

Protocol IIF-MC-RHCR (b)

A 24-Week Multicenter, Randomized, Double-Blind, Parallel-Group Study Comparing the Efficacy and Safety of Ixekizumab to Guselkumab in Patients with Moderate-to-Severe Plaque Psoriasis

NCT03573323

Approval Date: 07-Dec-2018

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Ixekizumab (LY2439821)

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Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 07-Dec-2018 GMT

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## 1. Synopsis

### Title of Study:

A 24-week multicenter, randomized, double-blind, parallel-group study comparing the efficacy and safety of ixekizumab to guselkumab in patients with moderate-to-severe plaque psoriasis.

### Rationale:

In early studies of biologics targeting the tumor necrosis factor (TNF) pathway to treat patients with chronic plaque psoriasis (hereafter, Ps), significant clinical improvement was obtained at a 75% clearance of skin from baseline (Psoriasis Activity and Severity Index; PASI 75). Newer biologics targeting the interleukin (IL)-17 or IL-23 immune pathway have raised the level of expected improvement to almost clear (at least a 90% improvement from baseline in PASI score; PASI 90) or completely clear (a 100% improvement from baseline in PASI score; PASI 100) skin, and studies suggest that this improvement is attainable in a high proportion of patients (Papp et al. 2005; Reich et al. 2005; Leonardi et al. 2008; Menter et al. 2008; Papp et al. 2008; Langley et al. 2014; Griffiths et al. 2015; Krueger et al. 2015; Lebwohl et al. 2015; Papp et al. 2015; Blauvelt et al. 2017; Reich et al. 2017).

As new drugs targeting these pathways come to the market, there is a need to directly compare the efficacy and safety, as well as rapidness of efficacy, between products to better inform dermatologists and patients regarding drug selection.

Study I1F-MC-RHCR (RHCR) is a 24-week study to compare the efficacy and safety, as well as rapidness of efficacy, between ixekizumab and guselkumab in patients with moderate-to-severe Ps. The primary efficacy endpoint of this trial is the percentage of patients reaching 100% improvement from baseline (complete clearance) in PASI score, as demonstrated by PASI 100 at Week 12.

### Objective(s)/Endpoints:

Objectives	Endpoints
<b>Primary</b> To assess whether ixekizumab is superior to guselkumab at Week 12 in the treatment of patients with moderate-to-severe Ps, as measured by PASI 100	<ul style="list-style-type: none"> <li>The proportion of patients achieving PASI 100 at Week 12</li> </ul>
<b>Major Secondary</b> To assess whether ixekizumab is superior to guselkumab in the treatment of patients with moderate-to-severe Ps at different time points, as measured by: <ul style="list-style-type: none"> <li>PASI 75</li> </ul>	<ul style="list-style-type: none"> <li>The proportion of patients achieving PASI 75 at Week 2</li> </ul>
<ul style="list-style-type: none"> <li>PASI 90</li> </ul>	<ul style="list-style-type: none"> <li>The proportion of patients achieving PASI 90 at Weeks 4 and 8</li> </ul>
<ul style="list-style-type: none"> <li>PASI 100</li> </ul>	<ul style="list-style-type: none"> <li>The proportion of patients achieving PASI 100 at Weeks 4, 8 and 24</li> </ul>

Objectives	Endpoints
<ul style="list-style-type: none"> <li>• Static Physician Global Assessment score of 0 (sPGA [0])</li> </ul>	<ul style="list-style-type: none"> <li>• The proportion of patients achieving sPGA (0) at Week 12</li> </ul>
<ul style="list-style-type: none"> <li>• PASI 50</li> </ul>	<ul style="list-style-type: none"> <li>• The proportion of patients achieving PASI 50 at Week 1</li> </ul>

Abbreviations: PASI = Psoriasis Area and Severity Index; Ps = plaque psoriasis; sPGA = Static Physician Global Assessment.

**Summary of Study Design:**

Study RHCR is a multicenter, randomized, double-blind, parallel-group Phase 4 study with 4 study periods in patients with chronic moderate-to-severe Ps.

**Treatment Groups and Duration:**

There are 2 treatment groups in this study. Patients will be randomized at Week 0 to receive either:

- (i) Ixekizumab: 80 mg subcutaneous (SC) injection. At Week 0, 160 mg starting dose (two 80 mg injections), followed by 80 mg every 2 weeks (Q2W) from Weeks 2 through 12, and then followed by 80 mg every 4 weeks (Q4W) thereafter (i.e., at Weeks 16 and 20).

or

- (ii) Guselkumab: 100 mg SC injection. At Weeks 0 and 4, 100 mg injection, followed by 100 mg every 8 weeks (Q8W) thereafter (i.e., at Weeks 12 and 20).

The study duration for the 4 study periods are: Screening Period (Period 1; up to 28 days); Induction Dosing Period (Period 2; 12 weeks); Extension Period (Period 3; 12 weeks); Post-Treatment Follow-Up Period (Period 4; at least 12 weeks after the date of patients’ early termination visit [ETV] or last regularly scheduled visit).

**Number of Patients:**

Approximately 960 patients are planned to be randomized.

**Statistical Analysis:**

The total sample size for this study will be 960 patients randomized at a 1:1 ratio, stratified by site, into the double-blind Induction Dosing Period (Period 2) to ixekizumab or guselkumab. With 480 patients per treatment group, the study will have approximately 98% power to test the superiority of ixekizumab to guselkumab for PASI 100 at Week 12. The power calculation is based on the assumption of 35.3% and 23.0% response rate at Week 12 for the ixekizumab and guselkumab treatment groups, respectively. A 2-sided Fisher’s exact test at significance level 0.05 is assumed.

For the Induction Dosing Period (Period 2), unless otherwise specified, 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 Cochran-Mantel-Haenszel (CMH) test stratified by pooled site, 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, pooled site, baseline value, visit, treatment-by-visit interaction and baseline value-by-visit as fixed factors. A secondary analysis for continuous efficacy and health outcomes variables will be made using analysis of covariance (ANCOVA) adjusting for pooled site and baseline value.

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

## 2. Schedule of Activities

Table RHCR.2.1. Schedule of Activities

## Screening (Period 1) and Induction Dosing Period (Period 2)

	Screening (Period 1)	Induction Dosing (Period 2)							
		Baseline							
CRF Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9
Study Week		W0	W1	W2	W4	W6	W8	W10	W12
Study Days	-28 to -5 d	0 d	7 ± 1 d	14 ± 1 d	28 ± 3 d	42 ± 3d	56 ± 3 d	70 ± 3 d	84 ± 3d
Informed consent	X								
Complete medical history	X								
Demographics <sup>a</sup>	X								
Physical examination <sup>b</sup>	X								
Weight	X	X							X
Height		X							
Chest x-ray (local) <sup>c</sup>	X								
Inclusion/exclusion criteria <sup>d</sup>	X	X							
Randomization		X							
Concomitant medications	X	X	X	X	X	X	X	X	X
Review preexisting conditions/AEs	X	X	X	X	X	X	X	X	X
Administer study drug <sup>e</sup>		X		X	X	X	X	X	X
Dispense study drug		X		X	X	X	X	X	X
Study drug compliance <sup>f</sup>		X		X	X	X	X	X	X
Dispense Study Drug Administration Log		X		X	X	X	X	X	X
Collect, review, and enter data from Study Drug Administration Log		X		X	X	X	X	X	X

Screening (Period 1) and Induction Dosing Period (Period 2)

	Screening (Period 1)	Induction Dosing (Period 2)							
		Baseline							
CRF Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9
Study Week		W0	W1	W2	W4	W6	W8	W10	W12
Study Days	-28 to -5 d	0 d	7 ± 1 d	14 ± 1 d	28 ± 3 d	42 ± 3d	56 ± 3 d	70 ± 3 d	84 ± 3d
<b>Efficacy Measures</b>									
<i>Clinician-Rated or -Administered Assessments</i>									
PASI	X	X	X	X	X	X	X	X	X
BSA	X	X	X	X	X	X	X	X	X
sPGA	X	X	X	X	X	X	X	X	X
C-SSRS Baseline	X								
C-SSRS Since Last Visit		X	X	X	X	X	X	X	X
Self-Harm Supplement Form and Self-Harm Follow-Up Form	X	X	X	X	X	X	X	X	X
Physician Global Assmt Disease Activity VAS <sup>g</sup>		X							X
PGA-F		X							
<i>Patient-Rated Assessments</i>									
Itch NRS	X	X	X	X	X	X	X	X	X
Skin Pain VAS	X	X	X	X	X	X	X	X	X
DLQI		X		X	X	X	X		X
PatGA		X	X	X	X	X	X	X	X
Patient Assmt of Pain VAS <sup>h</sup>		X							X
Patient Global Assmt Disease Activity VAS <sup>h</sup>		X							X
<b>Laboratory Tests</b>									
Administer QuantiFERON <sup>®</sup> -TB Gold <sup>i</sup>	X								
FSH <sup>j</sup>	X								
HIV/HCV	X								
HBV <sup>k</sup>	X	X							X
Serum pregnancy test <sup>l</sup>	X								
Urine pregnancy test <sup>m</sup>		X			X		X		X
Serum chemistry	X	X							X
Hematology	X	X			X				X
Urinalysis	X	X							
Immunogenicity testing <sup>n</sup>		X							

**Extension Period (Period 3) and Post Treatment Follow-Up Period (Period 4)**

	Extension (Period 3)				Post Treatment Follow-Up (Period 4)		
CRF Visit Number	V10	V11	V12	ETV	V801	V802	V803
Study Week	W16	W20	W24		LV + W4	LV + W12	LV + W24
Study Days	112 ± 5 d	140 ± 5 d	168 ± 5 d		± 4 d	± 4 d	± 4 d
Weight			X	X			
Concomitant medications	X	X	X	X	X	X	X
Review preexisting conditions/AEs	X	X	X	X	X	X	X
Administer study drug <sup>e</sup>	X	X					
Dispense study drug	X	X					
Study drug compliance <sup>f</sup>	X	X					
Dispense Study Drug Administration Log	X	X					
Collect, review, and enter data from Study Drug Administration Log	X	X	X	X			
<b>Efficacy Measures</b>							
<i>Clinician-Rated or -Administered Assessments</i>							
PASI	X	X	X	X			
BSA	X	X	X	X			
sPGA	X	X	X	X			
C-SSRS Since Last Visit	X	X	X	X	X	X	X
Self-Harm Supplement Form and Self-Harm Follow-Up Form	X	X	X	X	X	X	X
Physician Global Assmt Disease Activity VAS <sup>g</sup>			X	X			
PGA-F			X	X			
<i>Patient-Rated Assessments</i>							
Itch NRS	X	X	X	X			
Skin Pain VAS	X	X	X	X			
DLQI	X		X	X			
PatGA	X	X	X	X			
Patient Assmt of Pain VAS <sup>h</sup>			X	X			
Patient Global Assmt Disease Activity VAS <sup>h</sup>			X	X			
<b>Laboratory Tests</b>							
HBV <sup>k</sup>			X	X		X	
Urine pregnancy test <sup>m</sup>	X	X	X	X			
Serum chemistry			X	X			
Hematology	X		X	X	X	X	X

Abbreviations: AE = adverse event; BSA = body surface area; CRF = case report form; C-SSRS = Columbia- Suicide Severity Rating Scale; d = day; DLQI = Dermatology Life Quality Index; ETV = early termination visit; FSH= follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV



= human immunodeficiency virus; LV = last visit; NRS = numeric rating scale; Patient Assmt of Pain = Patient's Assessment of Pain; Patient Global Assmt Disease Activity = Patient's Global Assessment of Disease Activity; PASI = Psoriasis Area and Severity Index; PatGA = Patient's global assessment of disease severity; PGA-F = Physician's Global Assessment of Fingernail Psoriasis; PK = pharmacokinetics; sPGA = static Physician's Global Assessment; TB = tuberculosis; V = visit; VAS = visual analog scale; W = week.

- a Includes year of birth, gender, and ethnicity.
- b Complete physical at screening (excluding pelvic, rectal, and breast examinations). Physicals should include symptom-directed physical, as well as an examination of heart, lungs, and abdomen, and visual examination of the skin.
- c To be performed if not done in the prior 6 months.
- d Patients who test positive for latent TB at screening may be re screened following appropriate treatment. Additionally, patients who do not qualify at baseline under Exclusion Criterion [34] (active or recent infection) may be re-screened (1 time).
- e See [Table RHCR.7.1](#). All patients should remain under observation for at least 1 hour after study drug administration to monitor safety at Week 0.
- f Designated Unblinded Site Personnel will be responsible for handling and dispensing of all study drugs (ixekizumab, guselkumab, and placebo).
- g Administered only to patients with PsA at the baseline (W0) visit.
- h To be completed only by patients with PsA at the baseline (W0) visit.
- i Patients who test positive for latent TB at screening may be re-screened. QuantiFERON® may be performed by a Lilly-designated or local laboratory. See [Section 9.4.4](#) for detailed description of QuantiFERON®-TB Gold .
- j FSH test performed for women  $\geq 40$  and  $< 60$  years of age who have had a cessation of menses for at least 12 months to confirm non-childbearing potential ( $\geq 40$  mIU/mL).
- k All patients will be tested for HBV at screening. Patient who meet criteria for HBV monitoring (see [Section 9.4.6.3](#)) will be identified by the central laboratory at baseline and monitored according to the study schedule.
- l To be performed for females of childbearing potential only. Additional urine pregnancy testing can be performed at the investigator's decision. Patients determined to be pregnant will be discontinued from treatment and will no longer be administered study drug.
- m To be performed for females of childbearing potential only. Patients determined to be pregnant will be discontinued from treatment and will no longer be administered study drug.
- n To analyze change from baseline, the immunogenicity sample collected at baseline (W0) will be used. For any patient who experiences a potential systemic allergic/hypersensitivity reaction during the study as judged by the investigator, a sample will also be collected when possible to be tested for immunogenicity and PK. Samples from patients treated with guselkumab will not be analyzed for anti guselkumab antibodies. These samples will be discarded at the end of the study.

## 3. Introduction

### 3.1. Study Rationale

In early studies of biologics targeting the tumor necrosis factor (TNF) pathway to treat patients with chronic plaque psoriasis (Ps), significant clinical improvement was obtained at a 75% clearance of skin from baseline (Psoriasis Activity and Severity Index; PASI 75). Newer biologics targeting the interleukin (IL)-17 or IL-23 immune pathway have raised the level of expected improvement to almost clear (at least a 90% improvement from baseline in PASI score; PASI 90) or completely clear (a 100% improvement from baseline in PASI score; PASI 100) skin, and studies suggest this improvement is attainable in a high proportion of patients (Papp et al. 2005; Reich et al. 2005; Leonardi et al. 2008; Menter et al. 2008; Papp et al. 2008; Langley et al. 2014; Griffiths et al. 2015; Krueger et al. 2015; Lebwohl et al. 2015; Papp et al. 2015; Blauvelt et al. 2017; Reich et al. 2017).

As new drugs targeting these pathways come to the market, there is a need to directly compare the efficacy and safety, as well as rapidness of efficacy, between products to better inform dermatologists and patients regarding drug selection.

Study IIF-MC-RHCR (RHCR) is a 24-week study to compare the efficacy and safety, as well as rapidness of efficacy, between ixekizumab and guselkumab in patients with moderate-to-severe Ps. The primary efficacy endpoint of this study is the percentage of patients reaching 100% improvement from baseline (complete clearance) in PASI score, as demonstrated by PASI 100 at Week 12.

### 3.2. Background

Psoriasis is a common, lifelong and life-shortening, chronic inflammatory skin disease manifested by prototypic red, thick, and scaly plaques. Plaque psoriasis is the most common form and has been shown to have a significant impact on the overall health of patients. Along with an association with inflammatory arthritis in the form of psoriatic arthritis (PsA), Ps is associated with increased risk for multiple comorbid conditions, including myocardial infarction (MI) and stroke, metabolic syndrome, diabetes mellitus, chronic renal insufficiency, and liver abnormalities (Yeung et al. 2013). The life span of patients with moderate-to-severe Ps may be shortened by as many as 5 years, partly due to association with comorbidities (Gelfand et al. 2006; Ryan and Kirby 2015).

The worldwide prevalence of Ps is 2% to 3% (Christophers 2001; International Federation of Psoriasis Associations [IFPA] 2017; National Psoriasis Foundation [NPF] 2018). Almost one-third of patients with Ps in the United States (US) suffer from moderate-to-severe disease (Dubin et al. 2003). Certain symptoms, such as itching, can especially impact the quality of life and is detrimental to work productivity and sleep (Zimolag et al. 2009; Gowda et al. 2010; Janowski et al. 2014; Lebwohl et al. 2014).

Early treatments for Ps obtained 50% to 75% improvement in skin clearance; however, expectations for treatment goals of efficacy are expected to be higher as new and more efficacious therapies have emerged. Recent studies of biologics which block the IL-17 or IL-23

pathways, both central to Ps pathogenesis (Leonardi et al. 2012; Langley et al. 2014; Sofen et al. 2014; Gordon et al. 2015; Griffiths et al. 2015; Krueger et al. 2015; Lebwohl et al. 2015; Papp et al. 2015), have demonstrated substantial efficacy. Complete skin clearance and improved long-term efficacy have increasingly become the desired treatment outcomes (Gniadecki et al. 2015; Bartos et al. 2016). Some studies have suggested that increased levels of clearance resulted in greater improvement in quality of life (Takeshita et al. 2014; Vishwanathan et al. 2015; Feldman et al. 2016; Fairchild et al. 2017).

Ixekizumab (LY2439821) is a humanized immunoglobulin G (IgG) subclass 4 monoclonal antibody (MAb) designed and engineered to selectively inhibit 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 the other members of the IL-17 family (IL-17B, IL-17C, IL-17D, IL-17E, or IL-17F).

Ixekizumab has demonstrated efficacy at both short- and long-term time points, with a favorable safety profile (Griffiths et al. 2015, Gordon et al. 2016, Strober et al. 2017). In all 3 pivotal Phase 3 studies (the UNCOVER studies), ixekizumab was superior to placebo with respect to all primary and major secondary endpoints. In the UNCOVER studies, 32% to 42% of patients who received treatment with ixekizumab had complete resolution (PASI 100 or static Physician Global Assessment [sPGA] score of 0; versus [vs.] none in the placebo group) of their Ps at Week 12; high levels of clinical response were maintained with continued exposure to ixekizumab 80 mg Q4W through Week 60 with at least 50% of patients maintaining or attaining PASI 100 (Gordon et al. 2016). In the UNCOVER-2 and UNCOVER-3 studies, ixekizumab had greater efficacy than etanercept, a TNF inhibitor (TNFi); 40.5% of patients treated with ixekizumab 80 mg Q2W, compared with 5.3% of etanercept-treated patients, achieved PASI 100 after 12 weeks (Griffiths et al. 2015, Gordon et al. 2016). In a Phase 3 head-to-head study (IXORA-S), ixekizumab demonstrated superiority over the IL-12/23 antagonist ustekinumab in patients with moderate-to-severe Ps at Week 12; this trend was maintained through Week 52. The majority (76.5%) of ixekizumab-treated patients sustained a PASI 90 response through 1 year, and over half of ixekizumab-treated patients (52.2%) had completely clear skin at Week 52. The corresponding rates for the ustekinumab-treated patients were 59.0% and 35.5%, respectively.

Guselkumab is a fully human IgG subclass 1 lambda monoclonal antibody that binds to the p19 subunit of IL-23; it inhibits the intracellular and downstream signaling of IL-23, which is required for terminal differentiation and survival of T helper (Th)17 cells.

In 2 recent Phase 3 studies, VOYAGE 1 (Blauvelt et al. 2017) and VOYAGE 2 (Reich et al. 2017), guselkumab treatment (administered as a single 100-mg injection initially, 4 weeks later and subsequently every 8 weeks [Q8W]) resulted in statistically significant improvements in efficacy compared with placebo and superiority to adalimumab, a TNFi, in the treatment of moderate-to-severe Ps (Gordon et al. 2018). In the VOYAGE 1 study, compared with placebo, significantly higher proportions of patients taking guselkumab achieved Investigator Global Assessment (IGA; co-primary endpoint) 0/1 (6.9% vs. 85.1%) and PASI 90 (co-primary

endpoint; 2.9% vs. 73.3%) at Week 16. In addition, the proportions achieving IGA 0 (1.1% vs. 47.7%) and PASI 100 (0.6% vs. 37.4%) were significantly higher for guselkumab vs. placebo at Week 16. Compared with adalimumab, a higher proportion of patients in the guselkumab group achieved IGA 0/1 (85.1% vs. 65.9%) and PASI 90 (73.3% vs. 49.7%) at Week 16. Significantly better responses to guselkumab compared with adalimumab were maintained at Week 24 and at Week 48; PASI 100 responses in the guselkumab group were also significantly better than those in the adalimumab group at Weeks 24 and 48. The results of VOYAGE 2 study confirmed the results of VOYAGE 1. Guselkumab was superior to placebo at the Week 16 co-primary endpoints (IGA 0/1 and PASI 90). Guselkumab was also superior to adalimumab at the Week 16 endpoints (IGA 0/1, PASI 75/90) and at Week 24 (IGA 0, PASI 90, and PASI 100).

Adalimumab is one of the earliest biologics approved for Ps and targets the TNF pathway. Guselkumab, being one of the most recent biologics, targets the IL-23 pathway. As the IL-17/23 pathway has been shown to be selectively important in the pathogenesis of Ps (Leonardi et al. 2012; Langley et al. 2014; Sofen et al. 2014; Gordon et al. 2015; Griffiths et al. 2015; Krueger et al. 2015; Lebwohl et al. 2015; Papp et al. 2015), the results of the VOYAGE studies (guselkumab [IL-23p19 antagonist]) are not surprising, nor are the results of the UNCOVER-2 and -3 studies that demonstrated superior efficacy of ixekizumab (IL-17A antagonist) compared to the TNFi etanercept. These studies help inform dermatologists that newer biologics have superior efficacy compared to older biologics targeting the TNF pathway and, thus, are a good choice for treating patients who desire nearly clear or completely clear skin.

To date, there is no publication comparing biologics for the treatment of Ps that inhibit IL-23 (specifically IL-23p19) vs. those that inhibit IL-17; thus expectations of efficacy between these 2 types of new biologics are not well delineated. Studies of ixekizumab suggest equal, if not superior ability compared to guselkumab to achieve PASI 90 (as shown in the VOYAGE studies). Ixekizumab also demonstrated a high percentage of patients achieving PASI 100, and a rapid onset of skin improvement after administration of ixekizumab (UNCOVER). Comparing these 2 classes of biologics in a study, in which both are tested with the same endpoints and measured at the same time, will provide important information to clinicians trying to determine which drug class is the best for a given patient. The purpose of this study is to compare efficacy and safety, as well as rapidness of efficacy, of ixekizumab and guselkumab.

### 3.3. Benefit/Risk Assessment

Ixekizumab has been demonstrated to be safe and effective for the treatment of patients with moderate-to-severe chronic Ps and active PsA. The risk profile for patients within this study is anticipated to be consistent with the known safety experience for ixekizumab described in the currently approved labeling of Taltz® (Taltz package insert, 2018).

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of ixekizumab are found in the Investigator's Brochure (IB). Information on AEs expected to be related to the study drug may be found in Section 6.2 (Development Core Safety Information) of the IB. Information on SAEs that are expected in the study population independent of drug exposure and that will be assessed by the

sponsor in aggregate periodically during the course of the study, may be found in Section 5 (Effects in Humans) of the IB.

The known and expected benefits, risks, and SAEs for guselkumab are outlined in the United States Package Insert (USPI) for Tremfya® (Tremfya USPI package insert, 2017; Canada Product Monograph, 2017).

## 4. Objectives and Endpoints

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

**Table RHCR.4.1. Objectives and Endpoints**

Objectives	Endpoints
<p><b>Primary</b> To assess whether ixekizumab is superior to guselkumab at Week 12 in the treatment of patients with moderate-to-severe Ps, as measured by PASI 100</p>	<ul style="list-style-type: none"> <li>The proportion of patients achieving PASI 100 at Week 12</li> </ul>
<p><b>Major Secondary</b> To assess whether ixekizumab is superior to guselkumab in the treatment of patients with moderate-to-severe Ps at different time points, as measured by:</p> <ul style="list-style-type: none"> <li>PASI 75</li> </ul>	<ul style="list-style-type: none"> <li>The proportion of patients achieving PASI 75 at Week 2</li> </ul>
<ul style="list-style-type: none"> <li>PASI 90</li> </ul>	<ul style="list-style-type: none"> <li>The proportion of patients achieving PASI 90 at Weeks 4 and 8</li> </ul>
<ul style="list-style-type: none"> <li>PASI 100</li> </ul>	<ul style="list-style-type: none"> <li>The proportion of patients achieving PASI 100 at Weeks 4, 8 and 24</li> </ul>
<ul style="list-style-type: none"> <li>sPGA [0]</li> </ul>	<ul style="list-style-type: none"> <li>The proportion of patients achieving sPGA (0) at Week 12</li> </ul>
<ul style="list-style-type: none"> <li>PASI 50</li> </ul>	<ul style="list-style-type: none"> <li>The proportion of patients achieving PASI 50 at Week 1</li> </ul>
<p><b>Exploratory</b> To assess whether ixekizumab is superior to guselkumab in the treatment of patients with moderate-to-severe Ps at different time points, as measured by:</p> <ul style="list-style-type: none"> <li>sPGA score of 0 and 1 (sPGA [0, 1])</li> </ul>	<ul style="list-style-type: none"> <li>The proportion of patients with a static sPGA (0,1) with at least a 2-point improvement from baseline at Weeks 4, 8, 12, 24</li> </ul>
<ul style="list-style-type: none"> <li>Itch NRS: <ul style="list-style-type: none"> <li>Responder</li> <li>Change from baseline</li> <li>Score of 0 (Itch NRS [0])</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>The proportion of patients achieving the Itch NRS Responder definition at Weeks 4, 8, 12, and 24 (restricted to those patients with Itch NRS score <math>\geq 4</math> points at baseline)</li> <li>Change from baseline in Itch NRS score at Weeks 4, 8, 12, and 24</li> <li>The proportion of patients achieving Itch NRS (0) at Weeks 4, 8, 12, and 24 (restricted to those patients with Itch NRS score <math>&gt; 0</math> at baseline)</li> </ul>

Objectives	Endpoints
<ul style="list-style-type: none"> <li>• Skin Pain VAS                             <ul style="list-style-type: none"> <li>○ Skin Pain VAS (0)</li> <li>○ Change from baseline</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>○ The proportion of patients achieving Skin Pain VAS (0) at Weeks 4, 8, 12, and 24 (restricted to those patients with Skin Pain VAS score &gt;0 at baseline)</li> <li>○ Change from baseline in Skin Pain VAS score at Weeks 4, 8, 12, and 24</li> </ul>
<ul style="list-style-type: none"> <li>• DLQI (0,1)</li> </ul>	<ul style="list-style-type: none"> <li>• The proportion of patients achieving DLQI (0,1) at Weeks 2, 4, 8, 12, and 24 (restricted to those patients with DLQI score &gt;1 at baseline)</li> </ul>

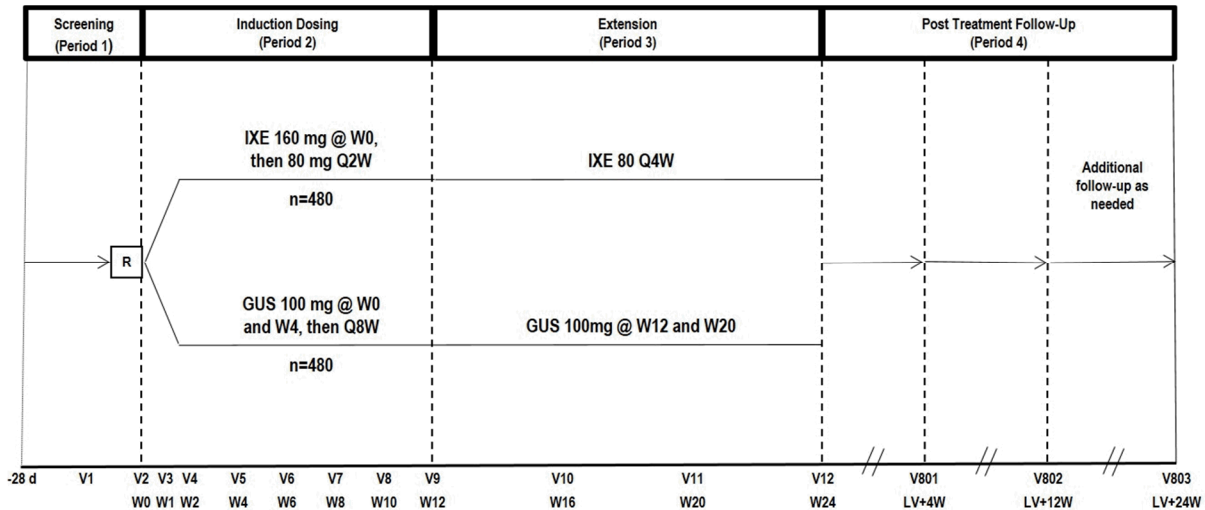
Abbreviations: DLQI = Dermatology Life Quality Index; NRS = Numeric Rating Scale; PASI = Psoriasis Area and Severity Index; Ps = plaque psoriasis; sPGA = static Physician Global Assessment; VAS = visual analog scale.

## 5. Study Design

### 5.1. Overall Design

Study RHCR is a multicenter, randomized, double-blind, parallel-group Phase 4 study with 4 study periods in patients with chronic moderate-to-severe Ps.

Study governance considerations are described in detail in [Appendix 3](#).



Abbreviations: GUS = guselkumab; IXE = ixekizumab; LV = last visit; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous; R = randomization; V = study visit; W = week.

**Figure RHCR.1. Illustration of study design for clinical protocol RHCR.**

The following treatment groups will be assessed in this study:

- Ixekizumab: 80 mg SC injection. At Week 0, 160 mg starting dose (two 80 mg injections), followed by 80 mg Q2W from Weeks 2 through 12, and then followed by 80 mg Q4W thereafter (i.e., at Weeks 16 and 20).
- Guselkumab: 100 mg SC injection. At Weeks 0 and 4, 100 mg injection, followed by 100 mg Q8W thereafter (i.e., at Weeks 12 and 20).

The study will consist of 4 periods:

- **Period 1 (Section 5.1.1): Screening Period** (Visit 1) will assess patient eligibility and occurs approximately 5 to 28 days prior to Period 2 (baseline; Week 0 [Visit 2]).
- **Period 2 (Section 5.1.2): Induction Dosing Period** occurring from Week 0 (baseline; Visit 2) to Week 12 (Visit 9).
- **Period 3 (Section 5.1.3): Extension Period** occurring after Week 12 (Visit 9) to Week 24 (Visit 12).
- **Period 4 (Section 5.1.4): Post-Treatment Follow-Up Period** occurring from last treatment period Visit 12 (Week 24) or ETV, for a minimum of 12 weeks following that visit.



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

Patients discontinuing from the study drug who have received at least 1 dose of study drug will continue to the ETV before proceeding to the Post-Treatment Follow-Up Period (Period 4). For the management of patient safety, all patients should be monitored through Period 4 at least as frequently as indicated on the Schedule of Activities (Section 2).

Treatment assignments will remain blinded to investigators, study site personnel directly involved in patient efficacy and safety assessments, and patients.

Designated Unblinded Site Personnel are responsible for receipt of study drug shipments, dispensing study drug, administering study drug, recording information in the Study Drug Administration Log, and confirming treatment assignments.

Unblinded Site Personnel are also responsible for maintaining the blind of the patient (e.g., by means of a blindfold or other appropriate physical barrier means communicated to the sponsor for final approval). Designated Unblinded Site Personnel will not be involved in any clinical aspects of the study, including clinical evaluations and AE assessments. It is critical that the blind is maintained throughout the study (24 weeks).

All treatment groups are described in Section 7.1, Table RHCR.7.1, and administration of the study drug is described in Section 7.1, Table RHCR.7.2.

Excluded and restricted therapies are detailed in Section 7.8.

Section 10.3.7 outlines the information regarding interim analyses, including the primary database lock at Week 12.

### **5.1.1. Screening Period (Period 1)**

The duration of the Screening Period will be 5 to 28 days before the Induction Dosing Period (Period 2) and consists of 1 screening visit (Visit 1) to assess patient eligibility. The patient will sign the informed consent form (ICF) before any study assessments, examinations, or procedures are performed.

All inclusion and exclusion criteria are provided in Sections 6.1 and 6.2, respectively. Screening procedures (including complete medical history and demographics) will be performed according to the Schedule of Activities (Section 2). At Visit 1, a QuantiFERON®-TB Gold test assay may be performed by a Lilly-designated or local laboratory (Section 9.4.4).

Patients who test positive for latent tuberculosis (TB) at screening may be re-screened one time following appropriate treatment as described in Section 9.4.4.

Additionally, patients who do not qualify at screening under Exclusion Criteria [34] may be re-screened (1 time), as described in Section 7.3 with approval of Lilly Medical Team (clinical research scientist[CRS]/ clinical research physician [CRP]).

### **5.1.2. Induction Dosing Period (Period 2)**

The Induction Dosing Period (Period 2) will be a double-blind treatment period that will occur from Week 0 (baseline; Visit 2) to Week 12 (Visit 9).

At Week 0 (baseline, Visit 2), routine safety assessments, laboratory tests, and clinical efficacy assessments will be performed on eligible patients, according to the Schedule of Activities (Section 2).

Patients will be randomized at a 1:1 ratio, to 1 of 2 treatment groups according to commercially prescribed dosing.

Please refer to Section 7.1, Table RHCR.7.1, and Table RHCR.7.2 for a full description of treatment groups and dosing during Period 2.

Training of administration of study drug is outlined in Sections 7.1.1.

Patients who discontinue from study drug for any reason during this period will continue to the ETV before entering the Post-Treatment Follow-Up Period (Period 4; Section 5.1.4).

### **5.1.3. Extension Period (Period 3)**

The Extension Period (Period 3) will be a double-blind treatment period that will occur from Week 12 (Visit 9) up to Week 24 (Visit 12).

During Period 3, safety and efficacy parameters in participating patients will continue to be evaluated according to the Schedule of Activities (Section 2).

Please refer to Section 7.1, Table RHCR.7.1, and Table RHCR.7.2 for a full description of treatment groups and dosing during Period 3.

Patients who discontinue from study drug for any reason during Period 3 will continue to the ETV before entering the Post-Treatment Follow-Up Period (Period 4; Section 5.1.4).

### **5.1.4. Post-Treatment Follow-Up Period (Period 4)**

All patients receiving at least 1 dose of study drug will enter the Post-Treatment Follow-Up Period (Period 4) for a minimum of 12 weeks, beginning after their last regularly scheduled visit (or the date of their ETV).

Required study visits should occur at 4 weeks (Visit 801) and at 12 weeks (Visit 802) after the last regularly scheduled visit (or the date of the patient's ETV), except for patients with a concurrent infection that requires systemic anti-infective therapy (described in Section 9.4.6.1).

If, at Visit 802, a patient's neutrophil count is  $\geq 1500$  cells/ $\mu\text{L}$  or greater than or equal to the patient's baseline neutrophil count, the patient's participation in the study will be considered complete unless the investigator determines additional follow-up may be necessary. An additional study visit (Visit 803) 12 weeks after Visit 802 may be required. Additional visits before Visit 803 may be required for appropriate patient management (described in Section 9.4.6.1).

For patients who have entered Period 4, Ps therapy is allowed, as determined appropriate by the investigator. These allowed Ps therapies include the treatment patients received during the double-blind trial.

## 5.2. Number of Participants

Approximately 1300 participants will be screened to achieve 960 randomized participants (480 randomized participants per treatment group). Based on experience from the previous UNCOVER-1, -2, -3, and IXORA-S trials, a 5% dropout rate is anticipated.

Patients with previous biologic use can be included in the study provided all inclusion/exclusion criteria, including the washout period(s), as specified in Sections 6.1 and 6.2 of this protocol are respected. Patients with previous exposure to another IL-17 antagonist(s) will be limited to approximately 15% of the total patient population.

## 5.3. End of Study Definition

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

## 5.4. Scientific Rationale for Study Design

This study will examine the effect of ixekizumab vs. that of the active comparator (guselkumab) on patients with moderate-to-severe Ps.

Guselkumab was chosen as the active comparator, as it:

- demonstrates a good safety profile (Blauvelt et al. 2017; Reich et al. 2017),
- is given as SC injection, and
- represents an important class of drugs for Ps treatment.

During the Induction Dosing Period (Period 2), patients randomized to ixekizumab (80 mg Q2W) will be compared with patients randomized to guselkumab (100 mg at Week 0 and 4). During the Extension Period (Period 3), guselkumab 100 mg Q8W (starting at Week 12) and ixekizumab 80 mg Q4W will be studied.

Traditionally PASI 75 has been considered the gold standard to measure drug efficacy in Ps. However, data suggested that only higher levels of clinical response (>90% improvement) are associated with normalization of patients' health-related quality of life. While these levels of clearance are rarely provided by conventional drugs and TNFi, they are more consistently obtained with IL-23 antagonists and IL-17 antagonists. Therefore, in this trial, the efficacy of ixekizumab and guselkumab in treating patients with Ps will be measured by the PASI 100 response at Week 12. This measurement and the Week 12 endpoint are in alignment with efficacy endpoints for currently approved Ps therapies, as well as regulatory guidance (EMA 2004).

The Extension Period (Period 3) will permit collection of data for the assessment of longer-term safety and efficacy data of ixekizumab compared to guselkumab.

The Post-Treatment Follow-Up Period (Period 4) is for safety monitoring following the last treatment period and study visit.

### **5.5. Justification for Dose**

The general approach to dosing ixekizumab in this study is to use the commercially approved dosing regimen for treatment of adults with moderate-to-severe Ps (Taltz USPI [WWW]; Canada Product Monograph [WWW]).

The guselkumab dosing regimen used in this study (100 mg at Weeks 0, 4, 12, and 20) is the approved dose for the treatment of adults with moderate-to-severe Ps (Tremfya USPI package insert, 2017; Canada Product Monograph [WWW]).

## 6. Study Population

This study will include patients with moderate-to-severe chronic Ps who have given written informed consent approved by Eli Lilly and Company (Lilly), or its designee, and the ethics review board (ERB) governing the site.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened in the following circumstances: patients who test positive for latent TB at screening may be re-screened following appropriate treatment, as described in Section 9.4.4. Additionally, patients who do not qualify at screening under Exclusion Criteria [34] may be re-screened once,  $\geq 4$  weeks after documented resolution of symptoms. When re-screening is performed, the individual must sign a new ICF and will be assigned a new identification number.

Study investigator(s) will review patient records and/or patient history and screening test results/measurements to determine if the patient meets all inclusion and exclusion criteria to qualify for participation in the study. All screening activities must be completed and reviewed before the patient is randomized.

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

### 6.1. Inclusion Criteria

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

- [1] Patient with chronic plaque psoriasis based on a diagnosis for at least 6 months before baseline (Week 0; Visit 2), as determined by the investigator.
- [2] Are a candidate for phototherapy and/or systemic therapy.
- [3] Have both an sPGA score of  $\geq 3$  and a PASI score  $\geq 12$  at screening (Visit 1) and at baseline (Week 0, Visit 2).
- [4] Have  $\geq 10\%$  body surface area (BSA) involvement at screening (Visit 1) and baseline (Week 0, Visit 2).
- [5] Are patients 18 years or older.
- [6] If a male patient, agree to use a reliable method of birth control during the study.
- [7] Female patients:  
Participants of child-bearing age or child-bearing potential who are sexually active who test negative for pregnancy must be counseled and agree to use either 1 highly effective method of contraception or 2 acceptable methods of contraception combined for the duration of the study and for at least 12 weeks following the last dose of study drug, or remain abstinent during the study and for at least 12 weeks following the last dose of study drug.

If the highly effective contraceptive methods are contraindicated or strictly declined by patient, acceptable birth control methods may be considered. These may include combination of both of the following methods:

- Male or female condom with spermicide
  - Cap, diaphragm, or sponge with spermicide
1. Highly effective methods of contraception (use 1 form):
    - a. combined oral contraceptive pill and mini-pill
    - b. NuvaRing®
    - c. implantable contraceptives
    - d. injectable contraceptives (such as Depo-Provera®)
    - e. intrauterine device (such as Mirena® and ParaGard®)
    - f. contraceptive patch—ONLY women <198 pounds or 90 kg
    - g. abstinence from sex
    - h. vasectomy—for men in clinical studies
  2. Effective methods of contraception (use 2 forms combined)
    - male condom with spermicide
    - female condom with spermicide
    - diaphragm with spermicide
    - cervical sponge
    - cervical cap with spermicide

Females who are not of childbearing potential include those who have undergone or who have:

- female sterilization
- hysterectomy
- menopause- as confirmed by diagnostically elevated follicle-stimulating hormone (FSH) at baseline.
- Müllerian agenesis (Mayer–Rokitansky–Küster–Hauser syndrome [also referred to as congenital absence of the uterus and vagina])

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

## 6.2. Exclusion Criteria

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

- [9] Have predominant pattern of pustular, erythrodermic, and/or guttate forms of psoriasis.
- [10] Have a history of drug-induced psoriasis.
- [11] Had a clinically significant flare of psoriasis during the 12 weeks before baseline (Week 0, Visit 2).

Medications/Therapies

- [12] Use of tanning booths for at least 4 weeks before baseline (Week 0, Visit 2) and during the study, per investigator assessment.
- [13] Concurrent or recent use of any biologic agent within the following periods prior to baseline (Week 0, Visit 2): etanercept <28 days; infliximab, adalimumab, certolizumab pegol, or alefacept <60 days; golimumab <90 days; rituximab <12 months; secukinumab <5 months; or any other biologic agent (e.g., ustekinumab) <5 half-lives.
- [14] Have prior use of IL-23p19 antagonists (e.g., guselkumab, tildrakizumab, risankizumab), or have any condition or contraindication as addressed in the local labeling for guselkumab that would preclude the patient from participating in this protocol.
- [15] Have previously completed or withdrawn from this study, participated in any other study with ixekizumab or guselkumab, have participated in any study investigating IL-23p19 antagonists, or have received treatment with ixekizumab.
- [16] Have previously failed to respond to an IL-17 antagonist, per investigator assessment.

Vaccinations

- [17] Have had a live vaccination within 12 weeks of baseline (Week 0, Visit 2), or intend to have a live vaccination during the course of the study or within 15 weeks of completing treatment in this study, or have participated in a vaccine clinical study within 12 weeks of 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 before therapy.

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

- [18] Have had a vaccination with Bacillus Calmette-Guérin (BCG) within 12 months of baseline (Week 0, Visit 2) or intend to have vaccination with BCG during the course of the study or within 5 half-life of completing treatment in this study.

Medical Status and Medical History

- [19] 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.
- [20] Are currently enrolled in any other clinical study involving a study drug or any other type of medical research judged not to be scientifically or medically compatible with this study.

- [21] Have had any major surgery within 8 weeks of baseline (Week 0, Visit 2) or will require major surgery during the study that, in the opinion of the investigator in consultation with Lilly, would pose an unacceptable risk to the patient.
- [22] Have current or a history of lymphoproliferative disease, or signs or symptoms of lymphoproliferative disease within 5 years of baseline (Week 0, Visit 2); or have active or history of malignant disease within 5 years of baseline (Week 0, Visit 2), except for basal cell carcinoma, squamous cell carcinoma, skin Bowen's disease or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks or carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed.
- (Note: patients with history of malignancy with no evidence of recurrence or active disease within 5 years of baseline may participate in the study).
- [23] Presence of significant uncontrolled cerebro-cardiovascular (e.g., MI, arrhythmias, unstable angina, unstable arterial hypertension, moderate-to-severe [New York Heart Association class III/IV] heart failure, or cerebrovascular accident), respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic or neuropsychiatric disorders or abnormal laboratory values at screening (Visit 1) that, in the opinion of the investigator, pose an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.
- [24] Have had fluid overload, MI, or new onset ischemic heart disease (e.g., unstable angina), uncompensated heart failure, or in the opinion of the investigator other serious cardiac disease within 12 weeks of baseline (Week 0; Visit 2).
- [25] Presence of significant uncontrolled neuropsychiatric disorder, have recent history (within 30 days prior to screening [Visit 1] and any time between screening [Visit 1] and baseline randomization [Visit 2]) of a suicide attempt; or have active suicidal ideation with some intent to act with or without a specific plan (yes to question 4 or 5 on the "Suicidal Ideation" portion of the Columbia-Suicide Severity Rating Scale [C-SSRS]); or are clinically judged by the investigator to be at risk for suicide.
- [26] Have evidence of active or non-treated latent TB (refer to Section 9.4.4 for details on determining full TB exclusion criteria).
- [27] Are positive for human immunodeficiency virus (HIV) serology (positive for HIV antibody).
- [28] Have evidence of or test positive for hepatitis B virus (HBV) by testing positive for: 1) HBV surface antigen (HBsAg+); OR 2) anti-hepatitis B core antibody (HBcAb+) and are HBV deoxyribonucleic acid (DNA) positive.



Note: Patients who are HBsAg-, and HBcAb+ and HBV DNA negative may be enrolled in the study. Patients who meet these criteria at screening will be identified by the central laboratory and monitored during the study as detailed in Section 9.4.6.3.

- [29] 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 and 2) positive via a confirmatory test for HCV (e.g., HCV polymerase chain reaction).
- [30] Has any current unstable and/or clinically significant medical condition at Visit 1 that in the investigator's opinion could interfere with participation in the study.

#### Infections

- [31] Have had a serious infection (e.g., pneumonia, cellulitis, and sepsis), have been hospitalized, or have received intravenous antibiotics for an infection within 12 weeks of baseline (Week 0, Visit 2); have had a serious bone or joint infection within 24 weeks of baseline (Week 0, Visit 2); 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.
- [32] Have or have 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 jiroveci pneumonia, histoplasmosis, or coccidioidomycosis) or have a known immunodeficiency.
- [33] Have or have had a herpes zoster infection or any other clinically apparent varicella-zoster virus infection within 12 weeks of baseline (Week 0, Visit 2).
- [34] Have had 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 re-screened (1 time)  $\geq 4$  weeks after documented resolution of symptoms.

#### Clinical Laboratory Results

- [35] At screening (Visit 1), have a neutrophil count  $<1500$  cells/ $\mu\text{L}$  ( $<1.50 \times 10^3/\mu\text{L}$  or  $<1.50$  GI/L).
- [36] At screening (Visit 1), have a lymphocyte count  $<800$  cells/ $\mu\text{L}$  ( $<0.80 \times 10^3/\mu\text{L}$  or  $<0.80$  GI/L).
- [37] At screening (Visit 1), have a platelet count  $<100\,000$  cells/ $\mu\text{L}$  ( $<100 \times 10^3/\mu\text{L}$  or  $<100$  GI/L).

- [38] At screening (Visit 1), have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times (x) 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.)
- [39] At screening (Visit 1), have alkaline phosphatase (ALP) >3xULN or alkaline phosphatase >2.5xULN and total bilirubin >2xULN.
- [40] At screening (Visit 1), have a total white blood cell (WBC) count <3000 cells/ $\mu$ L (<3.00x10<sup>3</sup>/ $\mu$ L or <3.00 GI/L).
- [41] At screening (Visit 1), have hemoglobin <8.5 g/dL (85.0 g/L) for male patients and <8.0 g/dL (80 g/L) for female patients.
- [42] At screening (Visit 1), have clinical laboratory test results that are outside the normal reference range for the population and are considered clinically significant, per investigator assessment.
- [43] At screening (Visit 1), have serum creatinine level >2.0 mg/dL.

(Note: Laboratory tests should not be repeated unless there is a technical error or clinical reasons to believe a result may be erroneous.)

#### Other

- [44] Are women who are pregnant, or who are lactating (breast-feeding).
- [45] Have any other condition that precludes the patient from following and completing the protocol, in the opinion of the investigator.
- [46] 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.
- [47] Are Lilly employees or are employees of third-party organizations (TPOs) involved in the study.
- [48] Are unwilling or unable to comply with the use of a data collection device to directly record data from the subject.

### **6.2.1. Rationale for Exclusion of Certain Study Candidates**

Exclusion Criteria [12] through [16] exclude patients who have prior exposure to guselkumab, or any other IL-23p19 antagonist, or ixekizumab (note: see details in Sections 6.2 and 5.2), or any patients who are receiving treatment or concomitant medications that could have a negative impact on the safety of patients enrolled or confound the results of the study. Exclusion Criteria [17] through [43] exclude patients who would be at a greater safety risk, including patients at increased risk of infective complications or immunosuppression, if administered ixekizumab or guselkumab or whose data could confound the results of the study in the analysis of ixekizumab

and/or patients. Exclusion Criterion [44] provides protection to offspring. Exclusion Criteria [45], [46], and [47] reduce the potential bias that may be introduced at the study site.

The majority of the exclusion criteria are applied to reduce risks to patients by enrolling medically stable, relatively healthy (aside from the disease being studied) patients who are not receiving concomitant therapies that may impact their safety and/or confound effects when combined with the study drug being studied.

### **6.3. Lifestyle Restrictions**

See inclusion criteria [6] and [7] in Section [6.1](#) for birth control requirements.

## 7. Treatments

### 7.1. Treatments Administered

This study involves a double-blind comparison of 2 SC treatments, either ixekizumab or guselkumab, administered over a 24-week treatment period. Placebo injection will be utilized to maintain the blind for ixekizumab and guselkumab as described in [Table RHCR.7.1](#).

**Table RHCR.7.1. Treatment Regimens**

Randomized Treatment Group	Starting Dose W0	Dose W2-W12	Dose <sup>a</sup> W16-W20
Ixekizumab	Ixekizumab 80 mg 2xSC (total of 160 mg)	Ixekizumab 80 mg SC at W2, 4, 6, 8, 10, and 12	Ixekizumab 80 mg SC at W16 and 20
Guselkumab	Guselkumab 100 mg SC; Placebo	Guselkumab 100 mg SC at W4 and 12; Placebo at W2, 6, 8, and 10	Guselkumab 100 mg SC at W20; Placebo at W16

Abbreviations: SC = subcutaneous injection; W = Week.

<sup>a</sup> No dose is given at W14; therefore, W14 is not included in this table.

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

- explaining the correct use of the investigational agent(s) to site personnel/legal representative
- verifying that instructions are followed properly
- maintaining accurate records of study drug dispensing and collection
- returning all unused medication to Lilly or its designee at the end of the study

Note: In some cases, sites may destroy clinical trial material if during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures for disposing of clinical trial materials.

Designated Unblinded Site Personnel will be responsible for the handling, dispensing, and administering of all study drugs (ixekizumab, guselkumab, and placebo). Additional details regarding Unblinded Site Personnel responsibilities are provided in the Unblinded Site Personnel Dispensing and Dosing Instructions. Unblinded Site Personnel will not be involved in patient screening, enrollment, and any assessment of efficacy or safety. It is critical that the blind is maintained throughout the study (24 weeks).

#### Induction Dosing Period (Period 2) ([Table RHCR.7.2](#))

- Patients randomized to ixekizumab: At Week 0, a 160 mg starting dose of ixekizumab (two 80 mg injections), followed by ixekizumab 80 mg Q2W from Weeks 2 through 12.
- Patients randomized to guselkumab: At Weeks 0, 4, and 12, 100 mg injection of guselkumab. To maintain the blind, patients will receive 1 placebo injection at Weeks 0, 2, 6, 8, and 10.

**Extension Period (Period 3) (Table RHCR.7.2)**

- Patients randomized to ixekizumab: Ixekizumab 80 mg Q4W (i.e., at Weeks 16 and 20).
- Patients randomized to guselkumab: Guselkumab 100 mg Q8W (i.e., at Week 20). To maintain the blind, patients will receive 1 placebo injection at Week 16.

Table RHCR.7.2 presents the number of injections administered at each study week, for each dosing period, in the 2 treatment groups.

**Table RHCR.7.2. Ixekizumab and Guselkumab Treatment Group Dosing Summary for the Induction and Extension Periods**

Dosing Period	Study Week	Ixekizumab Treatment Group <sup>a,b</sup>		Guselkumab Treatment Group <sup>c</sup>		
		Ixekizumab (80 mg)	Total Number of Injections	Guselkumab (100 mg)	Placebo <sup>d</sup>	Total Number of Injections
Induction Dosing Period 2	0	2 <sup>a</sup>	2	1	1	2
	2	1	1	-	1	1
	4	1	1	1	-	1
	6	1	1	-	1	1
	8	1	1	-	1	1
	10	1	1	-	1	1
Extension Period 3	12	1	1	1	-	1
	16	1	1	-	1	1
	20	1	1	1	-	1
	24	-	-	-	-	-

Abbreviations: SC = subcutaneous; Q2W= every 2 weeks; Q4W= every 4 weeks; Q8W= every 8 weeks.

<sup>a</sup> A starting dose of 160 mg (Week 0) of ixekizumab will be given as 2 SC injections at Week 0.

<sup>b</sup> During the Induction Dosing Period, ixekizumab (80 mg) will be given as 1 SC injection Q2W (i.e., Weeks 2, 4, 6, 8, 10, and 12). During the Extension Period, ixekizumab (80 mg) will be given as 1 SC injection Q4W (i.e., Weeks 16 and 20).

<sup>c</sup> During the Induction Dosing Period (Period 2), guselkumab (100 mg) will be given as 1 SC injection at Weeks 0, 4 and 12. During the Extension Period (Period 3), guselkumab (100 mg) will be given as 1 SC injection Q8W (i.e., Week 20).

<sup>d</sup> Placebo (1 SC injection) will be given at Weeks 0, 2, 6, 8, and 10 during the Induction Dosing Period (Period 2). Placebo will be given at Week 16 during the Extension Period (Period 3).

### 7.1.1. Administration of Ixekizumab, Guselkumab and Placebo

All injections of ixekizumab, guselkumab, and placebo will be administered by the designated Unblinded Site Personnel.

**Training:** Training will be provided by the sponsor to the Unblinded Site Personnel; no training is required for patients.

**Administration:** Possible injection sites include the abdomen, thighs, and arms. The injections should not be administered in a psoriatic lesion. When multiple injections will be administered, the injections should be given in different areas.

Syringes should be at room temperature before injection (refer to the Unblinded Site Personnel Dispensing and Dosing Instructions).

Unblinded Site Personnel will record information in a Study Drug Administration Log, including the date, time, and anatomical location of administration of study drug (for treatment compliance), package number, who administered the study drug, and if applicable, the reason for which study drug was not administered or was not fully administered. Unblinded Site Personnel are also responsible to make sure patients remain blinded to treatment (i.e., patients must not see the syringe before, during or after the drug administration).

### **7.1.2. Observations after Study Drug Administration**

All patients should remain under observation for at least 1 hour after study drug administration to monitor safety at Week 0.

### **7.1.3. Packaging and Labelling**

The ixekizumab, guselkumab, and placebo solution for injection will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice and will be supplied with lot numbers, expiry dates, and certificates of analysis, as applicable.

Ixekizumab and placebo will be supplied as an injectable solution in 1-mL, single-dose, disposable manual syringe. Each syringe of ixekizumab is designed to deliver 80 mg of ixekizumab. The syringes (and contents) containing either ixekizumab or placebo will be visibly indistinguishable from each other. Guselkumab will be supplied as a single-dose 100 mg/mL disposable manual prefilled syringe.

Syringes will be supplied in cartons, with the appropriate quantity of syringes specific to the planned dispensing schedule of the study drug.

Unblinded Site Personnel will be responsible for handling and administering guselkumab, ixekizumab, and placebo to avoid unblinding.

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

## **7.2. Method of Treatment Assignment**

At Week 0 (Visit 2), patients who meet all criteria for enrollment at Visits 1 and 2 will be randomized at a 1:1 ratio to double-blind treatment groups (i.e., 80 mg ixekizumab or 100 mg guselkumab) as determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign blinded study drug to each patient. The Unblinded Site Personnel at the site will confirm that they have located the correct assigned study drug package by entering a confirmation number found on the package into the IWRS as described for Unblinded Site Personnel in the Unblinded Site Personnel Dispensing and Dosing Instructions.

Randomization will be stratified by site for this study.

### 7.3. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Individuals may be re-screened up to 1 time. Each time a re-screening is performed, the individual must sign a new ICF and will be assigned a new identification number.

Individuals may be re-screened in the following circumstances:

- Patients who test positive for latent TB at screening and have undergone documented subsequent treatment for at least 4 weeks (more details in Section 9.4.4).
- Patients who do not qualify at screening under exclusion criteria [34] may be re-screened once, 4 or more weeks after documented resolution of symptoms.
- Other reasons for re-screening must be discussed, approved and documented by the Lilly Medical Team (CRS/CRP).

#### 7.3.1. Selection and Timing of Doses

Patients will be assigned to treatment and will receive their assigned treatment as outlined in Sections 7.1.1.

Study drug should be administered on the same day of the week, at approximately the same time each day, as much as possible. The actual time of all dose administrations will be recorded in the subject's case report form (CRF). For injections not administered on the scheduled day of the week from Weeks 0 to 12, the missed dose should be administered within 3 days of the scheduled day; after Week 12, the missed dose should be administered within 5 days of the scheduled day. Dates of subsequent study visits should not be modified according to the delay of the injection of the missed scheduled dose. The doses at Weeks 0 to 12 should not be administered until after all assessments per the Schedule of Activities (Section 2) are completed.

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

### 7.4. Blinding

This is a double-blind study; patients and study site personnel performing assessments of outcomes will be blinded to study drug until all patients have completed the study. To preserve the blinding of the study, sponsor personnel will not see the randomization table and treatment assignments before the study is unblinded. Section 7.1 provides the dosing details pertinent to maintenance of the study blind. Emergency unblinding for AEs may be performed through an 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 will be recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or patient is prematurely unblinded, the patient must be discontinued from the study drug and should continue in the Post-Treatment

Follow-Up Period (Period 4). In cases for which there are ethical reasons to have the patient remain on the study drug, the investigator must obtain specific, documented approval from a Lilly CRS/CRP or representative for the patient to continue in the study.

Processes to maintain blinding during the interim analyses are described in Section 10.3.7.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. The patient safety must always be the first consideration in making such a determination. If a patient's treatment assignment is unblinded, Lilly must be notified immediately. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

## 7.5. Dosage Modification

Not applicable.

## 7.6. Preparation/Handling/Storage/Accountability

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

- confirming appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
- ensuring that only participants enrolled in the study may receive study drug and only authorized site staff may supply and administer study drug. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- the investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records).
- the study drug should be stored at 2°C to 8°C (36°F to 46°F) in its original carton to protect from light. Study drug should not be frozen. Sites will be required to monitor temperature of the on-site storage conditions of the study drug.

Details for the requirements for dispensing ixekizumab, guselkumab, and placebo syringes will be provided to the Unblinded Site Personnel in the Unblinded Site Personnel Dispensing and Dosing Instructions.

## 7.7. 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 requirements of the trial with the patient before randomization.

Throughout their participation in the treatment periods (Induction Dosing and Extension Periods), trained unblinded site personnel will record information in a Study Drug



Administration Log, including the date, time, and anatomical location of administration of study drug, syringe number, who administered the study drug, the reason if the study drug was not administered or not fully administered, and the count of empty study drug packaging. The time and day of each study drug administration (and other items included in the above paragraph) must be recorded into the electronic case report form (eCRF) by site personnel.

### **7.8. Concomitant Therapy**

All concomitant medication taken during the study must be recorded on the Concomitant Medication CRF at the study visits indicated in the Schedule of Activities (Section 2). Treatment with concomitant Ps therapies during the study will be permitted only as outlined in the inclusion and exclusion criteria (Sections 6.1 and 6.2, respectively) and as described in the paragraphs below. Patients taking permitted medications need to be documented to be in stable control. After trial enrollment, significant dose escalation of a concomitant medication should be discussed with Lilly medical before allowing patient to receive study drug.

[Table RHCR.7.3](#) summarizes concomitant medications that are and are not permitted and their conditions for use during the study.

**Table RHCR.7.3. Concomitant Medications Permitted/Not Permitted in the Study and Conditions for Use**

Drug Class	Permitted/Not Permitted During the Trial	Conditions for Use
Bath oils and oatmeal bath preparations	Permitted	Not to be used within 12 hours of a study visit.
NSAIDs, acetaminophen, or aspirin	Permitted	Allowed as needed.
Shampoos	Permitted	May not contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues. Not to be used within 12 hours of a study visit.
Topical moisturizers/emollients and other non-prescription topical products	Permitted	Do not contain urea, >3% salicylic acid, alpha- or beta-hydroxyl acids, corticosteroids, or vitamin D3 analogues. Not to be used within 12 hours of a study visit.
Topical steroids mild (such as hydrocortisone) are permitted  strong (such as mometasone), very strong (Betamethasone) <sup>a</sup> , and Halogenated steroids (clobetasone) are not permitted	Permitted  Not permitted	Permitted for use limited to the face, axilla, groin, and/or genitalia, as needed. These topical medications should not be used within approximately 24 hours before study visits requiring sPGA and PASI measures. More widespread use on large surfaces is not permitted.
Biologic agents other than study drug as part of this protocol	Not Permitted	Washout periods before baseline (Week 0, Visit 2); at least 5 half-lives
IL-17, IL-23p19 antagonists, other than the 2 products used as part of this protocol.	Not permitted	Must have never received ixekizumab or IL-23p19 antagonists; or participated in any study investigating IL-23p19 antagonists. Patient with previous exposure to another IL-17 antagonist(s) will be limited to approximately 15% of the total patient population.
Natalizumab or other agents targeting $\alpha 4$ integrin	Not permitted	Must have never received.
Phototherapy (including either oral and topical PUVA light therapy, UVB, or self-treatment with tanning beds or therapeutic sunbathing)	Not permitted	Must not have received within 4 weeks of baseline (Week 0, Visit 2).

**Concomitant Medications Permitted/Not Permitted in the Study and Conditions for Use**

Drug Class	Permitted/Not Permitted	Conditions for Use
Systemic nonbiologic psoriasis therapy (e.g., oral psoralens and ultraviolet A light therapy, cyclosporine, corticosteroids, MTX, oral retinoids, mycophenolate mofetil, thioguanine, hydroxyurea, sirolimus, azathioprine, fumaric acid derivatives, apremilast, and 1, 25 dihydroxy vitamin D3 and analogues)	Not permitted	Must not have received within 4 weeks of baseline (Week 0, Visit 2).
Vaccine, Bacillus Calmette-Guérin	Not permitted	Must not have received within 12 months of baseline (Week 0, Visit 2). Should not receive within 12 months of completed treatment in this study.
Vaccines, live	Not permitted	Must not have received within 12 weeks of baseline (Week 0, Visit 2). Should not receive within 15 weeks of completed treatment in this study.
Vaccines, nonlive seasonal and/or emergency	Permitted with conditions	Killed/inactive or subunit vaccines are expected to be safe; however, their efficacy with concomitant ixekizumab and guselkumab treatments is unknown. Check with Lilly Medical Team (CRS/CRP) before administration.

Abbreviations: CRS/CRP = clinical research scientist/clinical research physician; 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.

<sup>a</sup> Mason et al. 2002.

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

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.

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

## **7.9. Treatment after the End of the Study**

### **7.9.1. Treatment after Study Completion**

Study drug will not be made available after conclusion of the study to patients.

### **7.9.2. Special Treatment Considerations**

Patients will be screened for eligibility in the study as described in Sections 6.1 and 6.2 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.

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

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

Sometimes these reactions can be life-threatening. Proteins may also cause redness, itching, swelling, or pain locally at the injection site. Therefore, all patients should be closely monitored for signs or symptoms that could result from such reactions, be educated on the signs or symptoms of these types of reactions, and be instructed to contact the study site immediately if any of the symptoms are experienced following an injection. If a patient experiences an acute

allergic/hypersensitivity reaction after an injection of study drug, 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 (e.g., injection-site erythema, injection-site pruritus). Patients who develop clinically significant systemic allergic/hypersensitivity reactions following administration of study drug who do not respond to symptomatic medication, or have a reaction that results in clinical sequelae (e.g., hospitalization), should be discontinued from study drug and not receive further doses of study drug, with or without premedication (Section 8.1). Medications considered appropriate for premedication include (but are not restricted to) acetaminophen/paracetamol up to 1000 mg and antihistamines (e.g., oral diphenhydramine, 50 mg) given 30 to 60 minutes before study drug injection. Patients may self-premedicate at home before administration of study drug, as directed by the investigator. All such premedications will be recorded as concomitant therapy. Corticosteroids are not permitted as agents for premedication.

## 8. Discontinuation Criteria

### 8.1. Discontinuation from Study drug

#### 8.1.1. *Permanent Discontinuation from Study drug*

Possible reasons leading to permanent discontinuation of study drug:

- **Subject Decision**
  - the patient requests to discontinue study drug.
- **Discontinuation due to a hepatic event or liver test abnormality.**
  - Patients who are discontinued from study drug due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via CRF.

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

- ALT or AST >8x ULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN and total bilirubin level (TBL) >2xULN or international normalized ratio (INR) >1.5
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3xULN
- ALP >2.5xULN and TBL >2xULN
- ALP >2.5xULN 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 study drug in the following circumstances:

- Neutrophil (segmented) counts (see safety monitoring for neutropenia Section 9.4.6.1):
  - <500 cells/ $\mu$ L
  - $\geq$ 500 and <1000 cells/ $\mu$ L (based on 2 test results; the second test performed within 1 week from knowledge of the initial result)
  - $\geq$ 1000 and <1500 cells/ $\mu$ L (based on 3 test results as specified in Section 9.4.6.1) AND an infection that is not fully resolved
- Total WBC count <2000 cells/ $\mu$ L
- Lymphocyte count <200 cells/ $\mu$ L
- Platelet count <50,000 cells/ $\mu$ L
- 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 study drug and appropriate measures being taken. In this case, Lilly or its designee is to be notified immediately via email and the event is to be documented.

- Clinically significant systemic hypersensitivity reaction following SC administration of study drug that does not respond to symptomatic medication or results in clinical sequelae
- The patient becomes pregnant
- The patient develops a malignancy (Note: patients may be allowed to continue if they develop no more than 2 non-melanoma skin cancers during the study)
- if the patient develops active suicidal ideation with some intent to act with or without a specific plan (yes to question 4 or 5 on the “Suicidal Ideation” portion of the C-SSRS),

-OR-

if the patient develops suicide-related behaviors as recorded on the C-SSRS,

then it is recommended that the patient be assessed by a psychiatrist or appropriately trained professional to assist in deciding whether the patient is to be discontinued from the study.

Patients discontinuing from the study drug prematurely for any reason should complete AE and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

### **8.1.2. 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, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on study drug. If the investigator and the sponsor CRP 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 study drug. Safety follow-up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

## **8.2. Discontinuation from the Study**

Patients will be discontinued in the following circumstances:

- enrollment in any other clinical study involving an study drug or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice

- investigator decision
  - the investigator decides that the patient should be discontinued from the study
  - if the patient for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for the treatment of the study indication, discontinuation from the study occurs before introduction of the new agent
- subject decision
  - the patient requests to be withdrawn from the study

Patients discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

### **8.3. Lost to Follow-Up**

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

Lilly personnel will not be involved in any attempts to collect vital status information.



## 9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing). All study assessments except for the C-SSRS, Self-Harm, and Self-Harm Follow-Up will be completed electronically.

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

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

### 9.1. Efficacy Assessments

#### 9.1.1. Primary Efficacy Assessments

The primary efficacy endpoint is PASI 100 response at Week 12 (Visit 9).

##### 9.1.1.1. Psoriasis Area and Severity Index

The PASI is an accepted primary efficacy measurement for this phase of development of Ps 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 Ps up to 72 for the most severe disease (Fredriksson and Pettersson 1978). The PASI has been the most frequently used endpoint and measure of Ps 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 Ps (PASI 100), have become additional endpoints because of the increasing recognition of the association of higher clearance with greater health-related quality of life (Puig 2015).

#### 9.1.2. Major Secondary Efficacy Assessments

##### 9.1.2.1. Static Physician Global Assessment

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

#### 9.1.3. Other Efficacy Assessments

##### 9.1.3.1. Percentage of Body Surface Area

The investigator will evaluate the percentage involvement of Ps 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) (Thomas and Finlay 2007).

### **9.1.3.2. Physician's Global Assessment of Disease Activity Visual Analog Scale (for Patients with PsA)**

The investigator will be asked to give an overall assessment of the severity of the patient's current PsA activity using a 100-mm horizontal visual analog scale (VAS), where 0 represents no disease activity and 100 represents extremely active disease. The investigator making the assessment must be a rheumatologist or medically qualified physician. The same assessor should preferably perform the Physician's Global Assessment of Disease Activity VAS for a given patient to minimize inter-observer variation.

### **9.1.3.3. PGA-F Physician's Global Assessment of Fingernail Psoriasis**

The Physician's Global Assessment of Fingernail Psoriasis (PGA-F), was developed for clinicians to evaluate the severity of fingernail abnormalities in patients with nail psoriasis. The scale assesses the nail bed and nail matrix signs of disease on a 0 to 4 scale (0 - clear, 1 - minimal, 2 - mild, 3 - moderate, 4 - severe).

## **9.1.4. Health Outcome Endpoints**

### **9.1.4.1. Itch Numeric Rating Scale**

The Itch NRS is a patient-administered single-item 11-point horizontal scale anchored at 0 and 10, with 0 representing "no itch" and 10 representing "worst itch imaginable." Patients indicate their overall severity of itching from Ps by circling the number that best describes the worst level of itching in the past 24 hours.

### **9.1.4.2. Skin Pain Visual Analog Scale**

The Skin Pain VAS is a patient-administered scale designed to measure skin pain from Ps using a 100-mm horizontal VAS. Overall severity of a patient's skin pain from Ps at the present time is indicated by placing a single mark on the horizontal scale (0 = no skin pain; 100 = severe skin pain).

### **9.1.4.3. Patient's Global Assessment of Disease Severity**

The Patient's Global Assessment of Disease Severity 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 Ps "today" from 0 (clear), no Ps; to 5 (severe).

### **9.1.4.4. Dermatology Life Quality Index**

The Dermatology Life Quality Index (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 score of 0 or 1 suggests no impact on patients' life.

**9.1.4.5. Patient's Assessment of Pain Visual Analog Scale (for Patients with PsA)**

The patient will be asked to assess his or her current level of joint pain by marking a vertical tick on a 100-mm horizontal VAS where the left end represents no joint pain and the right end represents worst possible joint pain. Results will be expressed in millimeters measured between the left end of the scale and the crossing point of the vertical line of the tick; this procedure is applicable for all VAS used in the trial.

**9.1.4.6. Patient's Global Assessment of Disease Activity Visual Analog Scale (for Patients with PsA)**

The patient's overall assessment of his or her PsA activity will be recorded using the 100-mm horizontal VAS where the left end represents no disease activity and the right end represents extremely active disease activity.

**9.1.5. Appropriateness of Assessments**

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

**9.2. Adverse Events**

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the study drug or the study, or that caused the patient to discontinue the study drug 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.

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, study drug, via eCRF.

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

A "reasonable possibility" means that there is a cause and effect relationship between the study drug, 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 study drug 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 discontinuations of treatment.

Study site personnel must alert Lilly or its designee within 24 hours of the investigator **unblinding** a patient's treatment group assignment for any reason.

### **9.2.1. Serious Adverse Events**

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the patient has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF, but prior to receiving study drug, the SAE should be reported to the sponsor per SAE reporting requirements and timelines (see Section 9.2) 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. Patients with a serious hepatic AE should have additional data collected using the eCRF.

Pregnancy (during maternal or paternal exposure to study drug) 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 disposition CRF 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 drug or study participation, the investigator must promptly notify Lilly.

Data on occurrence of SAEs up to and including the patient's last study visit will be collected, regardless of the investigator's opinion of causation, in the clinical data collection database and the pharmacovigilance system at the sponsor.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB.

#### **9.2.1.1. Suspected Unexpected Serious Adverse Reactions**

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

#### **9.2.1.2. Adverse Events of Special Interest**

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

Adverse events of special interests for ixekizumab are the following:

- cytopenias (leukopenia, neutropenia, and thrombocytopenia)
- liver function test changes/enzyme elevations (ALT, AST, bilirubin, and ALP)
- infections
- injection-site reactions
- allergic reactions/hypersensitivities
- cerebro-cardiovascular events
- malignancies
- inflammatory bowel disease (IBD)
- 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 cerebro-cardiovascular 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.

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

The role of the external CECs is to adjudicate defined clinical events in a blinded, consistent, and unbiased manner throughout the course of a study. The purpose of the CEC for adjudication of cerebro-cardiovascular events and the CEC for adjudication of suspected IBD events is to ensure that all reported events are evaluated uniformly by a single group.

### **9.2.2. Complaint Handling**

Lilly collects product complaints on study drugs 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.

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly or delegate will be reported.

The designated Unblinded Site Personnel must be responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee
- filing the product complaint and associated records in a secure location, separate from blinded site staff

If the investigative site is asked to return the product for investigation, the designated Unblinded Site Personnel will return a copy of the product complaint form with the product.

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

## **9.3. Treatment of Overdose**

Refer to the IB.

## 9.4. Safety

### 9.4.1. Laboratory Tests

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

With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by the central vendor, if a central vendor is used for the clinical trial.

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

### 9.4.2. Immunogenicity Assessments

Samples for immunogenicity testing including a pharmacokinetic sample will be collected at Visit 2, and at later time points in case of event judged by the investigator to be a potential systemic allergic/hypersensitivity reaction, when possible. Venous blood samples (approximately 10 mL) will be collected in tubes and used to determine antibody production against ixekizumab. The actual date of each sampling will be recorded on the laboratory requisition. To analyze change from baseline, the exploratory sample collected at Visit 2 will be used. If analyzed, the samples will be evaluated in validated immunogenicity assays at an external vendor in a screening assay and if positive a neutralizing ADA assay. Assay validation details are available upon request.

Samples from patients treated with guselkumab will not be analyzed for anti-guselkumab antibodies. These samples will be discarded at the end of the study. 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 or for a shorter period if local regulations and ERBs allow, at a facility selected by the sponsor, to enable further analysis of immune responses to ixekizumab. This duration will allow the sponsor to respond to regulatory requests related to the study drug. Any samples remaining after 15 years will be destroyed.

#### 9.4.2.1. Ixekizumab Serum Concentration

Immunogenicity samples may also be analyzed for ixekizumab serum concentrations to facilitate the interpretation of the immunogenicity data if needed. Analysis of samples collected from guselkumab-treated patients is not planned. Samples sent for ixekizumab serum concentration analysis will be tested at a laboratory approved by Lilly or its designee. Concentrations of immunoreactive ixekizumab in human serum will be determined by a validated method.

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

### 9.4.3. Physical Examination

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

Any clinically significant findings from a complete physical examination that result in a diagnosis are to be reported to Lilly or its designee as AEs via eCRF.

### 9.4.4. Chest X-Ray and Tuberculosis Testing

An anterior-posterior view chest x-ray will be obtained, unless the x-ray or results from a chest x-ray obtained within 6 months before 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 prior to randomization.

In addition, patients will be tested at screening as indicated in Section 2 for evidence of active or latent TB using the QuantiFERON®-TB Gold test (according to “*Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, United States*” [CDC (WWW)], or other published regional recommendations as applicable). This may be performed by a Lilly-designated or local laboratory. If the QuantiFERON®-TB Gold test is indeterminate, 1 retest is allowed and must be done by QuantiFERON®-TB Gold. If the retest is indeterminate, then the patient will be excluded from the study.

Patients with documentation of a negative test result within 3 months before baseline (Week 0, Visit 2) do not need a TB screen at Visit 1.

However, patients with a positive QuantiFERON®-TB Gold test at screening but with no other evidence of active TB may be re-screened 1 time and may be enrolled without repeating a QuantiFERON®-TB GOLD test if the following conditions are met:

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

If re-screening occurs within 6 months of the date of the screening chest x-ray, there is no need for repeat of chest x-ray for considering enrollment. Patients who have a documented history of completing an appropriate TB treatment regimen with no history of re-exposure to TB since their treatment was completed and no evidence of active TB will be eligible to participate in the study. Patients who have had household contact with a person with active TB will be excluded, unless appropriate and documented prophylaxis for TB was given.



### 9.4.5. **Columbia-Suicide Severity Rating Scale**

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicidal ideation and/or behavior during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if suicidal ideation and/or behavior occurred. The C-SSRS is administered by an appropriately trained healthcare professional with at least 1 year of patient care/clinical experience or some or all of the patients may have this data solicited through electronic patient-reported outcomes (ePRO) technology. The tool was developed by the National Institute of Mental Health trial group (TASA) for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events. Patients will be assessed according to the Schedule of Activities (Section 2). The Self-Harm Supplement Form is a 1-question form that asks for the number of suicidal or nonsuicidal self-injurious behaviors the patient has experienced since the last assessment. For each unique event identified, a questionnaire (Self-Harm Follow-Up Form) which collects supplemental information on the self-injurious behavior is to be completed. The Self-Harm Supplement Form will be completed according to the Schedule of Activities (Section 2).

The non-leading AE collection should occur prior to the collection of the C-SSRS. If a suicide-related event is discovered during the C-SSRS, but was not captured during the non-leading AE collection, sites should not change the AE form. If an event is serious or leads to discontinuation, this is an exception where the SAE and/or AE leading to discontinuation should be included on the AE form and the process for reporting SAEs should be followed.

### 9.4.6. **Safety Monitoring**

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

#### 9.4.6.1. **Neutropenia**

**During treatment with study drug**, patients with neutrophil counts  $<1500$  cells/ $\mu\text{L}$  should be managed for neutropenia as follows:

- $<500$  cells/ $\mu\text{L}$  ( $<0.50 \times 10^3/\mu\text{L}$  or  $<0.50$  GI/L), see discontinuation criteria (Section 8.1.1)
- $\geq 500$  cells/ $\mu\text{L}$  and  $<1000$  cells/ $\mu\text{L}$  ( $\geq 0.50 \times 10^3/\mu\text{L}$  and  $<1.00 \times 10^3/\mu\text{L}$  or  $\geq 0.50$  GI/L and  $<1.00$  GI/L), see discontinuation criteria (Section 8.1.1)
- $\geq 1000$  cells/ $\mu\text{L}$  and  $<1500$  cells/ $\mu\text{L}$  ( $\geq 1.00 \times 10^3/\mu\text{L}$  and  $<1.50 \times 10^3/\mu\text{L}$  or  $\geq 1.00$  GI/L and  $<1.50$  GI/L), and the patient has a concurrent infection that requires systemic anti-infective therapy (e.g., antibiotic, antifungal agent, and antiviral agent):
  - The dose of study drug 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  $\geq 1500$  cells/ $\mu\text{L}$  ( $\geq 1.50 \times 10^3/\mu\text{L}$  or  $\geq 1.50 \times 10^3/\mu\text{L}$ ) and the infection has resolved or is resolving, the patient may resume dosing of study drug and evaluation at scheduled visits. If the neutrophil count remains  $\geq 1000$  cells/ $\mu\text{L}$  and  $<1500$  cells/ $\mu\text{L}$  ( $\geq 1.00 \times 10^3/\mu\text{L}$  and  $<1.50 \times 10^3/\mu\text{L}$  or  $\geq 1.00$  GI/L and  $<1.50$  GI/L), study drug 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  $\geq 1000$  cells/ $\mu\text{L}$  and  $< 1500$  cells/ $\mu\text{L}$  ( $\geq 1.00 \times 10^3/\mu\text{L}$  and  $< 1.50 \times 10^3/\mu\text{L}$  or  $\geq 1.00$  GI/L and  $< 1.50$  GI/L), and:

- a. the infection has not fully resolved, the patient will be discontinued from the study.
  - b. the infection has resolved, the patient may resume dosing and evaluation at scheduled visits. However, if resumption of dosing is not deemed appropriate by the investigator, the patient will be discontinued from the study.
- $\geq 1000$  cells/ $\mu\text{L}$  and  $< 1500$  cells/ $\mu\text{L}$  ( $\geq 1.00 \times 10^3/\mu\text{L}$  and  $< 1.50 \times 10^3/\mu\text{L}$  or  $\geq 1.00$  GI/L and  $< 1.50$  GI/L), and the patient has no concurrent infection that requires systemic anti-infective therapy (e.g., antibiotic, antifungal agent, and 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  $\geq 1500$  cells/ $\mu\text{L}$  ( $\geq 1.50 \times 10^3/\mu\text{L}$  or  $\geq 1.50$  GI/L). If the patient has 3 or more postbaseline neutrophil counts of  $\geq 1000$  cells/ $\mu\text{L}$  ( $\geq 1.00 \times 10^3/\mu\text{L}$  or  $\geq 1.00$  GI/L) and  $< 1500$  cells/ $\mu\text{L}$  ( $< 1.50 \times 10^3/\mu\text{L}$  or  $< 1.50$  GI/L), no value of  $< 1000$  cells/ $\mu\text{L}$  ( $< 1.00 \times 10^3/\mu\text{L}$  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. Management of neutropenia during the Post-Treatment Follow-Up Period (Period 4) is described below.

If, **at the last scheduled visit or ETV**, the patient's neutrophil count is  $< 1500$  cells/ $\mu\text{L}$  ( $< 1.50 \times 10^3/\mu\text{L}$  or  $< 1.50$  GI/L) and less than the patient's baseline neutrophil count, the following measures should be taken:

- [1] 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 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.
- [2] 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 Period 4 design at 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.

[3] For Visit 801 and subsequent visits, the following monitoring applies:

- As long as a patient's neutrophil count is  $<1000$  cells/ $\mu\text{L}$  ( $<1.00 \times 10^3/\mu\text{L}$  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  $\geq 1000$  cells/ $\mu\text{L}$  and  $<1500$  cells/ $\mu\text{L}$  ( $\geq 1.00 \times 10^3/\mu\text{L}$  and  $<1.50 \times 10^3/\mu\text{L}$  or  $\geq 1.00$  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  $\geq 1500$  cells/ $\mu\text{L}$  ( $\geq 1.50 \times 10^3/\mu\text{L}$  or  $\geq 1.50$  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 determines additional follow-up may be necessary.

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

#### **9.4.6.2. Hepatic**

If a study patient experiences elevated ALT  $\geq 3 \times \text{ULN}$ , ALP  $\geq 2 \times \text{ULN}$ , or elevated TBL  $\geq 2 \times \text{ULN}$ , liver testing ([Appendix 4](#)) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

##### **9.4.6.2.1. Hepatic Safety Data Collection**

Additional safety data should be collected via the eCRF if 1 or more of the following conditions occur:

- elevation of serum ALT to  $\geq 5 \times \text{ULN}$  on 2 or more consecutive blood tests
- elevated serum TBL to  $\geq 2 \times \text{ULN}$  (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to  $\geq 2 \times \text{ULN}$  on 2 or more consecutive blood tests
- patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be a SAE

### 9.4.6.3. Hepatitis B Monitoring

Patients who are negative for hepatitis B surface antigen (HBsAg-) and positive for anti-hepatitis B core antibody (HBcAb+) at screening, regardless of other hepatitis B testing results, will have a serum HBV DNA obtained to be analyzed by the central laboratory. Patients who are determined to be HBV DNA negative (undetectable) may be enrolled into the study with required HBV DNA monitoring every 3 to 4 months during treatment and 12 weeks after the last dose of ixekizumab. Patients who are found to be HBV DNA positive (detectable) at screening will be excluded from the trial (see “*Interpretation of Hepatitis B Serologic Test Results*” [CDC resources page (WWW)], or other published regional recommendations as applicable).

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

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

Upon discontinuation from study drug, the patient should be discontinued from the study. Any patient who discontinued the study for any reason will complete the ETV before entering the Post-Treatment Follow-Up Period (Period 4).

## 9.5. Pharmacokinetics

See Section [9.4.2.1](#).

## 9.6. Pharmacodynamics

Not applicable.

## 9.7. Pharmacogenomics or Genetics

Not applicable.

## 9.8. Biomarkers

Not applicable.

## 9.9. Health Economics or Medical Resource Utilization and Health Economics

Not applicable.

## 10. Statistical Considerations

### 10.1. Sample Size Determination

Approximately 960 patients will be randomized at a 1:1 ratio to ixekizumab 80 mg Q2W and guselkumab 100 mg Q8W. With 480 patients per treatment group, this study will have 98% power to test the superiority of ixekizumab 80 mg Q2W to guselkumab 100 mg Q8W for PASI 100 at Week 12. The following assumptions were used for the power calculation response rate at Week 12: 35.3% and 23.0% for ixekizumab and guselkumab group, respectively. A 2-sided Fisher’s exact test at significance level 0.05 is assumed. These assumptions are based on the ixekizumab and guselkumab clinical studies in Ps (Griffiths et al. 2015; Gordon et al. 2016; Blauvelt et al. 2017; Reich et al. 2017).

This study is also powered at 95% to test the superiority of ixekizumab for PASI 100 at Week 24 assuming the response rate of ixekizumab and guselkumab at 56% and 44%, respectively.

### 10.2. Populations for Analyses

Unless otherwise specified, efficacy and health outcome analyses will be conducted on the intent-to-treat (ITT) population; whereas, safety analyses will be conducted on the safety population defined below:

Population	Description
Intent-to-Treat Population	All randomized patients, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Patients will be analyzed according to the treatment to which they were assigned.
Safety	All randomized participants who take at least 1 dose of study drug. Participants will be included in the treatment group to which they were randomized. In the event of a treatment error, participants will be analyzed according to the treatment they actually received.

### 10.3. Statistical Analyses

#### 10.3.1. General Statistical Considerations

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

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

Unless otherwise specified, efficacy, and health outcome analyses will be conducted on the ITT population. This set includes all data from all randomized patients according to the treatment the patients were assigned, regardless of whether they received the treatment or not.

The randomization to treatment groups is stratified by site as described in Section 7.2. Study sites with fewer than 5 randomized patients per treatment group will be pooled for statistical analysis purposes. All efficacy and health outcomes analyses will use pooled sites.

All tests of treatment effects will be 2-sided, unless otherwise stated.

The Induction Dosing Period (Period 2) starts at the first injection of study drug at Week 0 (Visit 2) and ends prior to the first injection of study drug at Week 12 or the ETV (between Weeks 0 and 12).

Baseline will be defined as the last available value before the first injection for efficacy, health outcomes, and safety analyses. In most cases, this will be the measure 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 the randomization date will be used. Change from baseline will be calculated as the visit value of interest 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.

The primary analysis method for treatment comparisons of categorical efficacy, health outcomes variables at specific time points will be made using a Cochran-Mantel-Haenszel (CMH) test stratified by pooled site. Missing data will be imputed using the nonresponder imputation (NRI) method. The 95% confidence interval (CI) associated with the treatment response rate, and treatment difference will be provided. Secondary analysis will be conducted using a Fisher's exact test.

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, pooled site, baseline value, visit, treatment-by-visit interaction and baseline value-by-visit as fixed factors. A secondary analysis for continuous efficacy and health outcomes variables will be made using analysis of covariance (ANCOVA) adjusting for pooled site and baseline value.

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

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.

### **10.3.2. Treatment Group Comparability**

#### **10.3.2.1. Patient Disposition**

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

Patient disposition will be summarized for each treatment period. Reasons for discontinuation from the study will be tabulated by treatment randomized. A detailed description of patient disposition will be provided at the end of the study.

#### **10.3.2.2. Patient Characteristics**

Patient characteristics and baseline clinical measures will be recorded and summarized by treatment group. Baseline characteristics will include gender, age, height, weight, race, duration of disease, previous nonbiologic systemic therapy, and previous biologic therapy. Baseline clinical and health outcome measurements will include sPGA, PASI, BSA, Itch NRS, DLQI, skin pain and patient global assessment, PGA-F, physician's global assessment of disease activity VAS, patient's assessment of pain VAS, patient's global assessment of disease activity VAS, and C-SSRS.

Comparisons between treatment groups will be conducted using Fisher's exact test and analysis of variance (ANOVA) for categorical data and continuous data, respectively.

#### **10.3.2.3. Concomitant Therapy**

Previous and concomitant medications will be summarized for patients who enter each treatment period and presented by World Health Organization Anatomic Therapeutic Class (WHOATC) Level 4 and generic name.

#### **10.3.2.4. Treatment Compliance**

Treatment compliance with study drug will be summarized for each treatment period separately. Overall compliance with therapy is defined to be missing no more than 20% of the expected doses and not missing 2 consecutive doses. A patient will be considered compliant overall for each study period if he/she is missing no more than 20% of the expected doses and not missing 2 consecutive doses. Proportions of patients compliant by visit and overall will be compared between treatment groups. Detailed analytical method for comparison will be defined in the statistical analysis plan (SAP).

### **10.3.3. Efficacy Analyses**

#### **10.3.3.1. Primary Analyses**

The primary analysis, that is, the proportion of patients who achieve PASI 100 at Week 12, will be based on the ITT population.

Treatment comparisons between ixekizumab treatment group and guselkumab in the proportion of patients achieving a PASI 100 response at Week 12 will be made using the CMH test stratified by pooled site. Missing data will be imputed using the NRI method. The 95% CI associated with the treatment response rate, and treatment difference will be provided.

Secondary analyses for PASI 100 at Week 12 will be conducted using Fisher's exact test.

#### **10.3.3.2. Major Secondary Analyses**

[Table RHCR.10.1](#) summarizes the primary and major secondary outcomes and analysis methods. All analyses listed will be performed based on the ITT Population unless otherwise specified.

A graphical multiple testing strategy for the primary and major secondary objectives will be implemented to control the overall family-wise type I error rate at a 2-sided  $\alpha$  level of 0.05. Detail multiplicity control will be detailed in SAP.

**Table RHCR.10.1. Primary and Major Secondary Outcome Analyses**

	Outcome Measure	Primary Analytical Method	Secondary Analytical Method
Primary Efficacy Endpoint	PASI 100 at Week 12	CMH test with NRI	Fisher's exact test with NRI
Major Secondary Endpoints	PASI 75 at Week 2	CMH test with NRI	Fisher's exact test with NRI
	PASI 90 at Week 4	CMH test with NRI	Fisher's exact test with NRI
	PASI 100 at Week 4	CMH test with NRI	Fisher's exact test with NRI
	PASI 100 at Week 8	CMH test with NRI	Fisher's exact test with NRI
	PASI 90 at Week 8	CMH test with NRI	Fisher's exact test with NRI
	sPGA (0) at Week 12	CMH test with NRI	Fisher's exact test with NRI
	PASI 100 at Week 24	CMH test with NRI	Fisher's exact test with NRI
	PASI 50 at Week 1	CMH test with NRI	Fisher's exact test with NRI

Abbreviations: CMH = Cochran-Mantel-Haenszel; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; sPGA = static Physician Global Assessment.

### 10.3.3.3. Exploratory Efficacy Analyses

The exploratory endpoints listed in [Table RHCR.4.1](#) will be analyzed as appropriate. Details of analyses will be included in the SAP.

### 10.3.4. Safety Analyses

Safety will be assessed by summarizing and analyzing AEs including adjudicated cerebro-cardiovascular events, laboratory analytes including neutrophil counts, and C-SSRS. The duration of treatment exposure will also be summarized.

The safety analyses will focus on comparison of ixekizumab to guselkumab for the Induction Dosing Period (Period 2). Safety data will also be separately summarized for the combined Induction Dosing Period (Period 2) and Extension Period (Period 3), as well as Post-Treatment Follow-Up (Period 4). All safety analyses will be conducted on the Safety Population.

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

#### 10.3.4.1. Adverse Events

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



baseline and on or prior to the date of the last visit within the treatment period. Both the date/time of the event onset and the date/time of the first study drug injection are considered when determining TEAEs. Treatment-emergent adverse events will be assigned to the treatment period in which they first occurred or worsened. A follow-up emergent AE (FEAE) is defined as an event that first occurred or worsened in severity after the date of Week 24 or the ETV. For events that are gender specific, the denominator and computation of the percentage will include only patients from the given gender.

An overall summary of AEs will be provided for each of the treatment periods, including the number and percentage of patients who experienced TEAEs, TEAEs by maximum severity, deaths, SAEs, TEAEs related to study drug, discontinuations from the treatment due to an AE, and treatment-emergent AESIs. Treatment-emergent AEs (all, by maximum severity, and TEAEs possibly related to study drug by the investigator), SAEs including deaths, and AEs that lead to treatment discontinuation will be summarized and analyzed by MedDRA System Organ Class, and Preferred Term.

In addition to general safety parameters, safety information on specific topics of AESIs will also be presented. Potential AESIs will be identified by a standardized MedDRA query or a Lilly defined MedDRA preferred term listing.

Follow-up emergent adverse events, SAEs including deaths, and AEs that lead to study discontinuation will be summarized for Post-Treatment Follow-Up Period (Period 4).

#### 10.3.4.2. 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 (see below). 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 post baseline.
- 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 post baseline.
  - 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 post baseline.

#### 10.3.4.3. Other Safety Evaluations

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

Further details for these analyses will be provided in the SAP.

### **10.3.5. Evaluation of Immunogenicity**

For patients randomized to ixekizumab who experience a potential systemic allergic/hypersensitivity event during the study, an immunogenicity sample will be collected and evaluated for ADA compared to a stored baseline sample if possible. Immunogenicity samples will not be evaluated for anti-guselkumab antibodies.

### **10.3.6. Other Analyses**

#### **10.3.6.1. Subgroup Analyses**

The effect of the following baseline characteristics on the primary efficacy endpoint, PASI 100 at Week 12, will be assessed:

- Demographics (e.g., gender, age, weight, and race)
- Disease characteristics (e.g., disease severity, duration of disease, and age of onset)
- Previous treatment for Ps (e.g., previous use of nonbiologic systemic therapy, and previous use of biologic therapy)

Detailed description of the subgroup variables will be provided in the SAP. Additional subgroup analyses on efficacy or subgroup analyses on safety may be performed as deemed appropriate and necessary.

### **10.3.7. Interim Analyses**

One interim analysis is planned when all patients have completed their Week 12 visit or ETV. The interim analysis will include all data collected by the cutoff date, including the data from the Extension Period (Period 3) and the Post Treatment Follow-Up Period (Period 4). The analyses from the Week 12 lock will be treated as a primary analysis because all primary and major secondary objectives, except for PASI 100 at Week 24, will be assessed at this time.

Prior to a Week 12 database lock, all members of the study team will be blinded to the treatment allocations. At the time of the Week 12 database lock, study team members that do not have direct access to study sites will have access to the unblinded treatment allocation and unblinded data. Study team members that have direct access to study sites and data collection will remain blinded to the treatment allocations until all patients have completed the study (or discontinued on or prior to Week 24) and final database lock has occurred. Site staff, clinical monitors, and patients will remain blinded to the patient treatment allocation until after final database lock.

Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded. All investigators, patients and personnel in contact with study sites will be kept blinded to treatment assignments until final CSR is complete.

Additional analyses and snapshots of study data may be performed after all patients complete Period 3 (Week 24 or ETV) to fulfill the need for regulatory interactions or publication purposes.

Unblinding details are specified in the unblinding plan section of the SAP or a separate unblinding plan document.

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## 12. Appendices

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## Appendix 1. Abbreviations and Definitions

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Term	Definition
<b>ADA</b>	anti-drug antibody
<b>AE</b>	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.
<b>AESI</b>	adverse events of special interest
<b>ALT</b>	alanine aminotransferase
<b>ALP</b>	alkaline phosphatase
<b>ANCOVA</b>	analysis of covariance
<b>AST</b>	aspartate aminotransferase
<b>BCG</b>	Bacillus Calmette-Guérin
<b>Blinding/masking</b>	<p>A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not.</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>
<b>BSA</b>	body surface area
<b>CEC</b>	Clinical Events Committee
<b>CFR</b>	Code of Federal Regulations
<b>CI</b>	confidence interval
<b>CIOMS</b>	Council for International Organizations of Medical Sciences
<b>CMH</b>	Cochran-Mantel-Haenszel
<b>complaint</b>	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.
<b>compliance</b>	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.



<b>consent</b>	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
<b>CRF/eCRF</b>	Case report form/electronic case report form: Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
<b>CRP/CRS</b>	clinical research physician/clinical research scientist: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, CRS, global safety physician or other medical officer.
<b>CSR</b>	clinical study report
<b>C-SSRS</b>	Columbia-Suicide Severity Rating Scale
<b>DLQI</b>	dermatology life quality index
<b>DNA</b>	deoxyribonucleic acid
<b>DSM-IV</b>	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
<b>EDC</b>	electronic data capture
<b>EMA</b>	European Medicines Agency
<b>ERB/IRB</b>	Ethical review board/institutional review board: A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
<b>end of study (trial)</b>	End of study (trial) is the date of the last visit or last scheduled procedure shown in the Schedule of Events for the last patient.
<b>enroll</b>	The act of assigning a patient to a treatment. Patient who are enrolled in the study are those who have been assigned to a treatment.
<b>enter</b>	Patient entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
<b>ETV</b>	Early Termination Visit
<b>FSH</b>	Follicle-stimulating hormone
<b>GCP</b>	good clinical practice
<b>HBcAb</b>	anti-hepatitis B virus core antibody
<b>HBsAg</b>	hepatitis B virus surface antigen
<b>HBV</b>	hepatitis B virus
<b>HCV</b>	hepatitis C virus

<b>HIV</b>	human immunodeficiency virus
<b>IB</b>	Investigator's Brochure
<b>IBD</b>	inflammatory bowel disease
<b>ICF</b>	informed consent form
<b>ICH</b>	International Council for Harmonisation
<b>IGA</b>	Investigator Global Assessment
<b>IgG</b>	immunoglobulin G
<b>IL</b>	interleukin
<b>Informed consent</b>	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
<b>interim analysis</b>	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.
<b>informed consent</b>	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
<b>INR</b>	international normalized ratio
<b>ITT</b>	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.
<b>IWRS</b>	interactive voice-response system/interactive web-response system
<b>LS</b>	least-squares
<b>MAb</b>	monoclonal antibody
<b>MedDRA</b>	Medical Dictionary for Regulatory Activities
<b>MI</b>	myocardial infarction
<b>MMRM</b>	mixed model for repeated measures
<b>MTX</b>	methotrexate
<b>NRI</b>	nonresponder imputation

<b>NRS</b>	numeric rating scale
<b>PASI</b>	Psoriasis Area and Severity Index
<b>PASI 50/75/90</b>	at least a ( $\geq$ )50%/75%/90% improvement in PASI score from baseline
<b>PASI 100</b>	a 100% improvement in PASI score from baseline
<b>PatGA</b>	Patient's global assessment of disease severity
<b>PGA-F</b>	Physician's Global Assessment of Fingernail Psoriasis
<b>PK</b>	pharmacokinetics
<b>PPS</b>	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.
<b>PRO/ePRO</b>	patient-reported outcomes/electronic patient-reported outcomes
<b>Ps</b>	plaque psoriasis
<b>PsA</b>	psoriatic arthritis
<b>Q2W</b>	every 2 weeks
<b>Q4W</b>	every 4 weeks
<b>Q8W</b>	every 8 weeks
<b>randomize</b>	The process of assigning patients to an experimental group on a random basis.
<b>re-screen</b>	To screen a patient who was previously declared a screen failure for the same study.
<b>SAE</b>	serious adverse event
<b>SAP</b>	statistical analysis plan
<b>SC</b>	subcutaneous
<b>sPGA</b>	static Physician Global Assessment
<b>screen</b>	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.
<b>study drug</b>	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.
<b>SUSARs</b>	suspected unexpected serious adverse reactions
<b>TB</b>	tuberculosis

<b>TBL</b>	total bilirubin level
<b>TEAE</b>	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
<b>Th</b>	T helper
<b>TNF</b>	tumor necrosis factor
<b>TNFi</b>	TNF inhibitor
<b>TPO</b>	third-party organization
<b>ULN</b>	upper limit of normal
<b>USPI</b>	United States Package Insert
<b>VAS</b>	visual analog scale
<b>WBC</b>	white blood cell

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## Appendix 2. Clinical Laboratory Tests

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**Hematology<sup>a,b</sup>**

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

**Urinalysis (dipstick)<sup>a,b</sup>**

color  
 Specific gravity  
 pH  
 Protein  
 Glucose<sup>g</sup>  
 Ketones  
 Bilirubin  
 Urobilinogen  
 Blood  
 Nitrite  
 Urine creatinine  
 Leukocyte esterase  
 Urinalysis (microscopic):  
 Sediment, cells, casts

**Other Tests<sup>a</sup>**

Human immunodeficiency virus antibody (HIV)<sup>c,d</sup>  
 Hepatitis B Surface antigen (HBsAg)<sup>c,d</sup>  
 Anti-Hepatitis B Core antibody (HBcAb)<sup>c,d</sup>  
 Anti-Hepatitis B Surface antibody (HBsAb)<sup>d</sup>  
 Anti-Hepatitis C antibody<sup>c,d</sup>  
 HBV DNA<sup>c,d</sup>

Tuberculosis<sup>d</sup>

**Serum Chemistry<sup>a,b</sup>**

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<sup>g</sup>  
 Albumin  
 Cholesterol (total)  
 Total protein  
 CPK  
 Triglycerides  
 Gamma-Glutamyl Transferase (GGT)

**Immunogenicity**

Ixekizumab serum concentration

Pregnancy Test (serum and urine)<sup>e</sup>  
 Follicle stimulating hormone (FSH)<sup>d,f</sup>

**Clinical Safety Laboratory Tests**

Abbreviations: CPK = creatine phosphokinase; DNA = deoxyribonucleic acid; HBV = hepatitis B virus; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cells.

- a Assayed by sponsor-designated laboratory.
- b Unscheduled blood chemistry, urinalysis, and hematology panels may be performed at the discretion of the investigator.
- c See exclusion criteria (Section 6.2).
- d Test required at Visit 1 only to determine eligibility of patient for the study (note: with the exception of those patients who require further HBV monitoring [Section 9.4.6.3]).
- e 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 24. 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 study drug (see Section 8.1.1).
- f Women  $\geq 40$  and <60 years of age who have had a cessation of menses for  $\geq 12$  months will have an FSH test confirming nonchildbearing potential ( $\geq 40$  mIU/mL). FSH test will be performed centrally.
- g non-fasting glucose.

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**Appendix 3. Study Governance Considerations**

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

### ***Appendix 3.1.1. Informed Consent***

The investigator is responsible for:

- ensuring that the patient understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of study drug.
- 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 patients willingness to continue his or her participation in the study.
- ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

### ***Appendix 3.1.2. Recruitment***

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes.

### ***Appendix 3.1.3. Ethical Review***

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

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

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

- the protocol and related amendments and addenda, current Investigator Brochure (IB) and updates during the course of the study
- informed consent form
- other relevant documents (e.g., curricula vitae, advertisements)



**Appendix 3.1.4. Regulatory Considerations**

This study will be conducted in accordance with the protocol and with the:

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

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

**Appendix 3.1.5. Investigator Information**

Physicians with a specialty in dermatology or other relevant specialties with appropriate experience in diagnosis and treatment of patients with psoriasis will participate as investigators in this clinical trial.

**Appendix 3.1.6. Protocol Signatures**

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

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

**Appendix 3.1.7. Final Report Signature**

The investigator will sign the final clinical study report (CSR) for this study, indicating agreement with the analyses, results, and conclusions of the report.

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 investigator with the most analyzable and enrolled patients will serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

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

## Appendix 3.2. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate
- provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and verify data reported to detect potential errors

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

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

### **Appendix 3.2.1. Data Capture System**

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture (EDC) system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Clinical outcome assessment (COA) data (questionnaires) will be collected by the investigator site personnel from the patient, via a paper source document and will be transcribed by the investigator site personnel into the EDC system.

Additionally, electronic Clinical Outcome Assessment (eCOA) data (questionnaires, scales, rating scales etc.) will be directly recorded by the subject/investigator site personnel, into an instrument (e.g., hand held tablet). The eCOA data will serve as the source documentation and the investigator does not maintain a separate, written or electronic record of these data.

Data collected via the sponsor-provided data capture system(s) will be stored at a third-party site. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly Clinical Laboratory Results Modernization database.

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

### **Appendix 3.3. Study and Site Closure**

#### ***Appendix 3.3.1. Discontinuation of Study Sites***

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

#### ***Appendix 3.3.2. Discontinuation of the Study***

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

#### ***Appendix 3.4. Publication Policy***

The publication policy for Study IIF-MC-RHCR is described in the letters of agreement between the Sponsor and the investigators and institutions.

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## Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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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

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#### Hepatic Hematology<sup>a</sup>

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

#### Hepatic Chemistry<sup>a</sup>

Total bilirubin  
Direct bilirubin  
Alkaline phosphatase  
ALT  
AST  
  
GGT  
CPK

#### Haptoglobin<sup>a</sup>

#### Hepatic Serologies<sup>a,b</sup>

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<sup>a</sup>

#### Alkaline Phosphatase Isoenzymes<sup>a</sup>

#### Anti-smooth muscle antibody (or anti-actin antibody)<sup>a</sup>

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

<sup>a</sup> Assayed by Lilly-designated or local laboratory.

<sup>b</sup> Reflex/confirmation dependent on regulatory requirements and/or testing availability.

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**Appendix 5. Protocol Amendment I1F-MC-RHCR(b)  
Summary: A 24 Week Multicenter, Randomized, Double  
Blind, Parallel Group Study Comparing the Efficacy and  
Safety of Ixekizumab to Guselkumab in Patients with  
Moderate to Severe Plaque Psoriasis**

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## **Overview**

Protocol I1F-MC-RHCR(a) A 24 Week Multicenter, Randomized, Double Blind, Parallel Group Study Comparing the Efficacy and Safety of Ixekizumab to Guselkumab in Patients with Moderate to Severe Plaque Psoriasis has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

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

**Amendment Summary for Protocol I1F-MC-RHCR Amendment (b)**

Section # and Name	Description of Change	Brief Rationale
5.1 Overall Design	Added the following clarification to “the other appropriate means” of patient blinding by the Unblinded Site Personnel: “physical barrier means communicated to the sponsor for final approval.”	Improve clarity
5.2 Number of Participants	Rephrased 1 <sup>st</sup> sentence of the 2 <sup>nd</sup> paragraph and replaced “treatment with” with “exposure to” in the last sentence of the 2 <sup>nd</sup> paragraph.	Improve clarity
6.2 Exclusion Criteria	<u>Exclusion criteria # [15]</u> Removed the restriction of participation in any study investigating other IL-17 antagonists.	Based on recent protocol review and feedback received, a decision was made to be consistent regarding the current or recent use of other IL-17 antagonists. This amendment is to be consistent with the eligible population despite of the source of the exposure. Prior exposure to other IL-17 antagonist in clinical trial settings will be allowed as long as all other inclusion/exclusion criteria are respected; especially > 5 half-lives washout period before baseline visit (Week 0, Visit 2). As specified in Section 5.2 of the protocol, the patient population with previous exposure to another IL-17 antagonist(s) will be limited to approximately 15% of the total patient population.

Section # and Name	Description of Change	Brief Rationale
6.2 Exclusion Criteria	<p><u>Exclusion criteria # [22]</u>                      Added the following clarifications:                      “except for basal cell carcinoma, squamous cell carcinoma, skin Bowen’s disease or actinic keratosis that have been treated with no evidence of recurrence in the past 12 weeks or carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed.”</p>	<p>This addition is to clarify that subjects with the types of non-invasive malignancies and Non-Melanoma Skin Cancers (NMSC), as described in the clarification, can be included in this study, if they have been successfully treated with no evidence of recurrence. This is similar to other biologicals psoriasis studies and aligned with both products labels. In Lilly’s opinion, including such patients in this short study (24 weeks of active treatment periods) will not pose an increased risk of such events since similar populations have previously participated in other biological psoriasis studies.</p>
6.2.1 Rationale for Exclusion of Certain Study Candidates	<p>Removed IL-17 antagonist from the description of exclusion criteria and editorial changes.</p>	<p>For content consistency as a result of changes made to Exclusion Criteria #[15].</p>
7.8 Concomitant Therapy	<p><u>Table RHCR.7.3</u>                      Drug Class “IL 17, IL-23p19 antagonists, other than the 2 products used as part of this protocol”:                      Removed IL-17 and replaced “treatment with” with “exposure to” in the description of Condition for Use.</p>	<p>For content consistency as a result of changes made to Exclusion Criteria #[15] and improve clarity.</p>

## Revised Protocol Sections

<b>Note:</b> Deletions have been identified by <del>strikethroughs</del> . Additions have been identified by the use of <u>underscore</u> .
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### 5.1. Overall Design

Unblinded Site Personnel are also responsible for maintaining the blind of the patient (e.g., by means of a blindfold or other appropriate physical barrier means communicated to the sponsor for final approval).

### 5.2. Number of Participants

Patients with previous biologic use (~~note: except concurrent or recent use of any biologic agent < 5 half-lives~~) will be can be included in the study provided all inclusion/exclusion criteria, including the washout period(s), as specified in (see Sections 6.1 and 6.2)-of this protocol are respected. Patients with previous ~~treatment with~~ exposure to another IL-17 antagonist(s) will be limited to approximately 15% of the total patient population.

### 6.2. Exclusion Criteria

- [15] Have previously completed or withdrawn from this study, participated in any other study with ixekizumab or guselkumab, have participated in any study investigating ~~other IL-17 or~~ IL-23p19 antagonists, or have received treatment with ixekizumab.
- [22] Have current or a history of lymphoproliferative disease, or signs or symptoms of lymphoproliferative disease within 5 years of baseline (Week 0, Visit 2); or have active or history of malignant disease within 5 years of baseline (Week 0, Visit 2), except for basal cell carcinoma, squamous cell carcinoma, skin Bowen's disease or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks or carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed.

(Note: patients with history of malignancy with no evidence of recurrence or active disease within 5 years of baseline may participate in the study).

#### 6.2.1 Rationale for Exclusion of Certain Study Candidates

Exclusion Criteria [12] through [16] exclude patients who have prior exposure to: guselkumab, or any IL-23p19 antagonist, or ixekizumab or any IL-17 antagonist (note: see details in Sections 6.2 and 5.2), or any patients who are receiving treatment or concomitant medications that could have a negative impact on the safety of patients enrolled or confound the results of the study.



7.8. Concomitant Therapy

**Table RHCR.7.3. Concomitant Medications Permitted/Not Permitted in the Study and Conditions for Use**

IL-17, IL-23p19 antagonists, other than the 2 products used as part of this protocol.	Not permitted	Must have never received ixekizumab or IL-23p19 antagonists; or participated in any study investigating <del>IL-17</del> , and IL-23p19 antagonists. Patient with previous <del>treatment</del> <u>with exposure</u> to another IL-17 antagonist(s) will be limited to approximately 15% of the total patient population.
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Leo Document ID = 3370197c-0e46-4820-9021-8de9b79bc46c

Approver: PPD [REDACTED]  
Approval Date & Time: 07-Dec-2018 18:47:26 GMT  
Signature meaning: Approved

Approver: PPD [REDACTED]  
Approval Date & Time: 07-Dec-2018 19:02:47 GMT  
Signature meaning: Approved