseline is considered clinically relevant (Basra et al. 2008).

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

The Short-Form (36) Health Survey (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 (MCS) scores and physical component summary (PCS), 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 will be used, which has a 1-week recall period (SF-36 Health Survey Update [WWW]).

8.1.3. Exploratory Efficacy Assessments

8.1.3.1. Clinician Reported Assessments

8.1.3.1.1. (Overall) Psoriasis Area and Severity Index

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. 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 quality of life (HRQoL) (Puig 2015).

8.1.3.1.2. Percentage of Body Surface Area

The investigator 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) (Van Voorhees et al. 2009).

8.1.3.1.3. Fitzpatrick Skin Type Assessment

The Fitzpatrick Skin Type is a skin classification system that classifies the typical response of different types of skin to ultraviolet light. Types range from the very fair (Type I) to the very dark (Type VI).

8.1.3.1.4. Binary Questions on Psoriasis Location**8.1.3.1.4.1. Overall**

Studying psoriasis involvement in the face, pubis, inguinal creases, gluteal cleft, and perianal area is of considerable interest for patients. These are locations that bear high potential for stigmatization and negative impact on quality of life. In addition, it is important to confirm that association of psoriasis on nails, scalp, axillae, and inframammary folds that have been correlated with genital involvement in past studies (Ryan et al. 2015). To this end, binary responses (yes/no) will be noted at baseline, Week 4, 12, 24, 52, or ETV whether the patient currently has visible psoriasis on face, inframammary fold, axilla, scalp, nail, pubis, perianal region, gluteal cleft and inguinal creases.

8.1.3.1.4.2. Genital

The specific location of psoriasis in the genital area may differentially impact patients in terms of sexual avoidance and frequency as well as physical discomfort and pain. To this end, binary questions (yes/no) will be asked at each study visit whether the patient current has visible psoriasis in women on labia minora, labia majora, and/or perineum and in men on the penis (glans and/or shaft), scrotum, and/or perineum.

8.1.3.1.5. Binary Questions on Characteristics**8.1.3.1.5.1. Genital**

Publications related to genital psoriasis note that fissure, erosion, and ulcers may be present in the genital area. These characteristics may increase the pain and discomfort of genital psoriasis and also significantly impact sexual function and quality of life. Fissure, erosion, and ulcer are assessed collectively on the mGPASI but are not identified individually on the scale. To better understand which specific characteristics impact patients with psoriasis, information on presence of these characteristics will be recorded on the eCRF. Binary questions (yes/no) will be asked at each study visit regarding presence of fissure, erosion, and ulcer in the genital area (labia minora, labia majora, and perineum in female patients and penis, scrotum, and perineum in male patients).

8.1.3.1.5.2. Perianal/Gluteal Cleft

Little information is available regarding perianal characteristics in patients with psoriasis, and better understanding is needed. Fissures, abscess, ulcer, and skin tags may be present in the perianal area/gluteal cleft but have not been well studied in patients with psoriasis. However, perianal disease may significantly impact quality of life and add to discomfort/pain related to the

disease. To this end, binary questions (yes/no) will be asked periodically at study visits regarding presence in the perianal area of fissure, abscess, ulcer, and skin tags and in the gluteal cleft of fissure.

8.1.3.2. Combined Clinician/Patient Reported Assessment

The patient-reported portion of the questionnaire will be administered according to the Schedule of Activities ([Appendix 2](#)) in countries where this portion of the questionnaire has been translated into the native language of the region and linguistically validated.

8.1.3.2.1. Comprehensive Assessment of the Psoriasis Patient

An assessment of psoriasis severity, combining both clinician (exam) and patient-evaluation (patient reported outcome [PRO]; visual analog scale) to determine severity of overall plaque psoriasis as well as several subindices (scalp, nail, palmar-plantar, inverse, and genital). Each area is scored as 0 to 20 (0 to 10 for clinician assessment plus 0 to 10 for the higher of the 2 PROs). For this study, we will assess only the genital severity index. The genital severity score will range from 0 (clear/no impact) to 20 (severe genital psoriasis/worst imaginable pain and/or unable to be intimate at all).

8.1.3.3. Patient Reported Assessment

The patient-reported questionnaire will be administered according to the Schedule of Activities ([Appendix 2](#)) in countries where the questionnaire has been translated into the native language of the region and linguistically validated.

8.1.3.3.1. Touch Avoidance Numeric Rating Scale

The Touch Avoidance Numeric Rating Scale is a self-administered, single item scale that assesses touch avoidance over the past 2 weeks due to the look or feel of the patient's skin. The item is rated on scale of 0 (not at all) to 10 (very much).

8.1.4. Appropriateness of Assessments

8.1.4.1. Static Physician Global Assessment of Genitalia

The sPGA of Genitalia is a version of the sPGA scale used in Lilly's Phase 3 ixekizumab clinical trials that has been modified for the assessment of genital involvement as noted above (Section [8.1.2.1.2](#)). The instruction set directs clinicians to specifically evaluate plaque lesion severity in the genital area rather than the entire body. Instrument scoring is based on the identical categories and similar category descriptions of the sPGA scale but has been revised to reflect the importance of erythema in the presentation of genital psoriasis. The modifications to the scale were established with input from an Expert Consensus Development panel as well as clinical experts in genital psoriasis from 3 countries.

8.1.4.2. Modified Genital Psoriasis Area and Severity Index

The mGPASI was adapted from the standard PASI by Bissonnette et al. (2008) for use in male patients with genital psoriasis and later by Ryan et al. (2015) for use in male and female genital psoriasis patients. The PASI was modified to include erosion, fissure, and ulcer as part of the clinical assessment in order to capture some of the additional symptoms that may be present in genital psoriasis as described above. The mGPASI has been used to measure treatment effect in

an open-label treatment study of male patients with genital psoriasis (Bissonnette et al. 2008), as well as to measure severity of genital involvement in a recent cross-sectional study of male and female patients with genital psoriasis (Ryan et al. 2015). Ryan et al. (2015) found that patients with increased severity of genital disease, as measured quantitatively by the mGPASI, had more significant impairment of quality of life, independent of overall disease severity for all subjective patient reported quality of life assessments, including the Relationship and Sexuality Scale (RLSS), Center for Epidemiologic Studies Depression Scale (CED-S), and DLQI and was the only objective psoriasis measure which showed a significant correlation to all of these PROs. These studies demonstrated the utility of the mGPASI in quantifying the objective severity of genital psoriasis for use in future studies.

8.2. 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.

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via electronic data entry (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 via eCRF 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 decides whether he or she interprets the observed AEs as reasonably possibly related to the investigational product, study device, study procedure, to disease, or other concomitant treatment or pathologies. To assess the relationship of the AEs, the following is defined:

Reasonably Possibly **Related**: Reasonable possibility that there is a cause and effect relationship between the 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.

8.2.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

If an SAE occurs after signing the ICF, but prior to receiving investigational product, it needs to be reported **ONLY** if it is considered reasonably possibly related to study procedure.

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

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy 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.

8.2.2. Adverse Events of Special Interest

The following adverse events of special interest (AESIs) will be used to determine the safety and tolerability of ixekizumab over the range of doses selected for this clinical study.

AESIs for ixekizumab are:

- cytopenias (leukopenia, neutropenia, and thrombocytopenia)
- liver function test changes/enzyme elevations (ALT, AST, bilirubin, and alkaline phosphatase)
- infections
- injection-site reactions
- allergic reactions/hypersensitivities
- cerebrocardiovascular events
- malignancies
- inflammatory bowel disease
- depression

Sites will provide details on AEs as instructed on the eCRF. Investigators will also educate patients and/or caregivers about the symptoms of systemic allergic/hypersensitivity reactions and will provide instructions on the management and reporting of these reactions. Blood samples will be collected as soon as possible for any patient who experiences an AE of a potential systemic allergic/hypersensitivity reaction during the study as judged by the investigator. These samples may be tested for ADAs, other laboratory tests needed to elucidate the cause of the allergic/hypersensitivity reaction, and/or ixekizumab serum concentration.

Data on preferred terms associated with cerebrocardiovascular events (defined as death, cardiac ischemic event including MI and hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, coronary revascularization procedure, stroke/transient ischemic attack, peripheral revascularization procedure, peripheral arterial event, and hospitalization for hypertension) will be collected, and these events and any deaths will be adjudicated by an external Clinical Events Committee (CEC) made up of a chairperson, 2 cardiologists, and a neurologist. The role of the CEC is to adjudicate these defined clinical events in a blinded, consistent, and unbiased manner throughout the course of a study. The purpose of the CEC is to ensure that all events that have been reported are evaluated uniformly by a single group (the CEC).

8.2.2.1. Suspected Unexpected Serious Adverse Reactions

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.

8.2.3. Complaint Handling

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

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

8.3. Treatment of Overdose

Refer to the IB.

8.4. Safety Assessments

8.4.1. Electrocardiograms

For each patient, ECGs should be collected locally at screening according to the Schedule of Activities ([Appendix 2](#)). Electrocardiograms should be recorded according to the study specific recommendations included in the Manual of Operations for the study.

Electrocardiograms will be interpreted locally by a qualified physician. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational treatment should be reported to Lilly or its designee as an AE via eCRF.

8.4.2. Vital Signs

For each patient, vital signs measurements should be conducted according to the Schedule of Activities ([Appendix 2](#)) and following the study specific recommendations included in the Manual of Operations for the study. At baseline (Week 0) and Visit 7 (Week 12), BP and pulse should be measured prior to administration of the investigational product and again approximately 1 hour post-administration.

Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via eCRF.

8.4.3. Laboratory Tests

For each patient, laboratory tests detailed in ([Appendix 3](#)) should be conducted according to the Schedule of Activities ([Appendix 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.

8.4.4. Physical Examination

For each patient, a complete physical examination should be conducted according to the Schedule of Activities ([Appendix 2](#)) and following the study specific recommendations included in the Manual of Operations for the study.

Any clinically significant findings from a complete physical examination 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.

8.4.5. Chest X-Ray and Tuberculosis Testing

A posterior-anterior view chest x-ray will be obtained, unless the x-ray or results from a chest x-ray obtained within 6 months prior to the study are available. The chest x-ray or results will be reviewed by the investigator or designee to exclude patients with active TB infection.

In addition, patients will be tested at screening as indicated on the Schedule of Activities ([Appendix 2](#)) for evidence of active or latent TB indicated by a positive tuberculin PPD skin test response (≥ 5 mm induration, between approximately 2 and 3 days after test application, regardless of BCG vaccination history). In countries where an Interferon-Gamma Release Assay (QuantiFERON[®]-TB Gold test, and/or T-SPOT[®]) is available and in the judgment of the investigator preferred as an alternative to the PPD skin test for the evaluation of TB infection, it may be used instead of the PPD test (positive tests excluded) and may be read locally. If the QuantiFERON[®]-TB Gold test is indeterminate, or the T-SPOT[®] is invalid or borderline, 1 retest is allowed. If the retest for the QuantiFERON[®]-TB Gold test is indeterminate, or the retest for the T-SPOT[®] is invalid or borderline, then the patient is excluded from enrollment in the study.

Patients with documentation of a negative test result within 3 months prior to baseline (Week 0; Visit 2) do not need a TB screen at Visit 1. Documentation of this test result must include a record of the size of the induration response (< 5 mm induration). A PPD test recorded as negative without documenting the size of induration will result in a retest.

However, patients with a PPD skin test ≥ 5 mm induration or a positive QuantiFERON[®]-TB Gold or positive T-SPOT[®] test at screening, but no other evidence of active TB may be rescreened 1 time and may be enrolled without repeating a PPD or QuantiFERON[®]-TB Gold test or T-SPOT[®] if the following conditions are met:

- after receiving at least 4 weeks of appropriate latent TB infection (LTBI) therapy, with commitment by the patient and the investigator for the patient to complete a full course of prophylaxis for TB
- with no evidence of hepatotoxicity (ALT/AST must remain ≤ 2 times ULN) upon retesting of serum ALT/AST prior to randomization. Such patients must complete appropriate LTBI therapy during the course of the study in order to remain eligible
- meet all other inclusion/exclusion criteria for participation

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

Patients with positive TB test results on file: Patients with prior history of a positive TB test should not have a TB test performed at Visit 1. Documentation of this history and of at least 4 weeks of appropriate latent TB treatment prior to baseline (Week 0, Visit 2) 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 are eligible to participate in the study. Patients who have had household contact with a person with active TB are excluded, unless an appropriate and documented course of prophylaxis for TB was completed.

Any clinically significant findings from chest x-rays and/or tuberculosis testings 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.

8.4.6. Immunogenicity

Samples for immunogenicity testing, including samples that may be analyzed for ixekizumab concentration will be collected at time points indicated in the Schedule of Activities ([Appendix 2](#)). Additionally, blood samples for potential immunogenicity testing will be collected, as soon as possible, for any patient who experiences a potential systemic allergic/hypersensitivity reaction during the study as judged by the investigator. These samples may be tested for ADAs, ixekizumab serum concentration, and/or other laboratory tests needed to elucidate the cause of the allergic/hypersensitivity reaction.

8.4.7. Quick Inventory of Depressive Symptomatology—Self-Report (16 Items)

QIDS-SR16 is a self-administered, 16-item instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (APA 1994). A patient is asked to consider each statement as it relates to the way they have felt for the past 7 days. There is a 4-point scale for each item ranging from 0 to 3. The 16 items corresponding to 9 depression domains are summed to give a single score ranging from 0 to 27, with higher scores denoting greater symptom severity. The domains assessed by the instrument include: (1) sad mood, (2) concentration, (3) self-criticism, (4) suicidal ideation, (5) interest, (6) energy/fatigue, (7) sleep disturbance (initial, middle, and late insomnia or hypersomnia), (8) decrease/increase in appetite/weight, and (9) psychomotor agitation/retardation. Additional information and the QIDS-SR16 questions may be found at the University of Pittsburgh IDS/QIDS internet page [WWW]. A QIDS-SR16 assessment will be taken at times indicated in the Schedule of Activities ([Appendix 2](#)).

8.4.8. Safety Monitoring

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

If a study patient/subject experiences elevated ALT $\geq 3X$ ULN, ALP $\geq 2X$ ULN, or elevated TBL $\geq 2X$ 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](#).

8.4.8.1. Neutropenia

During treatment with investigational product, patients with neutrophil counts <1500 cells/ μL ($<1.50 \times 10^3/\mu\text{L}$ or <1.50 GI/L) should be managed for neutropenia as follows:

- <500 cells/ μL ($<0.50 \times 10^3/\mu\text{L}$ or <0.50 GI/L), see Discontinuation Criteria (Section 7.1)
- ≥ 500 cells/ μL and <1000 cells/ μL ($\geq 0.50 \times 10^3/\mu\text{L}$ and $<1.00 \times 10^3/\mu\text{L}$ or ≥ 0.50 GI/L and <1.00 GI/L), see Discontinuation Criteria (Section 7.1)
- ≥ 1000 cells/ μL and <1500 cells/ μL ($\geq 1.00 \times 10^3/\mu\text{L}$ and $<1.50 \times 10^3/\mu\text{L}$ or ≥ 1.00 GI/L and <1.50 GI/L), and the patient has a concurrent infection that requires systemic anti-infective therapy (for example, antibiotic, antifungal agent, antiviral agent):
 - The dose of investigational product 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 ($\geq 1.50 \times 10^3/\mu\text{L}$ or $\geq 1.50 \times 10^3/\mu\text{L}$) 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 ($\geq 1.00 \times 10^3/\mu\text{L}$ and $<1.50 \times 10^3/\mu\text{L}$ or ≥ 1.00 GI/L and <1.50 GI/L), 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 ($\geq 1.00 \times 10^3/\mu\text{L}$ and $<1.50 \times 10^3/\mu\text{L}$ or ≥ 1.00 GI/L and <1.50 GI/L), and:
 - the infection has not fully resolved, the patient will be discontinued from the study treatment and continue safety follow up.
 - the infection has resolved, the patient may resume dosing and evaluation at scheduled visits. However, if resumption of dosing is not deemed appropriate by the investigator, the patient will be discontinued from the study treatment and continue safety follow up .

- ≥ 1000 cells/ μL and < 1500 cells/ μL ($\geq 1.00 \times 10^3/\mu\text{L}$ and $< 1.50 \times 10^3/\mu\text{L}$ or ≥ 1.00 GI/L and < 1.50 GI/L), and the patient has no concurrent infection that requires systemic anti-infective therapy (for example, antibiotic, antifungal agent, antiviral agent):
 - Dosing may continue, and a repeat neutrophil count 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 ($\geq 1.50 \times 10^3/\mu\text{L}$ or ≥ 1.50 GI/L). If the patient has 3 or more postbaseline neutrophil counts of ≥ 1000 cells/ μL ($\geq 1.00 \times 10^3/\mu\text{L}$ or ≥ 1.00 GI/L) and < 1500 cells/ μL ($< 1.50 \times 10^3/\mu\text{L}$ or < 1.50 GI/L), no value of < 1000 cells/ μL ($< 1.00 \times 10^3/\mu\text{L}$ or < 1.00 GI/L), and no postbaseline infection requiring systemic anti-infective therapy, the patient may continue or resume further evaluation at scheduled visits, as deemed appropriate by the investigator.

If a patient without initial concurrent infection develops an infection that requires systemic anti-infective therapy, then the patient should be managed as indicated above for patients with concurrent infection.

If, at the last scheduled visit or ETV, the patient's neutrophil count is < 1500 cells/ μL ($< 1.50 \times 10^3/\mu\text{L}$ 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 4) design at Visits 801 (4 weeks post-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 4) 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 ($< 1.00 \times 10^3/\mu\text{L}$ or < 1.00 GI/L) at any follow up visit, the patient should return for visits at least Q4W (may require unscheduled visits).

- As long as a patient's neutrophil count is ≥ 1000 cells/ μL and < 1500 cells/ μL ($\geq 1.00 \times 10^3/\mu\text{L}$ and $< 1.50 \times 10^3/\mu\text{L}$ 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 (may require unscheduled visits).
- If, at Visit 802 or Visit 803, the patient's neutrophil count is ≥ 1500 cells/ μL ($\geq 1.50 \times 10^3/\mu\text{L}$ or ≥ 1.50 GI/L) or greater than or equal to the patient's baseline neutrophil count (whichever is lower), the patient's participation in the study will be considered complete unless the investigator deems additional follow-up may be necessary.

If, at Visit 803, the patient's neutrophil count remains < 1500 cells/ μL ($< 1.50 \times 10^3/\mu\text{L}$ or < 1.50 GI/L) and less than the patient's baseline neutrophil count, or if the investigator deems additional follow-up may be necessary, the investigator in consultation with Lilly, or qualified designee, will determine the appropriate management of the patient and the appropriate timing of additional contact(s) or visit(s).

8.4.8.2. Hepatitis B Monitoring

Patients that are HBcAb+ at screening, regardless of other hepatitis B testing results, will have a serum HBV DNA specimen obtained to be analyzed by the central laboratory. Such patients that 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 that are found to be HBV DNA positive (detectable) at screening will be excluded from the trial.

If the result of any subsequent HBV DNA testing is positive, the patient must be discontinued from the study treatment, should continue safety follow up, and should receive appropriate follow-up medical care, including consideration for antiviral therapy. A specialist physician in the care of patients with hepatitis (for example, infectious disease or hepatologist subspecialists) should be consulted and potentially start antiviral therapy prior to discontinuation of any immunosuppressant or immunomodulatory therapy (including investigational drug). Timing of discontinuation from the study and of any immunosuppressant/immunomodulatory therapy (including investigational product) needs to be based on the recommendations of the consulting specialist physician in conjunction with the investigator and medical guidelines/standard of care.

8.4.8.3. Hypertension

Patients who experience changes in BP (systolic BP at ≥ 160 mm Hg plus ≥ 20 mm Hg increase from baseline [Week 0; Visit 2]; and/or diastolic BP at ≥ 100 mm Hg plus ≥ 10 mm Hg increase from baseline) on 2 consecutive visits should receive intervention for the management of hypertension. See Section 7.1 for the discontinuation criterion related to hypertension.

8.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities ([Appendix 2](#)), blood samples of approximately 4 mL each will be collected to determine the serum concentrations of ixekizumab. These blood samples for PK analysis are matched to the timing of samples for the assessment of

immunogenicity. These samples are designed to be taken at trough, that is, immediately prior to dosing. It is expected that these PK samples will allow sufficient description of ixekizumab PK profiles at steady state throughout the study.

Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Samples collected for PK analysis will be tested at a laboratory approved by Lilly or its designee. Concentrations of immunoreactive ixekizumab in human serum will be determined by a validated method.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last patient visit for the study.

8.6. Pharmacodynamics

Not applicable

8.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities ([Appendix 2](#)) where local regulations and ERBs allow. These samples are not being collected to create a biobank for conducting unspecified disease or population genetic research either now or in the future.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to ixekizumab and to investigate genetic variants thought to play a role in psoriasis and/or associated autoimmune conditions. Assessment of variable response may include evaluation of AEs or differences in efficacy. These studies may include but are not limited to the IL-17 and IL-23 family and receptor and signaling pathways, to evaluate their association with observed response to ixekizumab.

All pharmacogenetic samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel. Samples will be destroyed according to a process consistent with local regulations.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by the sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, candidate gene studies, and epigenetic analyses.

Regardless of technology utilized genotyping data generated will be used only for the specific research scope described here.

8.8. Biomarkers

Serum, plasma, and mRNA samples for nongenetic biomarker research will be collected at the times specified in the Schedule of Activities ([Appendix 2](#)) where local regulations and ERBs allow.

Samples will be used for research on the drug target, disease process, pathways associated with psoriasis and/or associated autoimmune conditions, mechanism of action of ixekizumab, and/or research method or in validating diagnostic tools or assay(s) related to psoriasis and/or associated autoimmune conditions. Proteomic, gene-expression, genomic, epigenetic, or metabolomic analysis may be performed on these samples.

All biomarker samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel. Samples will be destroyed according to a process consistent with local regulations.

Samples will be retained for a maximum 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits, at a facility selected by the sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

8.8.1. Samples for Immunogenicity Research

Where local regulations and ERBs allow, blood samples for immunogenicity testing will be collected to determine antibody production against ixekizumab as specified in the Schedule of Activities ([Appendix 2](#)). The actual date of each sampling will be recorded at the study site. Immunogenicity will be assessed by a validated assay designed to perform in the presence of ixekizumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of ixekizumab.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if regulations and ERBs impose shorter time limits, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to ixekizumab.

8.8.2. Samples for Genital *Candida* Testing

Where local regulations and ERBs allow, genital skin swab samples for *Candida* testing will be collected and may be used to determine presence of *Candida* at baseline. Swabs will be collected from labia majora in women and glans penis in men.

Deficiency or inhibition of IL-17 has been linked to mucocutaneous candidiasis (Puel et al. 2011; Cosentyx package insert, 2015). In the Phase 3 trials of ixekizumab in the treatment of psoriasis, *Candida* infections were observed in approximately 3% of patients who received ixekizumab,

some of which involved the genital area. None of the *Candida* infections were SAEs or led to discontinuation of study treatment. None of the vulvovaginal candidiasis cases were considered severe, and none were considered related to investigational product by investigators.

Candida skin swabs will be tested at baseline for exploratory purposes to better understand colonization with *Candida* spp. of the genitalia of patients with psoriasis that involves the genital area. In general, these test results are not clinically informative without a clinical diagnosis of candidiasis, and the results will not be shared with investigators. If an investigator believes it is clinically indicated for patient management (per the local standard of care), then he/she may choose to take an additional skin swab to be evaluated per local procedures.

8.9. Health Economics

Not applicable

9. Statistical Considerations and Data Analysis

9.1. Determination of Sample Size

The total sample size for the study will be approximately 146 patients randomized at 1:1 ratio in the Blinded Treatment Period to ixekizumab Q2W and placebo (73 patients per treatment group).

No prior sPGA of Genitalia (primary outcome measure) data was available at the time of planning this study to guide sample size and power calculations because no biologic drug has been evaluated in a well-controlled clinical trial to date in patients with genital psoriasis. Therefore, based on the relevance and impact of sexual impairment in genital psoriasis, data from the assessment of DLQI Item 9 (How much has your skin caused any sexual difficulties?) outcomes in the ixekizumab Phase 2 and Phase 3 studies were used to calculate the sample size. Sample size was calculated assuming sexual impairment rates of 2% and 20% in the ixekizumab Q2W and placebo treatment groups, respectively. With these assumed rates, a sample size of 146 (73 per treatment group) is likely to achieve 94% power, based on a 2-sided Fisher's exact test at 0.05 level of significance.

9.2. General Statistical Considerations

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

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

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

Complete details of the planned analyses will be documented in the statistical analysis plan (SAP).

General Considerations for Analyses during Period 2 (Blinded Treatment Period)

Comparisons of ixekizumab Q2W dosing versus placebo will be performed for all outcome variables in Period 2. Baseline will be defined as the last available value before the first injection of the investigational product for both efficacy and safety analyses. In most cases, this will be the measurement recorded at Week 0 (Visit 2). For efficacy measures, if the patient does not take any injection, the last available value on or prior to randomization date will be used. Change from baseline at a particular visit will be calculated as the value at that visit minus the baseline value. For safety analyses using a baseline period, the baseline period is defined as the time from Visit 1 to the date/time of the first injection.

For outcome measures that are not collected at each postbaseline visit, data may exist at visits where the outcome measure was not scheduled to be collected, due to ETVs. In these situations,

data from the ETVs 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.

9.3. Analysis Population

Intent-to Treat Population: The intent-to-treat (ITT) population consists of all randomized patients. Even if the patients are not administered 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.

Safety Population: The safety population is defined as all randomized patients who received at least 1 dose of study treatment. Patients will be analyzed according to the dosing regimen to which they were assigned.

Open-Label Treatment Population: The open-label treatment population consists of all randomized patients who received at least 1 dose of study treatment during Period 3 and have entered the Open-Label Treatment Period. Patients will be analyzed according to the treatment group to which they were assigned in Period 2. All analyses for Period 3 (Open-Label Treatment Period) will be conducted on this analysis population.

Post-Treatment Follow-Up Population: 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. Patient data will be summarized according to the treatment group to which they were assigned in Period 2. Safety analyses for Period 4 (Post-Treatment Follow-Up Period) will be conducted on this analysis population.

9.3.1. Missing Data Imputation

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

Nonresponder Imputation (NRI)

Analysis of categorical efficacy and health outcome variables will be performed using 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 1 postbaseline observation will also be defined as nonresponders for the NRI analysis.

Last Observation Carried Forward (LOCF)

LOCF method will be used to impute missing data for only the major secondary continuous outcome variable. For patients having missing data at a visit, the last nonmissing postbaseline observation before the missing data will be carried forward to the corresponding time point of evaluation. Randomized patients without at least 1 postbaseline observation will not be included in LOCF analyses.

Modified Baseline Observation Carried Forward (mBOCF)

An mBOCF analysis will be performed on all continuous efficacy and health outcome variables. For patients discontinuing investigational product due to an AE, the baseline observation will be carried forward to the corresponding primary endpoint for evaluation. For patients discontinuing investigational product for any other reason, the last nonmissing postbaseline observation before discontinuation will be carried forward to the corresponding time point of evaluation. Randomized patients without at least 1 postbaseline observation will not be included for evaluation with the exception of patients discontinuing study treatment due to an AE.

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

9.3.2. Adjustment for Multiple Comparisons

A multiple testing strategy for the primary and the major secondary endpoint will be implemented to control the family-wise type I error rate at a 2-sided α level of 0.05. The following primary and major secondary endpoint will be sequentially tested in the following order to compare ixekizumab Q2W versus placebo, using the primary analysis method.

- Primary – Proportion of patients achieving sPGA of Genitalia (0,1) at Week 12
- Major Secondary – Mean change from baseline in the genital psoriasis itch NRS item within the GPSS at Week 12

The primary endpoint will be tested at 2-sided $\alpha = 0.05$. If the test for primary endpoint is significant, then the test for the major secondary endpoint will be performed. Otherwise the testing will stop.

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

9.4. Treatment Group Comparability

9.4.1. 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 for each treatment period and will include reasons for discontinuation. The reasons for discontinuation during Blinded Treatment Period (Period 2) will be compared between treatment groups using Fisher's exact test.

9.4.2. Patient Characteristics

Baseline characteristics, clinical, and health outcome measurements will be summarized for each population – ITT and Open-Label Treatment. Baseline characteristics will include gender, age, age category, weight, race, geographic region, baseline disease severity, duration of disease, previous nonbiologic systemic therapy, and previous biologic therapy. Baseline clinical and PRO measurements will include sPGA of Genitalia score, mGPASI total score, overall sPGA, overall PASI, BSA, GPSS total and item scores (including Genital Psoriasis Itch NRS), DLQI

total score, GPSIS subscales, SFQ items, PatGA-Genital, Touch avoidance NRS, SF-36, QIDS-SR16, and CAPP.

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

9.4.3. 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 4 and WHO preferred term. Treatment group comparisons in Period 2 will be conducted using Fisher's exact test.

9.4.4. Treatment Compliance

Treatment compliance with investigational product will be summarized for patients who enter Period 2. A patient will be considered compliant overall for each study period if he/she misses no more than 20% of the expected doses, does not miss 2 consecutive doses, and does not overdose (that is, take more injections at the same time point than specified in the protocol). Proportions of patients compliant overall will be compared between treatment groups during Period 2 using Fisher's exact test.

9.5. Primary and Secondary Analyses

9.5.1. Primary Analyses

- Categorical
 - Treatment comparisons of categorical efficacy and health outcome variables will be performed using a logistic regression model with treatment and BSA category as factors, using NRI method.
- Continuous
 - The primary analyses for all continuous efficacy and health outcome variables will be performed using MMRM. The model will include treatment, baseline BSA category, baseline value, visit, treatment-by-visit interaction, and baseline-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-square (LS) 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 12 will be tested. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, followed by the compound symmetry will be

used. This order is specified according to a decreasing number of covariance parameters in the structure.

9.5.2. Secondary Analyses

- **Categorical**
 - Secondary analysis on the categorical efficacy variables will be conducted using a Fisher's exact test.
 - A categorical, pseudo-likelihood-based MMRM for categorical repeated measures analysis may also be performed for the primary endpoint of sPGA of Genitalia (0, 1). The details of the analysis model will be presented in the SAP.
- **Continuous**
 - Secondary analyses for treatment comparisons on continuous outcome variables will be conducted using an analysis of covariance (ANCOVA) model and LOCF or mBOCF imputation methods. The ANCOVA model will include treatment, baseline BSA category, and baseline value. Type III sums of squares for the LS means will be used for the statistical comparison; the 95% CI will be reported.

9.5.3. Exploratory Analyses

The exploratory outcome measures will be analyzed using similar analysis methods described above. Complete details will be documented in the SAP.

9.6. Safety Analyses

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

The primary safety analyses will focus on comparisons of ixekizumab Q2W versus placebo in Period 2. Treatment comparisons of categorical safety outcome variables will be performed using Fisher's exact test. Treatment comparisons of continuous safety outcome variables will be performed using ANCOVA with treatment and baseline value in the model.

Summaries of safety data collected during the Open-Label Treatment Period and Post-Treatment Follow-Up Period will be presented separately. The categorical safety measures will be summarized with incidence rates. The mean change of the continuous safety measures will be summarized by visits.

Unless otherwise specified, the baseline for safety analyses in the Open-Label Treatment Period is defined as the last nonmissing assessment on or prior to Week 12 (Visit 7). Unless otherwise specified, the Post-Treatment Follow-Up Period Baseline is defined as the last nonmissing assessment on or prior to Week 52 (Visit 12) or ETV.

9.6.1. Adverse Events

Adverse events are classified based upon 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 15) or the ETV. For events that are gender specific, the denominator and computation of the percentage will only include patients from the given gender.

An overall summary of AEs will be provided for each treatment period. TEAEs, SAEs including deaths, AEs that led to investigational product discontinuation, and AEs by maximum severity and relationship to investigational product will be summarized by MedDRA system organ class (SOC) and preferred term (PT). TEAEs will also be summarized by PT sorted by decreasing frequency within SOC for all TEAEs, TEAEs by maximum severity, and TEAEs considered possibly related to investigational product.

FEAEs (all, by maximum severity, and FEAEs possibly related to investigational product by the investigator), SAEs including deaths, AEs that lead to study discontinuation will be summarized by MedDRA SOC and PT or by PT for the Post-Treatment Follow-Up Period (Period 4).

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

9.6.2. Clinical Laboratory Tests

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

- For categorical lab tests:
 - Treatment-emergent abnormal value = a change from normal at all baseline visits to abnormal at any time postbaseline.
- For continuous lab tests:
 - Treatment-emergent high value = a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time postbaseline.
 - Treatment-emergent low value = a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time postbaseline.

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

Vital signs will be presented as mean changes from baseline and as incidence of abnormal values and will be summarized for both predose and postdose at Week 0 (Visit 2) and Week 12 (Visit 7), as applicable.

The maximum postbaseline QIDS-SR16 total score will be summarized by treatment, and shift table will be produced for the change from baseline in QIDS-SR16 total score category.

Other covariate data, including body weight, will be descriptively summarized by treatment groups. Further analyses may be performed comparing the treatment groups.

9.7. Pharmacokinetic/Pharmacodynamic Analyses

Observed ixekizumab serum concentrations will be summarized by visits and corresponding time when sampling occurred.

As appropriate, the PK and the exposure-response relationship between ixekizumab exposure and clinically important efficacy measures (for example, sPGA or mGPASI) may be explored using graphical methods and/or a modeling approach. If a modeling approach is taken, data may be combined with data from other ixekizumab studies if appropriate.

The potential impact of immunogenicity on ixekizumab exposure and/or efficacy responses may be evaluated by graphical assessments, as appropriate, to compare drug exposure or efficacy responses between ADA negative and ADA positive patients at corresponding visits, or before and after ADA development for patients who developed ADA. Both treatment-emergent only and all ADA positive/negative patients may be explored. A similar approach may be taken if patients become neutralizing anti-drug antibody (NAb) positive.

Additional analyses may be performed upon receipt of the data. Data from this study may be combined with data from previous efficacy studies for additional population PK and/or exposure efficacy modelling if deemed appropriate.

9.8. Other Analyses

9.8.1. Subgroup Analyses

To assess consistency of results among the 2 subpopulations determined by baseline BSA category ($<10\%$ versus $\geq 10\%$ baseline BSA involvement), subgroup analysis will be conducted on sPGA of Genitalia (0,1) using the ITT population.

Other subgroups that may be evaluated include gender, age, weight, race, and geographic region. 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 (that is no inferential testing will be performed).

Additional subgroup analyses on efficacy or safety may be performed as deemed appropriate.

9.8.2. Immunogenicity Analyses

The analyses of ADA effects will be conducted on all evaluable patients within the defined safety population. Evaluable patients will be defined as either a) patients with an evaluable baseline sample and at least 1 evaluable postbaseline sample (that is, sample after administration of investigational product); or b) patients with no evaluable baseline sample whose evaluable postbaseline samples were all ADA negative. A treatment-emergent positive anti-drug antibody (TE-ADA+) patient will be defined as any occurrence of a greater than or equal to 4-fold or 2 dilution increase in immunogenicity titer over the baseline titer. This is equivalent to an increase in titer to $\geq 1:10$, in the case of a negative result at baseline.

The frequency and percentage (incidence) of patients with positive, negative, or inconclusive ADA at baseline and patients with positive, negative, or inconclusive TE-ADA postbaseline will be summarized by treatment group. Additional summarizations for patients who are TE-ADA+ will be done for patients who are TE-ADA persistent or transient positive; patients who are NAb positive, negative, or inconclusive; and for ADA titers.

Assessment of immunogenicity with respect to safety will include comparison of patients who experience TEAEs of systemic allergy/hypersensitivity and of injection-site reactions and also develop treatment-emergent ADA positive status with patients who experience the same types of TEAEs but who remain treatment-emergent ADA negative. ADA titers will also be evaluated in patients who experience these events.

9.9. Interim Analyses

An interim database lock and the unblinding of the sponsor will occur, and the analysis will be performed at the time (that is, a cut-off date) the last patient completes Visit 7 (Week 12), completes ETV, or discontinues from the Blinded Treatment Period (Period 2). This interim database lock will include all data collected by the cut-off date including data from the Open-Label Treatment Period and follow-up data from patients who have begun Post-Treatment Follow-Up Period (Period 4). Because the study will still be ongoing for the Open-Label Treatment Period and the Post-Treatment Follow-Up Period at the time of this database lock, the analysis will be referred to as an interim analysis. This interim analysis includes the final analysis for the Blinded Treatment Period (Period 2) of the study; therefore, there is no alpha adjustment due to this interim analysis. There will be no data monitoring committee.

A final database lock will occur after the Post-Treatment Follow-Up Period is completed. Site-level unblinding will occur after final database lock is complete.

Unblinding details will be specified in a separate unblinding plan document.

10. Study Governance Considerations

10.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

10.1.1. Informed Consent

The investigator is responsible for ensuring:

- that the patient understands the potential risks and benefits of participating in the study
- that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial

10.1.2. Ethical Review

The investigator must give assurance that the ERB was properly constituted and convened as required by International Conference on Harmonisation (ICH) guidelines and other applicable laws and regulations.

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

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

- the current IB and updates during the course of the study
- ICF
- relevant curricula vitae

10.1.3. Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third-party.

10.1.4. Investigator Information

Physicians with a specialty in dermatology or other specialties with appropriate experience (private practice, university, psoriasis research centers) will participate as investigators in this clinical trial.

10.1.5. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

10.1.6. Final Report Signature

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

The CSR coordinating investigator will be selected by the sponsor. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

10.2. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the 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.

10.2.1. Data Capture System

An electronic data capture system and an electronic source system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system. Some or all of a patient's data will be directly entered into the eCRF at the time that the information is obtained. In instances where direct data entry is not used, the site will maintain source documentation in the trial files, and the patient's data will be transcribed into the eCRF. Paper documentation provided by the patient will serve as the source document, including a SDAL, that will be identified and documented by each site in that site's study file.

In this study, patient-rated scales/questionnaires will be collected at office visits (and at home) directly via an electronic patient-reported outcome (ePRO) tablet device as part of an ePRO/Clinical Outcome Assessment (COA) system. Data entered into the ePRO/COA system will serve as the source data.

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

Any data collected within the ePRO instrument will serve as the source data and will be identified and documented by each site in that site's study file.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

10.3. Study and Site Closure

10.3.1. Discontinuation of Study Sites

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

10.3.2. Discontinuation of the Study

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

11. References

- [AAD] American Academy of Dermatology Work Group, Menter A, Korman NJ, Elmetts CA, Feldman SR, Gelfand JM, Gordon KB, Gottlieb A, Koo JY, Lebwohl M, Leonardi CL, Lim HW, Van Voorhees AS, Beutner KR, Ryan C, Bhushan R. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. *J Am Acad Dermatol*. 2011;65(1):137-174.
- [APA] American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-IV). 4th Ed. Washington DC: APA;1994.
- Andreassi L, Bilenchi R. Non-infectious inflammatory genital lesions. *Clin Dermatol*. 2014;32(2):307-314.
- Barchino-Ortiz L, Suárez-Fernández R, Lázaro-Ochaita P. Vulvar inflammatory dermatoses. *Actas Dermosifiliogr*. 2012;103(4):260-275.
- Basra MKA, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol*. 2008;159(5):997-1035.
- Bissonnette R, Nigen S, Bolduc C. Efficacy and tolerability of topical tacrolimus ointment for the treatment of male genital psoriasis. *J Cutan Med Surg*. 2008;12(5):230-234.
- Buechner SA. Common skin disorders of the penis. *BJU Int*. 2002;90(5):498-506.
- [CDA] Canadian Dermatology Association. Canadian guidelines for the management of plaque psoriasis. June 2009. Available at: <http://www.dermatology.ca/wp-content/uploads/2012/01/cdnpsoriasisguidelines.pdf>. Accessed: October 1, 2015.
- Cosentyx [package insert]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; 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 November 09, 2015.
- Farber EM, Nall L. Genital psoriasis. *Cutis*. 1992;50(4):263-266.
- Fouéré S, Adjadj L, Pawin H. How patients experience psoriasis: results from a European survey. *J Eur Acad Dermatol Venereol*. 2005;19(suppl 3):2-6.
- Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. *Dermatologica*. 1978;157(4):238-244.
- Greaves MW, Weinstein GD. Treatment of psoriasis. *N Engl J Med*. 1995;332(9):581-588.
- Griffiths CE, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, Cameron GS, Erickson J, Zhang L, Secrest RJ, Ball S, Braun DK, Osuntokun OO, Heffernan MP, Nickoloff BJ, Papp K; UNCOVER-2 and UNCOVER-3 investigators. Comparison of ixekizumab with etanercept

- or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet*. 2015;386(9993):541-551.
- Guglielmetti A, Conlledo R, Bedoya J, Ianiszewski F, Correa J. Inverse psoriasis involving genital skin folds: successful therapy with dapsone. *Dermatol Ther (Heidelb)*. 2012;2(1):15.
- [ISSVD] International Society for the Study of Vulvovaginal Disease (ISSVD) Patient Information Committee. Revised 2014. Available at: <http://issvd.org/wordpress/wp-content/uploads/2014/12/VULVAR-PSORIASIS.pdf>. Accessed October 1, 2015.
- Jemec GB, Baadsgaard O. Effect of cyclosporine on genital psoriasis and lichen planus. *J Am Acad Dermatol*. 1993;29(6):1048-1049.
- Krueger JG, Fretzin S, Suárez-Fariñas M, Haslett PA, Phipps KM, Cameron GS, McColm J, Katcherian A, Cueto I, White T, Banerjee S, Hoffman RW. IL-17A is essential for cell activation and inflammatory gene circuits in subjects with psoriasis. *J Allergy Clin Immunol*. 2012;130(1):145-154.
- Linden KG, Weinstein GD. Psoriasis: current perspectives with an emphasis on treatment. *Am J Med*. 1999;107(6):595-605.
- Martín Ezquerro G, Sánchez Regaña M, Herrera Acosta E, Umbert Millet P. Topical tacrolimus for the treatment of psoriasis on the face, genitalia, intertriginous areas and corporal plaques. *J Drugs Dermatol*. 2006;5(4):334-346.
- Mason A, Mason J, Cork M, Hancock H, Dooley G. Topical treatments for chronic plaque psoriasis: an abridged Cochrane systematic review. *J Am Acad Dermatol*. 2013;69(5):799-807.
- Meeuwis KA, de Hullu JA, de Jager ME, Massuger LF, van de Kerkhof PC, van Rossum MM. Genital psoriasis: a questionnaire-based survey on a concealed skin disease in the Netherlands. *J Eur Acad Dermatol Venereol*. 2010;24(12):1425-1430.
- Meeuwis KA, de Hullu JA, Massuger LF, van de Kerkhof PC, van Rossum MM. Genital psoriasis: a systematic literature review on this hidden skin disease. *Acta Derm Venereol*. 2011(a);91(1):5-11.
- Meeuwis KA, de Hullu JA, van de Nieuwenhof HP, Evers AW, Massuger LF, van de Kerkhof PC, van Rossum MM. Quality of life and sexual health in patients with genital psoriasis. *Br J Dermatol*. 2011(b);164(6):1247-1255.
- Meeuwis KA, van de Kerkhof PC, Massuger LF, de Hullu JA, van Rossum MM. Patients' experience of psoriasis in the genital area. *Dermatology*. 2012;224(3):271-276.
- Meeuwis KA, de Hullu JA, Inthout J, Hendriks IM, Sparreboom EE, Massuger LF, van de Kerkhof PC, van Rossum MM. Genital psoriasis awareness program: physical and psychological care for patients with genital psoriasis. *Acta Derm Venereol*. 2015;95(2):211-216.
- 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.

- Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, Gottlieb A, Koo JY, Lebwohl M, Lim HW, Van Voorhees AS, Beutner KR, Bhushan R, American Academy of Dermatology. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *J Am Acad Dermatol*. 2009;60(4):643-659.
- Puel A, Cypowyj S, Bustamante J, Wright JF, Liu L, Lim HK, Migaud M, Israel L, Chrabieh M, Audry M, Gumbleton M, Toulon A, Bodemer C, El-Baghdadi J, Whitters M, Paradis T, Brooks J, Collins M, Wolfman NM, Al-Muhsen S, Galicchio M, Abel L, Picard C, Casanova JL. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science*. 2011;332(6025):65-68.
- Puig L. PASI90 response: the new standard in therapeutic efficacy for psoriasis. *J Eur Acad Dermatol Venereol*. 2015;29(4):645-648.
- Rallis E, Nasiopoulou A, Kouskoulis C, Roussaki-Schulze A, Koumantaki E, Karpouzis A, Arvanitis A. Successful treatment of genital and facial psoriasis with tacrolimus ointment 0.1%. *Drugs Exp Clin Res*. 2005;31(4):141-145.
- Ryan C, Korman NJ, Gelfand JM, Lim HW, Elmets CA, Feldman SR, Gottlieb AB, Koo JY, Lebwohl MG, Leonardi CL, Van Voorhees AS, Bhushan R, Menter A. Research gaps in psoriasis: opportunities for future studies. *J Am Acad Dermatol*. 2014;70(1):146-167.
- Ryan C, Sadlier M, De Vol E, Patel M, Lloyd AA, Day A, Lally A, Kirby B, Menter A. Genital psoriasis is associated with significant impairment in quality of life and sexual functioning. *J Am Acad Dermatol*. 2015;72(6):978-983.
- Scott LJ, Dunn CJ, Goa KL. Calcipotriol ointment. A review of its use in the management of psoriasis. *Am J Clin Dermatol*. 2001;2(2):95-120.
- SF-36 Health Survey Update page. SF-36 web site. Available at: <http://www.sf-36.org/tools/sf36.shtml>. Accessed October 1, 2015.
- Stern RS. Genital tumors among men with psoriasis exposed to psoralens and ultraviolet A radiation (PUVA) and ultraviolet B radiation. The Photochemotherapy Follow-up Study. *N Engl J Med*. 1990;322(16):1093-1097.
- Stern RS, Laird N. The carcinogenic risk of treatments for severe psoriasis. Photochemotherapy Follow-up Study. *Cancer*. 1994;73(11):2759-2764.
- Stern RS, Bagheri S, Nichols K; PUVA Follow Up Study. The persistent risk of genital tumors among men treated with psoralen plus ultraviolet A (PUVA) for psoriasis. *J Am Acad Dermatol*. 2002;47(1):33-39.
- University of Pittsburgh. IDS/QIDS resource page. Available at: <http://www.ids-qids.org/>. Accessed October 1, 2015.
- Van Voorhees A, Feldman SR, Koo JYM, Lebwohl MG, Menter A. The psoriasis and psoriatic arthritis pocket guide. Portland: National Psoriasis Foundation; 2009.
- Weichert GE. An approach to the treatment of anogenital pruritus. *Dermatol Ther*. 2004;17(1):129-133.

Welsh BM, Berzins KN, Cook KA, Fairley CK. Management of common vulval conditions. *Med J Aust.* 2003;178(8):391-395.

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BCG	Bacillus Calmette-Guérin
BP	blood pressure
BSA	body surface area
blinding/masking	<p>A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, site level blinding will remain in effect until final database lock is complete.</p> <p>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.</p>
CEC	Clinical Events Committee
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
cGMP	current Good Manufacturing Practices
COA	Clinical Outcome Assessment
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
eCRF	electronic case report form: printed or electronic form for recording study participants' data during a clinical study, as required by the protocol

CRP	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.
CSR	clinical study report
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
ETV	early termination visit
FEAE	follow-up emergent adverse event
GCP	good clinical practice
GPSIS	Genital Psoriasis Sexual Impact Scale
GPSS	Genital Psoriasis Symptom Scale
HBcAb+	anti-hepatitis B core antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IL-17A	interleukin-17A
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	institutional review board

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.
IWRS	interactive web-response system
LTBI	latent tuberculosis infection
LOCF	last observation carried forward
LS	least-square
mBOCF	modified baseline observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mGPASI	modified Genital PASI
MI	myocardial infarction
MMRM	mixed-effects model for repeated measures
NAb	neutralizing anti-drug antibody
NRI	nonresponder imputation
NRS	numeric rating scale
PASI	Psoriasis Area and Severity Index
PASI 75	75% reduction in PASI from baseline
PK	pharmacokinetics
PPD	purified protein derivative
PPS	per-protocol set: The set of data generated by the subset of patients who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PRO/ePRO	patient-reported outcome/electronic patient-reported outcome
PT	preferred term
PUVA	psoralen and ultraviolet A
Q2W	every 2 weeks
Q4W	every 4 weeks
QIDS-SR16	Quick Inventory of Depressive Symptomatology–Self Report (16 items)

QTc	corrected QT interval
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
SDAL	study drug administration log
SF-36	Short-Form (36) Health Survey
SFQ	Sexual Frequency Questionnaire
SOC	system organ class
sPGA	static Physician Global Assessment
SUSARs	suspected unexpected serious adverse reactions
TB	tuberculosis
TBL	total bilirubin level
TE-ADA+	treatment-emergent positive anti-drug antibody
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
UVB	ultraviolet B
WBC	white blood cell

Appendix 2. Schedule of Activities

Schedule of Activities, Protocol I1F-MC-RHBQ

CRF Visit (V) Number	Screening		Baseline Randomization	Blinded Treatment Period (Period 2)				
	V1	V1	V2	V3	V4	V5	V6	V7
Weeks since Randomization			W0	W1	W2	W4	W8	W12
Study Days	-30 to -7 d	V1A: 2-3 d post-V1	1	7 ± 2d	14 ± 2d	28 ± 2d	56 ± 2d	84 ± 4d
Informed consent	X							
Complete medical history	X							
Demographics ^a	X							
Sociodemographics ^b			X					X
Physical examination ^c	X		X					X
Perianal/gluteal cleft characteristics examination	X		X					X
Inclusion/exclusion criteria ^d	X		X					
Body temperature			X					
Height			X					
Weight			X					X
Waist circumference			X					
Vital signs (BP and pulse)	X		X ^e	X	X	X	X	X ^e
Consumption habits ^f			X					
Concomitant medications	X		X	X	X	X	X	X
Review preexisting conditions/AEs			X	X	X	X	X	X
Randomization			X					
Administer IP on site			X					X

CRF Visit (V) Number	Screening		Baseline Randomization	Blinded Treatment Dosing Period (Period 2)				
	V1		V2	V3	V4	V5	V6	V7
Weeks since Randomization			W0	W1	W2	W4	W8	W12
Study Days	-30 to -7 d	V1A: 2-3 d post-V1	1	7 ± 2d	14 ± 2d	28 ± 2d	56 ± 2d	84 ± 4d
Dispense IP			X		X	X	X	X
Provide SDALg			X		X	X	X	X
Collect, review, and enter data from SDAL			X		X	X	X	X
Review e-diary				X	X	X	X	X
Dispense e-diary (includes GPSS, GPSIS, and SFQ)	X							
Collect e-diary								X
Clinical Efficacy/Health Outcomes								
sPGA (overall)	X		X	X	X	X	X	X
sPGA of Genitalia ^h	X		X	X	X	X	X	X
PASI (overall)	X		X	X	X	X	X	X
mGPASI ⁱ	X		X	X	X	X	X	X
BSA	X		X ^j	X	X	X ^j	X	X ^j
Fitzpatrick skin type			X					
GPSS ^k	Daily from Screening (V1) to Week 12 (V7)							X
GPSIS ^k	Weekly from Screening (V1) to Week 12 (V7)							X
SFQ ^k	Weekly from Screening (V1) to Week 12 (V7)							X
PatGA-Genital			X	X	X	X	X	X
Touch avoidance NRS			X		X	X	X	X

CRF Visit (V) Number	Screening		Baseline Randomization	Blinded Treatment Dosing Period (Period 2)				
	V1		V2	V3	V4	V5	V6	V7
Weeks since Randomization			W0	W1	W2	W4	W8	W12
Study Days	-30 to -7 d	V1A: 2-3 d post-V1	1	7 ± 2d	14 ± 2d	28 ± 2d	56 ± 2d	84 ± 4d
SF-36			X					X
DLQI			X		X	X	X	X
QIDS-SR16	X		X					X
CAPP (genital subindex)			X					X
Laboratory Tests								
Administer PPD/QuantiFERON®-TB Gold/T-SPOT®I	X							
Read PPD		X						
Chest x-ray ^m	X							
ECG	X							
HIV/HCV	X							
HBV ⁿ	X		X					X
FSH ^o	X							
Serum pregnancy test ^p	X							
Urine pregnancy test ^q			X			X	X	X
Serum chemistry	X		X			X		X
Lipid panel ^r			X			X		X
Hematology	X		X			X		X
TSH and free T4	X							

	Screening		Baseline Randomization	Blinded Treatment Dosing Period (Period 2)				
CRF Visit (V) Number	V1		V2	V3	V4	V5	V6	V7
Weeks since Randomization			W0	W1	W2	W4	W8	W12
Study Days	-30 to -7 d	V1A: 2-3 d post-V1	1	7 ± 2d	14 ± 2d	28 ± 2d	56 ± 2d	84 ± 4d
Genetic biomarker exploratory storage samples (DNA) ^S			X ^t					
Nonpharmacogenetic biomarker exploratory storage samples (serum, plasma, mRNA) ^S			X		X	X		X
Immunogenicity testing ^{S,u}			X		X	X		X
PK sample (trough) ^{S,v}			X		X	X		X
<i>Candida</i> skin swab ^w			X					

	Open-Label Treatment (Period 3)					ETV	Post-Treatment Follow-Up (Period 4) ^x		
							Required Follow-Up Visits	As-Needed Follow-Up Visits	
CRF Visit (V) Number	V8	V9	V10	V11	V12	ETVy	V801	V802	V803 ^z and onward
Weeks since Randomization	W16	W24	W28	W40	W52		LV + 4W	LV + 12W	LV + 24W
Study Days	112 ± 7d	168 ± 7d	196 ± 7d	280 ± 7d	364 ± 7d				
Sociodemographics ^b					X	X			
Physical examination ^c		X		X	X	X			
Perianal/gluteal cleft characteristics examination		X			X	X			
Weight					X	X			
Waist circumference					X	X			
Vital signs (BP and pulse)	X	X	X	X	X	X			
Concomitant medications	X	X	X	X	X	X			
Review preexisting conditions /AEs	X	X	X	X	X	X			
Dispense IP	X	X	X	X					
Provide SDAL ^g	X	X	X	X					
Collect, review, and enter data from SDAL	X	X	X	X	X	X			

	Open-Label Treatment (Period 3)					ETV	Post-Treatment Follow-Up (Period 4) ^x		
							Required Follow-Up Visits		As-Needed Follow-Up Visits
CRF Visit (V) Number	V8	V9	V10	V11	V12	ETVY	V801	V802	V803 ^z and onward
Weeks since Randomization	W16	W24	W28	W40	W52		LV + 4W	LV + 12W	LV + 24W
Study Days	112 ± 7d	168 ± 7d	196 ± 7d	280 ± 7d	364 ± 7d				
Review e-diary						X			
Collect e-diary						X			
Clinical Efficacy/Health Outcomes									
sPGA (overall)	X	X	X	X	X	X			
sPGA of Genitalia ^h	X	X	X	X	X	X			
PASI (overall)	X	X	X	X	X	X			
mGPASI ⁱ	X	X	X	X	X	X			
BSA	X	X ^j	X	X	X ^j	X ^j			
GPSS ^k	X	X	X	X	X	X			
GPSIS ^k	X	X	X	X	X	X			
SFQ ^k	X	X	X	X	X	X			
Touch avoidance NRS	X	X	X	X	X	X			
SF-36					X	X			
PatGA-Genital	X	X	X	X	X	X			

	Open-Label Treatment (Period 3)					ETV	Post-Treatment Follow-Up (Period 4) ^x		
							Required Follow-Up Visits		As-Needed Follow-Up Visits
CRF Visit (V) Number	V8	V9	V10	V11	V12	ETVy	V801	V802	V803 ^z and onward
Weeks since Randomization	W16	W24	W28	W40	W52		LV + 4W	LV + 12W	LV + 24W
Study Days	112 ± 7d	168 ± 7d	196 ± 7d	280 ± 7d	364 ± 7d				
DLQI	X	X	X	X	X	X			
QIDS-SR16		X		X	X	X			
CAPP (genital subindex)					X	X			
Laboratory Tests									
HBV ⁿ			X	X	X			X	
Urine pregnancy test ^q	X	X	X	X	X	X			
Serum chemistry	X		X	X	X	X	X	X	X
Hematology	X		X	X	X	X	X	X	X
Lipid panel ^r			X	X	X	X			
Nonpharmacogenetic biomarker exploratory storage samples (serum, plasma, mRNA) ^s					X	X			
Immunogenicity testing ^{s,u}		X			X		X	X	
PK sample (trough) ^{s,v}		X			X		X	X	

Abbreviations: AE = adverse event; BP = blood pressure; BSA = body surface area; CAPP = Comprehensive Assessment of the Psoriasis Patient; CRF = case report form; d = days; DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ETV = early termination visit; FSH = follicle-stimulating hormone; GPSS = Genital Psoriasis Symptoms Scale; GPSIS = Genital Psoriasis Sexual Impact Scale; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IP = investigational product; LV= last visit; mRNA = messenger ribonucleic acid; mGPASI = modified Genital PASI; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PatGA-Genital = Patient's Global Assessment of Genital Psoriasis; PK = pharmacokinetic; PPD = purified protein derivative; QIDS-SR16 = Quick Inventory of Depressive Symptomatology–Self Report (16 items); SDAL = Study Drug Administration Log; SFQ = Sexual Function Questionnaire; sPGA = static Physician's Global Assessment; T4 = thyroxine; TB = tuberculosis; TSH = thyroid stimulating hormone; V = study visit; W = study week.

- a Demographics includes recording of year of birth, gender, ethnicity, and race.
- b Sociodemographics includes recording information on marital and sexual partner status.
- c One complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed at screening. All physical examinations throughout the study should include a symptom directed physical as well as examination of heart, lungs, abdomen, and visual examination of the skin.
- d Patients who test positive for latent TB at screening may be rescreened (Section 8.4.5). Additionally, patients who do not qualify at screening under exclusion criteria [34, 38, 39, 50] may be rescreened (1 time) as described in Section 5.3.
- e At baseline (Week 0) and Visit 7 (Week 12), BP and pulse should be measured prior to administration of the investigational product and again approximately 1 hour post-administration.
- f Habits include recording of caffeine, alcohol, and tobacco consumption.
- g Patients will record information including the date, time, and location of administration of investigational product (for treatment compliance), syringe number, who administered the investigational product, and the reason if investigational product was not fully administered in the SDAL.
- h As part of sPGA of Genitalia, the investigator will record on the eCRF (yes/no) whether psoriasis is present in women on labia minora, labia majora, and/or perineum and in men on penis (glans and/or shaft), scrotum, and/or perineum.
- i As part of mGPASI, the investigator will record on the eCRF (yes/no) if fissure, erosion, and/or ulcer are present in the genital area (defined as labia minora, labia majora, perineum for female patients and on the penis, scrotum, perineum for male patients).
- j As part of BSA, the investigator will record if psoriasis is present on the face, inframammary fold, axilla, scalp, nail, pubis, perianal region, gluteal cleft, and inguinal creases in the eCRF (yes/no) at baseline (Week 0), Week 4, 12, 24, 52, or ETV.
- k Patients should complete the scales in the following order: 1. GPSS, 2. GPSIS, and 3. SFQ. An e-diary will be used to collect these PROs up to and including Week 12 (V7); thereafter, patients will answer these questions only at scheduled study visits. At Week 12 (V7), patients will complete these scales on site before completion of any other assessments.
- l See Section 8.4.5 for detailed description of QuantiFERON®-TB Gold, T-SPOT®, and PPD testing.
- m A chest x-ray will be taken at screening unless one has been obtained within the past 6 months (provided the x-ray and/or report are available for review).
- n All patients will be tested for HBV at screening. Patients who are HBsAg+ at screening are excluded. Patients who are HBcAb+ at screening, regardless of other HBsAb status, will have serum HBV DNA obtained to be analyzed by the central laboratory. Patients that are found to be HBV DNA positive (detectable) at screening will be excluded from the trial. Patients that are HBcAb+ at screening and HBV DNA negative (undetectable) may be enrolled into the study with required HBV DNA monitoring every 3 to 4 months as outlined above in the Schedule of Activities during treatment and 12 weeks after the last dose of ixekizumab. If the result of the HBV DNA testing is positive, the patient must be discontinued from the study treatment, should continue safety follow up, and should receive appropriate follow-up medical care (refer to Section 8.4.8.2 for further information regarding the timing of discontinuation).

- o FSH test performed for women ≥ 40 and < 60 years of age who have had a cessation of menses for at least 12 months to confirm nonchildbearing potential (≥ 40 mIU/mL). FSH test will be performed centrally.
- p To be performed for females of childbearing potential only. Serum pregnancy test will be done at Visit 1 only and will be performed centrally.
- q To be performed for females of childbearing potential only. Patients will undergo urine pregnancy self-testing at home on a monthly basis during periods between scheduled visits through Week 52. During these intervisit periods, the site must call the patient each month to obtain her pregnancy test results. Additional urine pregnancy testing can be performed at the investigator's discretion. Patients determined to be pregnant will be discontinued from treatment and will no longer be administered investigational product (see Section 7.1).
- r For the fasting lipid profile patients should not eat or drink anything except water for 12 hours prior to test. (For ETV: [1] If ETV is planned, then fasting lipid profile should be performed, and [2] if ETV is not planned and patient is not fasting, the lipid profile should not be performed.)
- s Samples will be collected as allowed by local regulations.
- t If the DNA sample is not collected at Visit 2 (Week 0), it can be collected at Visit 3 (Week 4).
- u Immunogenicity samples may also be analyzed for ixekizumab serum concentration to facilitate in the interpretation of the immunogenicity data. In addition, a blood sample will be collected, when possible, for any patient who experiences a potential systemic allergic/hypersensitivity reaction during the study as judged by the investigator (Section 8.4.6).
- v PK samples will be collected prior to administration of investigational product (Section 8.5).
- w Swab from labia majora for women and glans penis for men.
- x All patients receiving investigational product must enter into Period 4 and complete through Visit 802. Patients may be followed beyond Visit 802 for continued monitoring of their neutrophil counts or for other safety reasons.
- y If a patient discontinues study treatment early, the patient will complete the ETV and then enter the Post-Treatment Follow-Up Period.
- z This visit will only occur if a patient's neutrophil counts have not returned to the criteria defined in Section 8.4.8.1. or for other safety reasons.

Appendix 3. Clinical Laboratory Tests

Hematology^{a,b}

Hemoglobin
 Hematocrit
 Erythrocyte count (RBC)
 Mean cell volume (MCV)
 Mean cell hemoglobin concentration (MCHC)
 Leukocytes (WBC)
 Platelets

Absolute counts of:

Neutrophils, segmented
 Neutrophils, juvenile (bands)
 Lymphocytes
 Monocytes
 Eosinophils
 Basophils

Other Tests^a

Human immunodeficiency virus antibody (HIV)^c
 Hepatitis B Surface antigen (HBsAg)^{d,e}
 Anti-Hepatitis B Surface antibody (HBsAb)^{d,e}
 Anti-Hepatitis B Core antibody (HBcAb)^{d,e}
 Anti-Hepatitis C antibody^{c,d}
 HBV DNA^{c,f}
 Thyroid-stimulating hormone (TSH) and Free T4
 Ixekizumab serum concentration
 Exploratory storage samples (serum, plasma, DNA, & mRNA)

Purified Protein Derivative (PPD)^g

Serum Chemistry^{a,b}

Sodium
 Potassium
 Bicarbonate
 Chloride
 Phosphorus
 Total bilirubin
 Direct bilirubin
 Alkaline phosphatase
 Alanine aminotransferase (ALT/SGPT)
 Aspartate aminotransferase (AST/SGOT)
 Blood urea nitrogen (BUN)
 Uric acid
 Creatinine
 Calcium
 Glucose
 Albumin
 Cholesterol (total)
 Total protein

Triglycerides
 Gamma-Glutamyl Transferase (GGT)

Lipid Panel^{a,h}

Low Density Lipoprotein (LDL-C)
 High Density Lipoprotein (HDL)
 Very Low Density Lipoprotein (VLDL)

Pregnancy Test (serum and urine)ⁱ

Follicle-stimulating hormone (FSH)^j

Clinical Safety Laboratory Tests

Abbreviations: Ab = antibody; DNA = deoxyribonucleic acid; HBcAb = anti-hepatitis B core antibody; HBsAb = anti-hepatitis B surface antibody; HBsAb+ = positive for anti-hepatitis B surface antibody; HBsAg- = negative for hepatitis B surface antigen; HBV = hepatitis B virus; LDL-C = low density lipoprotein calculated; mRNA = messenger ribonucleic acid; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; T4 = thyroxine; TB = tuberculosis; WBC = white blood cells.

- a Assayed by sponsor-designated laboratory.
- b Unscheduled blood chemistry and hematology panels may be performed at the discretion of the investigator.
- c See exclusion criteria (Section 5.2).
- d Test required at Visit 1 only to determine eligibility of patient for the study.
- e Quantitative HBsAb testing will be done in those patients who are HBsAg-, HBcAb+, and HBsAb+ at screening.
- f Refer to hepatitis B monitoring (Section 8.4.8.2).
- g In countries where the QuantiFERON®-TB Gold test or T-SPOT® is available, it may be used instead of the PPD TB test and may be performed locally.
- h For the fasting lipid profile patients should not eat or drink anything except water for 12 hours prior to test.
- i Serum pregnancy test (women <60 years of age who are still of childbearing potential) and urine pregnancy test (women of childbearing potential). Patients will undergo urine pregnancy self-testing at home on a monthly basis during periods between scheduled visits until Week 52. During these intervisit periods, the site must call the patient each month to obtain her pregnancy test results. Additional urine pregnancy testing can be performed at the investigator's discretion. Patients determined to be pregnant will be discontinued from treatment and will no longer be administered investigational product (see Section 7.1).
- j Women ≥40 and <60 years of age who have had a cessation of menses for ≥12 months will have an FSH test confirming nonchildbearing potential (≥40 mIU/mL). FSH test will be performed centrally.

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

Hemoglobin
Hematocrit
RBC
WBC
Neutrophils, segmented
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets

Hepatic Chemistry^a

Total bilirubin
Direct bilirubin
Alkaline phosphatase
ALT
AST
GGT
CPK

Haptoglobin^a

Hepatic Coagulation^a

Prothrombin Time
Prothrombin Time, INR

Hepatic Serologies^{a,b}

Hepatitis A antibody, total
Hepatitis A antibody, IgM
Hepatitis B surface antigen
Hepatitis B surface antibody
Hepatitis B Core antibody
Hepatitis C antibody
Hepatitis E antibody, IgG
Hepatitis E antibody, IgM

Anti-nuclear antibody^a

Alkaline Phosphatase Isoenzymes^a

Anti-smooth muscle antibody (or anti-actin antibody)^a

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; CPK = creatine phosphokinase; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; RBC = erythrocyte count; WBC = leukocytes.

^a Assayed by Lilly-designated or local laboratory.

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

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