Protocol I1F-MC-RHCD(b)
Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Efficacy of Ixekizumab in Patients from 6 to Less than 18 Years of Age with Moderate-to-Severe Plaque Psoriasis

Confidential Information

Ixekizumab (LY2439821)

Study I1F-MC-RHCD is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study examining the effects of ixekizumab versus placebo in subjects from 6 to <18 years of age with moderate-to-severe plaque psoriasis (Psoriasis Area and Severity Index score ≥12, sPGA ≥3, and body surface area ≥10% at screening and baseline) and including etanercept as a reference group.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly: 30 November 2016
Amendment (a) Electronically Signed and Approved by Lilly: 20 July 2017

Amendment (b) Electronically Signed and Approved by Lilly on approval date provided below:

Approval Date: 22-Sep-2018 GMT

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1. Synopsis

Title of Study:
Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Efficacy of Ixekizumab in Patients from 6 to Less than 18 Years of Age with Moderate-to-Severe Plaque Psoriasis

Note that patients will be described as subjects throughout this document.

Rationale:
There is an unmet medical need for effective and safe therapies for children and adolescents with moderate-to-severe plaque psoriasis (Ps). Ixekizumab has been approved for the treatment of adults with moderate-to-severe plaque Ps and psoriatic arthritis (PsA) in a number of countries globally. It has also been approved for adults with Pustular Ps and Erythrodermic Ps in Japan and is currently being studied in adults with axial spondyloarthritis. This study is part of the European Pediatric Investigation Plan (PIP) and United States of America (USA) Pediatric Study Plan, and it is intended to investigate the safety, efficacy, and pharmacokinetics (PK) of ixekizumab in pediatric subjects (children and adolescents). Protocol Addendum I1F-MC-RHCD(1) describes additional PK sampling for a subgroup of subjects, which will be used to help define the PK of ixekizumab in pediatric subjects. Protocol Addendum I1F-MC-RHCD(2) states that in countries where etanercept is approved for severe pediatric plaque Ps treatment only (emerging markets and European countries), subjects may be randomized to etanercept. Protocol Addendum I1F-MC-RHCD(2) contains an active-controlled reference group (etanercept) during the Double-Blind Treatment Induction Period (Period 2). Additionally, subjects from European Union (EU) countries who meet the response criterion (defined as static Physician's Global Assessment [sPGA] [0,1]) at Week 60 will be re-randomized to ixekizumab or placebo (1:1 ratio) during a 48-Week Double-Blind, Randomized Withdrawal Period during Period 4.

Objectives/Endpoints:

Objectives	Endpoints
Co-Primary to assess whether ixekizumab Q4W is superior to placebo at Week 12 (Visit 7) in the treatment of pediatric subjects (children and adolescents) with moderate-to-severe plaque psoriasis as measured by PASI 75 and by sPGA (0,1)	• proportion of subjects achieving PASI 75 at Week 12 • proportion of subjects achieving sPGA (0,1) at Week 12
Gated Secondary to assess whether ixekizumab Q4W is superior to placebo as measured by: • PASI 90 • sPGA (0) • PASI 100 • Itch NRS • PASI 75 • sPGA (0,1)	• proportion of subjects achieving PASI 90 at Week 12 • proportion of subjects achieving sPGA (0) at Week 12 • proportion of subjects achieving PASI 100 at Week 12 • Proportion of subjects with an improvement of ≥4 in Itch NRS at Week 12 for subjects who had a baseline Itch NRS ≥4 • proportion of subjects achieving PASI 75 at Week 2 • proportion of subjects achieving sPGA (0,1) at Week 2

Objectives	Endpoints
Other Secondary to assess whether ixekizumab Q4W is superior to placebo	The following endpoints will be assessed at Week 12 and at each postbaseline visit during the Double-Blind Treatment Period: • proportion of subjects achieving PASI 50, PASI 75, PASI 90, and PASI 100 • proportion of subjects achieving sPGA (0,1) and sPGA (0) • change from baseline in itching severity (Itch NRS) score • CDLQI/DLQI (0,1) • change from baseline in NAPSI, PSSI, and/or PPASI score in case of nail, scalp, or hand/feet involvement
to summarize the efficacy of ixekizumab Q4W at Week 24 (Visit 10) and Week 48 (Visit 16) as measured by: • PASI 75 • sPGA (0,1) • PASI 90 • sPGA (0) • PASI 100	The following endpoints will be assessed: • proportion of subjects achieving PASI 75 at Weeks 24 and 48 • proportion of subjects achieving sPGA (0,1) at Weeks 24 and 48 • proportion of subjects achieving PASI 90 at Weeks 24 and 48 • proportion of subjects achieving sPGA (0) at Weeks 24 and 48 • proportion of subjects achieving PASI 100 at Weeks 24 and 48
to evaluate the potential development of anti-ixekizumab antibodies and its impact on subject efficacy of Ixekizumab	• PASI 75 and sPGA(0,1) at Week 12 correlated with treatment-emergent antidrug antibody titer (low, moderate, and high) and by NAb status
to measure ixekizumab exposure and characterize the pharmacokinetics of ixekizumab in pediatric subjects	• serum trough concentrations of ixekizumab
to assess the relationship between exposure and efficacy and exposure and immunogenicity	• model parameters for the exposure-response relationship between ixekizumab serum trough concentrations and efficacy endpoints (e.g., sPGA, PASI) at Week 12 • serum trough concentrations for ixekizumab antibody titer subgroups
to assess the safety of ixekizumab	• to evaluate the safety of ixekizumab, including but not limited to infections; injection-site reactions; B-, T-, and NK-cell levels; WBC count; RBC count; and laboratory values (hematology and chemistry [including ALT and AST]) during the course of the study

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; Nab = neutralizing antidrug antibody; NAPSI = Nail Psoriasis Severity Index; NK = natural killer; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PASI 50 = at least a 50% improvement from baseline in PASI score; PASI 75 = at least a 75% improvement from baseline in PASI score; PASI 90 = at least a 90% improvement from baseline in PASI score; PASI 100 = a 100% improvement from baseline in PASI score; PPASI = Palmoplantar Psoriasis Severity Index; PSSI = Psoriasis Severity Index; Q4W = every 4 weeks; RBC = red blood cell; sPGA = static Physician's Global Assessment; WBC = white blood cell.

Summary of Study Design:

Study I1F-MC-RHCD is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study examining the effects of ixekizumab versus placebo in subjects from 6 to <18 years of age with moderate-to-severe plaque Ps (Psoriasis Area and Severity Index [PASI] score ≥12, sPGA ≥3, and body surface area [BSA] ≥10% at screening and baseline). There is an active-controlled (etanercept) portion of the study design detailed in Protocol Addendum I1F-MC-RHCD(2).

Treatment Groups and Duration:

Subjects will receive placebo or ixekizumab during the Double-Blind Treatment Period (Induction Period) (Week 0 to Week 12) and open-label ixekizumab during the Maintenance Period (Week 12 to Week 60) and Extension Period (Week 60 to Week 108). The selected ixekizumab doses are: 1) 80 mg every 4 weeks (Q4W) (with a starting dose of 160 mg) for subjects >50 kg; 2) 40 mg Q4W (with a starting dose of 80 mg) for subjects 25 to 50 kg; and 3) 20 mg Q4W (with a starting dose of 40 mg) for subjects <25 kg.

Number of Subjects:

Approximately 195 subjects will be randomized to the study. Approximately 165 subjects will be randomized in a 2:1 ratio to receive ixekizumab (110 subjects) or placebo (55 subjects) during the Double-Blind Treatment Period. Approximately 30 subjects in countries where etanercept is approved for severe pediatric plaque Ps treatment only (emerging markets and European countries) will receive etanercept during the Double-Blind Treatment Period as described in Protocol Addendum I1F-MC-RHCD(2).

Statistical Analysis:

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. Comparisons between ixekizumab and placebo will be performed for all analyses in the Double-Blind Treatment Induction Period (Period 2). Change from baseline will be calculated as the visit value of interest minus the baseline value.

Efficacy Analyses:

Efficacy analyses will be conducted for the Double-Blind Treatment Induction Period (Period 2) and all ixekizumab treatment periods. The primary analysis will be based on the intent to treat (ITT) Population for Period 2, Induction. In addition, an analysis of the Per-Protocol Population will be used to support the primary efficacy analysis. Treatment comparisons in the proportion of subjects achieving at least a 75% improvement from baseline in PASI score (PASI 75) response and the proportion of subjects with sPGA (0,1) at Week 12 will be analyzed using Fisher's exact test.

Pharmacokinetics/Pharmacodynamics:

The PK of ixekizumab in pediatric subjects will be determined using population PK methods. The exposure-response relationship will be investigated between observed steady-state trough concentrations of ixekizumab and clinically important efficacy measures (e.g., sPGA and PASI endpoints).

Health Outcomes:

The following health outcomes/quality of life scales will be used: Itch NRS, DLQI, CDLQI, patient's global assessment of disease severity.

Safety Analyses:

Safety of ixekizumab, including but not limited to infections; injection-site reactions; B-, T-, and natural killer (NK)-cell levels; WBC count; RBC count; and laboratory values (hematology and chemistry [including ALT and AST]) will be assessed.

Safety analyses will be conducted for the Double-Blind Treatment Induction Period (Period 2) and for all ixekizumab treatment periods. Safety analysis will be based on the Safety Population. Safety will be assessed by summarizing and analyzing adverse events (AEs); laboratory analytes, including neutrophil counts; Children's Depression Rating Scale (CDRS); Columbia-Suicide Severity Rating Scale (C-SSRS); and vital signs. The duration of treatment will also be summarized.

Vaccination Effects:

Immunization history will be recorded at baseline, and any unexpected outcomes or effects related to standard-of-care vaccination will be summarized.

Interim Analyses:

Two interim analyses will be conducted. The first interim analysis of PK, safety, and select efficacy data on all subjects will be conducted after approximately 15 subjects have completed to Week 12 in the 25- to 50-kg weight group. A second interim analysis will be performed at the time (that is, a cutoff date) the last subject completes Study Period 2, Induction (Week 12) or at the Early Termination Visit. Additional analyses and snapshots of study data may be performed during and/or after completion of Period 3 and/or Period 4 to fulfill the need for regulatory interactions or publication purposes.

2. Schedule of Activities

Schedule of Activities, Protocol I1F-MC-RHCD
Screening (Period 1) and Double-Blind Treatment Induction Period (Period 2)

	Screening (Period 1)	Double-Blind Treatment Induction Period (Period 2)					
		Randomization					
Visit No	V1	V2	V3	V4	V5	V6	V7
Study Week		W0	W1	W4	W6	W8	W12
Study Days (Approximately)	-30 to -7 d	1	7 ± 2d	28 ± 2d	42 ± 2d	56 ± 2d	84 ± 2d
Informed consent and assent[a]	X						
Complete medical history[b]	X						
Immunization record	X	X	X	X	X	X	X
Demographics[c]	X						
Physical examination[d]	X						X
Height	X						X
Weight	X	X	X	X	X	X	X
Habits[e]	X						X
Inclusion/exclusion criteria[f]	X	X					
Vital signs (BP, pulse, body temperature)[g]	X	X		X		X	X
Concomitant medications	X	X	X	X	X	X	X
Review preexisting conditions/new conditions (AEs)[h]	X	X	X	X	X	X	X
Randomization		X					
Dispense study drug[i]		X		X		X	X
Administer study drug[i,k]		IXE 40, 80, or 160 mg or placebo		IXE 20, 40, or 80 mg or placebo		IXE 20, 40, or 80 mg or placebo	IXE 20, 40, 80, or 160 mg
sPGA	X	X	X	X	X	X	X
PASI/BSA	X	X	X	X	X	X	X
NAPSI[l]		X		X		X	X
PSSI[l]		X		X		X	X
PPASI[l]		X		X		X	X

	Screening (Period 1)	Double-Blind Treatment Induction Period (Period 2)					
		Randomization					
Visit No	V1	V2	V3	V4	V5	V6	V7
Study Week		W0	W1	W4	W6	W8	W12
Study Days (Approximately)	-30 to -7 d	1	7 ± 2d	28 ± 2d	42 ± 2d	56 ± 2d	84 ± 2d
Binary questions on psoriasis location		X		X		X	X
Tanner stage scale[m]	X						
CDLQI/DLQI		X		X		X	X
Patient's Global Assessment of Disease Severity		X		X		X	X
Children's Depression Rating Scale		X		X		X	X
Columbia–Suicide Severity Rating Scale/ Self-Harm Supplement Form[n]	X	X	X	X	X	X	X
Itch NRS		X	X	X		X	X
Laboratory Tests							
Administer PPD/ QuantiFERON®-TB Gold[o]	X						
Read PPD[o]	X						
Chest x-ray[p]	X						
Bone age imaging[q]		X					
ECG[r]	X						
HIV/HCV	X						
HBV[s]	X						X
Serum pregnancy test[t]	X						
Urine pregnancy test[t]		X		X		X	X
Serum chemistry	X	X		X			X
Hematology	X	X		X			X
Urinalysis	X	X		X			X
IgA, IgG, IgM	X	X		X			X

	Screening (Period 1)	Double-Blind Treatment Induction Period (Period 2)					
		Randomization					
Visit No	V1	V2	V3	V4	V5	V6	V7
Study Week		W0	W1	W4	W6	W8	W12
Study Days (Approximately)	-30 to -7 d	1	7 ± 2d	28 ± 2d	42 ± 2d	56 ± 2d	84 ± 2d
Cell flow cytometry panel (B, T, CD4+T, CD8+T, and NK cells)	X						X
Immunogenicity testing[u,v]		X		X		X	X
PK sample[w]		X		X		X	X

Schedule of Activities, Protocol I1F-MC-RHCD
Maintenance Period (Period 3)

Maintenance Period (Period 3)							
Visit No (V)	V8	V9	V10	V11	V12	V13	V14
Study Week	W16	W20	W24	W28	W32	W36	W40
Study Days (Approximately)	112 ± 7d	140 ± 7d	168± 7d	196± 7d	224± 7d	252± 7d	280± 7d
Height	X		X			X	
Weight	X	X	X	X	X	X	X
Habits[e]			X				
Vital signs (BP, pulse, body temperature)[g]	X	X	X	X	X	X	X
Immunization record	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Review preexisting conditions/new conditions (AEs)[h]	X	X	X	X	X	X	X
Dispense study drug[i]	X	X	X	X	X	X	X
Administer study drug	IXE 20, 40, or 80 mg						
sPGA	X	X	X	X	X	X	X
PASI/BSA	X	X	X	X	X	X	X
NAPSI[l]			X			X	
PSSI[l]			X			X	
PPASI[l]			X			X	
Binary questions on psoriasis location			X			X	
Tanner stage scale			X				
CDLQI/DLQI			X			X	
Patient's Global Assessment of Disease Severity			X			X	
Children's Depression Rating Scale			X			X	

Maintenance Period (Period 3)							
Visit No (V)	V8	V9	V10	V11	V12	V13	V14
Study Week	W16	W20	W24	W28	W32	W36	W40
Study Days (Approximately)	112 ± 7d	140 ± 7d	168± 7d	196± 7d	224± 7d	252± 7d	280± 7d
Columbia–Suicide Severity Rating Scale/Self-Harm Supplement Form[n]	X	X	X	X	X	X	X
Itch NRS			X			X	
Laboratory Tests							
HBV[s]			X			X	
Urine pregnancy test[t]	X	X	X	X	X	X	X
Serum chemistry			X			X	
Hematology			X			X	
Urinalysis			X			X	
IgA, IgG, IgM			X			X	
Immunogenicity testing[u,v]						X	
PK sample[w]						X	

Schedule of Activities, Protocol I1F-MC-RHCD
Maintenance Period (Period 3) and Extension Period (Period 4)

	Maintenance Period (Period 3)					Extension Period (Period 4)								
Visit No (V)	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28
Study Week	W44	W48	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96
Study Days (Approximately)	308 ± 7d	336 ± 7d	364 ± 7d	392 ± 7d	420 ± 7d	448 ± 7d	476 ± 7d	504 ± 7d	532 ± 7d	560 ± 7d	588 ± 7d	616 ± 7d	644 ± 7d	672 ± 7d
Physical examination[d]		X			X			X			X			X
Height		X			X			X			X			X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Habits[e]					X									
Vital signs (BP, pulse, body temperature)[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunization record	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review preexisting conditions/new conditions (AEs)[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer study drug	IXE 20, 40, or 80 mg													
sPGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PASI/BSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NAPSI[l]		X			X			X			X			X
PSSI[l]		X			X			X			X			X
PPASI[l]		X			X			X			X			X
Binary questions on psoriasis location		X			X			X			X			X
Tanner stage scale		X						X						X
CDLQI/DLQI		X			X			X			X			X

	Maintenance Period (Period 3)					Extension Period (Period 4)								
Visit No (V)	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28
Study Week	W44	W48	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96
Study Days (Approximately)	308 ± 7d	336 ± 7d	364 ± 7d	392 ± 7d	420 ± 7d	448 ± 7d	476 ± 7d	504 ± 7d	532 ± 7d	560 ± 7d	588 ± 7d	616 ± 7d	644 ± 7d	672 ± 7d
Patient's Global Assessment of Disease Severity		X			X			X			X			X
Children's Depression Rating Scale		X			X			X			X			X
Columbia–Suicide Severity Rating Scale/ Self-Harm Supplement Form[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Itch NRS		X			X			X			X			X
Laboratory Tests														
Assess for TB risk, signs, symptoms.			X											
HBV[s]		X			X			X			X			X
Urine pregnancy test[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry		X			X			X			X			X
Hematology		X			X			X			X			X
Urinalysis		X			X			X			X			X
IgA, IgG, IgM		X			X			X			X			X
Immunogenicity testing[u,v]						X								
PK sample[w]						X								

Schedule of Activities, Protocol I1F-MC-RHCD
Extension Period (Period 4) and Post-Treatment Follow-Up (Period 5)

	Extension Period (Period 4)			Post-Treatment Follow-Up (Period 5)[x]		
Visit No (V)	V29	V30	V31/ETV	V801	V802	V803[w]
Study Week	W100	W104	W108	LV + 4W	LV + 12W	LV + 24W
Study Days (Approximately)	700 ± 7d	728 ± 7d	756 ± 7d	± 4d	± 4d	± 4d
Physical examination[d]			X			
Height			X			
Weight	X	X	X			
Body temperature			X			
Vital signs (BP and pulse)[g]			X			
Immunization record	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Review preexisting conditions/new conditions (AEs)[h]	X	X	X	X	X	X
Bone age imaging			X			
Dispense study drug[i]	X	X				
Administer study drug	IXE 20, 40, or 80 mg					
sPGA	X	X	X			
PASI/BSA	X	X	X			
NAPSI[l]			X			
PSSI[l]			X			
PPASI[l]			X			
Binary questions on psoriasis location			X			
Tanner stage scale[m]			X			
CDLQI/DLQI			X			

	Extension Period (Period 4)			Post-Treatment Follow-Up (Period 5)[x]		
Visit No (V)	V29	V30	V31/ETV	V801	V802	V803[w]
Study Week	W100	W104	W108	LV + 4W	LV + 12W	LV + 24W
Study Days (Approximately)	700 ± 7d	728 ± 7d	756 ± 7d	± 4d	± 4d	± 4d
Patient's Global Assessment of Disease Severity			X			
Children's Depression Rating Scale			X			
Columbia–Suicide Severity Rating Scale/ Self-Harm Supplement Form[n]	X	X	X			
Itch NRS			X			
Laboratory Tests						
Assess for TB risk, signs, symptoms.		X				
HBV[s]			X			
Urine pregnancy test[t]	X	X	X			
Serum chemistry			X	X	X	X
Hematology			X	X	X	X
Urinalysis			X			
IgA, IgG, IgM			X			
Cell flow cytometry panel (B, T, CD4+T, CD8+T, and NK cells)			X			
Immunogenicity testing[u,v]			X		X	
PK sample[w]			X		X	

Schedule of Activities, Protocol I1F-MC-RHCD

Abbreviations: AE = adverse event; AESI = adverse event of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; d = days; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; ETV = Early Termination Visit; HBcAb+ = positive for anti-hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; IXE = ixekizumab (LY2439821); LV= last visit; NAPSI = Nail Psoriasis Severity Index; NK = natural killer; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PPASI = Palmoplantar Psoriasis Area and Severity Index; PPD = purified protein derivative; PK = pharmacokinetics; PSSI = Psoriasis Scalp Severity Index; Q4W = every 4 weeks; SC = subcutaneous; sPGA = static Physician's Global Assessment; TB = tuberculosis; ULN = upper limit of normal; V = study visit; W = study week.

[a] The parent or legal guardian will sign the informed consent form, and the subject will sign the assent form prior to any study assessments, examinations, or procedures being performed. An informed consent form should be signed by the subject when the legal age is reached as determined by the country regulations.

[b] Complete medical history, including TB exposure.

[c] Demographics include recording the full date of birth, sex, and ethnicity. In countries where we are not allowed to collect the full date of birth, (day, month, and year) we will make country specific adjustments to collect only month and year.

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

[e] Habits include recording of caffeine, alcohol, and tobacco consumption. This assessment is only required for subjects 12 years of age or older.

[f] Subjects who test positive for latent TB at screening may be rescreened following appropriate treatment. Additionally, subjects who do not qualify at screening under Exclusion Criterion [14] (active or recent infection) or Exclusion Criterion [16] (body temperature ≥38°C [100.5°F]) may be rescreened 1 time.

[g] At baseline (Week 0), BP and pulse should be measured at least 30 minutes pre- and postinjection. BP and pulse should be measured pre- and postinjection at the other visits.

[h] Inflammatory bowel disease will be assessed as an AESI. See Section 9.2.2 for a list of all AESIs.

[i] The study drug will be prepared by a trained clinical staff member who will be an unblinded member. Site staff will record information in the Study Drug Administration Logs, including the date, time, and anatomical location of administration of study drug (for treatment compliance); syringe number; who prepared and administered the study drug; and the reason if study drug was not fully administered.

[j] Subjects should remain under observation for at least 1 hour after dosing at Week 0 (Visit 2), Week 4 (Visit 4), Week 8 (Visit 6), Week 12 (Visit 7), and Week 16 (Visit 8) to monitor for safety. For subsequent injections during the study, and if no problems occurred with that injection, subjects will be observed for 15 minutes following injection.

[k] Subjects receiving ixekizumab 20 mg or 40 mg will receive 1 SC injection of ixekizumab at Week 0 (Visit 2) and 1 SC injection of ixekizumab Q4W at Weeks 4 and 8. Subjects receiving ixekizumab 80 mg will receive 2 SC injections of ixekizumab at Week 0 (Visit 2) and 1 SC injection of ixekizumab Q4W at Weeks 4 and 8.
Subjects receiving placebo for ixekizumab 20 mg or 40 mg will receive 1 SC injection of placebo at Week 0 (Visit 2) and 1 SC injection of placebo Q4W at Weeks 4 and 8. Subjects receiving placebo for ixekizumab 80 mg will receive 2 SC injections of placebo at Week 0 (Visit 2) and 1 SC injection of placebo Q4W at Weeks 4 and 8.

[l] If the subject has nail psoriasis, scalp psoriasis or palmoplantar psoriasis at baseline, then the NAPSI, PSSI or PPASI, respectively, will be administered at subsequent visits, as indicated in the Schedule of Activities.

[m] At tanner stage score 5, the site does not need to complete the scale with the subject any longer.

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

[o] QuantiFERON®-TB Gold test is preferred. For those subjects administered a PPD test, the subject will visit the site between 48 to 72 hours after PPD placement for the PPD read.

[p] A chest x-ray will be taken at screening, unless one has been obtained within the past 6 months (provided the x-ray and/or report are available for review). In Germany, a chest x-ray has to be performed within 6 months prior to signing informed consent indicating no evidence of TB.

[q] For the Bone age imaging at Visit 2, it is acceptable if the test is performed at Visit 1. In case test is performed in the last 6 months, it does not need to be repeated at Visit 2.

[r] Subjects must be supine for a minimum of 5 minutes before ECG collection and remain supine during ECG collection. ECGs may be obtained at additional times, when deemed clinically necessary.

[s] Subjects who are HBcAb+, HBsAb+, and HBV DNA– at screening will be tested for HBsAb levels at baseline, at 12-week intervals thereafter, and at the ETV, if applicable. Subjects who meet these criteria for HBsAb monitoring will be identified by the central laboratory. Subjects whose HBsAb levels are <200 mIU/mL at any postscreening visit will be tested for HBV DNA. Any enrolled subject who is HBcAb+, regardless of HBsAb status or level, and who experiences elevated ALT or AST >3 times ULN must undergo HBV DNA testing.

[t] To be performed for females of childbearing potential only (ages 12 and older or younger subjects per investigator assessment of full sexual maturity). Serum pregnancy test will be done at Visit 1 only and will be performed centrally. Subjects will undergo urine pregnancy testing at the clinic on a monthly basis during scheduled visits through Week 108. Additional urine pregnancy testing can be performed at the investigator's discretion. Subjects determined to be pregnant will be discontinued from treatment and will no longer be administered study drug.

[u] Where collection is allowed by local regulations.

[v] Immunogenicity samples may also be analyzed for ixekizumab serum concentration to facilitate in the interpretation of the immunogenicity data. In addition, a blood sample will be collected, when possible, for any subject who experiences a potential systemic allergic/hypersensitivity reaction during the study as judged by the investigator. At visits where study drug will be administered, immunogenicity samples will be collected prior to administration of study drug. Ideally, samples will be taken at approximately the same time for each collection.

[w] At visits where study drug will be administered, PK samples will be collected prior to administration of study drug.

[x] All subjects receiving study drug must enter into Period 5 and complete through Visit 802. Subjects may be followed beyond Visit 802 for continued monitoring of their neutrophil counts if determined by the Sponsor/investigator that additional monitoring is needed. If a subject discontinues study drug early, the subject will complete the ETV and then enter the Post-Treatment Follow-Up Period (Period 5).

[y] This visit will only occur if a subject's neutrophil counts have not returned to the defined criteria.

3. Introduction

3.1. Study Rationale

There is an unmet medical need for effective and safe therapies for children and adolescents with moderate-to-severe plaque Ps. Ixekizumab has been approved for the treatment of adults with moderate-to-severe plaque Ps and psoriatic arthritis (PsA) in a number of countries globally. It has also been approved for adults with Pustular Ps and Erythrodermic Ps in Japan, and is currently being studied in adults with axial spondyloarthritis. This study is part of the European PIP and USA Pediatric Study Plan, and it is intended to investigate the safety, efficacy, and PK of ixekizumab in pediatric subjects (children and adolescents). This study will assess specific response in the Pediatric Population. The risks and benefits in the Pediatric Population are expected to be similar to those in adults with plaque Ps. There is no specific difference in the mechanism of the disease; therefore, no difference in the safety profile is expected between adults, adolescents, and children.

Protocol Addendum I1F-MC-RHCD(1) describes additional PK sampling for a subgroup of subjects, which will be used to help define the PK of ixekizumab in pediatric subjects. Protocol Addendum I1F-MC-RHCD(2) states that in countries where etanercept is approved for severe pediatric plaque Ps treatment only (emerging markets and European countries), subjects may be randomized to etanercept. This addendum contains an active-controlled reference group (etanercept) during the Double-Blind Treatment Induction Period (Period 2). Additionally, subjects from EU countries who meet the response criterion (defined as sPGA [0,1]) at Week 60 will be re-randomized to ixekizumab or placebo (1:1 ratio) during a 48-Week Double-Blind, Randomized Withdrawal Period during Period 4.

3.2. Background

Pediatric plaque Ps affects approximately 1% of children and adolescents globally (Gelfand et al. 2005; Napolitano et al. 2016). It is estimated that 35% to 50% of adults with psoriasis developed their disease before 20 years of age (De Jager et al. 2009). In a report by Gelfand et al. (2005), the prevalence of plaque Ps in children in the United Kingdom was 0.55% for those aged 0 to 9 years and 1.37% for those aged 10 to 19 years. Pediatric plaque Ps is especially burdensome because it often presents on the face and scalp, as well as other highly visible areas. Nonbiologic topical therapies have been the mainstay of treatment due to lack of approved therapies for plaque Ps in children. Currently, there are few systemic therapies for pediatric plaque Ps, and most have significant side effects or are not as effective as desired (Bronckers et al. 2015).

Currently, there is an unmet medical need for effective and safe therapies for children and adolescents with moderate-to-severe psoriasis. Both the PIP and Pediatric Study Plan will focus on pediatric subjects with moderate-to-severe plaque Ps from 6 to <18 years of age.

3.3. Benefit/Risk Assessment

The mechanism of action of ixekizumab is similar in adults and children; therefore, it is expected that the benefit/risk ratio of participation in this study will be the same in children as it is in studies of adults. More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of ixekizumab (LY2439821) in adults are to be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

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

Table RHCD.1. Objectives and Endpoints

Objectives	Endpoints
Co-Primary to assess whether ixekizumab Q4W is superior to placebo at Week 12 (Visit 7) in the treatment of pediatric subjects (children and adolescents) with moderate-to-severe plaque psoriasis as measured by PASI 75 and by sPGA (0,1)	• proportion of subjects achieving PASI 75 at Week 12 • proportion of subjects achieving sPGA (0,1) at Week 12
Gated Secondary to assess whether ixekizumab Q4W is superior to placebo as measured by: • PASI 90 • sPGA (0) • PASI 100 • Itch NRS • PASI 75 • sPGA (0,1)	• proportion of subjects achieving PASI 90 at Week 12 • proportion of subjects achieving sPGA (0) at Week 12 • proportion of subjects achieving PASI 100 at Week 12 • improvement ≥4 for subjects who had a baseline Itch NRS score ≥4 • proportion of subjects achieving PASI 75 at Week 2 • proportion of subjects achieving sPGA (0,1) at Week 2
Other Secondary to assess whether ixekizumab Q4W is superior to placebo	The following endpoints will be assessed at Week 12 and at each postbaseline visit during the Double-Blind Treatment Period: • proportion of subjects achieving PASI 50, PASI 75, PASI 90, and PASI 100 • proportion of subjects achieving sPGA (0,1) and sPGA (0) • change from baseline in itching severity (Itch NRS) score • proportion of subjects achieving CDLQI/DLQI (0,1) • change from baseline in NAPSI, PSSI, and/or PPASI score in case of nail, scalp, or hand/feet involvement
to summarize the efficacy of ixekizumab Q4W at Week 24 (Visit 10) and Week 48 (Visit 16) as measured by: • PASI 75 • sPGA (0,1) • PASI 90 • sPGA (0) • PASI 100	The following endpoints will be assessed: • proportion of subjects achieving PASI 75 at Weeks 24 and 48 • proportion of subjects achieving sPGA (0,1) at Weeks 24 and 48 • proportion of subjects achieving PASI 90 at Weeks 24 and 48 • proportion of subjects achieving sPGA (0) at Weeks 24 and 48 • proportion of subjects achieving PASI 100 at Weeks 24 and 48
to evaluate the potential development of anti-ixekizumab antibodies and its impact on subject efficacy of Ixekizumab	• PASI 75 and sPGA(0,1) at Week 12 correlated with treatment-emergent antidrug antibody titer (low, moderate, and high) and

Objectives	Endpoints
	by NAb status
to measure ixekizumab exposure and characterize the pharmacokinetics of ixekizumab in pediatric subjects	• serum trough concentrations of ixekizumab
to assess the relationship between exposure and efficacy and exposure and immunogenicity	• model parameters for the exposure-response relationship between ixekizumab serum trough concentrations and efficacy endpoints (e.g., sPGA, PASI) at Week 12 • serum trough concentrations for ixekizumab antibody titer subgroups
to assess the safety of ixekizumab	• to evaluate the safety of ixekizumab, including but not limited to infections; injection-site reactions; B-, T-, and NK-cell levels; WBC count; RBC count; and laboratory values (hematology and chemistry [including ALT and AST]) during the course of the study
Tertiary/Exploratory to demonstrate normal growth and pubertal progression in children treated with ixekizumab during the course of the study	• weight, height, and BMI data will be merged to the Centers for Disease Control and Prevention standard growth data by age and gender to compare subjects' growth with normal values • shift table for tanner stage from maximum baseline to maximum postbaseline by gender
to evaluate the genital involvement of the subjects per the questionnaire Binary Questions on Psoriasis Location	• proportion of subjects achieving no psoriasis presence in each psoriasis location
to evaluate the patient's global assessment of disease severity	• proportion of subjects achieving patient's global assessment of disease severity 0 or 1
to evaluate the effect of ixekizumab on maintenance of efficacy and health outcomes during the open-label maintenance period and extension period.	• proportion of subjects achieving PASI 90 • proportion of subjects achieving sPGA (0) • proportion of subjects achieving PASI 100 • proportion of subjects achieving PASI 75 • proportion of subjects achieving sPGA (0,1) • improvement ≥4 for subjects who had a baseline Itch NRS score ≥4

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; Nab = neutralizing antidrug antibody; NAPSI = Nail Psoriasis Severity Index; NK = natural killer; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PASI 50 = at least a 50% improvement from baseline in PASI score; PASI 75 = at least a 75% improvement from baseline in PASI score; PASI 90 = at least a 90% improvement from baseline in PASI score; PASI 100 = a 100% improvement from baseline in PASI score; PPASI = Palmoplantar Psoriasis Severity Index; PSSI = Psoriasis Severity Index; Q4W = every 4 weeks; RBC = red blood cell; sPGA = static Physician's Global Assessment; WBC = white blood cell.

5. Study Design

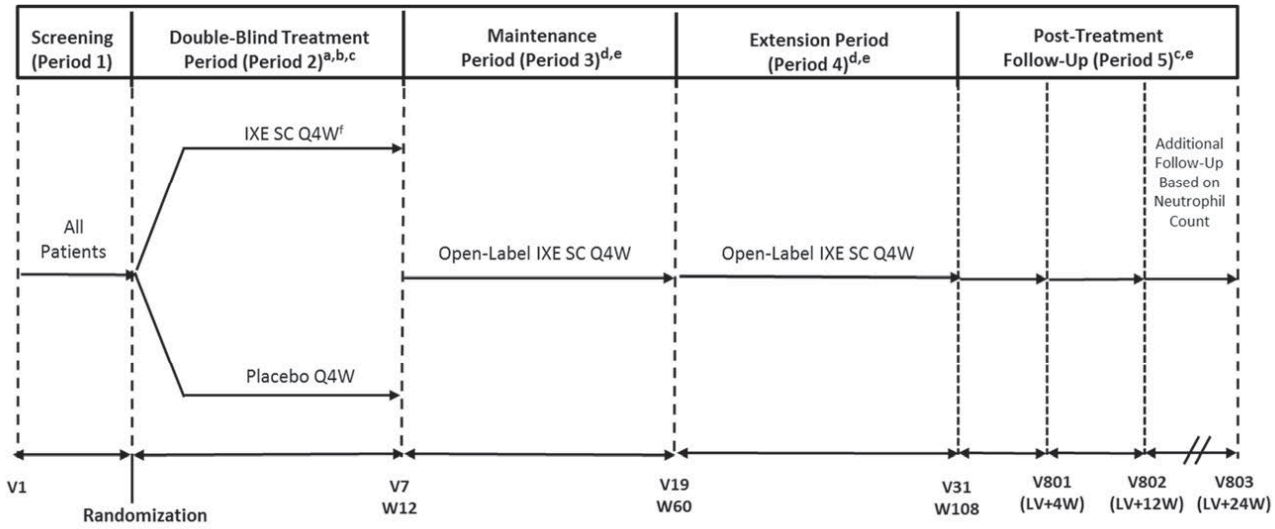
5.1. Overall Design

Study I1F-MC-RHCD (RHCD) is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study examining the effects of ixekizumab versus placebo in subjects from 6 to <18 years of age with moderate-to-severe plaque Ps (PASI score ≥12, sPGA ≥3, and BSA ≥10% at screening and baseline). There is an active-controlled (etanercept) reference arm portion of the study design detailed in Protocol Addendum I1F-MC-RHCD(2).

The study consists of 5 periods:

- **Period 1: Screening Period** (Visit 1) will assess subject eligibility and will occur approximately 7 to 30 days before Period 2, Induction (baseline; Week 0; Visit 2).
- **Period 2: Double-Blind Treatment Period** (Induction Period) will occur from Week 0 (baseline; Visit 2) to Week 12 (Visit 7) comparing ixekizumab with placebo in a double-blind fashion. Protocol Addendum I1F-MC-RHCD(2) describes etanercept as a reference control group for countries where etanercept is approved for treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.
- **Period 3: 48-Week Open-Label Maintenance Period** will occur from Week 12 (Visit 7) to Week 60 (Visit 19). Subjects randomized to the ixekizumab group during Period 2, Induction will maintain the dose received during the previous period. Subjects randomized to placebo during Period 2, Induction will receive ixekizumab at doses of 20, 40, or 80 mg based on weight. As part of Protocol Addendum I1F-MC-RHCD(2), subjects randomized to etanercept during the Double-Blind Treatment Period will begin treatment with ixekizumab after an 8-week washout period (to avoid, for safety reasons, increased risk with concurrent etanercept and ixekizumab exposures).
- **Period 4: Extension Period** will occur from Week 60 (Visit 19) to Week 108 (Visit 31). Subjects will continue with open-label treatment of the ixekizumab dose received during the previous period (Period 3). Protocol Addendum I1F-MC-RHCD(2) describes the 48-week Double-Blind Randomized Withdrawal Period for subjects from EU countries who meet response criteria during the Maintenance Period (defined as sPGA [0,1]). Subjects who enter the Double-Blind Randomized Withdrawal Period will be re-randomized to ixekizumab or placebo (1:1 ratio) at Week 60 (Visit 19).
- **Period 5: Post-Treatment Follow-Up Period** is for safety monitoring after treatment discontinuation for any subject receiving at least 1 dose of study drug. This period occurs from the last treatment period visit or Early Termination Visit (ETV) for up to 24 weeks following that visit.

Figure RHCD.1 illustrates the study design for the main study. Protocol Addendum I1F-MC-RHCD(2) contains the study design figure describing etanercept dosing and the Double-Blind Randomized Withdrawal Period. Appendix 3 contains the study governance considerations.



Abbreviations: IXE = ixekizumab (LY2439821); LV = date of last visit; PK = pharmacokinetic; Q4W = every 4 weeks; SC = subcutaneous; V = visit; W = week.
Footnotes on following page.

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

Illustration of study design for Clinical Protocol I1F-MC-RHCD

[a] Subjects will be randomized to either ixekizumab or placebo in a 2:1 ratio.

[b] Subjects receiving ixekizumab 20 mg or 40 mg will receive 1 SC injection of ixekizumab at Week 0 (Visit 2) and 1 SC injection of ixekizumab Q4W at Weeks 4 and 8. Subjects receiving ixekizumab 80 mg will receive 2 SC injections of ixekizumab at Week 0 (Visit 2) and 1 SC injection of ixekizumab Q4W at Weeks 4 and 8.
Subjects receiving placebo for ixekizumab 20 mg or 40 mg will receive 1 SC injection of placebo at Week 0 (Visit 2) and 1 SC injection of placebo Q4W at Weeks 4 and 8. Subjects receiving placebo for ixekizumab 80 mg will receive 2 SC injections of placebo at Week 0 (Visit 2) and 1 SC injection of placebo Q4W at Weeks 4 and 8.

[c] Immunogenicity and time-matched PK sample collection will occur as detailed in the Schedule of Activities (Section 2).

[d] Subjects randomized to ixekizumab during Period 2, Induction will receive 1 SC injection of ixekizumab and 1 SC injection of placebo at Week 12. Subjects randomized to the placebo group during Period 2, Induction will be assigned to receive ixekizumab at doses of 20, 40, or 80 mg based on weight. Subjects assigned to 20 mg will receive a starting dose of 40 mg, subjects assigned to 40 mg will receive a starting dose of 80 mg, and subjects assigned to 80 mg will receive a starting dose of 160 mg. All subjects will receive 2 SC injections of ixekizumab at Week 12 and 1 SC injection of ixekizumab Q4W at Week 16 and thereafter. Treatment with ixekizumab is weight based. If a subject changes weight category during the study, after completing the double blind treatment period (induction), the dose will be adjusted accordingly.

[e] All subjects receiving study drug must enter into Period 5 and complete through Visit 802. Subjects may be followed up beyond Visit 802 for continued monitoring of their neutrophil count if determined by the Sponsor/investigator that additional monitoring is needed.

[f] At Visit 2, randomization will occur based on the following weight groups: 1) <25 kg: randomization to ixekizumab 20 mg, receiving a starting dose of 40 mg; 2) 25 kg to 50 kg: randomization to ixekizumab 40 mg, receiving a starting dose of 80 mg; and 3) >50 kg: randomization to 80 mg, receiving a starting dose of 160 mg. A staggered approach to enrollment by weight group will be implemented with subjects 12 years of age or older and >50 kg enrolling initially to the study. If no safety concern is identified after an initial safety analysis of the first 12 weeks of treatment in the first 15 subjects >50 kg, subjects will start to enroll in the 25- to 50-kg group. Once data are obtained to Week 12 for approximately 15 subjects in the 25- to 50-kg group, an interim analysis of PK, safety, and efficacy data in all subjects in the study at that point will be performed to confirm doses for the remaining subjects in the study. Once confirmed, all weight groups will be open for enrollment.

5.1.1. Screening Period (Period 1)

The duration of the Screening Period is between approximately 7 and 30 days and consists of 1 visit (Visit 1) to assess subject eligibility. Subjects who have a PPD placed as part of their TB testing will have a second visit during this period to have PPD read. The parent or legal guardian will sign the informed consent form (ICF), and the subject will sign the assent form prior to any study assessments, examinations, or procedures being performed.

All inclusion and exclusion criteria are provided in Section 6.1 and 6.2, respectively. Screening procedures will be performed according to the Schedule of Activities (Section 2). At Visit 1, tuberculosis (TB) testing will be performed by one of the following methods:
1) QuantiFERON®-TB Gold or 2) purified protein derivative (PPD) skin test (Section 8.1.1). Subjects who are administered a PPD test at Visit 1 will visit the site between 48 to 72 hours after PPD placement for the PPD to be read. Subjects who are assessed as having latent TB at screening may be rescreened following appropriate treatment as described in Section 9.4.2.

Additionally, subjects who do not qualify at screening under Exclusion Criteria [28] or [29] may be rescreened (1 time) at least 4 weeks after documented resolution of symptoms. A serum pregnancy test, as applicable, will also be done at Visit 1.

5.1.2. 12-Week Double-Blind Treatment Induction Period (Period 2)

The Induction Period (Period 2) will be a Double-Blind Treatment Period that will occur from Week 0 (baseline; Visit 2) to Week 12 (Visit 7). Dosing will be as follows: subjects >50 kg will receive a starting dose of 160 mg, then 80 mg every 4 weeks (Q4W) thereafter; subjects 25 to 50 kg will receive a starting dose of 80 mg, then 40 mg Q4W thereafter; subjects <25 kg will receive a starting dose of 40 mg, then 20 mg Q4W thereafter. Evaluation of the co-primary endpoints will occur at Week 12.

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

Treatment assignment is discussed in Section 7.2.

Blinded dosing will occur at 4-week intervals throughout Period 2, Induction. See Section 7.1 and Table RHCD.2 for a full description of all dosing regimens. Subjects >50 kg will be administered 2 subcutaneous (SC) injections of ixekizumab or placebo at Week 0. Subjects 25 to 50 kg and <25 kg will receive 1 SC injection of ixekizumab or placebo at Week 0. All subjects will be administered 1 SC injection of ixekizumab or placebo Q4W at Week 4 and Week 8, regardless of their assigned dosage regimen.

The study drug will be prepared by unblinded study site personnel. All doses will be administered on-site.

Subjects should remain under observation for at least 1 hour after dosing at Week 0 (Visit 2) Week 4 (Visit 4), Week 8 (Visit 6), Week 12 (Visit 7), and Week 16 (Visit 8) to monitor for

safety. Following the first injection and if no problems occur with that injection, subjects will be observed for 15 minutes following injection at all other study visits.

Female subjects of childbearing potential (age 12 and older or younger subjects per investigator assessment of full sexual maturity) will undergo a urine pregnancy test at the clinic on a monthly basis during scheduled visits through Week 108. Additional urine pregnancy testing may be performed at the investigator's discretion. Subjects determined to be pregnant will be discontinued from treatment and will no longer be administered study drug (see Section 8.1).

Subjects who discontinue the study for any reason during this period will stop treatment and continue to the ETV prior to entering the Post-Treatment Follow-Up Period (Period 5).

5.1.3. 48-Week Open-Label Maintenance Period (Period 3)

Subjects will initiate the Maintenance Period as follows:

- Subjects randomized to the ixekizumab group during Period 2, Induction will maintain the dose received during the previous period. In addition, subjects will also receive 1 placebo injection at Week 12 to maintain the blind.
- Subjects randomized to the placebo group during Period 2, Induction will be assigned to receive ixekizumab based on weight. Table RHCD.2 provides details on the initial and subsequent doses.
- If a subject changes weight category following the Double-Blind Treatment Period, the ixekizumab dose associated with that weight will be administered. This may happen at any time during the Maintenance Period.
- For EU countries, please refer to Protocol Addendum RHCD(2).

5.1.4. 48-Week Extension Period (Period 4)

- Subjects will continue with open-label treatment of the ixekizumab dose received during the previous period (Period 3) and will receive an injection every Q4W through Week 104 (Visit 30). Subjects will receive the ixekizumab dose according to weight, which will be reassessed during this period. If a subject changes weight category, the ixekizumab dose associated with the most current weight will be administered. This may happen at any time during the Extension Period.

For EU countries, please refer to Protocol Addendum RHCD(2).

5.1.5. Post-Treatment Follow-Up Period (Period 5)

All subjects receiving study drug, including those who discontinue the study, will be monitored at approximately 4 and 12 weeks after the date of their final injection of study drug to monitor clinical safety, including neutrophil levels. If a subject's neutrophil count is ≥1500 cells/μL or greater than or equal to the subject's baseline neutrophil count at 12 weeks following the last injection of ixekizumab, the subject's participation in the study will be considered complete. If the subject's neutrophil count remains <1500 cells/μL at 24 weeks after the last injection, the investigator, in consultation with the Sponsor, will determine and be responsible for follow-up evaluations through appropriate healthcare options.

For subjects who completed or discontinued study treatment and have entered the Post-Treatment Follow-Up Period (Period 5), plaque Ps therapy with another agent is allowed after an appropriate washout period, as determined appropriate by the investigator (see Section 7.7).

5.2. Number of Participants

Approximately 195 subjects will be randomized to the study. Approximately 165 subjects will be randomized in a 2:1 ratio to receive ixekizumab (110 subjects) or placebo (55 subjects) during the Double-Blind Treatment Period. Approximately 30 subjects will receive etanercept during the Double-Blind Treatment Period as described in Protocol Addendum I1F-MC-RHCD(2).

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 subject.

5.4. Scientific Rationale for Study Design

Study RHCD includes 3 treatment periods: 1) a Double-Blind Treatment Induction Period (Period 2); 2) an Open-Label Maintenance Period in which all subjects receive ixekizumab (Period 3); and 3) an Open-Label Extension Period (Period 4) to determine the efficacy and safety of ixekizumab. During the 12-week blinded treatment period, ixekizumab Q4W is compared with placebo Q4W, whereas during the Open-Label Maintenance Period, all subjects are treated with ixekizumab Q4W. These period durations were chosen based on Phase 3 pivotal clinical studies conducted in adults with moderate-to-severe plaque Ps. The placebo-controlled Double-Blind Treatment Period is designed to minimize bias in the evaluation of ixekizumab in subjects with moderate-to-severe plaque Ps. Subjects may still receive treatment in the form of the allowed concomitant therapies as described in the study exclusion criteria (Section 6.2) and the concomitant therapy section (Section 7.7).

The efficacy of ixekizumab in treating plaque Ps will be measured by the PASI and sPGA and scales, with the primary efficacy endpoint at Week 12. These measures and the 12-week endpoint are in alignment with efficacy endpoints for currently approved plaque Ps therapies and with regulatory guidance (EMEA [WWW]). The Open-Label Maintenance Period and Extension Period will permit collection of data for the assessment of maintenance of efficacy and long-term safety data with ixekizumab.

The Post-Treatment Follow-Up Period (Period 5) is for safety monitoring following the last treatment period and study visit.

Study discontinuation criteria allow subjects to be discontinued at any time by investigator or subject decision if the subject is receiving insufficient benefit from study therapy or requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of plaque Ps (Section 8.1.1).

Clinical studies of plaque Ps require objective measurement of psoriasis disease activity/severity. The current gold standard for assessment of extensive psoriasis has been the PASI. The PASI is a measure of the average redness, thickness, and scaliness of the lesions (each graded on a

0-4 scale), weighted by the area of involvement. Clinicians typically consider at least 75% improvement in disease to be a clinically meaningful improvement indicative of success. Although the PASI has been the most widely used measure, it does have a number of limitations, one of which is its poor sensitivity to change for relatively small areas of involvement. Another major limitation of the PASI is that it is not routinely used by clinicians and therefore is poorly understood by both clinicians and subjects. Thus, the sPGA was added as a co-primary measure. The sPGA measures the physician's impression of the disease at a single point; it is a well-recognized clinical tool for assessing subject improvement. The PASI and sPGA were also used as co-primary endpoints in the ixekizumab Phase 3 studies in adult subjects with moderate-to-severe plaque Ps.

5.5. Justification for Dose

The efficacy, safety, and PK data from the Phase 2 and Phase 3 programs in adults with plaque Ps have been used to guide the dose and dosing regimen for investigation in pediatric subjects with plaque Ps. Weight was identified as an important covariate factor on clearance and volume terms in the adult population PK model. Therefore, the adult PK model and the adult sPGA time course exposure-response model were used to simulate the expected PK and PD responses across a range of ages and weights in pediatric subjects to support selection of the weight categories, doses, and dosing frequency proposed in this study. The recommended doses have been selected to target exposures in pediatric subjects to be within the range of exposures observed in the Phase 3 adult studies with the 80 mg every 2 weeks and 80 mg Q4W doses, which both had a positive benefit/risk ratio.

Simulations in pediatric subjects using the adult population PK model and the adult sPGA time course model were conducted. The weight distribution in the 6- to 18-year-old population was based on the Centers for Disease Control and Prevention (CDC) current growth charts (CDC [WWW]). In the PK model, the thigh was assumed as the injection site of drug administration because this location resulted in slightly higher exposure than arm and abdomen sites of administration (bioavailability estimates of 90% and 81%, respectively) and thus provides the most conservative estimate of exposure.

Results from the modeling and simulation support the following doses, dosing frequencies, and weight categories to be used in this study: 1) 80 mg Q4W (with a starting dose of 160 mg) for subjects >50 kg; 2) 40 mg Q4W (with a starting dose of 80 mg) for subjects 25 to 50 kg and; 3) 20 mg Q4W (with a starting dose of 40 mg) for subjects <25 kg.

Two interim analyses are planned for this study that will include an assessment of PK, safety, and select efficacy data from the initial subjects enrolled in this study to confirm the predictions. If necessary, dosage adjustments may be made for the remainder of the subjects based on this review (see Section 10.4.8 for more details of the interim analysis).

6. Study Population

The study population will consist of male and female subjects from 6 to <18 years of age with moderate-to-severe plaque Ps (PASI score ≥12, sPGA ≥3, and BSA ≥10% at screening and baseline).

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

6.1. Inclusion Criteria

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

Type of Subject and Disease Characteristics

[1] have a diagnosis of moderate-to-severe plaque-type psoriasis for at least 6 months prior to baseline (Week 0; Visit 2), as determined by the investigator

[2] have PASI score ≥12, sPGA ≥3, and BSA involvement ≥10% at screening (Visit 1) and baseline (Week 0; Visit 2)

[3] are candidates for phototherapy or systemic treatment or considered by the investigator as not adequately controlled by topical therapies

Subject Characteristics

[4] male and female subjects from 6 to <18 years of age at time of randomization

[4a] male subjects agree to use a reliable method of birth control during the study

[4b] female subjects:

Participants of childbearing age or childbearing 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
- Müllerian agenesis (Mayer–Rokitansky–Küster–Hauser syndrome [also referred to as congenital absence of the uterus and vagina])

[5] both the child or adolescent and a parent or legal guardian are able to understand and fully participate in the activities of the clinical study and sign their assent and consent, respectively, accordance to local guidelines.

[6] all immunizations are up-to-date in agreement with current immunization guidelines as noted by country specific pediatric authorities (e.g., the American Academy of Pediatrics). Note, subjects who are not up to date or have never been immunized are not to be enrolled in the trial.

6.2. Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria at screening:

Medical Conditions

[7] have pustular, erythrodermic, and/or guttate forms of plaque Ps

[8] subjects with drug-induced plaque Ps (e.g., a new onset of plaque Ps or an exacerbation of plaque Ps from beta-blockers, calcium channel blockers, or lithium)

[9] have clinical and/or laboratory evidence of untreated latent or active TB

[10] have evidence of or test positive for hepatitis B virus (HBV) by testing positive for 1) hepatitis B surface antigen (HBsAg+) or 2) anti-hepatitis B core antibody (HBcAb+) and are HBV DNA positive. (Note: Subjects who are HBcAb+ and HBV DNA negative may be enrolled in the study. Subjects who meet these criteria at screening will be identified by the central laboratory and monitored during the study)

[11] 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)

[12] have or had an infection typical of an immunocompromised host and/or that occurs with increased incidence in an immunocompromised host (including but not limited to *Pneumocystis jiroveci* pneumonia, histoplasmosis, or coccidioidomycosis) or have a known immunodeficiency

[13] have or had a herpes zoster or any other clinically apparent varicella-zoster virus infection within 12 weeks of baseline (Week 0; Visit 2)

[14] have any other active or recent infection, including chronic or localized infections, within 4 weeks of baseline (Week 0; Visit 2) that, in the opinion of the investigator, would pose an unacceptable risk to the subject if participating in the study; these subjects may be rescreened (1 time) 4 or more weeks after documented resolution of symptoms

[15] have sepsis or risk of sepsis

[16] have a body temperature ≥38°C (100.5°F) at baseline (Week 0; Visit 2); these subjects may be rescreened (1 time) ≥4 weeks after documented resolution of elevated temperature

[17] subjects with a documented history of immune deficiency syndrome (e.g., severe combined immunodeficiency syndrome, T-cell deficiency syndromes, B-cell deficiency syndromes, chronic granulomatous disease)

[18] subjects with a known history of malignancy; lymphoproliferative disease, including lymphoma; or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly unless ruled out by biopsy

[19] history of major immunologic reaction (such as serum sickness or anaphylactoid reaction) to an immunoglobulin G–containing agent (such as intravenous gamma globulin, a fusion protein, or monoclonal antibody)

[20] has had any major surgical procedure within 8 weeks prior to baseline (Week 0; Visit 2) or will require such during the study that, in the opinion of the investigator in consultation with Lilly or its designee, would pose an unacceptable risk to the subject

[21] presence of significant uncontrolled cerebrocardiovascular disorder (e.g., unstable arterial hypertension, moderate-to-severe [New York Heart Association class III/IV] heart failure, cerebrovascular accident); respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, or neurologic disorders; or abnormal laboratory values at screening that, in the opinion of the investigator, pose an unacceptable risk to the subject if participating in the study or of interfering with the interpretation of data

[22] presence of significant uncontrolled neuropsychiatric disorder that, in the opinion of the investigator, poses an unacceptable risk to the subject if participating in the study or of interfering with the interpretation of data; recent history of a suicide attempt (during the 30 days prior to screening); or marked yes to C-SSRS question 4 or 5 on ideation or yes to suicide behaviors

[23] had a serious infection (e.g., pneumonia, cellulitis); have been hospitalized; have received intravenous antibiotics for an infection within 12 weeks prior to baseline (Week 0; Visit 2); had a serious bone or joint infection within 24 weeks prior to baseline; have ever had an infection of an artificial joint; or are immunocompromised to an extent that participation in the study would pose an unacceptable risk to the subject

[24] have not had any immunizations, or are not up to date on immunizations recommended by country specific Pediatric guidance

[25] females of childbearing potential, who are sexually active and not on either 1 highly effective form of contraception or 2 effective forms of contraception (see Section 6.1. Inclusion Criteria 4b)

[26] females of childbearing potential, who are pregnant or intending to become pregnant or are breastfeeding

[27] have any other condition or laboratory values that, in the opinion of the investigator, preclude the subject from following and completing the protocol

[28] have evidence of precocious puberty at the time of study enrollment

[29] at screening, have a neutrophil count <1500 cells/μL (<1.50 x 103/μL or <1.50 GI/L), a lymphocyte count <800 cells/μL (<0.80 x 103/μL or <0.80 GI/L), or a platelet count <100,000 cells/μL (<100 x 103/μL or <100 GI/L)

[30] at screening, have ALT or AST >2.5 times the upper limit of normal (ULN). (Note: ALT and AST 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)

[31] at screening, have a total WBC count <3000 cells/μL (<3.00 x 103/μL or <3.00 GI/L), hemoglobin <8.5 g/dL (85.0 g/L) for male subjects, and hemoglobin <8.0 g/dL (80 g/L) for female subjects

Prior/Concomitant Therapy

[32] subjects previously treated with etanercept

[33] have used any therapeutic agent targeted at reducing interleukin-17

[34] have received other therapies within the specified time frames prior to screening (see below):

- adalimumab and infliximab 60 days, abatacept 90 days, anakinra 7 days, or any other biologic disease-modifying antirheumatic drug 5 half-lives
- systemic therapy for plaque Ps and PsA (other than above, e.g., methotrexate, cyclosporine) or phototherapy (e.g., photochemotherapy [psoralen plus ultraviolet A]) in the previous 4 weeks
- any investigational drugs in the previous 4 weeks or 5 half-lives, whichever is longer
- ultraviolet-A therapy, ultraviolet-B therapy, and topical treatments (except on face, scalp, and genital area during screening) in the previous 4 weeks

[35] had a live vaccination within 12 weeks prior to baseline (Week 0, Visit 2), intend to have a live vaccination during the course of the study or within 12 weeks of completing treatment in this study, or have participated in a vaccine clinical study within 12 weeks prior to baseline. Investigators should review the vaccination from Pediatric governance bodies nonlive vaccines intended to prevent infectious disease prior to therapy. (Note: killed/inactive or subunit vaccines are expected to be safe; however, their efficacy with concomitant ixekizumab treatment is unknown)

[36] are not up to date on all vaccinations according to country-specific guidance provided by pediatric governing bodies (e.g., the American Academy of Pediatrics), or have not had any vaccinations.

[38] if participating at a site where PPD is administered (rather than QuantiFERON®-TB Gold), had a vaccination with Bacillus Calmette-Guérin (BCG) within 12 months prior to baseline (Week 0, Visit 2) or intend to have vaccination with BCG during the study or within 12 months of completing treatment in this study

Prior/Concurrent Clinical Study Experience

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

[40] have participated, within the last 30 days, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 4 weeks or 5 half-lives (whichever is longer) should have passed

[41] have previously completed or withdrawn from this study or any other study investigating ixekizumab

Other Exclusions

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

6.3. Lifestyle Restrictions

Not applicable.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened 1 time. Those who test positive for latent TB at screening or who have a documented history of a positive TB test but no documented history of at least 4 weeks of appropriate latent TB treatment may be re-screened following appropriate treatment, as described in Section 9.4.2. The interval between re-screenings should be at least 1 month. Each time re-screening is performed, the individual must sign a new ICF and will be assigned a new identification number.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of ixekizumab administered by SC injection with placebo. The study drug should be at room temperature when injected. Possible injection sites include the abdomen, thigh, and upper arm (using the arm contralateral for blood samples for PK). The injection site should preferably not be in a psoriatic lesion and should be rotated to another area for subsequent doses at the same visit.

Table RHCD.2 shows the treatment regimens.

Table RHCD.2. Treatment Regimens

Regimen	Dose Week 0	Dose Week 4 and Week 8	Dose Week 12	Dose Week 16 through Week 104
Ixekizumab >50 kg	160 mg (administered as 2 80-mg SC injections)	80-mg Q4W SC injection	80-mg SC injection + a placebo injection at Week 12	80-mg Q4W SC injection
Ixekizumab 25-50 kg	80-mg SC injection	40-mg Q4W SC injection	40-mg SC injection + a placebo injection at Week 12	40-mg Q4W SC injection
Ixekizumab <25 kg	40-mg SC injection	20-mg Q4W SC injection	20-mg SC injection + a placebo injection at Week 12	20-mg Q4W SC injection
Placebo >50 kg	Placebo for ixekizumab 160 mg (administered as 2 placebo SC injections)	Placebo for ixekizumab 80-mg Q4W SC injection	Starting ixekizumab dose: 160-mg (administered as 2 80-mg SC injections)	80-mg Q4W SC injection
Placebo 25-50 kg	Placebo for ixekizumab 80-mg SC injection	Placebo for ixekizumab 40-mg Q4W SC injection	Starting ixekizumab dose: 80-mg (administered as 2 40-mg SC injections)	40-mg Q4W SC injection
Placebo <25 kg	Placebo for ixekizumab 40-mg SC injection	Placebo for ixekizumab 20-mg Q4W SC injection	Starting ixekizumab dose: 40-mg (administered as 2 20-mg SC injections)	20-mg Q4W SC injection

Abbreviations: Q4W = every 4 weeks; SC = subcutaneous.

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

- explaining the correct use of the study drug to the subject or the subject's caregiver
- verifying that instructions are followed properly
- maintaining accurate records of study drug dispensing and collection

- at the end of the study, returning all unused medication to Lilly or its designee, unless the Sponsor and sites have agreed that all unused medication is to be destroyed by the site, as allowed by local law

7.1.1. Packaging and Labeling

Clinical study materials will be labeled according to the country's regulatory requirements.

The study drug will be supplied by the Sponsor in accordance with current good manufacturing practices.

Ixekizumab and placebo for ixekizumab (excipients only) will be supplied as an injectable solution in 1-mL, single-dose, prefilled, disposable manual syringes with study-specific labels. Each syringe of ixekizumab is designed to deliver ixekizumab 80 mg.

Starting dose at Week 0: Subjects requiring the starting dose of 160 mg (ixekizumab or placebo to match) will receive two 80-mg SC injections. Subjects requiring the starting doses of 80 mg and 40 mg (ixekizumab or placebo to match) will receive 1 SC injection.

Starting dose at Week 12 for subjects who had been receiving placebo: Subjects requiring the starting dose of 160 mg ixekizumab will receive two 80-mg SC injections. Subjects requiring the starting dose of 80 mg ixekizumab will receive two 40-mg SC injections. Subjects requiring the starting dose of 40 mg ixekizumab will receive two 20-mg SC injections.

Ongoing injections: Subjects requiring a lower dose of ixekizumab or placebo will have the dose prepared by injecting the contents of the 80-mg syringe into an empty sterile vial, then withdrawing and administering the required volume with a disposable syringe (0.5 mL for 40 mg and 0.25 mL for 20 mg). The syringes (and contents) containing either ixekizumab or matching placebo will be visibly indistinguishable from each other.

Syringes will be supplied in cartons, with the appropriate quantity of syringes specific to the planned dispensing schedule of the study drug. Clinical study materials will be labeled according to the country's regulatory requirements. All study drug will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

7.2. Method of Treatment Assignment

Subjects who meet all enrollment criteria at Visit 1 and Visit 2 will be randomized in a 2:1 ratio to double-blind treatment with ixekizumab or placebo at Week 0 (Visit 2). Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign cartons containing double-blind study drug to each subject. Study site personnel will confirm that they have located the correct carton by entering a confirmation number into the IWRS.

To achieve between-group comparability for region, the randomization will be stratified by region (United States/Canada, European countries, and the rest of the world).

During the Maintenance and Extension periods, all subjects will receive open-label treatment with ixekizumab.

7.2.1. Selection and Timing of Doses

Subjects will be randomized to treatment and will receive their assigned study drug as outlined in Sections 7.1 and 7.2.

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

The actual time and site of all dose administrations will be recorded in the subject's case report form (CRF).

7.3. Blinding

The Double-Blind Treatment Induction Period (Period 2) is double-blinded; subjects and study site personnel will be blinded to treatment assignments.

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

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

If an investigator, study site personnel performing assessments, or subject is accidentally unblinded, the subject must be discontinued from the study. If there are ethical reasons for the subject to remain in the study, the investigator must obtain specific approval from a Lilly clinical research physician (CRP) or designated clinical research scientist (CRS) for the subject to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining whether unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly-designated CRP/CRS prior to unblinding a subject's treatment assignment, unless this could delay emergency treatment of the subject. If a subject's treatment assignment is unblinded, Lilly must be notified immediately.

7.4. Dosage Modification

During the Double-Blind Treatment Induction Period (Period 2), subjects will receive treatment regimen based on their baseline weight category and are not allowed to modify the treatment regimen during this treatment period. At each visit following the Double-Blind Treatment Period, the subject's ixekizumab dose will be modified if the subject changes weight categories.

The first interim analysis will confirm whether exposures are as expected and whether exposure-response is similar in pediatric subjects to response in adults. Review of the data at this interim could lead to dosing regimen modification for some or all ongoing and future subjects based on the findings. Any changes to dosing regimens recommended by the DMC will be reviewed by the Lilly Senior Management Designee who will determine whether changes will be implemented.

The interim analyses are described in further detail in Section 10.4.8.

7.5. Preparation/Handling/Storage/Accountability

Study drug will be supplied by Lilly or its representative in accordance with current good manufacturing practices and will be supplied with lot numbers, expiration dates, and certificates of analysis, as applicable.

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

7.6. Treatment Compliance

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

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

Subject compliance with the study drug will be assessed at each visit. Compliance will be assessed by the number of injections needed versus the number of injections administered to the subjects. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

7.7. Concomitant Therapy

Previous plaque Ps therapies and all concomitant medication taken during the study must be recorded in the electronic CRF (eCRF). Treatment with plaque Ps therapies during the study is permitted only as outlined in the inclusion/exclusion criteria (Sections 6.1 and 6.2) and as described in the paragraphs below. Subjects taking permitted medications should be on chronic stable doses at the baseline visit (Week 0; Visit 2) as specified in Section 6.2.

The following therapies will not be permitted during the study:

- plaque Ps therapy as described in the inclusion/exclusion criteria (Section 6.1 and Section 6.2)
- any biologic therapy within the washout period specified in Section 6.2
- concomitant medications as described in the exclusion criteria

- live vaccines
- phototherapy

The following medications will be permitted during the study:

Topical Steroids: Topical steroids (that is, nonhalogenated steroids/topical calcineurin inhibitors administered no more than twice daily) will be permitted for use limited to the face, axilla, and/or genitalia, as needed. These topical medications should not be used within approximately 24 hours prior to study visits.

Vaccines: Use of nonlive seasonal vaccinations and/or emergency vaccinations (such as rabies or tetanus vaccinations) is allowed.

Other Concomitant Therapies: The following will be allowed as needed: shampoos that do not contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues; topical moisturizers/emollients and other nonprescription topical products that do not contain urea, >3% salicylic acid, alpha- or beta-hydroxyl acids, corticosteroids, or vitamin D3 analogues; and bath oils and oatmeal bath preparations.

Additional drugs are to be avoided during the study, unless required to treat an AE or for treatment of an ongoing medical problem. If the need for concomitant medication arises for an AE or for appropriate medical management (including the limited use of therapeutic agents which, if used under treatment regimens other than for treating an AE or for appropriate medical management, might be considered plaque Ps therapies), the investigator should base decisions on the subject and clinical factors. Any additional medication, whether prescription or over-the-counter, used at baseline (Week 0; Visit 2) and/or during the course of the study must be documented with the start and stop dates on the Concomitant Medications eCRF.

Subjects will maintain their usual medication regimen for other concomitant diseases throughout the study, unless specifically excluded in the protocol. Subjects taking concomitant medications should be on stable doses at 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. Additional systemic drugs are to be avoided during the study, unless required to treat an AE. Other medications may be allowed if approved by the Sponsor or its designee.

For subjects who discontinued study treatment and have entered the Post-Treatment Follow-Up Period (Period 5), plaque Ps therapy with another agent, as determined appropriate by the investigator, is allowed. Any changes in medications not addressed above should be discussed with the investigator. Subjects should be instructed to consult the investigator or other appropriate study personnel at the study site before taking any new medications or supplements.

7.8. Treatment after the End of the Study

7.8.1. Continued Access

Ixekizumab will not be made available by the Sponsor at the conclusion of the study to subjects if the product is commercially available in countries where the subject resides.

7.8.2. Special Treatment Considerations

Subjects 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. Subjects 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 subjects are to be closely monitored for signs or symptoms that could result from such reactions, educated on the signs or symptoms of these types of reactions, and instructed to contact the study site immediately if any of the symptoms are experienced following an injection. If a subject experiences an acute allergic/hypersensitivity reaction after an injection of study drug, he or she is to be managed appropriately and given instruction to receive relevant supportive care. Additionally, for an event judged by the investigator to be a potential systemic allergic/hypersensitivity reaction, a blood sample is to be drawn as soon as possible to test for antidrug antibodies (ADAs) (Section 9.4.7).

For subjects who experience a potential allergic/hypersensitivity reaction, consideration for any premedication for future injections will be agreed upon between the investigator and the Sponsor. Examples of potential allergic/hypersensitivity reactions that might merit premedication include mild-to-moderate skin rashes, mild-to-moderate generalized pruritus and/or urticaria, and mild to-moderate injection-site reactions (e.g., injection-site erythema, injection site pruritus). Subjects who develop clinically significant systemic allergic/hypersensitivity reactions following administration of study drug that do not respond to symptomatic medication or result in clinical sequelae or hospitalization are to be discontinued from study treatment and not receive further doses of study drug, with or without premedication (see 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 after all efficacy assessments have been completed for a given visit and 30 to 60 minutes prior to study drug SC injection for visits where injections are administered at the clinic. For all other injections, subjects may self-premedicate at home prior to administration of study drug, as directed by the investigator. All such premedications will be recorded as concomitant medications. Corticosteroids are not permitted as agents for premedication.

7.8.3. Permanent Discontinuation from Study Treatment

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

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN and total bilirubin level (TBL) >2xULN or prothrombin time >1.5xULN
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3xULN
- ALP >2.5x ULN 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, subjects will be discontinued from the study drug under the following circumstances:

- neutrophil (segmented) counts:
  - <500 cells/μL
  - ≥500 and <1000 cells/μL (based on 2 test results; the second test performed within 1 week from knowledge of the initial result)
  - ≥1000 and <1500 cells/μL (based on 3 test results) and an infection that is not fully resolved
- total WBC count <2000 cells/μL
- lymphocyte count <200 cells/μL
- platelet count <50,000 cells/μL
- Refer to Appendix 5, which describes the 95 percentile BP for age and gender and median height. If subject BP readings is greater than 95 percentile at 3 consecutive study visits, study drug must be held until the subject's BP is further assessed. Following that assessment, a decision will be made by Lilly CRP/CRS as to whether the subject should remain on the trial.
- the subject experiences a severe AE or an SAE or has a clinically significant change in a laboratory value that, in the opinion of the investigator, merits discontinuation of the study drug and appropriate measures being taken. This includes evidence of active viral hepatitis or active TB. In such cases, Lilly or its designee is to be notified immediately

- clinically significant systemic hypersensitivity reaction following SC administration of study drug that does not respond to symptomatic medication or results in clinical sequelae
- subject becomes pregnant
- subject develops a malignancy
- subject has a positive TB test using PPD or QuantiFERON®-TB Gold and is assessed as having latent TB infection (see Section 9.4.2), and/or develops symptoms or signs of tuberculosis
- any subject who has a change in disease phenotype at any time (e.g., a change to pustular psoriasis)
- if the subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for the treatment of plaque Ps, discontinuation from study treatment occurs prior to introduction of the new agent
- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- the investigator or attending physician decides that the subject should be withdrawn from study treatment
- the subject (or caregiver) requests withdrawal from study treatment
- the patient, at any time during the study, scores a ≥5 for Item 13 on the CDRS-R
  -OR
- develops active suicidal ideation with some intent to act with or without a specific plan (yes to question 4 or 5 on the "Suicidal Ideation" portion of the Columbia–Suicide Severity Rating Scale [C-SSRS])
  -OR
- develops suicide-related behaviors as recorded on the C-SSRS.
- It is recommended that the subject be assessed by ~~a psychiatrist or~~ an appropriately trained professional (e.g., psychiatrist, clinical psychologist, social worker etc.) to assist in deciding whether the subject is to be discontinued from the study.
- the investigator or Lilly stops the subject's participation in the study or Lilly stops the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)

All subjects who discontinue from study treatment are encouraged to complete the follow-up period of the study.

8. Discontinuation Criteria

The reason for and date of discontinuation from study drug and reason for and date of discontinuation from study participation will be collected for all randomized subjects.

Subjects who discontinue study drug early will have end-of-therapy procedures performed as shown in the Schedule of Activities (Section 2) and will enter the Post-Treatment Follow-Up Period.

Missing data may compromise the integrity of the study and undermine the altruistic contribution of study subjects to answer the scientific questions being addressed in the study. Complete information from each subject is critical to achieving the fullest understanding of the potential benefits and risks of ixekizumab. Subjects should make every effort to stay in the study, to attend scheduled visits, and to take study drug as medically appropriate.

Subjects who meet any of the criteria described in Section 8.1 will be discontinued from study treatment.

8.1. Discontinuation from Study Treatment

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

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

The criteria for enrollment must be followed explicitly. If the Sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Sponsor CRP/CRS and the investigator to determine whether the subject may continue in the study. If both agree it is medically appropriate for the subject to continue, the investigator must obtain documented approval from the Sponsor CRP/CRS to allow the inadvertently enrolled subject to continue in the study with or without treatment with study drug.

8.2. Discontinuation from the Study

Reasons that may lead to permanent discontinuation include:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- investigator decision
    - the investigator decides that the subject should be discontinued from the study
    - if the subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent

- subject decision
    - the subject or the subject's designee (e.g., parent or legal guardian) requests withdrawal from the study

8.3. Lost to Follow-Up

A subject 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. Study site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit or who were otherwise unable to be followed up by the study site.

9. Study Assessments and Procedures

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

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

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

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessments

The co-primary efficacy endpoints are PASI 75 and sPGA (0,1) at Week 12.

The PASI is an accepted primary efficacy measurement for this phase of development of plaque Ps treatments (EMEA [WWW]). The PASI combines assessments of the extent of body-surface involvement in 4 anatomical regions (head and neck, trunk, arms, and legs) and the severity of scaling, redness, and plaque induration/infiltration (thickness) in each region, yielding an overall score of 0 for no plaque Ps to 72 for the most severe disease (Fredriksson and Pettersson 1978). 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 plaque Ps (a 100% improvement from baseline in PASI score [PASI 100]) are additional endpoints due to increasing recognition of the association of higher clearance with greater health-related quality of life (Puig 2015).

The sPGA is the physician's global assessment of the subject's plaque Ps lesions at a given time point. The sPGA is recommended as an endpoint to assess efficacy in the treatment of plaque Ps (EMEA [WWW]). Plaques are assessed for induration, erythema, and scaling, and an overall rating of plaque Ps severity is given using the anchors of clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).

9.1.2. Secondary Efficacy Assessments

9.1.2.1. Nail Psoriasis Severity Index (NAPSI)

If the subject has fingernail/toenail plaque Ps at baseline, the NAPSI will be used. The NAPSI is a numeric, reproducible, objective tool for evaluation of fingernail/toenail plaque Ps. This scale is used to evaluate the severity of fingernail/toenail bed plaque Ps matrix plaque Ps by area of involvement in the fingernail/toenail unit. In this study, both fingernail and toenail involvement will be assessed. The fingernail/toenail is divided into imaginary horizontal and longitudinal lines into quadrants. Each nail is given a score for fingernail/toenail bed plaque Ps (0 to 4) and nail matrix plaque Ps (0 to 4) depending on the presence (score of 1) or absence (score of 0) of any of the features of fingernail or toenail bed and matrix plaque Ps in each quadrant. The

NAPSI score is the sum of scores in the fingernail and toenail bed and matrix from each quadrant (maximum of 8). Each fingernail and toenail is evaluated, and the sum of all the fingernails and toenails is the total NAPSI score (range: 0 to 160).

9.1.2.2. Psoriasis Scalp Severity Index

If the subject has scalp plaque Ps at baseline, the Psoriasis Scalp Severity Index (PSSI) will be used. The PSSI is a composite score derived from the sum of scores for erythema, induration, and desquamation multiplied by a score for the extent of scalp area involved (range: 0 to 72).

9.1.2.3. Palmoplantar Psoriasis Area and Severity Index

If the subject has palmoplantar plaque Ps at baseline, the Palmoplantar Psoriasis Severity index (PPASI) will be used. The PPASI is a composite score derived from the sum of scores for erythema, induration, and desquamation multiplied by a score for the extent of palm and sole area involvement (range: 0 to 72).

9.1.2.4. Percentage of Body Surface Area

The investigator will evaluate the percentage involvement of plaque Ps on each subject's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), in which 1% corresponds to the size of the subject's hand (including the palm, fingers, and thumb) (Van Voorhees et al. 2009).

9.1.2.5. Binary Questions on Psoriasis Location

The binary questions for psoriasis location will define specific locations of plaque Ps. This assessment will be used as a secondary endpoint and will be especially helpful to delineate the presence of psoriasis on the face and in the genital area. There are no specific scales to assess plaque Ps in these locations.

9.1.3. Health Outcomes/Quality of Life Measures

9.1.3.1. Itch Numeric Rating Scale

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

9.1.3.2. Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) will be completed by subjects aged 17 years and older.

The DLQI is a simple, subject-administered, 10-question, validated, quality-of-life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Response categories include "not at all," "a lot," and "very much," with corresponding scores of 1, 2, and 3, respectively, and unanswered ("not relevant") responses scored as "0." The recall period is "over the last week," totals range from 0 to 30 (less to more impairment), and a 5-point change from baseline is considered clinically relevant (Basra et al. 2008).

9.1.3.3. Children's Dermatology Life Quality Index

The Children's Dermatology Life Quality Index (CDLQI) questionnaire will be completed by subjects aged 6 to 16 years of age.

The Children's Dermatology Life Quality Index (CDLQI) questionnaire is designed for use in children (subjects from 4 to 16 years of age) (Lewis-Jones and Finlay 1995; Waters et al. 2010; Salek et al. 2013). It consists of 10 items, 6 of which are headings (symptoms and feelings, leisure, school or holidays, personal relationships, sleep, and treatment). The CDLQI is calculated by summing the score of each question, resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. The severity banding for CDLQI scores is:

0-1 = no effect on child's life

2-6 = small effect

7-12 = moderate effect

13-18 = very large effect

19-30 = extremely large effect

The CDLQI is self-explanatory and can be simply handed to the subject who is asked to complete it with the help of a parent or guardian. It is usually completed in 1 to 2 minutes. The recall period is "over the last week," total scores range from 0 to 30 (less to more impairment), and a 5-point change from baseline is considered clinically relevant (Basra et al. 2008).

The Dermatology Life Index (DLQI) will be completed by subjects aged 17 years and older. The Children's Dermatology Life Quality Index (CDLQI) questionnaire will be completed by subjects aged 6 to 16 years of age. The sites will use the appropriate version according to the age and transition from CDLQI to DLQI when the subject turn 17 years old, with the exception during the double blind treatment period (induction).

9.1.3.4. Patient's Global Assessment of Disease Severity

The patient's global assessment of disease severity is a subject-administered single-item scale in which subjects are asked to rank, by circling a number on a 0-to-5 NRS, the severity of their plaque Ps "today" from 0 (clear) = no plaque Ps to 5 (severe) = the worst their plaque Ps has ever been.

9.1.4. Appropriateness of Assessments

All of the clinical and safety assessments in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant. Immunogenicity monitoring will provide information for future development of ixekizumab.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of subjects 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 subjects.

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate healthcare option, AEs that are serious or otherwise medically important, considered related to the study drug or the study, or that caused the subject to discontinue the study drug before completing the study. The subject should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF and assent are signed, study site personnel will record via CRF the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, study 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 and study drug via eCRF.

The investigator will interpret and document whether an AE has a reasonable possibility of being related to the study drug, the 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, the study device, and/or a study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgical procedures and nonsurgical interventions should not be reported as AEs, unless the underlying medical condition has worsened during the study.

If a subject's study drug is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via CRF, clarifying, if possible, the circumstances leading to any dosage modifications or discontinuation of treatment.

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of death)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect

- considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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

Although all AEs occurring after signing the ICF are recorded in the CRF and each AE is to be assessed as to whether it meets any of the above serious criteria, the submission of SAE reports to the Sponsor begins after the subject has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF but prior to receiving study drug, it needs to be reported to the Sponsor ONLY if it is considered reasonably possibly related to study procedure.

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

Pregnancy (during maternal or paternal exposure to study drug) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported according to the SAE reporting process to provide data to the Sponsor 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 subject summary 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 or she considers the event reasonably possibly related to study treatment or study participation, the investigator must promptly notify Lilly.

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 are assessed as being related to study drug or procedure. United States 21 CFR 312.32 and EU Clinical Trial Directive 2001/20/EC and the associated detailed guidance or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Adverse Events of Special Interest

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

AESIs for ixekizumab are:

- cytopenias (leukopenia, neutropenia, and thrombocytopenia)
- liver biochemical test changes/enzyme elevations (ALT, AST, bilirubin, and ALP)
- infection
- immunogenicity
- injection-site reactions
- allergic reactions/hypersensitivities
- cerebrocardiovascular events
- malignancies
- depression
- inflammatory bowel disease
- interstitial lung disease

If infections, injection-site reactions, or allergic/hypersensitivity reactions are reported, study sites will provide details on these events as instructed on the eCRF. Investigators will also educate subjects and/or caregivers about the symptoms of allergic/hypersensitivity reactions and will provide instructions on dealing with these reactions (see also Section 7.8). A blood sample will be collected when possible for any subject who experiences an AE of allergic reactions/hypersensitivities during the study.

Data on suspected inflammatory bowel disease, 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 Clinical Events Committee (CEC) composed of gastroenterologists with expertise in inflammatory bowel disease. The role of the CEC is to adjudicate defined clinical events in a blinded, consistent, and unbiased manner throughout a study. The importance of the CEC is to ensure that all events that have been reported are evaluated uniformly by a single group.

9.2.3. Complaint Handling

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

Subjects will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug so that the situation can be assessed.

9.3. Treatment of Overdose

Refer to the ixekizumab IB and/or Product Label for the adult indication (ixekizumab and/or comparator).

9.4. Safety

9.4.1. Physical Examination

One complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed at screening (Visit 1). This examination will determine whether the subject 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 adverse event (TEAE) assessment. All physical examinations throughout the study should include a symptom-directed physical evaluation as well as an examination of the heart, lungs and abdomen and a visual examination of the skin.

9.4.2. Chest X-Ray and Tuberculosis Testing

A posterior-anterior view chest x-ray will be obtained, unless the x-ray or results from a chest x-ray obtained within 6 months prior to the study are available. The chest x-ray or results will be reviewed by the investigator or designee and considered along with the subject's medical history, assessment of risk factor for *M. tuberculosis* infection and physical examination to exclude subjects with active TB infection. In Germany, a chest x-ray has to be performed within 6 months prior to signing informed consent indicating no evidence of TB.

In addition, subjects will be tested at screening as indicated in the Schedule of Activities (Section 2) for evidence of *M. tuberculosis* infection. A positive tuberculin PPD skin test response for this study is defined as ≥5-mm induration between 48 and 72 hours after PPD application, regardless of BCG vaccination history. In countries where an interferon-gamma release assay (QuantiFERON®-TB Gold test) is available and, in the judgment of the investigator, is preferred as an alternative to the PPD skin test for the evaluation of *M. tuberculosis* infection, it may be used instead of the PPD test and may be read locally. If the QuantiFERON®-TB Gold test is indeterminate, 1 retest is allowed. If the retest for the QuantiFERON®-TB Gold test is indeterminate, the subject is excluded from enrollment in the study.

Subjects with documentation of a negative PPD or QuantiFERON®-TB Gold test (TB test) result within 3 months prior to baseline (Week 0; Visit 2) are not required to have a TB test at Visit 1 unless medical history, including assessment for TB infection risk factors, chest x-ray or physical examination indicates that testing should be done. Documentation of this test result must include a record of the size of the induration response (<5-mm induration) or the laboratory report of the QuantiFERON®-TB Gold test result. A PPD test recorded as negative without documenting the size of induration will require a retest.

Subjects with a PPD skin test ≥5 mm in duration or a positive QuantiFERON®-TB Gold but no evidence of active TB, and subjects who have a documented history of a positive TB test but no documented history of completion of a full, appropriate latent TB treatment course, who are assessed as having latent TB infection may be re-screened 1 time and may be enrolled without repeating a PPD or 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 ≤2x ULN) upon retesting of serum ALT/AST prior to randomization,
- commitment by the subject and the caregiver for the subject to complete a full course of standard prophylaxis for TB, and

- meet all other inclusion/exclusion criteria for participation.

Such subjects must complete appropriate latent TB infection therapy to remain eligible for continued study participation. If rescreening occurs within 6 months of the screening chest x-ray, a repeat of chest x-ray for considering enrollment is not required.

If a subject with a positive PPD or QuantiFERON®-TB Gold is fully assessed by the investigator and the investigator determines that the subject has no risk factors for and no symptoms or signs of *M. tuberculosis* infection, the Investigator may contact the Lilly Medical Monitor to discuss the possibility of a false-positive test result.

Subjects with positive TB test results on file: Subjects with a documented prior history of a positive TB test and subjects who have a documented history of completion of an appropriate TB treatment regimen for latent or active TB should not have a TB test performed at Visit 1. Such subjects with no history of re-exposure to TB since their treatment was completed and no evidence of active TB are eligible to participate in the study. Subjects who have had household contact with a person with active TB are excluded unless an appropriate and documented course of prophylaxis for TB was completed.

Subjects are to be monitored on a regular basis for any symptoms or signs of active TB and for any new risk factors for TB infection, with full medical evaluation including TB testing when medically indicated. Subjects that exhibit symptoms of active TB should be referred to a specialist in the care of subjects with TB.

Any clinically significant findings from chest x-rays and/or TB testing that result in a diagnosis and that occur after the subject signs the ICF should be reported to Lilly or its designee as an AE via eCRF.

9.4.3. Electrocardiograms

For each subject, 1 electrocardiogram (ECG) should be collected according to the Schedule of Activities (Section 2). The ECG should be recorded according to the study-specific recommendations included in the ECG Manual for the study. Subjects must be supine for a minimum of 5 minutes before ECG collection and remain supine during ECG collection.

A single ECG will be obtained at Visit 1 and read by a qualified physician (the investigator or qualified designee) at the study site to determine whether the subject meets entry criteria. The screening (Visit 1) ECG will subsequently be electronically transmitted to the centralized ECG vendor designated by the Sponsor. The centralized ECG vendor's cardiologist will complete an ECG overread before randomization to confirm that the subject meets entry criteria.

ECGs may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high quality records.

ECGs after Visit 1 will be interpreted by a qualified physician at the study site as soon after ECG collection as possible, ideally while the subject is still present, for immediate subject management should any clinically relevant findings be identified.

If a clinically significant quantitative or qualitative change from screening (Visit 1) is identified after randomization, the investigator will assess the subject for symptoms (e.g., palpitations, near syncope, syncope) and determine whether the subject can continue in the study. The investigator or qualified designee is responsible for determining whether any change in subject management is needed and must document his or her review of the ECG printed at the time of evaluation. Any clinically significant findings from ECGs that result in a diagnosis of untoward cardiac event and that occur after the subject receives the first dose of the study drug should be reported to Lilly or its designee as an AE via CRF.

The investigator (or qualified designee) must document his or her review of the ECG printed at the time of evaluation, the final overread ECG report issued by the central ECG laboratory, and any alert reports.

9.4.4. Bone Imaging

A Bone Age Imaging X-ray will be performed on the left hand twice at Visit 2 (Week 0) and Visit 31 (Week 108) according to schedule of activities. ICH guidelines require that we monitor the growth and development of pediatric subjects systematically for all drugs studied in this age group (ICH guidelines). The bone age indicates the level of biological and structural maturity and can deviate from chronological age calculated from the date of birth. Pubertal progress will be monitored by clinical tanner staging in association with longitudinal growth.

9.4.5. Vital Signs

Vital sign measurements should be conducted according to the Schedule of Activities (Section 2).

Any clinically significant findings from vital sign measurement that result in a diagnosis and that occur after the subject receives the first dose of study drug should be reported to Lilly or its designee as an AE via CRF. To be collected as per standard clinical practice.

9.4.6. Laboratory Tests

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

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

9.4.7. Immunogenicity

Samples for immunogenicity testing will be collected at time points indicated in the Schedule of Activities (Section 2) and for an event judged by the investigator to be a potential systemic allergic/hypersensitivity reaction, when possible. Venous blood samples (approximately 2 mL) will be collected into tubes and used to determine antibody production against ixekizumab. The actual date of each sampling will be recorded on the laboratory requisition.

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. Treatment-emergent immunogenicity is defined as any occurrence of a 4-fold or 2-dilution increase in titer over the pretreatment baseline titer. In the case of a negative result at baseline, treatment-emergent immunogenicity is defined as an increase in titer to ≥1:10.

Samples may be stored for a maximum of 15 years following last subject visit to enable further analysis of immune responses to ixekizumab. The duration allows the Sponsor to respond to regulatory requests related to the study drug.

Blood samples for PK assessment will be time-matched to immunogenicity samples for analysis of ixekizumab serum concentrations to facilitate in the interpretation of the immunogenicity data (see Section 9.5).

9.4.8. Safety-Related Immune Markers

Interleukin-17 is believed to play a role in neutrophil homeostasis and in neutrophil-dependent host defense against extracellular infections (Happel et al. 2003; Huang et al. 2004; Milner et al. 2008). Neutrophil counts will therefore serve as a safety marker in the current investigation.

Ixekizumab is not expected to affect the numbers of B, T, and NK lymphocytes or serum immunoglobulin subclasses A, G, and M (IgA, immunoglobulin G, and immunoglobulin M, respectively) in peripheral blood. However, since this is a novel immunomodulatory drug, these parameters will be measured in subjects according to the Schedule of Activities (Section 2).

9.4.9. Children's Depression Rating Scale

The Children's Depression Rating Scale–Revised (CDRS-R) (Poznanski and Mokros 1996) is the most widely used rating scale for assessing severity of depression and change in depressive symptoms for clinical research studies in children and adolescents with depression. The CDRS-R was originally developed as a rating scale for children aged 6 to 12 years. It is a 17-item scale, with items ranging from 1 to 5 or 1 to 7 (the total score is the sum of the 17 items and ranges from 17-113, with higher scores indicating more depressive symptoms) and is rated by a clinician via interviews with the child and parent or legal guardian. A score of ≥40 is indicative of depression, whereas a score ≤28 is often used to define remission (minimal or no symptoms) (Mayes et al. 2010). Subjects will be assessed according to the Schedule of Activities (Section 2).

9.4.10. Columbia–Suicide Severity Rating Scale

Children aged 11 years and younger will use the Children CSSRS form and those 12 years and older will use the Adult CSSRS. The sites will use the appropriate version according to the age and transition from one version to the other when the subject turns 12 years old, with the exception during the double-blind treatment period (Period 2, Induction).

The C-SSRS (Posner et al. 2007; C-SSRS website [WWW]) is a scale that captures the occurrence, severity, and frequency of suicide-related ideations and behaviors during the

assessment period. The C-SSRS must be administered by appropriately trained study site personnel. The tool was developed by the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study Group as a counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events. Subjects will be assessed according to the Schedule of Activities (Section 2).

The Self-Harm Supplement Form is a 1-question eCRF questionnaire that is completed at any visit, including baseline visits, asking for the number of suicidal or nonsuicidal self-injurious behaviors the subject experienced since last assessment. For each unique event identified, a questionnaire (Self-Harm Follow-Up Form), which collects supplemental information on the self-injurious behavior, must be completed. This information is then documented in the eCRF.

9.4.11. Tanner Stage Scale

The Tanner Stage Scales are a series of line drawings that are designed to aid the investigator in appropriately assessing the sexual maturity of the subject. Data gathered will be assessed to determine that no pubertal disruption has occurred during the study. Although the line drawings were originally intended for child self-assessment; evidence suggests that pubertal assessment by the child or the parents/legal guardian is not a reliable measure of exact pubertal staging and should be augmented by a physical examination (Rasmussen et al. 2015). The drawings will be used by the dermatologist investigator as an aid. Subjects will be assessed according to the Schedule of Activities (Section 2).

9.4.12. Safety Monitoring

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

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

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the DMC (an advisory group for this study formed to protect the integrity of data; refer to Section 10.4.8, Interim Analyses) can conduct additional analyses of the safety data.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 2 mL each will be collected to determine the serum concentrations of ixekizumab. Two additional PK samples will be taken during Period 2, Induction in subjects who participate in the PK/PD addendum (see Protocol Addendum I1F-MC-RHCD[1] for details).

A maximum of 3 samples may be drawn at additional time points during the study if warranted and agreed upon between both the investigator and Sponsor. Instructions for the collection and handling of blood samples will be provided by the Sponsor. The actual date and 24-hour clock time of each sampling will be recorded.

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

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

9.6. Pharmacodynamics

Not applicable.

9.7. Pharmacogenomics

Not applicable.

9.8. Biomarkers

Not applicable.

9.9. Medical Resource Utilization and Health Economics

Not applicable.

10. Statistical Considerations

10.1. Bone Imaging

A Bone Age Imaging X-ray will be done on the left hand twice. ICH guidelines require that we monitor the growth and development of pediatric subjects systematically for all drugs studied in this age group (ICH guidelines). The bone age indicates the level of biological and structural maturity and can deviate from chronological age calculated from the date of birth. Pubertal progress is generally monitored by clinical tanner staging in association with longitudinal growth.

10.2. Sample Size Determination

Sample size of this study is based on the regulatory requirements from the European Medicine's Agency Paediatric Investigation Plan for ixekizumab. The regulatory requirements for the number of subjects in each treatment group were: (1) at least 170 randomized subjects (at least 90 to ixekizumab, at least 25 to etanercept, and at least 55 to placebo) and (2) at least 30% of subjects from the EU.

For this study, approximately 195 subjects will be randomized. Approximately 165 subjects will be randomized in a 2:1 ratio to receive ixekizumab (110 subjects) or placebo (55 subjects) during the Double-Blind Treatment Period. Approximately 30 subjects will be randomized to etanercept; details are described in the Protocol Addendum I1F-MC-RHCD(2).

The study will have >99% power to test the superiority of ixekizumab to placebo for PASI 75 and for sPGA (0,1) at Week 12 based on the 2-sided Fisher exact test at a significance level of 0.05. The following assumptions were used for the power calculations for both sPGA (0,1) and PASI 75 responses rates based on ixekizumab clinical studies in adult subjects with moderate-to-severe plaque Ps efficacy data (Griffiths et al. 2015; Gordon et al. 2016): 80% response for ixekizumab and 10% response for placebo for both PASI 75 and sPGA (0,1).

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
ITT	All randomized subjects, even if the subject does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Unless otherwise specified, efficacy and health outcomes analyses will be conducted on the ITT Population during the Double-Blind Treatment Induction Period (Period 2). Subjects will be analyzed according to the treatment to which they were assigned.
Per-Protocol	All randomized subjects who do not have significant protocol violations. Subjects will be analyzed according to the treatment to which they were assigned. The co-primary analyses (PASI 75 and sPGA [0,1]) will be repeated using the per-protocol set during the Double-Blind Treatment Period.
Safety	All randomized participants who take at least 1 dose of double-blind study treatment. Subjects will be analyzed according to the treatment to which they were assigned. Safety analyses for the Post-Treatment Follow-Up Period will be conducted on the Follow-Up Population, defined as all randomized subjects who received at least 1 dose of study treatment

	and have entered the Post-Treatment Follow-Up Period.
All Ixekizumab	All randomized subjects who receive at least 1 dose of ixekizumab. Efficacy and safety analyses will be conducted on this population.

Abbreviations: ITT = intent to treat; PASI 75 = at least a 75% improvement from baseline in Psoriasis Area and Severity Index score; sPGA = static Physician's Global Assessment.

10.4. Statistical Analyses

10.4.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee.

Efficacy and safety analyses will be conducted for the Double-Blind Treatment Induction Period (Period 2) and all ixekizumab treatment periods (defined as the total time subject is receiving ixekizumab during the study).

Unless otherwise specified, efficacy and health outcomes analyses during Period 2, Induction will be conducted on the ITT Population. Efficacy and health outcomes will be summarized during the overall ixekizumab treatment period for ~~all~~ subjects who are randomized to ixekizumab group at Week 0 and combining all the ixekizumab treatment periods.

Safety analyses during the Period 2, Induction will be conducted on the Safety Population. Safety analyses during the overall ixekizumab treatment period will be conducted for all subjects who receive at least 1 dose of ixekizumab and combining all the ixekizumab treatment periods.

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. Comparisons between ixekizumab and placebo will be performed for all analyses in the Double-Blind Treatment Induction Period (Period 2).

Unless otherwise specified, baseline for efficacy and health outcomes during Period 2, Induction and during the overall ixekizumab treatment period is at or prior to the first injection of study drug. In most cases, this will be the measure recorded at Week 0 (Visit 2).If the subject does not receive any injection, the last available value on or prior to randomization date will be used. Change from baseline will be calculated as the visit value of interest minus the baseline value.

Unless otherwise specified, baseline for safety during Period 2, Induction is defined as follows: for categorical data, baseline includes all available values before the first injection at Week 0; for continuous data, baseline is the last available value before the first injection at Week 0. Baseline for categorical safety data during the overall ixekizumab treatment period is defined as all available values if ixekizumab is received at Week 0 and the last available value prior to first dose of ixekizumab when ixekizumab is administered after Period 2, Induction.

For the Post-Treatment Follow-Up Period (Period 5), baseline is defined as the last nonmissing assessment on or prior to entering Period 5, that is, on or prior to Week 108 or ETV.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis

methods described in the protocol and the justification for making the change will be described in the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

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

10.4.2. Analysis Methods

The primary analyses method for categorical data comparison between treatments will be the Fisher's exact test. Difference of the proportions and the 95% CI of the difference will be included.

Secondary analyses for the co-primary efficacy measures PASI 75 and sPGA (0,1) will be conducted using a logistic regression analysis with treatment group, region, baseline sPGA score (severity of the psoriasis), and baseline weight category (<25 kg, ≥25 to ≤50 kg, >50 kg) as factors. The odds ratio and the corresponding 95% CI will be reported.

The analyses for the continuous efficacy and health outcomes variables will be made using analysis of covariance (ANCOVA) and using a mixed model for repeated measures (MMRM) analysis). The ANCOVA model includes treatment, region, baseline sPGA score, baseline weight category, and baseline value. Type III sums of squares for the least-squares means will be used for the statistical comparison; the 95% CI will be reported.

When the MMRM is used, the model will include treatment, region, baseline sPGA score, baseline weight category, baseline value, visit, treatment-by-visit, and baseline-by-visit interactions as fixed factors. The covariance structure to model the within-subject errors will be unstructured. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III tests for the least-squares means will be used for the statistical comparison; the 95% CI will be reported. Treatment comparisons at Week 12 and all other postbaseline visits in Period 2, Induction will be reported. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, followed by the compound symmetry will be used. This order is specified according to a decreasing number of covariance parameters in the structure. The sandwich estimator (Diggle et al. 1994) for the covariance estimation will be used by specifying the EMPIRICAL option in SAS PROC MIXED. When sandwich estimation is used, the Kenward-Roger approximation for denominator degrees of freedom cannot be used. Instead, DDFM= BETWITHIN option will be used to estimate denominator degrees of freedom.

Treatment comparisons of time to relapse (sPGA $\geq$ 2) will be conducted using the log-rank test as described in Protocol Addendum I1F-MC-RHCD(2).

10.4.2.1. Missing Data Imputation

The methods for imputation of missing data to be used in this study are in accordance with the precedent set in other Phase 3 plaque Ps studies (Griffiths et al. 2015; Gordon et al. 2016).

10.4.2.2. Nonresponder Imputation

Analysis of categorical efficacy and health outcomes variables will be assessed using a nonresponder imputation (NRI) method. Subjects will be considered nonresponders for the NRI analysis if they do not meet the clinical response criteria or have missing clinical response data at the analysis time point. Randomized subjects without at least 1 postbaseline observation will also be defined as nonresponders for the NRI analysis.

10.4.2.3. Last Observation Carried Forward

A last observation carried forward analysis will be performed on all continuous efficacy and health outcomes variables as a secondary analysis. For subjects having missing data at the visit, the last nonmissing postbaseline observation before the missing data will be carried forward to the corresponding time point for evaluation. Subjects who have a baseline and at least 1 postbaseline observation will be included for evaluation.

10.4.3. Adjustment for Multiple Comparisons

A multiple testing strategy for the co-primary and major secondary objectives will be implemented to control the family-wise Type I error rate at a 2-sided α level of 0.05. The primary and key secondary comparisons will be tested by using the primary analysis method, Fisher exact test, with NRI missing data imputation approach.

A gatekeeping approach will be used for multiple comparisons to control the family-wise error rate. The following endpoints will be tested:

- Primary 1: Proportion of subjects achieving PASI 75 at Week 12
- Primary 2: Proportion of subjects achieving sPGA (0,1) at Week 12
- Secondary 1: Proportion of subjects achieving PASI 90 at Week 12
- Secondary 2: Proportion of subjects achieving sPGA (0) at Week 12
- Secondary 3: Proportion of subjects achieving PASI 100 at Week 12
- Secondary 4: Proportion of subjects achieving ≥4 point improvement at Week 12for subjects who had a baseline Itch NRS ≥4
- Secondary 5: Proportion of subjects achieving PASI 75 at Week 2
- Secondary 6: Proportion of subjects achieving sPGA (0,1) at Week 2

The Primary 1 will first be tested at 2-sided α=0.05. If successful, the test for Primary 2 will be performed at 2-sided α=0.05. Otherwise, the test will stop. If the Primary 2 endpoint is successful, the Secondary 1 endpoint will be tested. The test will continue to the last endpoint if all the prior tests are successful. If a test is not successful, all subsequent tests will not be performed.

10.4.3.1. Subject Disposition

All subjects who discontinue from study treatment and from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for discontinuation will be given. Subject disposition will be summarized for each treatment period with reasons for

discontinuation. The reasons for discontinuation during Period 2, Induction will be compared between treatment groups using Fisher's exact test.

10.4.3.2. Subject Characteristics

The subject's age, gender, ethnicity, weight, height, BMI, habits, and other demographic characteristics will be recorded. Baseline disease severity (including sPGA score and PASI score), age of plaque Ps onset, disease location (nails, scalp, hands, and feet), and previous plaque Ps therapy type will also be recorded and reported.

Subject baseline characteristics will be summarized by treatment group and overall for the ITT population. Comparisons between treatment groups for the ITT population will be conducted using Fisher's exact test for categorical data and an analysis of variance model with treatment group as a factor for continuous data.

10.4.3.3. Concomitant Therapy

Previous and concomitant medications will be summarized for subjects for Period 2, Induction will be presented by World Health Organization Anatomic Therapeutic Class Level 4 and preferred term. Previous plaque Ps therapy will be summarized according to the type (topical, biologics, nonbiologics, phototherapy, and so on). The comparisons between treatment groups in Period 2, Induction will be conducted using Fisher's exact test.

10.4.3.4. Treatment Compliance

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

10.4.4. Efficacy Analyses

10.4.4.1. Co-Primary Analyses

The co-primary analyses will be based on the ITT Population for Period 2, Induction. In addition, an analysis of the Per-Protocol Population will be used to support the primary efficacy analyses.

Treatment comparisons in the proportion of subjects achieving PASI 75 response and sPGA (0,1) response at Week 12 will be analyzed using Fisher's exact test. Missing data will be imputed using the NRI method described in Section 10.4.2.2. Table RHCD.3 includes the co-primary analysis variables and the methods.

10.4.4.2. Major Secondary Analyses

Unless otherwise specified, the major secondary analyses at Week 12 will be based on the ITT Population for Period 2, Induction. The major secondary comparisons will be tested based on the gatekeeping approach described in Section 10.4.3. Treatment comparisons in the proportion of subjects achieving a response at Week 12 will be analyzed using Fisher's exact test. Missing

data will be imputed using the NRI method described in Section 10.4.2.2. Table RHCD.3 includes the secondary analysis variables and the methods.

10.4.4.3. Other Secondary Analyses

Unless otherwise specified, the other secondary analyses for Period 2, Induction will be based on the ITT Population and safety population. There will be no adjustment for multiple comparisons for other secondary analyses.

The other secondary analyses include the secondary analyses and comparisons for the co-primary efficacy outcomes PASI 75 and sPGA (0,1) and the analyses for secondary efficacy outcomes. Table RHCD.3 includes the secondary analysis variables and methods. The detailed methods are specified in Section 10.4.2.2. The treatment comparisons include ixekizumab versus placebo at Week 12 and all other postbaseline visits during Period 2, Induction (the time course of response to treatment).

Table RHCD.3. Efficacy Analyses

Efficacy Measure	Variable	Analysis
PASI	PASI 75 (co-primary efficacy outcome)	Fisher's exact test with NRI (primary analysis); Logistic regression
	PASI 90 (major secondary efficacy outcome)	Fisher's exact test with NRI
	PASI 100 (major secondary efficacy outcome)	Fisher's exact test with NRI
	Change from baseline percent improvement	ANCOVA with LOCF MMRM
sPGA	sPGA (0,1) (co-primary efficacy outcome)	Fisher's exact test with NRI (primary analysis); Logistic regression
	sPGA (0) (major secondary efficacy outcome)	Fisher's exact test with NRI
BSA	Change from baseline	ANCOVA with LOCF MMRM
NAPSI (subjects with baseline nail involvement)	Change from baseline	ANCOVA with LOCF MMRM
PSSI (subjects with baseline scalp involvement)	Change from baseline	ANCOVA with LOCF MMRM
PPASI (subjects with baseline palmoplantar involvement)	Change from baseline	ANCOVA with LOCF MMRM
Binary questions on psoriasis location (by subjects who have psoriasis presence within the specified psoriasis location)	Achieving resolution of psoriasis within the specified psoriasis location	Fisher's exact test with NRI

Abbreviations: ANCOVA = analysis of covariance; BSA = body surface area; LOCF = last observation carried forward; MMRM = mixed model for repeated measures; NAPSI = Nail Psoriasis Severity Index; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; PASI 75 = at least a 75% improvement from baseline in PASI score; PASI 90 = at least a 90% improvement from baseline in PASI score; PASI 100 = a 100% improvement from baseline in PASI score; PPASI = Palmoplantar Psoriasis Area and Severity Index; PSSI = Psoriasis Scalp Severity Index; sPGA = static Physician's Global Assessment.

10.4.5. Safety Analyses

Safety of ixekizumab, including but not limited to infections; injection-site reactions; B-, T-, and NK-cell levels; WBC count; RBC count; and laboratory values (hematology and chemistry [including ALT and AST]) will be assessed.

Exposure to study drug; AEs; laboratory analytes, including neutrophil counts and immunogenicity; CDRS; C-SSRS; and vital signs will be summarized.

Immunization history will be summarized at baseline, and any unexpected outcomes or effects related to standard-of-care vaccination will be summarized.

For Period 2, Induction, the safety data will be summarized and analyzed with treatment comparisons of ixekizumab versus placebo.

For all ixekizumab treatment periods combined (Periods 2, 3, and 4), safety data will be summarized.

During the Post-Treatment Follow-Up Period (Period 5), safety data will be summarized.

The categorical safety measures will be summarized with frequencies. The mean change of the continuous safety measures will be summarized.

10.4.5.1. Adverse Events

AEs are classified based on the Medical Dictionary for Regulatory Activities (MedDRA). A TEAE is defined as an event that first occurred or worsened in severity after baseline and on or prior to the date of the last visit within the treatment period. Both the date/time of the event and the date/time of the dose (that is, injection) are considered when determining TEAEs. A follow-up emergent AE is defined as an event that first occurred or worsened in severity after subject discontinuation from treatment. For events that are gender-specific, the denominator and computation of the percentage will only include subjects from the given gender.

An overall summary of AEs will be provided for Period 2, Induction and all ixekizumab treatment periods combined. The AE summary includes the number and percentage of subjects who experienced at least 1 TEAE, TEAEs by maximum severity, death, SAEs, TEAEs related to study drug, discontinuations from treatment due to an AE, and treatment-emergent AESIs. TEAEs (all, by maximum severity), 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 AEs, SAEs including deaths, and AEs that lead to study discontinuation will be summarized by MedDRA system organ class and preferred term for Period 5.

10.4.5.2. Clinical Laboratory Tests

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

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

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

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

Vital signs will be analyzed as mean changes from baseline and as incidence of treatment-emergent abnormal values.

CDRS total scores will be analyzed as mean changes from baseline.

C-SSRS responses will be listed by subject and visit. Only subjects that show suicidal ideation/behavior or self-injurious behavior without suicidal intent will be displayed (i.e., if a subject answers are all "no" for the C-SSRS, then that subject will not be displayed).

Weight, height, and tanner stage data will be summarized for every visit.

Weight, height, and BMI data will be merged to the CDC standard growth data by age and gender to compare subjects' growth with the standard.

Shift tables for tanner stage from maximum baseline to maximum postbaseline by gender will be presented.

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

Further analyses may be performed.

10.4.6. Pharmacokinetic/Pharmacodynamic Analyses

Observed ixekizumab serum trough concentrations will be summarized by time point across the study. The PK parameters of ixekizumab in pediatric subjects will be determined using population PK methods.

The exposure-response relationship will be investigated between steady-state trough concentrations of ixekizumab and clinically important efficacy measures (e.g., sPGA and PASI endpoints) at Week 12 using graphical methods and, if appropriate, modeling methods. If applicable, the potential impact of immunogenicity on ixekizumab exposure and/or efficacy responses may be evaluated by graphical assessments, as appropriate, to compare drug exposure or efficacy responses between ADA-negative and ADA-positive subjects at corresponding visits or before and after ADA development for subjects who develop ADA. Both treatment-emergent

only and all ADA positive/negative subjects may be evaluated. A similar approach may be taken if subjects become neutralizing antibody positive.

Additional analyses may be performed upon receipt of the data. The data from this study may be combined with data from previous adult studies if needed for model development.

10.4.7. Other Analyses

10.4.7.1. Health Outcomes/Quality of Life Measures

The analyses of health outcomes variables for Period 2, Induction will be based on the ITT Population, unless otherwise specified. There will be no adjustment for multiple comparisons.

Table RHCD.4 includes the health outcomes variables and methods.

Table RHCD.4. Analyses of Health Outcomes Variables

Health Outcome and Quality-of-Life Measure	Variable	Analysis
Itch NRS	Improvement ≥4 for subjects who had a baseline Itch NRS ≥4	Fisher's exact test with NRI
	Change from baseline	ANCOVA with LOCF MMRM
CDLQI/DLQI	Achieving CDLQI/DLQI total score 0 or 1	Fisher's exact test with NRI
Patient's global assessment of disease severity	Achieving patient's global assessment of disease severity 0 or 1	Fisher's exact test with NRI

Abbreviations: ANCOVA = analysis of covariance; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; LOCF = last observation carried forward; MMRM = mixed model for repeated measures; NRI = nonresponder imputation; NRS = numeric rating scale.

10.4.7.2. Subgroup Analyses

Subgroup analysis will be conducted for PASI 75 and sPGA (0,1) using the ITT Population for Period 2, Induction.

Subgroups to be evaluated may include gender, age, weight, ethnicity, region, geographic region, baseline disease severity, duration of disease, previous nonbiologic systemic therapy, and previous biologic therapy. Detailed descriptions of the subgroup variables will be provided in the statistical analysis plan.

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

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

10.4.8. Interim Analyses

Two interim analyses will be conducted.

A staggered approach to enrollment by weight group will be used so that a minimum of 15 subjects 12 years of age or older and >50 kg will be enrolled and safety evaluated for the initial 12 weeks of dosing before opening enrollment in the middle weight group (25 to 50 kg). When approximately 15 subjects have enrolled in the middle weight group and completed up to Week 12, an analysis of all available PK data will be conducted to confirm that exposures are within the range expected. All safety data from these subjects will also be analyzed at this time in addition to select efficacy data. Doses for the remaining subjects in the study will be confirmed based on these analyses. Once confirmed, all weight groups will be open for enrollment of the remaining subjects needed to complete the study.

The first interim analysis of PK, safety, and efficacy data on all subjects will be conducted after approximately 15 subjects in the 25- to 50-kg weight group have completed to Week 12. The analysis will include all data available at this time—that is, it will include data from subjects in both weight groups who have enrolled at the time of the interim. The analysis of the data will be conducted by statisticians and PK/PD scientists external to the study team (statistical assessment center). The statistical assessment center will provide the analyses to a DMC consisting of members external to Lilly. The DMC will recommend whether changes to weight-based dosing are necessary based on the analysis. This committee will consist of a minimum of 3 members including a physician with an expertise in dermatology, a statistician, and an additional clinician(s) or PK/PD expert. No member of the DMC may have contact with study sites. Only the DMC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their subjects.

Study sites will receive information about interim results ONLY if they need to know for the safety of their subjects.

The second interim database lock and unblinding will occur and the analysis will be performed at the time (that is, a cutoff date) the last subject completes Study Period 2, Induction (Week 12) or ETV. This interim database lock will include all data collected by the cutoff date including follow-up data from subjects that have begun Periods 3, 4, or 5. Because the study will still be ongoing at the time of this database lock, the analysis will be referred to as an interim analysis. This interim analysis includes the final analysis for the Double-Blind Treatment Induction Period (Period 2, Induction) of the study; therefore, there is no alpha adjustment due to this interim analysis. The DMC is not needed for this interim analysis.

Additional analyses and snapshots of study data may be performed during and/or after completion of Period 3 and/or Period 4 to fulfill the need for regulatory interactions or publication purposes.

Enrollment of each geographic region will be closely monitored. If 120 subjects from the United States and Canada complete the 12-week Double-Blind Randomized Period and if other regions are behind in reaching their enrollment goal, an additional interim analysis may be conducted to include only the subjects from the United States and Canada to meet the US submission timeline. The DMC is not needed for this interim analysis. The details will be documented in the unblinding plan and the statistical analysis plan. A final database lock will occur after the Post-Treatment Follow-Up Period is completed.

Unblinding details are specified in the unblinding plan.

11. References

Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The dermatology life quality index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol*. 2008;159(5):997-1035.

Bronckers IM, Paller AS, van Geel MJ, van de Kerkhof PC, Seyger MM. Psoriasis in children and adolescents: diagnosis, management and comorbidities. *Pediatr Drugs.* 2015;17(5):373-384.

[CDC] Centers for Disease Control and Prevention resources page. National Center for Health Statistics. Data table of weight-for-age charts. Available at: http://www.cdc.gov/growthcharts/html_charts/wtage.htm. Accessed October 20, 2016.

[C-SSRS] Columbia–Suicide Severity Rating Scale web site. Available at: http://www.cssrs.columbia.edu. Accessed January 13, 2016.

De Jager ME, Van de Kerkhof PC, De Jong EM, Seyger MM. Epidemiology and prescribed treatments in childhood psoriasis: a survey among medical professionals. *J Dermatolog Treat.* 2009;20(5):254-258.

Diggle PJ, Liang KY, Zeger SL. Analysis of longitudinal data. Oxford: Clarendon Press; 1994.

[EMEA] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. November 18, 2004; CHMP/EWP/2454/02 corr. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003329.pdf. Accessed October 19, 2016.

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

Gelfand JM, Weinstein R, Porter SB, Niemann AL, Berlin JA, Margolis DJ. Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. *Arch Dermatol.* 2005;141(12):1537-1541.

Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, Reich K, Amato D, Ball SG, Braun DK, Cameron GS, Erickson J, Konrad RJ, Muram TM, Nickoloff BJ, Osuntokun OO, Secrest RJ, Zhao F, Mallbris L, Leonardi CL; UNCOVER-1 Study Group; UNCOVER-2 Study Group; UNCOVER-3 Study Group. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med.* 2016;375(4):345-356.

Griffiths CE, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, Cameron GS, Erickson J, Zhang L, Secrest RJ, Ball S, Braun DK, Osuntokun OO, Heffernan MP, Nickoloff BJ, Papp K; UNCOVER-2 and UNCOVER-3 investigators. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet*. 2015;386(9993):541-551.

Happel KI, Zheng M, Young E, Quinton LJ, Lockhart E, Ramsay AJ, Shellito JE, Schurr JR, Bagby GJ, Nelson S, Kolls JK. Cutting edge: roles of toll-like receptor 4 and IL-23 in IL-17 expression in response to Klebsiella pneumoniae infection. *J Immunol*. 2003;170(9):4432-4436.

Huang W, Na L, Fidel PL, Schwarzenberger P. Requirement of interleukin-17A for systemic anti-Candida albicans host defense in mice. *J Infect Dis*. 2004;190(3):624-631.

Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *Br J Dermatol.* 1995;132(6):942-949.

Mayes TL, Bernstein IH, Haley CL, Kennard BD, Emslie GJ. Psychometric properties of the Children's Depression Rating Scale-Revised in adolescents. *J Child Adolesc Psychopharmacol.* 2010;20(6):513-516.

Milner JD, Brenchly JM, Laurence A, Freeman AF, Hill BJ, Elias KM, Kanno Y, Spalding C, Elloumi HZ, Paulson ML, Davis J, Hsu A, Asher AI, O'Shea J, Holland SM, Paul WE, Douek DC. Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. *Nature*. 2008;452(7188):773-776.

Napolitano M, Megna M, Balato A, Ayala F, Lembo S, Villani A, Balato N. Systemic treatment of pediatric psoriasis: a review. *Dermatol Ther (Heidelb).* 2016;6(2):125-142.

National Institutes of Health. The Fourth Report on The Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Revised May 2005. Available at: https://www.nhlbi.nih.gov/files/docs/resources/heart/hbp_ped.pdf. Accessed Mar 20, 2017.

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

Poznanski EO, Mokros HB. Children's depression rating scale, revised (CDRS-R). Los Angeles: Western Psychological Services; 1996.

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

Rasmussen AR, Wohlfahrt-Veje C, Tefre de Renzy-Martin K, Hagen CP, Tinggaard J, Mouritsen A, Mieritz MG, Main KM. Validity of self-assessment of pubertal maturation. *Pediatrics.* 2015;135(1):86-93.

Salek MS, Jung S, Brincat-Ruffini LA, MacFarlane L, Lewis-Jones MS, Basra MK, Finlay AY. Clinical experience and psychometric properties of the Children's Dermatology Life Quality Index (CDLQI), 1995-2012. *Br J Dermatol.* 2013;169(4):734-759.

Van Voorhees A, Feldman SR, Koo JYM, Lebwohl MG, Menter A. The psoriasis and psoriatic arthritis pocket guide. National Psoriasis Foundation. 2009. Available at: https://www.psoriasis.org/sites/default/files/accessing-health-care/FY10_Pocket_Guide_WEB.pdf. Accessed November 18, 2016.

Waters A, Sandhu D, Beattie P, Ezughah F, Lewis-Jones S. Severity stratification of Children's Dermatology Life Quality Index (CDLQI) scores [abstract]. *Br J Dermatol.* 2010;163(suppl 1):121.

12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	antidrug antibody
AE	adverse event: Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCG	Bacillus Calmette-Guérin
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa, or when the Sponsor is aware of the treatment but the investigator and/his staff and the subject are not. A double-blind study is one in which neither the subject 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.
BP	blood pressure
BSA	body surface area
CDC	Centers for Disease Control and Prevention
CDLQI	Children's Dermatology Life Quality Index
CDRS	Children's Depression Rating Scale
CEC	Clinical Events Committee
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.

CSR	clinical study report
C-SSRS	Columbia–Suicide Severity Rating Scale
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the assent/informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
ETV	Early Termination Visit
EU	European Union
GCP	good clinical practice
HBcAb+	positive for anti-hepatitis B core antibody
HBsAg+	positive for hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
ITT	intent to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
Lilly	Eli Lilly and Company

MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
NK	natural killer
NRI	nonresponder imputation
PASI	Psoriasis Area and Severity Index
PASI 100	a 100% improvement from baseline in PASI score
PASI 75	at least a 75% improvement from baseline in PASI score
PASI 90	at least a 90% improvement from baseline in PASI score
PD	pharmacodynamic(s)
PIP	Pediatric Investigation Plan
PK	pharmacokinetic(s)
PPASI	Palmoplantar Psoriasis Severity Index
PPD	purified protein derivative
Ps	psoriasis
PsA	psoriatic arthritis
PSSI	Psoriasis Scalp Severity Index
Q4W	every 4 weeks
RBC	red blood cell
SAE	serious adverse event
SC	subcutaneous(ly)
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
sPGA	static Physician's Global Assessment
study drug	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, 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.
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis

TBL	total bilirubin level
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, which and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
USA	United States of America
WBC	white blood cell

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a,b]	**Clinical Chemistry**[a-c]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Bicarbonate
Mean cell hemoglobin concentration	Chloride
Leukocytes (WBC)	Phosphorus
Neutrophils, segmented	Total bilirubin
Neutrophils, juvenile (bands)	Direct bilirubin
Lymphocytes	Alkaline phosphatase
Monocytes	Alanine aminotransferase
Eosinophils	Aspartate aminotransferase
Basophils	Blood urea nitrogen
Platelets	Creatinine
	Uric acid
	Calcium
	Random blood glucose
	Albumin
Urinalysis[a]	Cholesterol (total)
Specific gravity	Total protein
pH	Triglycerides
Protein	GGT
Glucose	
Ketones	**Pregnancy Test** (females only, serum and urine)[c,d]
Blood	**Other Tests**[a]
Urobilinogen	Human immunodeficiency virus antibody
Bilirubin	Hepatitis B virus DNA
Nitrite	Hepatitis B surface antigen (HBsAg)
Urine creatinine	Hepatitis B surface antibody
Leukocyte esterase	Hepatitis B core antibody
Color	Hepatitis C virus
	Serum immunoglobulins (IgA, IgG, and IgM)
Cell Flow Cytometry	PPD/QuantiFERON®-TB Gold
	Immunogenicity testing
B cells, T cells, CD4+ T cells, CD8+ T cells, NK cells	PK sample

Abbreviations: GGT = gamma-glutamyl transferase; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; NK = natural killer; PK = pharmacokinetic; PPD = purified protein derivative; RBC = red blood cell; TB = tuberculosis; WBC = white blood cell.

a Assayed by Lilly-designated laboratory.

b Results will be confirmed by the central laboratory at the time of initial testing.

c Serum pregnancy test will be done at Visit 1 only and will be performed centrally. Subjects will undergo urine pregnancy testing at the clinic on a monthly basis during scheduled visits through Week 108. Additional urine pregnancy testing can be performed at the investigator's discretion.

d As appropriate for age.

Appendix 3. Study Governance Considerations

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

Appendix 3.1.1. Informed Consent

The investigator is responsible for ensuring:

- that the subject understands the potential risks and benefits of participating in the study
- that informed consent is given by each subject 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 subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the study.

A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, the child may be required to give documented assent, if capable.

Appendix 3.1.2. Ethical Review

The investigator or an appropriate local representative 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 and Assent Form must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

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

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

Appendix 3.1.3. Regulatory Considerations

This study will be conducted in accordance with:

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

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

Appendix 3.1.4. Investigator Information

Physicians with a specialty in dermatology or pediatric dermatology will participate as investigators in this clinical study.

Appendix 3.1.5. Protocol Signatures

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

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

Appendix 3.1.6. Final Report Signature

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

The 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
- Conduct Sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate case report form (CRF) data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

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

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

Appendix 3.2.1. Data Capture System

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

Any data for which paper documentation provided by the subject will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the subject may include, for example, a paper diary to collect patient-reported outcome measures (e.g., a rating scale), a daily dosing schedule, or an event diary.

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

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

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

Appendix 3.3.2. Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with subjects in consultation with the Lilly, or its designee, clinical research physician.

Hepatic Monitoring Tests

Hepatic hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic chemistry	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Antinuclear antibody[a]**
AST	
GGT	**Alkaline phosphatase isoenzymes[a]**
CPK	
	Anti–smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

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

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

Appendix 5. Blood Pressure Levels for Children with Median Height by Age and Gender

		Boy		Girl	
Age (Year)	Hypertension Stage	Systolic BP (mmHg) (supine or sitting – forearm at heart level)	Diastolic BP (mmHg) (supine or sitting – forearm at heart level)	Systolic BP (mmHg) (supine or sitting – forearm at heart level)	Diastolic BP (mmHg) (supine or sitting – forearm at heart level)
6	Prehypertension	≥110 and <114	≥70 and <74	≥108 and <111	≥70 and <74
	Stage 1	≥114 and <126	≥74 and <87	≥111 and <124	≥74 and <86
	Stage 2	≥126	≥87	≥124	≥86
7	Prehypertension	≥111 and <115	≥72 and <76	≥109 and <113	≥71 and <75
	Stage 1	≥115 and <127	≥76 and <89	≥113 and <125	≥75 and <87
	Stage 2	≥127	≥89	≥125	≥87
8	Prehypertension	≥112 and <116	≥73 and <78	≥111 and <115	≥72 and <76
	Stage 1	≥116 and <128	≥78 and <91	≥115 and <127	≥76 and <88
	Stage 2	≥128	≥91	≥127	≥88
9	Prehypertension	≥114 and <118	≥75 and <79	≥113 and <117	≥73 and <77
	Stage 1	≥118 and <130	≥79 and <92	≥117 and <129	≥77 and <89
	Stage 2	≥130	≥92	≥129	≥89
10	Prehypertension	≥115 and <119	≥75 and <80	≥115 and <119	≥74 and <78
	Stage 1	≥119 and <132	≥80 and <93	≥119 and <131	≥78 and <91
	Stage 2	≥132	≥93	≥131	≥91
11	Prehypertension	≥117 and <121	≥76 and <80	≥117 and <121	≥75 and <79
	Stage 1	≥121 and <134	≥80 and <93	≥121 and <133	≥79 and <92
	Stage 2	≥134	≥93	≥133	≥92
12	Prehypertension	≥120 and <123	≥76 and <81	≥119 and <123	≥76 and <80
	Stage 1	≥123 and <136	≥81 and <94	≥123 and <135	≥80 and <93
	Stage 2	≥136	≥94	≥135	≥93
13	Prehypertension	≥120 and <126	≥77 and <81	≥120 and <124	≥77 and <81
	Stage 1	≥126 and <138	≥81 and <94	≥124 and <137	≥81 and <94
	Stage 2	≥138	≥94	≥137	≥94
14	Prehypertension	≥120 and <128	≥78 and <82	≥120 and <126	≥78 and <82
	Stage 1	≥128 and <141	≥82 and <95	≥126 and <138	≥82 and <95
	Stage 2	≥141	≥95	≥138	≥95
15	Prehypertension	≥120 and <131	≥79 and <83	≥120 and <127	≥79 and <83
	Stage 1	≥131 and <143	≥83 and <96	≥127 and <139	≥83 and <96
	Stage 2	≥143	≥96	≥139	≥96
16	Prehypertension	≥120 and <134	≥80 and <84	≥120 and <128	≥80 and <84
	Stage 1	≥134 and <146	≥84 and <97	≥128 and <140	≥84 and <96
	Stage 2	≥146	≥97	≥140	≥96

17	Prehypertension	≥120 and <136	≥80 and <87	≥120 and <129	≥80 and <84
	Stage 1	≥136 and <148	≥87 and <99	≥129 and <141	≥84 and <96
	Stage 2	≥148	≥99	≥141	≥96

Abbreviations: BP = blood pressure; mmHg = millimeters of mercury.

Source: [NIH] The Fourth report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Revised May 2005.

Appendix 6. Protocol Amendment I1F-MC-RHCD(b) Summary: Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate Safety, Tolerability and Efficacy of Ixekizumab in Patients from 6 to Less than 18 Years of Age with Moderate-to-Severe Plaque Psoriasis

Overview

Protocol I1F-MC-RHCD (a) Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate Safety and Efficacy of Ixekizumab in Patients from 6 to Less than 18 Years of Age 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 major changes and rationale for the changes made to this protocol are as follows:

- Addition of language that allows for additional interim analysis
- Updated language so that sites are not required to take oral body temperature
- Clarified that when patient is at tanner stage score 5, the site does not need to complete the scale with the patient any longer
- Clarified the timing of Bone age imaging so that it is acceptable if this test is done at either Visit 1 or 2 and if it is done in the last 6 months then it does not need to be repeated
- Clarified that vital signs need to be taken at least 30 mins before injection instead of approximately 30 mins before injection
- Updated the exclusion criterion so that patients with lymphoproliferative and other malignant disorders are excluded from study participation unless it is ruled out by biopsy
- Updated the exclusion criterion that specifies the time frame of receiving other therapies to state that these time frames are with respect to screening time
- Corrected the title of Appendix 6.
- Removed reference to QIDS on the list of reasons for discontinuation
- Corrected the wording about washout which says screening and baseline which is not consistent in the protocol
- Updated inclusion criteria language that ‘Lilly employees’ cannot participate
- Removed statement that the injection cannot be done over the plaques

- Updated that Ixekizumab is currently approved for PsA. Additionally it is also approved in Japan for PsO and Pustular Ps and Erythrodermic PsO.

Revised Protocol Sections

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

1. Synopsis

Rationale:

There is an unmet medical need for effective and safe therapies for children and adolescents with moderate-to-severe plaque psoriasis (Ps). Ixekizumab has been approved for the treatment of adults with moderate-to-severe plaque Ps and psoriatic arthritis (PsA) in a number of countries globally. It has also been approved for adults with ~~psoriatic arthritis (PsA)~~ Pustular Ps and Erythrodermic Ps in Japan and is currently being studied in adults with axial spondyloarthritis.

Interim Analyses:

Two interim analyses will be conducted. The first interim analysis of PK, safety, and select efficacy data on all subjects will be conducted after approximately 15 subjects have completed to Week 12 in the 25- to 50-kg weight group. A second interim analysis will be performed at the time (that is, a cutoff date) the last subject completes Study Period 2, Induction (Week 12) or at the Early Termination Visit. Additional analyses and snapshots of study data may be performed during and/or after completion of Period 3 and/or Period 4 to fulfill the need for regulatory interactions or publication purposes.

2. Schedule of Activities

Schedule of Activities, Protocol I1F-MC-RHCD
Screening (Period 1) and Double-Blind Treatment Induction Period (Period 2)

	Screening (Period 1)	Double-Blind Treatment Induction Period (Period 2)					
		Randomization					
Visit No	V1	V2	V3	V4	V5	V6	V7
Study Week		W0	W1	W4	W6	W8	W12
Study Days (Approximately)	-30 to -7 d	1	7 ± 2d	28 ± 2d	42 ± 2d	56 ± 2d	84 ± 2d
Informed consent and assent[a]	X						
Complete medical history[b]	X						
Immunization record	X	X	X	X	X	X	X
Demographics[c]	X						
Physical examination[d]	X						X
Height	X						X
Weight	X	X	X	X	X	X	X
Habits[e]	X						X
Inclusion/exclusion criteria[f]	X	X					
Vital signs (BP, pulse, body temperature)[g]	X	X		X		X	X
Concomitant medications	X	X	X	X	X	X	X
Review preexisting conditions/new conditions (AEs)[h]	X	X	X	X	X	X	X
Randomization		X					
Dispense study drug[i]		X		X		X	X
Administer study drug[j,k]		IXE 40, 80, or 160 mg or placebo		IXE 20, 40, or 80 mg or placebo		IXE 20, 40, or 80 mg or placebo	IXE 20, 40, 80, or 160 mg
sPGA	X	X	X	X	X	X	X
PASI/BSA	X	X	X	X	X	X	X
NAPSI[l]		X		X		X	X

	Screening (Period 1)	Double-Blind Treatment Induction Period (Period 2)					
		Randomization					
Visit No	V1	V2	V3	V4	V5	V6	V7
Study Week		W0	W1	W4	W6	W8	W12
Study Days (Approximately)	-30 to -7 d	1	7 ± 2d	28 ± 2d	42 ± 2d	56 ± 2d	84 ± 2d
PSSI[l]		X		X		X	X
PPASI[l]		X		X		X	X
Binary questions on psoriasis location		X		X		X	X
Tanner stage scale [m]	X						
CDLQI/DLQI		X		X		X	X
Patient's Global Assessment of Disease Severity		X		X		X	X
Children's Depression Rating Scale		X		X		X	X
Columbia–Suicide Severity Rating Scale/ Self-Harm Supplement Form[m n]	X	X	X	X	X	X	X
Itch NRS		X	X	X		X	X
Laboratory Tests							
Administer PPD/ QuantiFERON®-TB Gold[n o]	X						
Read PPD[n o]	X						
Chest x-ray[o p]	X						
Bone age imaging [q]		X					
ECG[p r]	X						
HIV/HCV	X						
HBV[q s]	X						X
Serum pregnancy test[r t]	X						
Urine pregnancy test[r t]		X		X		X	X
Serum chemistry	X	X		X			X
Hematology	X	X		X			X
Urinalysis	X	X		X			X

	Screening (Period 1)	Double-Blind Treatment Induction Period (Period 2)					
		Randomization					
Visit No	V1	V2	V3	V4	V5	V6	V7
Study Week		W0	W1	W4	W6	W8	W12
Study Days (Approximately)	-30 to -7 d	1	7 ± 2d	28 ± 2d	42 ± 2d	56 ± 2d	84 ± 2d
IgA, IgG, IgM	X	X		X			X
Cell flow cytometry panel (B, T, CD4+T, CD8+T, and NK cells)	X						X
Immunogenicity testing[s] [u,t] [v]		X		X		X	X
PK sample[tt] [w]		X		X		X	X

Schedule of Activities, Protocol I1F-MC-RHCD
Maintenance Period (Period 3)

Maintenance Period (Period 3)							
Visit No (V)	V8	V9	V10	V11	V12	V13	V14
Study Week	W16	W20	W24	W28	W32	W36	W40
Study Days (Approximately)	112 ± 7d	140 ± 7d	168± 7d	196± 7d	224± 7d	252± 7d	280± 7d
Height	X		X			X	
Weight	X	X	X	X	X	X	X
Habits[e]			X				
Vital signs (BP, pulse, body temperature)[g]	X	X	X	X	X	X	X
Immunization record	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Review preexisting conditions/new conditions (AEs)[h]	X	X	X	X	X	X	X
Dispense study drug[i]	X	X	X	X	X	X	X
Administer study drug	IXE 20, 40, or 80 mg						
sPGA	X	X	X	X	X	X	X
PASI/BSA	X	X	X	X	X	X	X
NAPSI[l]			X			X	
PSSI[l]			X			X	
PPASI[l]			X			X	
Binary questions on psoriasis location			X			X	
Tanner stage scale			X				
CDLQI/DLQI			X			X	
Patient's Global Assessment of Disease Severity			X			X	
Children's Depression Rating Scale			X			X	

Maintenance Period (Period 3)							
Visit No (V)	V8	V9	V10	V11	V12	V13	V14
Study Week	W16	W20	W24	W28	W32	W36	W40
Study Days (Approximately)	112 ± 7d	140 ± 7d	168± 7d	196± 7d	224± 7d	252± 7d	280± 7d
Columbia–Suicide Severity Rating Scale/Self-Harm Supplement Form[m] [n]	X	X	X	X	X	X	X
Itch NRS			X			X	
Laboratory Tests							
HBV[qq]			X			X	
Urine pregnancy test[r] [t]	X	X	X	X	X	X	X
Serum chemistry			X			X	
Hematology			X			X	
Urinalysis			X			X	
IgA, IgG, IgM			X			X	
Immunogenicity testing[s] [u,t] [v]						X	
PK sample[u] [w]						X	

Schedule of Activities, Protocol I1F-MC-RHCD
Maintenance Period (Period 3) and Extension Period (Period 4)

	Maintenance Period (Period 3)					Extension Period (Period 4)								
Visit No (V)	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28
Study Week	W44	W48	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96
Study Days (Approximately)	308 ± 7d	336 ± 7d	364 ± 7d	392 ± 7d	420 ± 7d	448 ± 7d	476 ± 7d	504 ± 7d	532 ± 7d	560 ± 7d	588 ± 7d	616 ± 7d	644 ± 7d	672 ± 7d
Physical examination[d]		X			X			X			X			X
Height		X			X			X			X			X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Habits[e]					X									
Vital signs (BP, pulse, body temperature)[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunization record	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review preexisting conditions/new conditions (AEs)[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer study drug	IXE 20, 40, or 80 mg													
sPGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PASI/BSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NAPSI[l]		X			X			X			X			X
PSSI[l]		X			X			X			X			X
PPASI[l]		X			X			X			X			X
Binary questions on psoriasis location		X			X			X			X			X
Tanner stage scale		X						X						X
CDLQI/DLQI		X			X			X			X			X

	Maintenance Period (Period 3)					Extension Period (Period 4)								
Visit No (V)	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28
Study Week	W44	W48	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96
Study Days (Approximately)	308 ± 7d	336 ± 7d	364 ± 7d	392 ± 7d	420 ± 7d	448 ± 7d	476 ± 7d	504 ± 7d	532 ± 7d	560 ± 7d	588 ± 7d	616 ± 7d	644 ± 7d	672 ± 7d
Patient's Global Assessment of Disease Severity		X			X			X			X			X
Children's Depression Rating Scale		X			X			X			X			X
Columbia–Suicide Severity Rating Scale/ Self-Harm Supplement Form[mm n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Itch NRS		X			X			X			X			X
Laboratory Tests														
Assess for TB risk, signs, symptoms.			X											
HBV[qq rr]		X			X			X			X			X
Urine pregnancy test[ss tt]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry		X			X			X			X			X
Hematology		X			X			X			X			X
Urinalysis		X			X			X			X			X
IgA, IgG, IgM		X			X			X			X			X
Immunogenicity testing[uu tt vv]						X								
PK sample[ww xx yy]						X								

Schedule of Activities, Protocol I1F-MC-RHCD
Extension Period (Period 4) and Post-Treatment Follow-Up (Period 5)

	Extension Period (Period 4)			Post-Treatment Follow-Up (Period 5)[v–w]		
Visit No (V)	V29	V30	V31/ETV	V801	V802	V803[w]
Study Week	W100	W104	W108	LV + 4W	LV + 12W	LV + 24W
Study Days (Approximately)	700 ± 7d	728 ± 7d	756 ± 7d	± 4d	± 4d	± 4d
Physical examination[d]			X			
Height			X			
Weight	X	X	X			
Body temperature			X			
Vital signs (BP and pulse)[g]			X			
Immunization record	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Review preexisting conditions/new conditions (AEs)[h]	X	X	X	X	X	X
Bone age imaging			X			
Dispense study drug[i]	X	X				
Administer study drug	IXE 20, 40, or 80 mg					
sPGA	X	X	X			
PASI/BSA	X	X	X			
NAPSI[l]			X			
PSSI[l]			X			
PPASI[l]			X			
Binary questions on psoriasis location			X			
Tanner stage scale [m]			X			
CDLQI/DLQI			X			

	Extension Period (Period 4)			Post-Treatment Follow-Up (Period 5)[v]-[w]		
Visit No (V)	V29	V30	V31/ETV	V801	V802	V803[w]
Study Week	W100	W104	W108	LV + 4W	LV + 12W	LV + 24W
Study Days (Approximately)	700 ± 7d	728 ± 7d	756 ± 7d	± 4d	± 4d	± 4d
Patient's Global Assessment of Disease Severity			X			
Children's Depression Rating Scale			X			
Columbia–Suicide Severity Rating Scale/ Self-Harm Supplement Form[m]-[n]	X	X	X			
Itch NRS			X			
Laboratory Tests						
Assess for TB risk, signs, symptoms.		X				
HBV[q]-[s]			X			
Urine pregnancy test[r]-[t]	X	X	X			
Serum chemistry			X	X	X	X
Hematology			X	X	X	X
Urinalysis			X			
IgA, IgG, IgM			X			
Cell flow cytometry panel (B, T, CD4+T, CD8+T, and NK cells)			X			
Immunogenicity testing[s]-[u],[t]-[v]			X		X	
PK sample[u]-[w]			X		X	

Schedule of Activities, Protocol I1F-MC-RHCD

Abbreviations: AE = adverse event; AESI = adverse event of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; d = days; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; ETV = Early Termination Visit; HBcAb+ = positive for anti-hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; IXE = ixekizumab (LY2439821); LV= last visit; NAPSI = Nail Psoriasis Severity Index; NK = natural killer; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PPASI = Palmoplantar Psoriasis Area and Severity Index; PPD = purified protein derivative; PK = pharmacokinetics; PSSI = Psoriasis Scalp Severity Index; Q4W = every 4 weeks; SC = subcutaneous; sPGA = static Physician's Global Assessment; TB = tuberculosis; ULN = upper limit of normal; V = study visit; W = study week.

[a] The parent or legal guardian will sign the informed consent form, and the subject will sign the assent form prior to any study assessments, examinations, or procedures being performed. An informed consent form should be signed by the subject when the legal age is reached as determined by the country regulations.

[b] Complete medical history, including TB exposure.

[c] Demographics include recording the full date of birth, sex, and ethnicity. In countries where we are not allowed to collect the full date of birth, (day, month, and year) we will make country specific adjustments to collect only month and year.

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

[e] Habits include recording of caffeine, alcohol, and tobacco consumption. This assessment is only required for subjects 12 years of age or older.

[f] Subjects who test positive for latent TB at screening may be rescreened following appropriate treatment. Additionally, subjects who do not qualify at screening under Exclusion Criterion [14] (active or recent infection) or Exclusion Criterion [16] (~~oral~~ body temperature ≥38°C [100.5°F]) may be rescreened 1 time.

[g] At baseline (Week 0), BP and pulse should be measured ~~approximately~~ at least 30 minutes pre- and postinjection. BP and pulse should be measured pre- and postinjection at the other visits.

[h] Inflammatory bowel disease will be assessed as an AESI. See Section 9.2.2 for a list of all AESIs.

[i] The study drug will be prepared by a trained clinical staff member who will be an unblinded member. Site staff will record information in the Study Drug Administration Logs, including the date, time, and anatomical location of administration of study drug (for treatment compliance); syringe number; who prepared and administered the study drug; and the reason if study drug was not fully administered.

[j] Subjects should remain under observation for at least 1 hour after dosing at Week 0 (Visit 2), Week 4 (Visit 4), Week 8 (Visit 6), Week 12 (Visit 7), and Week 16 (Visit 8) to monitor for safety. For subsequent injections during the study, and if no problems occurred with that injection, subjects will be observed for 15 minutes following injection.

k Subjects receiving ixekizumab 20 mg or 40 mg will receive 1 SC injection of ixekizumab at Week 0 (Visit 2) and 1 SC injection of ixekizumab Q4W at Weeks 4 and 8. Subjects receiving ixekizumab 80 mg will receive 2 SC injections of ixekizumab at Week 0 (Visit 2) and 1 SC injection of ixekizumab Q4W at Weeks 4 and 8.
Subjects receiving placebo for ixekizumab 20 mg or 40 mg will receive 1 SC injection of placebo at Week 0 (Visit 2) and 1 SC injection of placebo Q4W at Weeks 4 and 8. Subjects receiving placebo for ixekizumab 80 mg will receive 2 SC injections of placebo at Week 0 (Visit 2) and 1 SC injection of placebo Q4W at Weeks 4 and 8.

l If the subject has nail psoriasis, scalp psoriasis or palmoplantar psoriasis at baseline, then the NAPSI, PSSI or PPASI, respectively, will be administered at subsequent visits, as indicated in the Schedule of Activities.

m At tanner stage score 5, the site does not need to complete the scale with the subject any longer.

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

~~n~~ o QuantiFERON®-TB Gold test is preferred. For those subjects administered a PPD test, the subject will visit the site between 48 to 72 hours after PPD placement for the PPD read.

~~o~~ p A chest x-ray will be taken at screening, unless one has been obtained within the past 6 months (provided the x-ray and/or report are available for review). In Germany, a chest x-ray has to be performed within 6 months prior to signing informed consent indicating no evidence of TB.

q For the Bone age imaging at Visit 2, it is acceptable if the test is performed at Visit 1. In case test is performed in the last 6 months, it does not need to be repeated at Visit 2.

~~p~~ r Subjects must be supine for a minimum of 5 minutes before ECG collection and remain supine during ECG collection. ECGs may be obtained at additional times, when deemed clinically necessary.

~~q~~ s Subjects who are HBcAb+, HBsAb+, and HBV DNA– at screening will be tested for HBsAb levels at baseline, at 12-week intervals thereafter, and at the ETV, if applicable. Subjects who meet these criteria for HBsAb monitoring will be identified by the central laboratory. Subjects whose HBsAb levels are <200 mIU/mL at any postscreening visit will be tested for HBV DNA. Any enrolled subject who is HBcAb+, regardless of HBsAb status or level, and who experiences elevated ALT or AST >3 times ULN must undergo HBV DNA testing.

~~r~~ t To be performed for females of childbearing potential only (ages 12 and older or younger subjects per investigator assessment of full sexual maturity). Serum pregnancy test will be done at Visit 1 only and will be performed centrally. Subjects will undergo urine pregnancy testing at the clinic on a monthly basis during scheduled visits through Week 108. Additional urine pregnancy testing can be performed at the investigator's discretion. Subjects determined to be pregnant will be discontinued from treatment and will no longer be administered study drug.

~~s~~ u Where collection is allowed by local regulations.

~~t~~ v Immunogenicity samples may also be analyzed for ixekizumab serum concentration to facilitate in the interpretation of the immunogenicity data. In addition, a blood sample will be collected, when possible, for any subject who experiences a potential systemic allergic/hypersensitivity reaction during the study as judged by the investigator. At visits where study drug will be administered, immunogenicity samples will be collected prior to administration of study drug. Ideally, samples will be taken at approximately the same time for each collection.

~~u~~ w At visits where study drug will be administered, PK samples will be collected prior to administration of study drug.

~~v~~ x All subjects receiving study drug must enter into Period 5 and complete through Visit 802. Subjects may be followed beyond Visit 802 for continued monitoring of their neutrophil counts if determined by the Sponsor/investigator that additional monitoring is needed. If a subject discontinues study drug early, the subject will complete the ETV and then enter the Post-Treatment Follow-Up Period (Period 5).

~~w~~ y This visit will only occur if a subject's neutrophil counts have not returned to the defined criteria.

3.1 Study Rationale

There is an unmet medical need for effective and safe therapies for children and adolescents with moderate-to-severe plaque Ps. Ixekizumab has been approved for the treatment of adults with moderate-to-severe plaque Ps and PsA in a number of countries globally. It ~~is currently being studied in adults with PsA in the United States and European Union, has already~~ has also been approved for adults ~~with PsA in Japan~~ with Pustular Ps and Erythrodermic Ps in Japan, and is currently being studied in adults with axial spondyloarthritis. This study is part of the European PIP and USA Pediatric Study Plan, and it is intended to investigate the safety, efficacy, and PK of ixekizumab in pediatric subjects (children and adolescents). This study will assess specific response in the Pediatric Population. The risks and benefits in the Pediatric Population are expected to be similar to those in adults with plaque Ps. There is no specific difference in the mechanism of the disease; therefore, no difference in the safety profile is expected between adults, adolescents, and children.

3.2. Background

Pediatric plaque Ps affects approximately 1% of children and adolescents globally (Gelfand et al. 2005; Napolitano et al. 2016). It is estimated that 35% to 50% of adults with psoriasis developed their disease before 20 years of age (De Jager et al. 2009). In a report by Gelfand et al. (2005), the prevalence of plaque Ps in children in the United Kingdom was 0.55% for those aged 0 to 9 years and 1.37% for those aged 10 to 19 years. Pediatric plaque Ps is especially burdensome because it often presents on the face and scalp, as well as other highly visible areas. Nonbiologic topical therapies have been the mainstay of treatment due to lack of approved therapies for plaque Ps in children. Currently, there are few systemic therapies for pediatric plaque Ps, and most have significant side effects or are not as effective as desired (Bronckers et al. 2015).

Currently, there is an unmet medical need for effective and safe therapies for children and adolescents with moderate-to-severe psoriasis. Both the PIP and Pediatric Study Plan will focus on pediatric subjects with moderate-to-severe plaque Ps from 6 to <18 years of age.

~~This study will explore specific response in the Pediatric Population. The risks and benefits in the Pediatric Population are expected to be similar to those in adults with plaque Ps. There is no specific difference in the mechanism of the disease; therefore, no difference in the safety profile is expected between adults, adolescents, and children.~~

6.2 Exclusion Criteria

[16] have a~~n oral~~ body temperature ≥38°C (100.5°F) at baseline (Week 0; Visit 2); these subjects may be rescreened (1 time) ≥4 weeks after documented resolution of elevated temperature

[18] subjects with a known history of malignancy; lymphoproliferative disease, including lymphoma; or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly unless ruled out by biopsy

[34] have received other therapies within the specified time frames prior to screening (see below)~~below~~:

- adalimumab and infliximab 60 days, abatacept 90 days, anakinra 7 days, or any other biologic disease-modifying antirheumatic drug 5 half-lives ~~prior to baseline~~
- systemic therapy for plaque Ps and PsA (other than above, e.g., methotrexate, cyclosporine) or phototherapy (e.g., photochemotherapy [psoralen plus ultraviolet A]) in the previous 4 weeks
- any investigational drugs in the previous 4 weeks or 5 half-lives, whichever is longer
- ultraviolet-
- A therapy, ultraviolet-B therapy, and topical treatments (except on face, scalp, and genital area during screening) in the previous 4 weeks

~~[43] are employees of Lilly or its designee or are employees of third-party organizations involved in the study~~

7.1 Treatments Administered

This study involves a comparison of ixekizumab administered by SC injection with placebo. The study drug should be at room temperature when injected. Possible injection sites include the abdomen, thigh, and upper arm (using the arm contralateral for blood samples for PK). The injection site should preferably not be in a psoriatic lesion and should be rotated to another area for subsequent doses at the same visit.

7.8.3 Permanent Discontinuation from Study Treatment

- The patient, at any time during the study, scores a ≥5 for Item 13 ~~3 for Item 12 (Thoughts of Death or Suicide)~~ on the ~~QIDS-SR16~~CDRS-R
  -OR
- develops active suicidal ideation with some intent to act with or without a specific plan (yes to question 4 or 5 on the "Suicidal Ideation" portion of the Columbia–Suicide Severity Rating Scale [C-SSRS])
  -OR
- develops suicide-related behaviors as recorded on the C-SSRS.

10.4.2 Analysis Methods

The primary analyses method for categorical data comparison between treatments will be the Fisher's exact test. Difference of the proportions and the 95% CI of the difference will be included.

Secondary analyses for the co-primary efficacy measures PASI 75 and sPGA (0,1) will be conducted using a logistic regression analysis with treatment group, region, baseline sPGA score (severity of the psoriasis), and baseline weight category (<25 kg, ≥25 to ≤50 kg, >50 kg) as factors. The odds ratio and the corresponding 95% CI will be reported.

The ~~primary~~ analyses for the continuous efficacy and health outcomes variables will be made using analysis of covariance (ANCOVA) and using a mixed model for repeated measures (MMRM) analysis). The ANCOVA model includes treatment, region, baseline sPGA score, baseline weight category, and baseline value. Type III sums of squares for the least squares means will be used for the statistical comparison; the 95% CI will be reported.

~~A secondary analysis for continuous efficacy and health outcomes variables will be made using a mixed model for repeated measures (MMRM) analysis.~~ When the MMRM is used, the model will include treatment, region, baseline sPGA score, baseline weight category, baseline value, visit, treatment-by-visit, and baseline-by-visit interactions as fixed factors. The covariance structure to model the within-subject errors will be unstructured. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III tests for the least-squares means will be used for the statistical comparison; the 95% CI will be reported. Treatment comparisons at Week 12 and all other postbaseline visits in Period 2, Induction will be reported. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, followed by the compound symmetry will be used. This order is specified according to a decreasing number of covariance parameters in the structure. The sandwich estimator (Diggle et al. 1994) for the covariance estimation will be used by specifying the EMPIRICAL option in SAS PROC MIXED. When sandwich estimation is used, the Kenward-Roger approximation for denominator degrees of freedom cannot be used. Instead, DDFM= BETWITHIN option will be used to estimate denominator degrees of freedom.

Treatment comparisons of time to relapse (sPGA $\geq$ 2) will be conducted using the log-rank test as described in Protocol Addendum I1F-MC-RHCD(2).

Additional analyses and snapshots of study data may be performed during and/or after completion of Period 3 and/or Period 4 to fulfill the need for regulatory interactions or publication purposes.

10.4.8 Interim Analysis

Additional analyses and snapshots of study data may be performed during and/or after completion of Period 3 and/or Period 4 to fulfill the need for regulatory interactions or publication purposes.

Appendix 6. Protocol Amendment I1F-MC-RHCD(b) Summary: Multicenter, ~~Double~~ Double-Blind, Randomized, Placebo-Controlled Study to Evaluate Safety, Tolerability and Efficacy of Ixekizumab in Patients from 6 to Less than 18 Years of Age with Moderate-to-Severe Plaque Psoriasis

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Approver: PPD
Approval Date & Time: 21-Sep-2018 19:31:15 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 22-Sep-2018 13:11:47 GMT
Signature meaning: Approved

1. Protocol Addendum I1F-MC-RHCD(2.1) Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Efficacy of Ixekizumab in Patients from 6 to Less than 18 Years of Age with Moderate-to-Severe Plaque Psoriasis

Ixekizumab (LY2439821)

This addendum is to be performed in addition to all procedures required by protocol I1F-MC-RHCD or any subsequent amendments to that protocol.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Addendum (2) Electronically Signed and Approved by Lilly:
30 November 2016

Revised Protocol Addendum (2.1) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 20-Jul-2017 GMT

2. Table of Contents

Protocol Addendum I1F-MC-RHCD(2.1) Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Efficacy of Ixekizumab in Patients from 6 to Less than 18 Years of Age with Moderate-to-Severe Plaque Psoriasis

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List of Attachments

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3. Rationale for Addendum

The following addition is being made to Protocol I1F-MC-RHCD (RHCD) for pediatric subjects with plaque psoriasis (Ps). This addendum is to be performed in addition to all procedures required by Protocol RHCD or any subsequent amendments to that protocol.

The following addition will apply in countries where etanercept is approved for severe pediatric psoriasis treatment only (emerging markets and European countries) and where subjects may be randomized to etanercept:

- **Period 2: Double-Blind Treatment Period**: Where applicable, 30 subjects will be randomized to etanercept (Enbrel®), an open-label reference arm. Placebo will not be given to match etanercept. Subjects will only receive placebo to match ixekizumab. To maintain statistical validity, a blinded assessor will conduct the efficacy assessments in countries where etanercept will be administered. Subjects randomized to etanercept during the Double-Blind Treatment Period (Period 2) will begin treatment with ixekizumab during the 48-Week Open-Label Maintenance Period (Period 3) after an 8-week washout period (to avoid increased risks with concurrent etanercept and ixekizumab exposures).

The following addition will also apply for subjects from European (EU) countries:

- **Period 4: 48-Week Double-Blind, Randomized Withdrawal Period**: Subjects from EU countries who meet the response criterion (defined as static Physician's Global Assessment [sPGA] [0,1]) at Week 60 will be rerandomized to ixekizumab or placebo (1:1 ratio). Subjects who are rerandomized to ixekizumab will receive ixekizumab 20, 40, or 80 mg every 4 weeks (Q4W) according to their weight at the time of rerandomization. Upon disease relapse to Ps (sPGA $\geq$2), subjects will receive ixekizumab 20, 40, or 80 mg Q4W according to their weight.

The parent or legal guardian will sign the informed consent form (ICF), and the subject will sign the assent form prior to any study assessments, examinations, or procedures being performed.

4. Protocol Additions

The underlined and ~~strikethrough~~ text in the following sections show the additions and deletions applicable to subjects participating in this addendum. Additionally, the revised Schedule of Activities and study design figure are presented in Attachment 1 and Attachment 2, respectively.

4.1. Use of Etanercept during the Double-Blind Treatment Period (Period 2)

4. Objectives and Endpoints

Objectives	Endpoints
Other Secondary to compare the efficacy of ixekizumab Q4W and etanercept at Week 12 (Visit 7) as measured by PASI 75 and by sPGA (0,1) in countries where etanercept is approved	• proportion of subjects achieving PASI 75 at Week 12 • proportion of subjects achieving sPGA (0,1) at Week 12

Abbreviations: PASI 75 = at least a 75% improvement from baseline in Psoriasis Area and Severity Index score; Q4W = every 4 weeks; sPGA = static Physician's Global Assessment.

5.1. Overall Design

- **Period 2: Double-Blind Treatment Period** (Induction Period) will occur from Week 0 (baseline; Visit 2) to Week 12 (Visit 7) comparing ixekizumab to placebo in a double-blind fashion and to etanercept (as a reference arm).
- **Period 3: 48-Week Open-Label Maintenance Period** will occur from Week 12 (Visit 7) to Week 60 (Visit 19). Subjects randomized to etanercept during Period 2 will receive ixekizumab at doses of 20, 40, or 80 mg according to their weight after an etanercept 8-week washout period is complete. The etanercept washout period will be from Week 12 through Week 20.
- **Period 4: Extension Period** will occur from Week 60 (Visit 19) to Week 108 (Visit 31). Subjects from countries outside of the EU, irrespective of response, and nonresponders from the EU will continue with open-label treatment with the ixekizumab dose received during the previous period (Period 3). Subjects from the EU who meet response criteria (defined as those with sPGA [0,1]) will be rerandomized to ixekizumab or placebo in the Double-Blind, Randomized Withdrawal Period.
  (See Section 4.2 of this protocol addendum for details on the Double-Blind, Randomized Withdrawal Period.)

5.1.2. 12-Week Double-Blind Treatment Period (Period 2)

Subjects randomized to etanercept will be administered etanercept 0.8 mg/kg, not exceeding 50 mg per dose, every week from Week 0 through Week 11.

7.1. Treatments Administered

This study involves a comparison of ixekizumab administered by subcutaneous (SC) injection with placebo and with etanercept (as a reference arm). ~~The investigational product (~~Ixekizumab, etanercept, and placebo should be at room temperature when injected. Possible injection sites include the abdomen, thigh, and upper arm (using the arm contralateral for blood samples for PK). The injection site should not be in a psoriatic lesion and should be rotated to another area for subsequent doses at the same visit. Placebo will not be given to match etanercept. To maintain statistical validity, a blinded assessor will conduct the efficacy assessments in countries where etanercept will be administered.

After training by the clinical staff, injections of etanercept will be self-administered by the subject or caregiver.

Training: For training purposes, the proper procedures for preparation of the needed dose of etanercept and administration of the initial injection will be performed by clinical staff at Week 0 (Visit 2). Each subject must return to the clinical site for all injections and be trained to self-inject etanercept under the supervision of the investigator until the investigator judges the subject sufficiently competent to perform the self-injections independently. After this time, the subject will be allowed to self-inject at home.

Administration: If the subject is unable to perform the injection, a caregiver may inject etanercept to the subject. In this case, the caregiver will also be trained to inject etanercept to the subject at the study site until the investigator judges the caregiver sufficiently competent to inject. All subsequent injections will be administered by the subject or caregiver.

Table RHCD.3 shows the etanercept treatment regimen.

Table RHCD.3. Etanercept Treatment Regimen

Regimen	Dose Week 0 through Week 11	Week 12 through Week 20
Etanercept	0.8 mg/kg, not exceeding 50 mg per dose	No injections because of the washout period

7.1.1. Packaging and Labeling

Etanercept (Enbrel®) will be supplied by the sponsor or its designee in accordance with cGMP. Etanercept will be supplied in 2 presentations to be administered based on subject weight:

- Powder for solution for injection in a single-dose vial and diluent for reconstitution. Each vial contains 25 mg of etanercept.
- Solution for injection in a single-dose, prefilled, disposable manual syringe. Each syringe of etanercept is designed to deliver 50 mg of etanercept.

7.2. Method of Treatment Assignment

Subjects from countries where etanercept is approved for severe pediatric psoriasis treatment only (emerging markets and European countries) who meet all criteria for enrollment at Visit 1 and Visit 2 will be randomized to double-blind treatment at Week 0 (Visit 2) in a 2:2:1 ratio to ixekizumab, etanercept, or placebo until approximately 75 subjects with severe psoriasis from etanercept-approved countries are randomized to ixekizumab (30 subjects), etanercept (30 subjects), and placebo (15 subjects).

7.3. Blinding

Etanercept will be administered open label during Period 2 and a blinded assessor will be used (see Section 7.1).

7.5. Preparation/Handling/Storage/Accountability

Instructions for the preparation of etanercept will be provided by the sponsor.

7.6. Treatment Compliance

Etanercept: The subject or caregiver will record information in a Study Drug Administration Log, including the date, time, and anatomical location of administration of etanercept (for treatment compliance); carton number; who prepared and administered the investigational product; and the reason if investigational product was not fully administered.

10.3.1. General Statistical Considerations

During the Double-Blind Treatment Period, approximately 75 subjects with severe psoriasis from etanercept-approved countries will be randomized to ixekizumab (30 subjects), etanercept (30 subjects), and placebo (15 subjects) in a 2:2:1 ratio.

Study RHCD (2) will have approximately 85% power to test the superiority of ixekizumab to etanercept for sPGA (0,1) and at least a 75% improvement from baseline in Psoriasis Area and Severity Index score (PASI 75) at Week 12 based on the 2-sided Fisher exact test at significance level of 0.05. The study will have approximately 45% power to test the superiority of etanercept to placebo for PASI 75 at Week 12 based on the 2-sided Fisher exact test at significance level of 0.05. The following assumptions were used for the power calculations for both sPGA (0,1) and PASI 75 response rates based on ixekizumab clinical studies in adult subjects with moderate-to-severe plaque psoriasis (Ps) efficacy data (Griffiths et al. 2015; Gordon et al. 2016): 80% responders for ixekizumab, 40% responders for etanercept, and 10% for placebo.

Subjects with severe psoriasis in countries where etanercept is used as a reference arm will be included in the treatment comparisons of ixekizumab and etanercept for the Double-Blind Treatment Period.

For subjects with severe psoriasis in countries where etanercept is used as a reference arm, treatment comparisons in the proportion of subjects achieving PASI 75 or sPGA (0,1) at Week 12 will be analyzed using Fisher's exact test. Missing data will be imputed using the nonresponder imputation method (NRI).

Further details will be described in the SAP.

4.2. Double-Blind Randomized Withdrawal Period in Subjects in EU Countries

4. Objectives and Endpoints

Objectives	Endpoints
to assess whether ixekizumab Q4W is superior to placebo for EU subjects during the Double-Blind Randomized Withdrawal Period	• time to relapse to moderate severity (sPGA ≥2) during the Double-Blind, Randomized Withdrawal Period • proportion of subjects achieving sPGA (0,1) at Week 108 (Visit 31)

Abbreviations: Q4W = every 4 weeks; sPGA = static Physician's Global Assessment.

5.1. Overall Design

- **Period 4:**

  Extension Period will occur from Week 60 (Visit 19) to Week 108 (Visit 31). Subjects from countries outside of the EU, irrespective of response, and nonresponders from the EU will continue with open-label treatment with the ixekizumab dose received during the previous period.

  OR

  48-Week Double-Blind, Randomized Withdrawal Period will occur from Week 60 (Visit 19) to Week 108 (Visit 31) for subjects in the EU who meet the response criterion at Week 60 (defined as sPGA [0,1]). Subjects will be rerandomized to ixekizumab or placebo (1:1 ratio).

5.1.4. 48-Week Extension Period or Double-Blind, Randomized Withdrawal Period (Period 4)

Subjects from EU countries who meet the response criterion at Week 60 (defined as sPGA [0,1]) will be rerandomized to ixekizumab or placebo (1:1 ratio) at Visit 19 (Week 60). Subjects who

are rerandomized to ixekizumab will receive ixekizumab 20, 40, or 80 mg every 4 weeks (Q4W) according to their weight at the time of rerandomization. Upon disease relapse to Ps (sPGA ≥2), subjects will receive ixekizumab 20, 40, or 80 mg Q4W according to their weight. Subjects from EU countries who do not meet the response criterion at Week 60 will continue with open-label treatment with ixekizumab.

7.2. Method of Treatment Assignment

Subjects who meet response criteria (sPGA [0,1]) from EU countries will enter the Double-Blind Randomized Withdrawal Period and will be rerandomized to double-blind treatment at Week 60 (Visit 19) in a 1:1 ratio to ixekizumab or placebo. Subjects who are rerandomized to ixekizumab will receive ixekizumab 20, 40, or 80 mg Q4W according to their weight at the time of rerandomization. Subjects from EU countries who relapse (sPGA ≥2) during the Double-Blind Randomized Withdrawal Period will receive open-label treatment with ixekizumab according to their weight at the time of relapse.

7.3. Blinding

During the 48-Week Double-Blind, Randomized Withdrawal Period, subjects from EU countries who meet the response criterion at Week 60 (defined as sPGA [0,1]) will be rerandomized to double-blind ixekizumab or placebo (1:1 ratio).

10.3.1. General Statistical Considerations

During the Double-Blind, Randomized Withdrawal Period (Period 4), approximately 40 subjects from EU countries will be rerandomized to ixekizumab (20 subjects) and placebo (20 subjects) in a 1:1 ratio. The response criterion for rerandomization is sPGA (0,1) at Week 60.

The study will have approximately 95% power to test the superiority of ixekizumab to placebo in time to relapse (sPGA ≥2) based on the 2-sided log-rank test at a significance level of 0.05. The following assumptions were used for the power calculations: 20% relapse for ixekizumab and 85% relapse for placebo. Relapse rates were estimated based on ixekizumab clinical studies in adult subjects with moderate-to-severe Ps efficacy data (Griffiths et al. 2015; Gordon et al. 2016).

Unless otherwise specified, efficacy, health outcomes, and safety analyses for the Double-Blind, Randomized Withdrawal Period will be conducted on the Double-Blind, Randomized Withdrawal Period Population, defined as all rerandomized patients (i.e., subjects from countries in the EU who were rerandomized at Week 60) who received at least 1 dose of study treatment during Double-Blind, Randomized Withdrawal Period. Patients will be analyzed according to the treatment to which they were rerandomized.

Treatment comparisons of ixekizumab and placebo during the Double-Blind, Randomized Withdrawal Period will be performed for the Double-Blind, Randomized Withdrawal Period Population.

The time to relapse (loss of response; sPGA ≥2) during Double-Blind, Randomized Withdrawal Period (Period 4) is defined as:

> *Time to relapse (days) = date of first sPGA ≥ 2 during Period 4 – date of Week 60 rerandomization + 1.*

If a patient has not experienced relapse (sPGA ≥2) by completion or early discontinuation of Period 4, the patient will be censored at the date of their last visit during Period 4.

The number of patients at risk and experiencing a relapse event by each scheduled visit during Period 4 will be presented by treatment group. The Kaplan–Meier estimate of the proportion of patients relapsing will be presented for each visit. Treatment group comparisons will be performed using the log-rank test. For each treatment group, a Kaplan–Meier plot of the time to relapse will be provided.

Treatment comparisons in the proportion of subjects achieving sPGA (0,1) at Week 108 will be analyzed using Fisher's exact test. Missing data will be imputed using the NRI.

Further details will be described in the SAP.

5. References

Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, Reich K, Amato D, Ball SG, Braun DK, Cameron GS, Erickson J, Konrad RJ, Muram TM, Nickoloff BJ, Osuntokun OO, Secrest RJ, Zhao F, Mallbris L, Leonardi CL; UNCOVER-1 Study Group; UNCOVER-2 Study Group; UNCOVER-3 Study Group. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med.* 2016;375(4):345-356.

Griffiths CE, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, Cameron GS, Erickson J, Zhang L, Secrest RJ, Ball S, Braun DK, Osuntokun OO, Heffernan MP, Nickoloff BJ, Papp K; UNCOVER-2 and UNCOVER-3 investigators. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet*. 2015;386(9993):541-551.

Attachment 1. Protocol Addendum RHCD(2.1) Schedule of Activities

Schedule of Activities, Protocol I1F-MC-RHCD(2.1)
Screening (Period 1) and Double-Blind Treatment Period (Period 2)

	Screening (Period 1)	Double-Blind Treatment Period (Period 2)					
		Randomization					
Visit No (V)	V1	V2	V3			V4	
Study Week		W0	W1	W2	W3	W4	W5
Study Days (Approximately)	-30 to -7 d	0	7 ± 2d	14 ± 2d	21 ± 2d	28 ± 2d	35 ± 2d
Informed consent and assent[a]	X						
Randomization		X					
Dispense study drug[i]		X	X			X	
Administer study drug[j,k]		**Group 1:** IXE 40, 80, or 160 mg or placebo **Group 2:** etanercept	**Group 1:** no injections **Group 2:** etanercept	**Group 1:** no injections **Group 2:** etanercept	**Group 1:** no injections **Group 2:** etanercept	**Group 1:** IXE 20, 40, or 80 mg or placebo **Group 2:** etanercept	**Group 1:** no injections **Group 2:** etanercept

Schedule of Activities, Protocol I1F-MC-RHCD(2.1)
Double-Blind Treatment Period (Period 2)

	Double-Blind Treatment Period (Period 2)						
Visit No (V)	V5		V6				V7
Study Week	W6	W7	W8	W9	W10	W11	W12
Study Days (Approximately)	42 ± 2d	49 ± 2d	56 ± 2d	63 ± 2d	70 ± 2d	77 ± 2d	84 ± 2d
Dispense IP[i]	X		X				
Administer IP[j,k]	**Group 1:** no injections **Group 2:** etanercept	**Group 1:** no injections **Group 2:** etanercept	**Group 1:** IXE 20, 40, or 80 mg or placebo **Group 2:** etanercept	**Group 1:** no injections **Group 2:** etanercept	**Group 1:** no injections **Group 2:** etanercept	**Group 1:** no injections **Group 2:** etanercept	**Group 1:** IXE 20, 40, 80, or 160 mg or placebo **Group 2:** no injections

Schedule of Activities, Protocol I1F-MC-RHCD(2.1)
Maintenance Period (Period 3)

Maintenance Period (Period 3)							
Visit No (V)	V8	V9	V10	V11	V12	V13	V14
Study Week	W16	W20	W24	W28	W32	W36	W40
Study Days (Approximately)	112 ± 7d	140 ± 7d	168± 7d	196± 7d	224± 7d	252± 7d	280± 7d
Dispense IP[i]	X	X	X	X	X	X	X
Administer IP	**Group 1:** IXE 20, 40, or 80 mg **Group 2:** no injections	**Group 1:** IXE 20, 40, or 80 mg **Group 2:** IXE 40, 80, or 160 mg	**All subjects:** IXE 20, 40, or 80 mg				

Schedule of Activities, Protocol I1F-MC-RHCD(2.1)
Maintenance Period (Period 3) and Extension Period or Double-Blind, Randomized Withdrawal Period (Period 4)

	Maintenance Period (Period 3)					**Extension Period or Double-Blind, Randomized Withdrawal Period (Period 4)**								
Visit No (V)	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28
Study Week	W44	W48	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96
Study Days (Approximately)	308 ± 7d	336 ± 7d	364 ± 7d	392 ± 7d	420 ± 7d	448 ± 7d	476 ± 7d	504 ± 7d	532 ± 7d	560 ± 7d	588 ± 7d	616 ± 7d	644 ± 7d	672 ± 7d
Randomization					X									
Dispense IP[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer IP	**All subjects:** IXE 20, 40, or 80 mg					**Group 1 (EU nonresponders and all OEU subjects):** Open-label IXE 20, 40, or 80 mg[w] **Group 2 (responders from EU countries):** Double-blind IXE 20, 40, or 80 mg or placebo[w]								

Schedule of Activities, Protocol I1F-MC-RHCD(2.1)
Extension Period (Period 4) and Post-Treatment Follow-Up (Period 5)

	Extension Period (Period 4)			**Post-Treatment Follow-Up Period (Period 5)[v]**		
Visit No (V)	V29	V30	V31/ ETV	V801	V802	V803[w]
Study Week	W100	W104	W108	LV + 4W	LV + 12W	LV + 24W
Study Days (Approximately)	700 ± 7d	728 ± 7d	756 ± 7d	± 4d	± 4d	± 4d
~~Telephone Visit~~	~~X~~	~~X~~				
Dispense IP[i]	X	X				
Administer IP	**Group 1 (nonresponders and OEU subjects):** Open-label IXE 20, 40, or 80 mg[w] **Group 2 (responders from EU countries):** Double-blind IXE 20, 40, 80 mg or placebo[w]					

Schedule of Activities, Protocol I1F-MC-RHCD(2.1)

Abbreviations: d = day; ETV = early termination visit; EU = European Union; IP = investigational product; IXE = ixekizumab; LV= date of last visit; OEU = outside the European Union; V = study visit; W = study week.

[a] The parent or legal guardian will sign the informed consent form (ICF), and the subject will sign the assent form prior to any study assessments, examinations, or procedures being performed. An ICF should be signed by the subject when the legal age is reached as determined by the country regulations.

[i] For training purposes, the proper procedures for preparation of needed dose of etanercept and administration of the initial injection will be performed by clinical staff at Week 0 (Visit 2). Each subject must return to the clinical site for all injections and be trained to self-inject etanercept under the supervision of the investigator until the investigator judges the subject sufficiently competent to perform the self-injections independently. After this time, the subject will be allowed to self-inject at home. If the subject is unable to perform the injection, a caregiver may inject etanercept to the subject. In this case, the caregiver will also be trained to inject etanercept to the subject at the study site until the investigator judges the caregiver sufficiently competent to inject. All subsequent injections will be administered by the subject or caregiver. The subject or the caregiver will record information in the Study Drug Administration Log, including the date, time, and anatomical location of administration of IP (for treatment compliance); carton number; who administered the IP; and the reason if IP was not fully administered.

[k] **Group 1:** Subjects receiving ixekizumab 20 mg or 40 mg will receive 1 SC injection of ixekizumab at Week 0 (Visit 2) and 1 SC injection of ixekizumab Q4W at Weeks 4 and 8. Subjects receiving ixekizumab 80 mg will receive 2 SC injections of ixekizumab at Week 0 (Visit 2) and 1 SC injection of ixekizumab Q4W at Weeks 4 and 8.

Subjects receiving placebo for ixekizumab 20 mg or 40 mg will receive 1 SC injection of placebo at Week 0 (Visit 2) and 1 SC injection of placebo Q4W at Weeks 4 and 8. Subjects receiving placebo for ixekizumab 80 mg will receive 2 SC injections of placebo at Week 0 (Visit 2) and 1 SC injection of placebo Q4W at Weeks 4 and 8.

Group 2: Subjects randomized to etanercept will receive etanercept every week (Q1W) at Week 0 through Week 11. After training by the clinical staff, injections of etanercept will be self-administered by the subject or caregiver, as described in Section 7.1.

[u] All subjects receiving IP must enter into the Post-Treatment Follow-Up Period (Period 5) and complete through Visit 802. Subjects may be followed beyond Visit 802 for continued monitoring of their neutrophil counts. If a subject discontinues IP early, the subject will complete the ETV and then enter the Post-Treatment Follow-Up Period (Period 5).

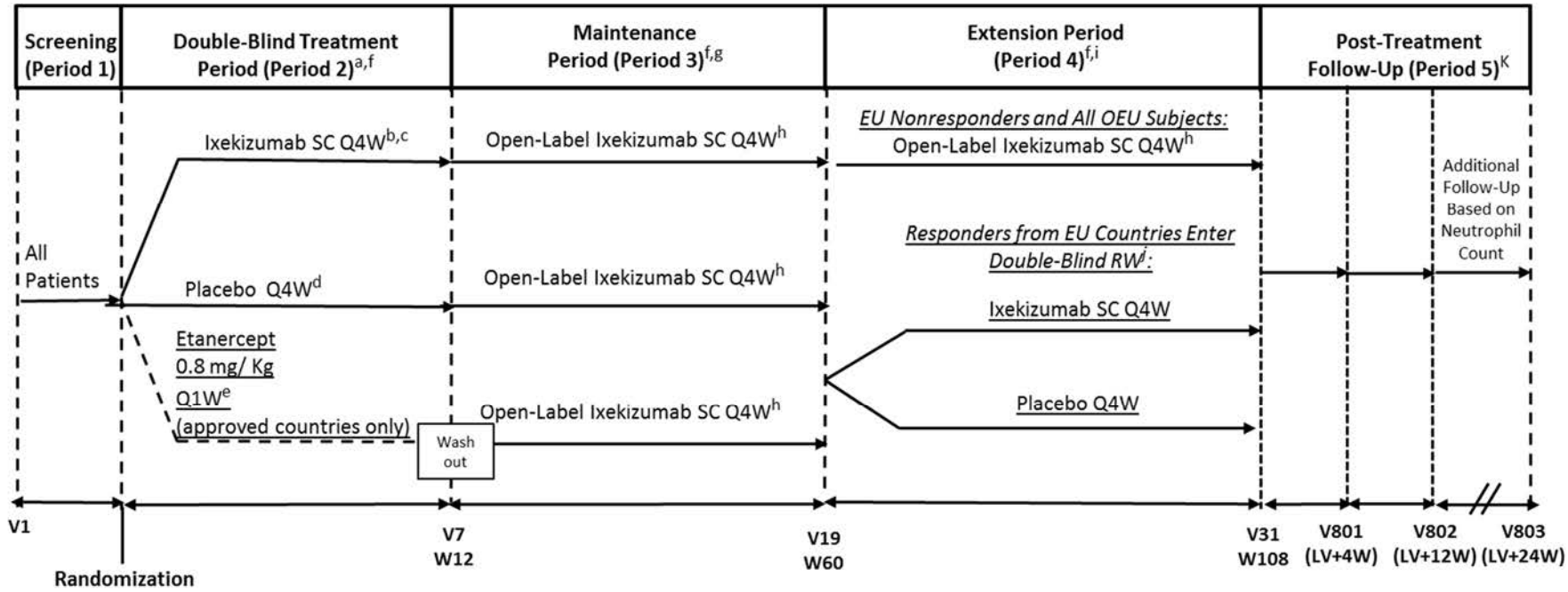
[v] This visit will only occur if a subject's neutrophil counts have not returned to the defined criteria.

[w] **Group 1:** All subjects from non-EU countries and nonresponders from EU countries will receive 1 SC injection of ixekizumab Q4W.

Group 2: Responders from EU countries will be rerandomized to either ixekizumab or placebo. Subjects will receive 1 SC injection Q4W. Subjects on placebo will receive ixekizumab upon disease relapse to psoriasis (sPGA ≥2).

Attachment 2. Protocol Addendum RHCD(2.1) Study Design

The figure below illustrates the study design for Protocol Addendum I1F-MC-RHCD(2.1).



Abbreviations: EU = European Union; LV = date of last visit; OEU = outside the European Union; Ps = plaque psoriasis ; Q1W = every week; Q4W = every 4 weeks; RW = randomized withdrawal; SC = subcutaneous; V = visit; W = weeks.

[a] Randomization will be stratified by region (United States/Canada, EU countries, and rest of the world) and by etanercept approval status: (1) Subjects with severe pediatric psoriasis (PASI ≥20 or sPGA ≥4) who are from countries where etanercept is approved for the treatment of severe pediatric psoriasis will be randomized to ixekizumab, etanercept, or placebo in a 2:2:1 ratio. (2) Per the main protocol, all other subjects (including those with moderate-to-severe Ps [PASI ≥12 and sPGA ≥3] from countries where etanercept is not approved for the treatment of severe pediatric psoriasis and subjects with moderate pediatric psoriasis [(PASI ≥12 to PASI <20) and sPGA = 3] in countries where etanercept is approved for the treatment of severe pediatric psoriasis) will be randomized to either ixekizumab or placebo in a 2:1 ratio.

[b] At Visit 2, randomization will occur according to the following weight groups: (1) <25 kg: randomization to ixekizumab 20 mg, receiving a starting dose of 40 mg; (2) 25 kg to 50 kg: randomization to ixekizumab 40 mg, receiving a starting dose of 80 mg; (3) >50 kg: randomization to 80 mg, receiving a starting dose of 160 mg. A staggered approach to enrollment by weight group will be implemented, with subjects aged 12 years or older and weighing >50 kg enrolling initially to the study. After an initial safety analysis of the first 12 weeks of treatment of 15 subjects weighing >50 kg and if no safety concern is identified, subjects will start to enroll in the 25- to 50-kg group. Once data for Week 12 for approximately 15 subjects in the 25- to 50-kg group is gathered, an interim analysis of PK, safety, and efficacy data for all subjects in the study at that point will be performed to confirm doses for future subjects in the study. Once confirmed, all weight groups will be open for enrollment.

Protocol Addendum RHCD(2) Study Design

[c] Subjects receiving ixekizumab 20 mg or 40 mg will receive 1 SC injection of ixekizumab at Week 0 (Visit 2) and 1 SC injection of ixekizumab Q4W at Weeks 4 and 8. Subjects receiving ixekizumab 80 mg will receive 2 SC injections of ixekizumab at Week 0 (Visit 2) and 1 SC injection of ixekizumab Q4W at Weeks 4 and 8.

[d] Subjects receiving placebo for ixekizumab 20 mg or 40 mg will receive 1 SC injection of placebo at Week 0 (Visit 2) and 1 SC injection of placebo Q4W at Weeks 4 and 8. Subjects receiving placebo for ixekizumab 80 mg will receive 2 SC injections of placebo at Week 0 (Visit 2) and 1 SC injection of placebo Q4W at Weeks 4 and 8.

[e] Subjects will be randomized to receive etanercept 0.8 mg/kg and up to a maximum of 50 mg per dose. All subjects will receive etanercept SC Q1W at Week 0 through Week 11.

[f] Unblinded site personnel will prepare the doses of ixekizumab and placebo.

[g] Subjects will initiate Maintenance Period as follows: (1) Subjects randomized to the ixekizumab arm during Period 2 will receive 1 SC injection of ixekizumab and 1 SC injection of placebo at Week 12. (2) Subjects randomized to the placebo arm during Period 2 will be assigned to receive ixekizumab at doses of 20, 40, or 80 mg according to weight and will receive 2 ixekizumab injections as follows—subjects assigned to 20 mg will receive a starting dose of 40 mg; subjects assigned to 40 mg will receive a starting dose of 80 mg; subjects assigned to 80 mg will receive a starting dose of 160 mg. All subjects will receive 2 SC injections at Week 12. (3) Subjects randomized to etanercept during Period 2 will receive no injections at Weeks 12 and 16. At Week 20, subjects will be assigned to receive ixekizumab at doses of 20, 40, or 80 mg according to their weight. Subjects assigned to 20 mg will receive a starting dose of 40 mg. Subjects assigned to 40 mg will receive a starting dose of 80 mg. Subjects assigned to 80 mg will receive a starting dose of 160 mg. Treatment with ixekizumab is weight based. If a subject changes weight category during the study and after the Double-Blind Treatment Period, the dose will be adjusted accordingly.

[h] All subjects will receive 1 SC injection of ixekizumab Q4W.

[i] Subjects from EU countries who meet the response criterion at Week 60 (defined as sPGA [0,1]) will be rerandomized to ixekizumab or placebo (1:1 ratio). Subjects from EU countries who do not meet response criteria and subjects from non-EU countries will continue with open-label treatment with ixekizumab.

[j] Subjects will receive ixekizumab upon disease relapse to psoriasis (sPGA ≥2).

[k] All subjects receiving investigational product must enter into the Post-Treatment Follow-Up Period (Period 5) and complete through Visit 802. Subjects may be followed beyond Visit 802 for continued monitoring of their neutrophil counts if needed or if determined by the sponsor/investigator that additional monitoring is needed.

Revised Protocol Addendum

Note:	Deletions have been identified by ~~strikethroughs~~. Addition to I1F-MC-RHCD(2) Clinical Protocol have been identified by the use of underscore. Additions to I1F-MC-RHCD(2.1) Clinical Protocol Addendum have been identified by the use of double underscore.

Attachment 2: Protocol Addendum RHCD(2.1) Study Design

[a] Randomization will be stratified by region (United States/Canada, EU countries, and rest of the world) and by etanercept approval status: (1) Subjects with severe pediatric psoriasis (PASI ≥20 or sPGA ≥4) who are from countries where etanercept is approved for the treatment of severe pediatric psoriasis will be randomized to ixekizumab, etanercept, or placebo in a 2:2:1 ratio. (2) Per the main protocol, all other subjects (including those with moderate-to-severe Ps [PASI ≥12 and sPGA ≥3] from countries where etanercept is not approved for the treatment of severe pediatric psoriasis and subjects with moderate pediatric psoriasis [(PASI ≥12 to PASI <20) and sPGA = 3] in countries where etanercept is approved for the treatment of severe pediatric psoriasis) will be randomized to either ixekizumab or placebo in a 2:1 ratio.

[b] At Visit 2, randomization will occur according to the following weight groups: (1) <25 kg: randomization to ixekizumab 20 mg, receiving a starting dose of 40 mg; (2) 25 kg to 50 kg: randomization to ixekizumab 40 mg, receiving a starting dose of 80 mg; (3) >50 kg: randomization to 80 mg, receiving a starting dose of 160 mg. A staggered approach to enrollment by weight group will be implemented, with subjects aged 12 years or older and weighing >50 kg enrolling initially to the study. After an initial safety analysis of the first 12 weeks of treatment of 15 subjects weighing >50 kg and if no safety concern is identified, subjects will start to enroll in the 25- to 50-kg group. Once data for Week 12 for approximately 15 subjects in the 25- to 50-kg group is gathered, an interim analysis of PK, safety, and efficacy data for all subjects in the study at that point will be performed to confirm doses for future subjects in the study. Once confirmed, all weight groups will be open for enrollment.

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Approver: PPD
Approval Date & Time: 19-Jul-2017 16:05:37 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 20-Jul-2017 13:03:12 GMT
Signature meaning: Approved

1. Statistical Analysis Plan: I1F-MC-RHCD: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Efficacy of Ixekizumab in Patients from 6 to Less than 18 Years of Age with Moderate-to-Severe Plaque Psoriasis

Ixekizumab (LY2439821) Pediatric Psoriasis

Study I1F-MC-RHCD is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study, examining the effects of ixekizumab versus placebo on PASI 75 and sPGA in subjects from 6 to <18 years of age with moderate to severe plaque psoriasis (PASI ≥12, sPGA ≥3, BSA ≥10%) at screening and baseline.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol I1F-MC-RHCD
(Phase 3)

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 06-June-2017
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly: 18-March-2019
Statistical Analysis Plan Version 3 electronically signed and approved by Lilly on date provided below.

Approval Date: 26-Jun-2019 GMT

2. Table of Contents

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3. Revision History

Statistical analysis plan (SAP) Version 1 was approved prior to unblinding of treatment assignments for Study Period 2.

Statistical Analysis Plan (SAP) Version 2 was approved prior to primary database lock (12 week).

Statistical Analysis Plan (SAP) Version 3 was approved after primary database lock and prior to submission database lock.

Revisions since Version 1:

Section	Action
Section 4.1 Study Objectives Table 4.1	Updated time point Week 2 to Week 4.
Section 6.1.1 Analysis Population Table 6.2	Updated abbreviations for placebo and etanercept arms.
Section 6.5. Multiple Comparisons/Multiplicity	Updated time point Week 2 to Week 4.
Section 6.8.1 Demographics and Baseline Characteristics	Updated age category criteria. Removed immunization history. Updated “Fingernail psoriasis” to “Nail psoriasis”.
Section 6.8.2 Historical Illness and Preexisting Conditions	Clarified definitions of historical illness and pre-existing conditions.
Section 6.11 Efficacy Analyses Table 6.3	Updated NAPSI definitions with toenail scores added. Corrected typo. Updated PSSI definition.
Section 6.11 Efficacy Analyses Table 6.4	Added logistic regression with NRI to categorical endpoints as secondary analysis method.
Section 6.11.2 Gated Secondary Efficacy Analyses	Updated time point Week 2 to Week 4.
Section 6.12 Health-Outcome/Quality-of-Life Analyses Table 6.5	Corrected definition of CDLQI question #7.
Section 6.12 Health-Outcome/Quality-of-Life Analyses Table 6.6	Added logistic regression with NRI to categorical endpoints as secondary analysis method.
Section 6.14.1 Extent of Exposure	Removed by-patient listing for extent of exposure.
Section 6.14.2.1 Common Adverse Events	Removed.
Section 6.14.3.1 Special Safety Topics Including Adverse Events of Special Interest Table 6.7	Text updates for definition/derivation of AESIs to be consistent with PSAP V8 Removed duplicated or unnecessary analyses Changed Covance to performing lab reference range Wording updates per most recent PSAP for Infections, Allergic Reactions/Hypersensitivities, Injection Site Reactions, IBD, ILD.

Section	Action
Section 6.14.4 Clinical Laboratory Evaluation	Removed by-patient listings.
Section 6.14.9 Tanner Stage Scale	Removed analysis for Period 2.
Section 6.15.1 Efficacy Subgroup Analyses	Updated age category criteria. Updated duration of disease category.
Section 6.16 Protocol Violations Table 6.12	Updated important protocol violations per most recent Trial Issue Management Plan.
Section 6.17 Interim Analyses and Data Monitoring	Added additional interim analyses to fulfill the need for regulatory interactions or publication purposes.
Section 6.18 Planned Exploratory Analyses	Updated psychometric analyses of the Itch NRS.
References	Updated references
Appendices 3-6	Updated per PSAP V8.

Revisions since Version 2:

Section	Action
Section 6.16 Protocol Violations Table 6.12	Updated important protocol violations per most recent Trial Issue Management Plan (to incorporate post-hoc change after the primary database lock).

4. Study Objectives

Table RHCD.4.1. Study Objectives

Objectives	Endpoints
Co-Primary To assess whether ixekizumab Q4W is superior to placebo at Week 12 (Visit 7) in the treatment of pediatric subjects (children and adolescents) with moderate-to-severe plaque psoriasis as measured by PASI 75 and by sPGA (0,1)	• Proportion of subjects achieving PASI 75 at Week 12 • Proportion of subjects achieving sPGA (0,1) at Week 12
Gated Secondary To assess whether ixekizumab Q4W is superior to placebo as measured by: • PASI 90 • sPGA (0) • PASI 100 • Itch NRS • PASI 75 • sPGA (0,1)	• Proportion of subjects achieving PASI 90 at Week 12 • Proportion of subjects achieving sPGA (0) at Week 12 • Proportion of subjects achieving PASI 100 at Week 12 • Improvement ≥4 for subjects who had a baseline Itch NRS score ≥4 at Week 12 • Proportion of subjects achieving PASI 75 at Week 4 • Proportion of subjects achieving sPGA (0,1) at Week 4
Other Secondary To assess whether ixekizumab Q4W is superior to placebo	The following endpoints will be assessed at Week 12 and at each postbaseline visit during the Double-Blind Treatment Period: • Proportion of subjects achieving PASI 50, PASI 75, PASI 90, and PASI 100 • Proportion of subjects achieving sPGA (0,1) and sPGA (0) • Change from baseline in itching severity (Itch NRS) score • CDLQI/DLQI (0,1) • Change from baseline in NAPSI, PSSI, and/or PPASI score in case of nail, scalp, or hand/feet involvement
To summarize the efficacy of ixekizumab Q4W at Week 24 (Visit 10) and Week 48 (Visit 16) as measured by: • PASI 75 • sPGA (0,1) • PASI 90 • sPGA (0) • PASI 100	The following endpoints will be assessed: • Proportion of subjects achieving PASI 75 at Weeks 24 and 48 • Proportion of subjects achieving sPGA (0,1) at Weeks 24 and 48 • Proportion of subjects achieving PASI 90 at Weeks 24 and 48 • Proportion of subjects achieving sPGA (0) at Weeks 24 and 48 • Proportion of subjects achieving PASI 100 at Weeks 24 and 48
To evaluate the potential development of anti-ixekizumab antibodies and its impact on subject efficacy of ixekizumab	• PASI 75 and sPGA(0,1) at Week 12 correlated with treatment-emergent antidrug antibody titer (low, moderate, and high) and by NAb status
To measure ixekizumab exposure and characterize the pharmacokinetics of ixekizumab in pediatric subjects	• Serum trough concentrations of ixekizumab
To assess the relationship between exposure and efficacy and exposure and immunogenicity	• Model parameters for the exposure-response relationship between ixekizumab serum trough concentrations and efficacy endpoints (for example, sPGA, PASI) at Week 12

Objectives	Endpoints
	• Serum trough concentrations for ixekizumab antibody titer subgroups
To assess the safety of ixekizumab	• To evaluate the safety of ixekizumab, including but not limited to: infections; injection-site reactions; B-, T-, and NK-cell levels; WBC count; RBC count; and laboratory values (hematology and chemistry [including ALT and AST]) during the course of the study
To demonstrate normal growth and pubertal progression in children treated with ixekizumab during the course of the study	• Weight, height, and BMI data will be merged to the Centers for Disease Control and Prevention standard growth data by age and gender to compare subjects' growth with normal values • Shift table for Tanner stage from maximum baseline to maximum postbaseline by gender
To evaluate the genital involvement of the subjects per the questionnaire Binary Questions on Psoriasis Location	• Proportion of subjects achieving no psoriasis presence in each psoriasis location
To evaluate the patient's global assessment of disease severity	• Proportion of subjects achieving patient's global assessment of disease severity 0 or 1
To evaluate the effect of ixekizumab on maintenance of efficacy and health outcomes during the open-label maintenance period and extension period.	• Proportion of subjects achieving PASI 90 • Proportion of subjects achieving sPGA (0) • Proportion of subjects achieving PASI 100 • Proportion of subjects achieving PASI 75 • Proportion of subjects achieving sPGA (0,1) • Improvement ≥4 for subjects who had a baseline Itch NRS score ≥4

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; NAb = neutralizing antidrug antibody; NAPSI = Nail Psoriasis Severity Index; NK = natural killer; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PASI 50 = at least a 50% improvement from baseline in PASI score; PASI 75 = at least a 75% improvement from baseline in PASI score; PASI 90 = at least a 90% improvement from baseline in PASI score; PASI 100 = a 100% improvement from baseline in PASI score; PPASI = Palmoplantar Psoriasis Severity Index; PSSI = Psoriasis Severity Index; Q4W = every 4 weeks; RBC = red blood cell; sPGA = static Physician's Global Assessment; WBC = white blood cell.

Table RHCD.4.2. Protocol Addendum I1F-MC-RHCD(2) Study Objectives

Objectives	Endpoints
Other Secondary To compare the efficacy of ixekizumab Q4W and etanercept at Week 12 (Visit 7) as measured by PASI 75 and by sPGA (0,1) in countries where etanercept is approved	• Proportion of subjects achieving PASI 75 at Week 12 • Proportion of subjects achieving sPGA (0,1) at Week 12
To assess whether ixekizumab Q4W is superior to placebo for EU subjects during the Double-Blind, Randomized Withdrawal Period	• Time to relapse to moderate severity (sPGA ≥2) during the Double-Blind, Randomized Withdrawal Period • Proportion of subjects achieving sPGA (0,1) at Week 108 (Visit 31)

Abbreviations: EU = European Union; PASI 75 = at least a 75% improvement from baseline in Psoriasis Area and Severity Index score; Q4W = every 4 weeks; sPGA = static Physician's Global Assessment.

5. Study Design

5.1. Summary of Study Design

Study I1F-MC-RHCD (RHCD) is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study examining the effects of ixekizumab versus placebo in subjects from 6 to <18 years of age with moderate-to-severe plaque psoriasis (Ps) (Psoriasis Area and Severity Index [PASI] score ≥12, static Physician's Global Assessment [sPGA] ≥3, and body surface area [BSA] ≥10% at screening and baseline). Protocol Addendum I1F-MC-RHCD(1) specifies the pharmacokinetics (PK) collection schedule and how the data from the approximately 24 subjects participating in the PK addendum will be used. Protocol Addendum I1F-MC-RHCD(2) specifies the details for the active-controlled (etanercept) portion of the study design, as well as a double-blind, randomized withdrawal period for subjects from European Union (EU) countries.

The study consists of 5 periods:

- **Period 1: Screening Period** (Visit 1) will assess subject eligibility and will occur approximately 7 to 30 days before Period 2 (baseline; Week 0; Visit 2).
- **Period 2: Double-Blind Treatment Period** (Induction Period) will occur from Week 0 (baseline; Visit 2) to Week 12 (Visit 7), comparing ixekizumab with placebo in a double-blind fashion. The dose of ixekizumab will not be adjusted during this period. Protocol Addendum I1F-MC-RHCD(2) describes etanercept as a reference control group for countries where etanercept is approved for treatment of chronic severe Ps in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.
- **Period 3: 48-Week, Open-Label Maintenance Period** will occur from Week 12 (Visit 7) to Week 60 (Visit 19). Subjects randomized to the ixekizumab group during Period 2 will maintain the dose received during the previous period. Subjects randomized to placebo during Period 2 will receive ixekizumab at doses of 20, 40, or 80 mg, based on weight. As part of Protocol Addendum I1F-MC-RHCD(2), subjects randomized to etanercept during the Double-Blind Treatment Period will begin treatment with ixekizumab after an 8-week washout period (to avoid, for safety reasons, increased risk with concurrent etanercept and ixekizumab exposures). If a subject changes weight category following the Double-Blind Treatment Period, the ixekizumab dose associated with that weight will be administered. This may happen at any time during the Maintenance Period.
- **Period 4: Extension Period** will occur from Week 60 (Visit 19) to Week 108 (Visit 31). Subjects will continue with open-label treatment of the ixekizumab dose received during the previous period (Period 3). Protocol Addendum I1F-MC-RHCD(2) describes the 48-week Double-Blind, Randomized Withdrawal Period for subjects from EU countries who meet response criteria during the Maintenance Period (defined as sPGA [0,1]). Subjects who enter the Double-Blind, Randomized Withdrawal Period will be re-randomized to ixekizumab or placebo (1:1 ratio) at Week 60 (Visit 19). Subjects who are re-randomized to

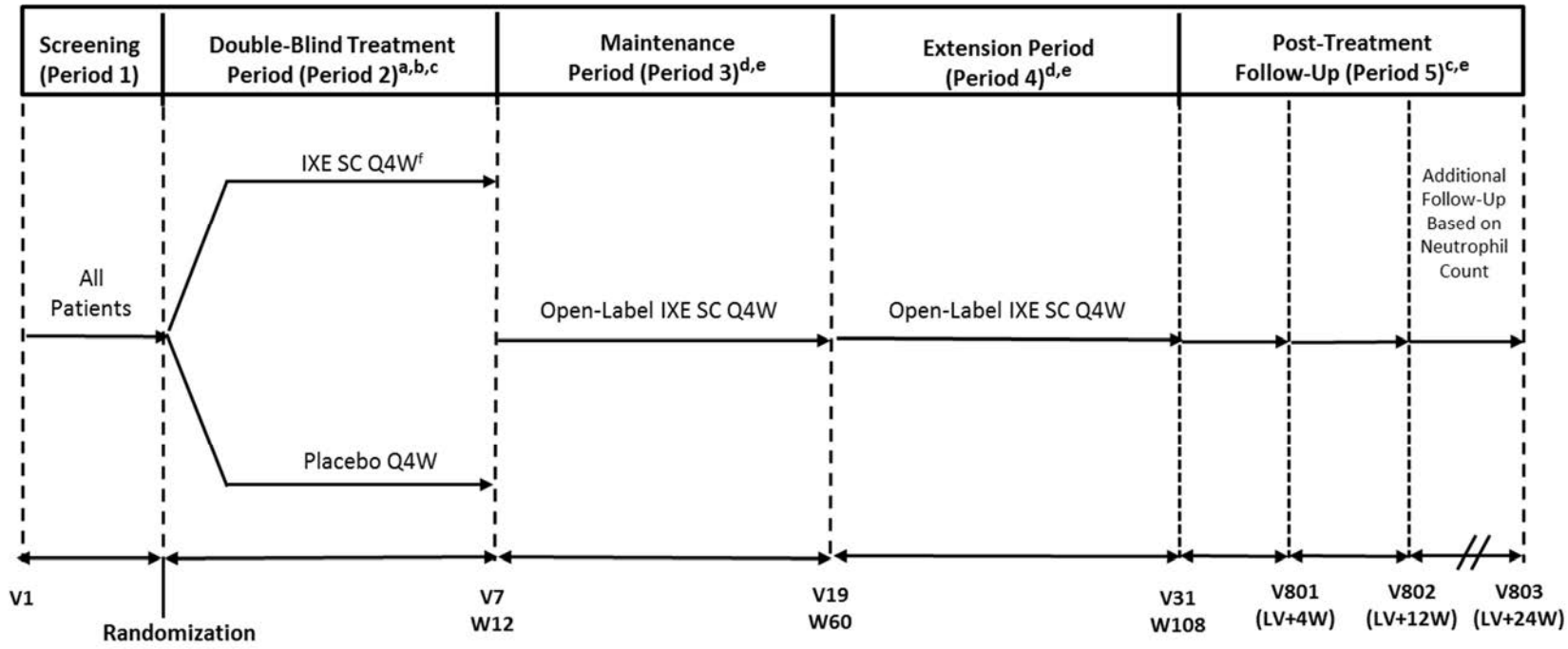
ixekizumab will receive ixekizumab 20, 40, or 80 mg every 4 weeks (Q4W) according to their weight at the time of re-randomization.

- **Period 5: Post-Treatment Follow-Up Period** is for safety monitoring after treatment discontinuation for any subject receiving at least 1 dose of study drug. This period occurs from the last treatment period visit or Early Termination Visit (ETV) for up to 24 weeks following that visit.

The underlined text in the following sections show the additions and deletions applicable to subjects participating in Protocol Addendum I1F-MC-RHCD(2).

- **Period 2: Double-Blind Treatment Period** (Induction Period) will occur from Week 0 (baseline; Visit 2) to Week 12 (Visit 7), comparing ixekizumab to placebo in a double-blind fashion (all countries) and to etanercept (as a reference arm – all countries except North America). The dose will remain the same in this treatment period.
- **Period 3: 48-Week, Open-Label Maintenance Period** will occur from Week 12 (Visit 7) to Week 60 (Visit 19). Subjects randomized to etanercept during Period 2 will receive ixekizumab at doses of 20, 40, or 80 mg, according to their weight after an etanercept 8-week washout period is complete. The etanercept washout period will be from Week 12 through Week 20. If a subject changes weight category following the Double-Blind Treatment Period, the ixekizumab dose associated with that weight will be administered. This may happen at any time during the Maintenance Period.
- **Period 4: Extension Period** will occur from Week 60 (Visit 19) to Week 108 (Visit 31). Subjects from countries outside of the EU, irrespective of response, and nonresponders from the EU will continue with open-label treatment with the ixekizumab dose received during the previous period (Period 3). Subjects from the EU who meet response criteria at Week 60 (defined as those with sPGA [0,1]) will be re-randomized to ixekizumab or placebo in the Double-Blind, Randomized Withdrawal Period. Subjects will receive the ixekizumab dose according to weight, which will be reassessed during this period.

Figure RHCD.5.1 and Figure RHCD.5.2 illustrate the study design for the main protocol and the protocol addendum (2).



Abbreviations: IXE = ixekizumab (LY2439821); LV = date of last visit; PK = pharmacokinetic(s); Q4W = every 4 weeks; SC = subcutaneous; V = visit; W = week.

Footnotes on following page.

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

Illustration of study design for Clinical Protocol I1F-MC-RHCD

[a] Subjects will be randomized to either ixekizumab or placebo in a 2:1 ratio.

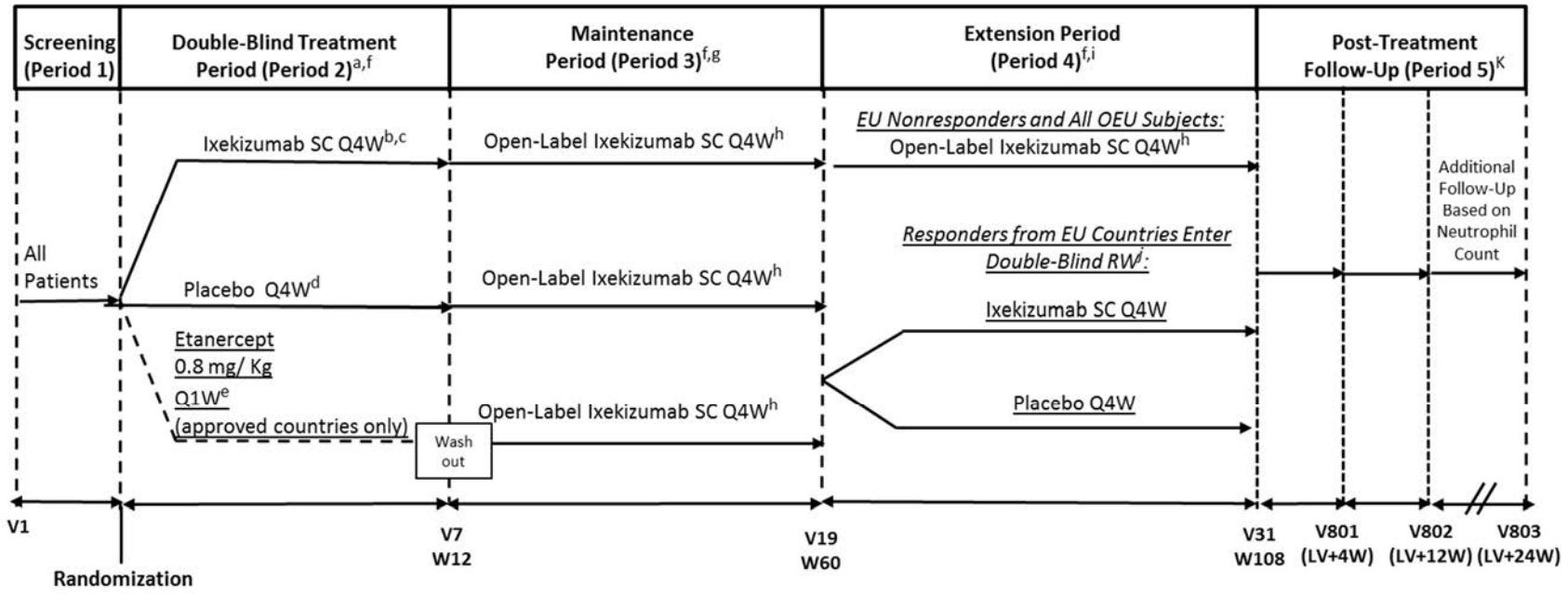
[b] Subjects receiving ixekizumab 20 mg or 40 mg will receive 1 SC injection of ixekizumab at Week 0 (Visit 2) and 1 SC injection of ixekizumab Q4W at Weeks 4 and 8. Subjects receiving ixekizumab 80 mg will receive 2 SC injections of ixekizumab at Week 0 (Visit 2) and 1 SC injection of ixekizumab Q4W at Weeks 4 and 8. Subjects receiving placebo for ixekizumab 20 mg or 40 mg will receive 1 SC injection of placebo at Week 0 (Visit 2) and 1 SC injection of placebo Q4W at Weeks 4 and 8. Subjects receiving placebo for ixekizumab 80 mg will receive 2 SC injections of placebo at Week 0 (Visit 2) and 1 SC injection of placebo Q4W at Weeks 4 and 8.

[c] Immunogenicity and time-matched PK sample collection will occur as detailed in the Schedule of Activities (Section 2) of the Protocol

[d] Subjects randomized to ixekizumab during Period 2 will receive 1 SC injection of ixekizumab and 1 SC injection of placebo at Week 12. Subjects randomized to the placebo group during Period 2 will be assigned to receive ixekizumab at doses of 20, 40, or 80 mg, based on weight. Subjects assigned to 20 mg will receive a starting dose of 40 mg, subjects assigned to 40 mg will receive a starting dose of 80 mg, and subjects assigned to 80 mg will receive a starting dose of 160 mg. All subjects will receive 2 SC injections of ixekizumab at Week 12 and 1 SC injection of ixekizumab Q4W at Week 16 and thereafter. Treatment with ixekizumab is weight-based. If a subject changes weight category during the study, the dose will be adjusted accordingly.

[e] All subjects receiving study drug must enter into Period 5, and complete through Visit 802. Subjects may be followed up beyond Visit 802 for continued monitoring of their neutrophil count if determined by the Sponsor/investigator that additional monitoring is needed.

[f] At Visit 2, randomization will occur based on the following weight groups: 1) <25 kg: randomization to ixekizumab 20 mg, receiving a starting dose of 40 mg; 2) 25 kg to 50 kg: randomization to ixekizumab 40 mg, receiving a starting dose of 80 mg; and 3) >50 kg: randomization to 80 mg, receiving a starting dose of 160 mg. A staggered approach to enrollment by weight group will be implemented with subjects >12 years and >50 kg enrolling initially to the study. If no safety concern is identified after an initial safety analysis of the first 12 weeks of treatment in the first 15 subjects >50 kg, subjects will start to enroll in the 25- to 50-kg group. Once data are obtained to Week 12 for approximately 15 subjects in the 25- to 50-kg group, an interim analysis of PK, safety, and efficacy data in all subjects in the study at that point will be performed to confirm doses for the remaining subjects in the study. Once confirmed, all weight groups will be open for enrollment.



Abbreviations: EU = European Union; LV = date of last visit; OEU = outside the European Union; PASI = Psoriasis Area and Severity Index PK = pharmacokinetic(s); Ps = plaque psoriasis ; Q1W = every week; Q4W = every 4 weeks; RW = randomized withdrawal; SC = subcutaneous; sPGA = static Physician's Global Assessment; V = visit; W = weeks.

Footnotes on following page.

Figure RHCD.5.2. Illustration of study design for Protocol Addendum I1F-MC-RHCD(2).

[a] Randomization will be stratified by region (United States/Canada, EU countries, and rest of the world) and by etanercept approval status: 1) Subjects with severe pediatric Ps (PASI ≥20 or sPGA ≥4) who are from countries where etanercept is approved for the treatment of severe pediatric Ps will be randomized to ixekizumab, etanercept, or placebo in a 2:2:1 ratio. 2) Per the main protocol, all other subjects (including those with moderate-to-severe Ps [PASI ≥12 and sPGA ≥3] from countries where etanercept is not approved for the treatment of severe pediatric Ps, and subjects with moderate pediatric Ps [12 ≤PASI <20 and sPGA = 3] in countries where etanercept is approved for the treatment of severe pediatric Ps) will be randomized to either ixekizumab or placebo in a 2:1 ratio.

[b] At Visit 2, randomization will occur according to the following weight groups: 1) <25 kg: randomization to ixekizumab 20 mg, receiving a starting dose of 40 mg; 2) 25 kg to 50 kg: randomization to ixekizumab 40 mg, receiving a starting dose of 80 mg; 3) >50 kg: randomization to 80 mg, receiving a starting dose of 160 mg. A staggered approach to enrollment by weight group will be implemented, with subjects aged >12 years and weighing >50 kg enrolling initially to the study. After an initial safety analysis of the first 12 weeks of treatment of 15 subjects weighing >50 kg, and if no safety concern is identified, subjects will start to enroll in the 25- to 50-kg group. Once data for Week 12 for approximately 15 subjects in the 25- to 50-kg group is gathered, an interim analysis of PK, safety, and efficacy data for all subjects in the study at that point will be performed to confirm doses for future subjects in the study. Once confirmed, all weight groups will be open for enrollment.

[c] Subjects receiving ixekizumab 20 mg or 40 mg will receive 1 SC injection of ixekizumab at Week 0 (Visit 2) and 1 SC injection of ixekizumab Q4W at Weeks 4 and 8. Subjects receiving ixekizumab 80 mg will receive 2 SC injections of ixekizumab at Week 0 (Visit 2) and 1 SC injection of ixekizumab Q4W at Weeks 4 and 8.

[d] Subjects receiving placebo for ixekizumab 20 mg or 40 mg will receive 1 SC injection of placebo at Week 0 (Visit 2) and 1 SC injection of placebo Q4W at Weeks 4 and 8. Subjects receiving placebo for ixekizumab 80 mg will receive 2 SC injections of placebo at Week 0 (Visit 2) and 1 SC injection of placebo Q4W at Weeks 4 and 8.

[e] Subjects will be randomized to receive etanercept 0.8 mg/kg and up to a maximum of 50 mg per dose. All subjects will receive etanercept SC Q1W at Week 0 through Week 11.

[f] Unblinded site personnel will prepare the doses of ixekizumab and placebo.

[g] Subjects will initiate Maintenance Period as follows: (1) Subjects randomized to the ixekizumab arm during Period 2 will receive 1 SC injection of ixekizumab and 1 SC injection of placebo at Week 12. (2) Subjects randomized to the placebo arm during Period 2 will be assigned to receive ixekizumab at doses of 20, 40, or 80 mg, according to weight, and will receive 2 ixekizumab injections as follows—subjects assigned to 20 mg will receive a starting dose of 40 mg; subjects assigned to 40 mg will receive a starting dose of 80 mg; subjects assigned to 80 mg will receive a starting dose of 160 mg. All subjects will receive 2 SC injections at Week 12. (3) Subjects randomized to etanercept during Period 2 will receive no injections at Weeks 12 and 16. At Week 20, subjects will be assigned to receive ixekizumab at doses of 20, 40, or 80 mg, according to their weight. Subjects assigned to 20 mg will receive a starting dose of 40 mg. Subjects assigned to 40 mg will receive a starting dose of 80 mg. Subjects assigned to 80 mg will receive a starting dose of 160 mg. Treatment with ixekizumab is weight-based. If a subject changes weight category during the study and after the Double-Blind Treatment Period, the dose will be adjusted accordingly.

[h] All subjects will receive 1 SC injection of ixekizumab Q4W.

[i] Subjects from EU countries who meet the response criterion at Week 60 (defined as sPGA [0,1]) will be re-randomized to ixekizumab or placebo (1:1 ratio). Subjects from EU countries who do not meet response criteria and subjects from non-EU countries will continue with open-label treatment with ixekizumab.

[j] Subjects will receive ixekizumab upon disease relapse to Ps (sPGA ≥2).

[k] All subjects receiving investigational product must enter into the Post-Treatment Follow-Up Period (Period 5) and complete through Visit 802. Subjects may be followed beyond Visit 802 for continued monitoring of their neutrophil counts if needed or if determined by the Sponsor/investigator that additional monitoring is needed.

5.2. Determination of Sample Size

5.2.1. Clinical Protocol RHCD

Sample size of this study is based on the regulatory requirements from the European Medicine's Agency Paediatric Investigation Plan for ixekizumab. The regulatory requirements for the number of subjects in each treatment group were: (1) at least 170 randomized subjects (at least 90 to ixekizumab, at least 25 to etanercept, and at least 55 to placebo); and (2) at least 30% of subjects from the EU.

In the main protocol RHCD, approximately 165 subjects will be randomized in a 2:1 ratio to receive ixekizumab (110 subjects) or placebo (55 subjects) during the Double-Blind Treatment Period. The study will have >99% power to test the superiority of ixekizumab to placebo for PASI 75 and for sPGA (0,1) at Week 12, based on the 2-sided Fisher's exact test at a significance level of 0.05. The following assumptions were used for the power calculations for both sPGA (0,1) and PASI 75 responses rates, based on ixekizumab clinical studies in adult subjects with moderate-to severe Ps efficacy data (Griffiths et al. 2015; Gordon et al. 2016): 80% response for ixekizumab and 10% response for placebo for both PASI 75 and sPGA (0,1).

5.2.2. Protocol Addendum RHCD(2)

During the Double-Blind Treatment Period, approximately 75 subjects with severe Ps from etanercept-approved countries will be randomized to ixekizumab (30 subjects), etanercept (30 subjects), and placebo (15 subjects) with 2:2:1 ratio.

Study RHCD(2) will have approximately 85% power to test the superiority of ixekizumab to etanercept for sPGA (0,1) and at least a 75% improvement from baseline in PASI score (PASI 75) at Week 12, based on the 2-sided Fisher's exact test at significance level of 0.05. The study will have approximately 45% power to test the superiority of etanercept to placebo for PASI 75 at Week 12, based on the 2-sided Fisher's exact test at significance level of 0.05. The following assumptions were used for the power calculations for both sPGA (0,1) and PASI 75 response rates, based on ixekizumab clinical studies in adult subjects with moderate-to-severe Ps efficacy data (Griffiths et al. 2015; Gordon et al. 2016): 80% responders for ixekizumab, 40% responders for etanercept, and 10% for placebo.

During the Double-Blind, Randomized Withdrawal Period (Period 4), approximately 40 subjects from EU countries will be re-randomized to ixekizumab (20 subjects) and placebo (20 subjects) with a 1:1 ratio. The response criterion for re-randomization is sPGA (0,1) at Week 60. The study will have approximately 95% power to test the superiority of ixekizumab to placebo in time to relapse, based on the 2-sided log-rank test at significance level of 0.05. The following assumptions were used for the power calculations: 20% relapse for ixekizumab; and 85% relapse for placebo. Relapse rates were estimated, based on ixekizumab clinical studies in adult subjects with moderate-to-severe Ps efficacy data (Griffiths et al. 2015; Gordon et al. 2016).

5.3. Method of Assignment to Treatment

Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign cartons containing double-blind study drug to each subject. Study site personnel will confirm that they have located the correct carton by entering a confirmation number into the IWRS.

5.3.1. Clinical Protocol RHCD

Subjects who meet all enrollment criteria at Visit 1 and Visit 2 will be randomized in a 2:1 ratio to double-blind treatment with ixekizumab or placebo at Week 0 (Visit 2).

To achieve between-group comparability for region, the randomization will be stratified by region (United States/Canada, European countries, and the rest of the world).

During the Maintenance and Extension periods, all subjects will receive open-label treatment with ixekizumab.

5.3.2. Protocol Addendum RHCD(2)

Subjects from countries where etanercept is approved for severe pediatric Ps treatment only who meet all criteria for enrollment at Visit 1 and Visit 2 will be randomized to double-blind treatment at Week 0 (Visit 2) in a 2:2:1 ratio to ixekizumab, etanercept, or placebo.

Subjects who meet response criteria (sPGA 0,1) from EU countries will enter the Double-Blind Randomized Withdrawal Period and will be re-randomized to double-blind treatment at Week 60 (Visit 19) in a 1:1 ratio to ixekizumab or placebo. Subjects who are re-randomized to ixekizumab will receive ixekizumab 20, 40, or 80 mg every 4 weeks (Q4W) according to their weight at the time of re-randomization. Subjects from EU countries who relapse (sPGA $\geq$2) during the Double-Blind Randomized Withdrawal Period will receive open-label treatment with ixekizumab according to their weight at the time of relapse.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (hereafter, Lilly, or its designee). The statistical analyses will be performed using SAS® Version 9.2 or higher.

Continuous data will be summarized in terms of the number of observations, mean, standard deviation (SD), minimum, median, and maximum. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to 1 more decimal place than the raw data recorded in the database. The SD will be reported to 2 more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be 4 for any summary statistic.

Categorical data will be summarized in terms of the number of patients in the Analysis Population, the number of patients providing data at the relevant time point, frequency counts, and the percentages corresponding to the appropriate method. Percentages will be presented to 1 decimal place. Percentages will not be presented for zero counts.

All confidence intervals (CIs) and statistical tests will be 2-sided unless, otherwise, specified. P-values which are greater than or equal to (≥) 0.001, and less than or equal to (≤) 0.999, will be presented to 3 decimal places. All other p-values which are less than 0.001 will be presented as <0.001, while p-values greater than 0.999 will be presented as >0.999. Confidence intervals will be presented to 1 more decimal place than the raw data.

Age, gender, and race will be reported on all by-patient listings unless, otherwise, specified. Gender will be abbreviated as follows: female (F); and male (M). Race will be abbreviated as follows: American Indian or Alaska Native (AI), Asian (AS), Black or African American (BL), Native Hawaiian or other Pacific Islander (NH), White (WH), and Multiple (MU).

6.1.1. Analysis Population

Table RHCD.6.1 provides the definitions for each analysis population for specific treatment periods. Table RHCD.6.2 summarizes the treatment groups and comparisons for each study period and analysis population.

Unless, otherwise, specified, efficacy and health-outcome analyses will be conducted for the Intent-to-treat (ITT) Population (per the main study) in Double-Blind Treatment Period (Period 2). In addition, the co-primary endpoints will be analyzed using the per-protocol set (PPS).

Select efficacy analyses will be conducted on the ITT Population-Etanercept Approved Countries (per Protocol Addendum[2]) in Double-Blind Treatment Period (Period 2).

Safety analyses for the Double-Blind Treatment Period (Period 2) will be conducted on the Safety Population. There are 2 safety populations: Safety Population (per the main study); and Safety Population-Etanercept Approved Countries (per Protocol Addendum[2]).

Unless, otherwise, specified, the efficacy and safety analyses for the Double-Blind, Randomized Withdrawal Period will be conducted on the Double-Blind, Randomized Withdrawal Period Population (per Protocol Addendum[2]).

Unless, otherwise, specified, during the Combined Treatment Periods (Periods 2, 3, and 4), efficacy and health-outcome analysis will be conducted on the ixekizumab Efficacy Primary Population.

Safety analyses during the Combined Treatment Periods (Periods 2, 3, and 4) will be conducted on the All Ixekizumab Safety Population

Unless, otherwise, specified, during Combined Treatment Periods 3 and 4, efficacy analysis will be conducted on the Ixekizumab Efficacy Secondary Population.

Safety analyses for the Post-Treatment Follow-Up Period (Period 5) will be conducted on the Follow-Up Population.

Table RHCD.6.1. Analysis Populations

Population	Period	Description
Intent-to-Treat (ITT) Population (per main study)	Double-Blind Treatment Period (Period 2)	All randomized subjects, even if the subject does not take the assigned treatment, does not receive the correct treatment, or, otherwise, does not follow the protocol. Unless, otherwise, specified, efficacy and health-outcome analyses will be conducted on the ITT Population during Double-Blind Treatment Period (Period 2). Subjects will be analyzed according to the treatment to which they were assigned.
Intent-to-Treat (ITT) – Etanercept Approved Countries (per Protocol Addendum[2])	Double-Blind Treatment Period (Period 2)	All randomized subjects per Protocol Addendum(2) in etanercept-approved countries (that is, subjects with severe psoriasis in countries where etanercept is used as a reference arm), even if the subject does not take the assigned treatment, does not receive the correct treatment, or, otherwise, does not follow the protocol. Subjects will be analyzed according to the treatment to which they were assigned.
Per-Protocol Set (per main study)	Double-Blind Treatment Period (Period 2)	All randomized subjects who do not have significant protocol violations (refer to Section 6.16). Subjects will be analyzed according to the treatment to which they were assigned. .
Safety Population (per main study)	Double-Blind Treatment Period (Period 2)	All randomized subjects who take at least 1 dose of double-blind study treatment. Subjects will be analyzed according to the treatment to which they were assigned.

Population	Period	Description
Safety Population – Etanercept-Approved Countries (per Protocol Addendum[2])	Double-Blind Treatment Period (Period 2) per Protocol Addendum(2)	All randomized subjects in Protocol Addendum(2) in etanercept countries who take at least 1 dose of double-blind study treatment per Protocol Addendum(2). Subjects will be analyzed according to the treatment to which they were assigned.
Double-Blind, Randomized Withdrawal Period Population	Randomized-Withdrawal Period (Period 4) per Protocol Addendum(2)	All re-randomized patients (that is, subjects from countries in the EU who were re-randomized at Week 60) who received at least 1 dose of study treatment during Double-Blind, Randomized Withdrawal Period.
Ixekizumab Efficacy Primary Population	Combined Treatment Periods (Periods 2, 3, and 4)	All subjects randomized to ixekizumab at Week 0 (Visit 2) and who received ixekizumab throughout their study participations. The following subjects are not included in this analysis population: (1) patients randomized to etanercept or placebo at Week 0; and (2) patients who are re-randomized to placebo during Period 4 per Protocol Addendum(2).
Ixekizumab Efficacy Secondary Population	Combined Treatment Periods 3 and 4	Patients initially randomized to placebo or etanercept who switch to ixekizumab during Period 3. The following data is not included in this analysis population: (1) patients initially randomized ixekizumab; (2) Period 4 data for patients re-randomized to placebo at Week 60.
All Ixekizumab Safety Population	Combined Treatment Periods.	All subjects who have at least 1 dose of ixekizumab, including patients in main protocol and Protocol Addendum(2).
Follow-Up Population	Post-Treatment Follow-Up Period (Period 5)	Safety analyses for Post-Treatment Follow-Up Period will be conducted on the Follow-Up Population, defined as all randomized subjects who received at least 1 dose of study treatment and have entered the Post-Treatment Follow-Up Period. Patients will be analyzed according to the last treatment they received before entering Period 5.

Abbreviations: EU = European Union.

Table RHCD.6.2. Treatment Groups and Comparisons for Each Study Period and Analysis Population

Study Period	Analysis Population	Treatment Group	Abbreviation	Comparison
Double-Blind Treatment Period (Period 2)	Intent-to-Treat Population; Per-Protocol Set; Safety Population	Ixekizumab Q4W	IXEQ4W	IXEQ4W vs. PBO IXEQ4W vs. ETN ETN vs. PBO
		Etanercept Q1W	ETN	
		Placebo Q4W	PBO	
Randomized-Withdrawal Period (Period 4)	Double-Blind, Randomized Withdrawal Period Population	Ixekizumab Q4W	IXEQ4W	IXEQ4W vs. PBO
		Placebo Q4W	PBO	
Combined Treatment Periods (Period 2, 3, 4)	Ixekizumab Efficacy Primary Population, All Ixekizumab Safety Population	Ixekizumab Q4W	IXEQ4W	NA
Combined Treatment Periods 3 and 4	Ixekizumab Secondary Primary Population	Placebo Q4W/ixekizumab Q4W	PBO/IXE	NA
		Etanercept Q4W/ixekizumab Q4W	ETN/IXE	
Post-Treatment Follow-Up Period (Period 5)	Follow-Up Population	Ixekizumab Q4W	IXEQ4W	No comparison
		Etanercept	ETN	
		Placebo Q4W	PBO	

Abbreviations: ETN = etanercept; IXE = ixekizumab; NA = not applicable; PBO = placebo; Q1W = every week; Q4W = every 4 weeks; vs. = versus.

6.1.2. Baseline Definition

For the Double-Blind Treatment Period (Period 2; ITT Populations), as well as the Combined Treatment Periods (Ixekizumab Efficacy Primary Population and Ixekizumab Efficacy Secondary Population), the baseline for efficacy and health-outcome analyses will be defined as the last available value before the first injection. In most cases, this will be the measure recorded at Week 0 (Visit 2). For efficacy and health-outcome measures, if the patient does not take any injection, the last available value on or prior to randomization date will be used.

Unless, otherwise, specified, baseline for safety during Period 2 is defined as follows: for categorical data, baseline includes all available values before the first injection at Week 0; for continuous data, baseline is the last available value before the first injection at Week 0.

Protocol Addendum I1F-MC-RHCD(2), for the Double-Blind Randomized Withdrawal Period in Subjects in EU Countries, the baseline for efficacy and health-outcome analyses will be defined as the measure recorded at Week 0 (Visit 2). For safety analysis, the baseline is defined as the last available values before the re-randomization (Week 60).

For safety analysis during the Combined Treatment Periods (Periods 2, 3, and 4; Ixekizumab Safety Population): patients who were initially randomized to ixekizumab at Week 0, baseline period is defined as the time from Visit 1 to the date/time of the first injection. For patients initially randomized to placebo or etanercept, baseline is defined as last available value prior to first dose of ixekizumab. For patients who get re-randomized to placebo during the Double-Blind Randomized Withdrawal Period (Protocol Addendum RHCD[2]), they may enter the rescue arm on ixekizumab after relapse. The baseline for this second ixekizumab exposure period will be the last nonmissing value during the placebo exposure period and prior to the ixekizumab injection. For patients who had 2 separate ixekizumab exposures, the baseline for the shift tables and standardized growth analyses in both exposure periods will be defined as the baseline for the first ixekizumab exposure period.

For the Post-Treatment Follow-Up Period (Period 5), the baseline is defined as the last nonmissing assessment on or prior to entering Period 5, that is, on or prior to Week 108, or ETV.

Change from baseline will be calculated as the visit value of interest minus the baseline value. If all baseline values are missing for a particular variable, then the change from baseline and the percent improvement from baseline will not be calculated.

6.1.3. Analysis Methods

6.1.3.1. Double-Blind Treatment Period (Period 2): Main Protocol

The primary analysis method for categorical data for treatment group comparisons will be Fisher's exact test. The difference of the proportions and the 95% CI of the difference will be included.

Secondary analyses for the primary efficacy measures, PASI 75 and sPGA(0,1), and other categorical efficacy and health outcome measures, will be conducted using a logistic regression analysis with treatment group, region, baseline sPGA score (severity of Ps), and baseline weight category (<25 kg, ≥25 to ≤50 kg, or >50 kg) as factors. The odds ratio and the corresponding 95% CI will be reported.

The analyses for the continuous efficacy and health-outcome variables will be made using analysis of covariance (ANCOVA) and mixed model for repeated measures (MMRM) analysis. The ANCOVA model includes treatment group, region, baseline sPGA score, baseline weight category, and baseline value. Type III sums of squares for the least-squares means will be used for the statistical comparison; the 95% CI will be reported.

When the MMRM is used, the model will include treatment, region, baseline sPGA score, baseline weight category, baseline value, visit, treatment-by-visit, and baseline-by-visit interactions as fixed factors. The covariance structure to model the within-subject errors will be unstructured. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III tests for the least-squares means will be used for the statistical comparison; the 95% CI will be reported. Treatment comparisons at Week 12 and all other postbaseline visits will be reported.

If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, followed by the compound symmetry will be used. This order is specified according to a decreasing number of covariance parameters in the structure. The sandwich estimator (Diggle et al. 1994) for the covariance estimation will be used by specifying the EMPIRICAL option in SAS PROC MIXED. When sandwich estimation is used, the Kenward-Roger approximation for denominator degrees of freedom cannot be used. Instead, the DDFM= BETWITHIN option will be used to estimate denominator degrees of freedom.

Fisher's exact test will be used for all adverse events (AEs), baseline characteristics, discontinuation, and other categorical safety data. The continuous baseline characteristics will be analyzed using an analysis of variance (ANOVA) model with treatment as a factor. Continuous vital sign data and laboratory values will be analyzed by an ANCOVA with treatment and baseline value in the model.

6.1.3.2. Double-Blind Treatment Period (Period 2): Protocol Addendum(2)

The analysis method for categorical data for treatment group comparisons will be Fisher's exact test. The difference of the proportions and the 95% CI of the difference will be included.

Fisher's exact test will be used for all AEs, baseline characteristics, discontinuation, and other categorical safety data. The continuous baseline characteristics will be analyzed using an ANOVA model with treatment as a factor. Continuous vital sign data and laboratory values will be analyzed by an ANCOVA with treatment and baseline value in the model.

6.1.3.3. Combined Treatment Periods

Data for the combined treatment periods will be summarized using descriptive statistics.

6.1.3.4. Double-Blind Randomized Withdrawal Period (Period 4)

The time to relapse (loss of response; sPGA ≥2) during Double-Blind, Randomized Withdrawal Period (Period 4) is defined as:

$$Time\ to\ relapse\ (days)$$

$$= date\ of\ first\ sPGA \geq 2\ during\ \text{Period 4} - date\ of\ Week\ 60\ rerandomization + 1$$

If a patient has not experienced relapse by completion or early discontinuation of Period 4, the patient will be censored at the date of his/her last visit during Period 4.

The number of patients at risk and experiencing a relapse event by each scheduled visit during Period 4 will be presented by treatment group. The Kaplan-Meier estimate of the proportion of patients relapsing will be presented for each visit. Treatment group comparisons will be performed using the log-rank test. For each treatment group, a Kaplan-Meier plot of the time to relapse will be provided.

The analysis method for categorical data for treatment group comparisons will be Fisher's exact test. The difference of the proportions and the 95% CI of the difference will be included.

Fisher's exact test will be used for all AEs, baseline characteristics, discontinuation, and other categorical safety data. The continuous baseline characteristics will be analyzed using an ANOVA model with treatment as a factor. Continuous vital sign data and laboratory values will be analyzed by an ANCOVA with treatment and baseline value in the model.

6.2. Adjustments for Covariates

Clinical Protocol RHCD (main study), the randomization at the beginning of the Double-Blind Treatment Period (Period 2) is stratified by geographic region. With the exception of the primary analysis (that is, Fisher's exact test), efficacy and health-outcome analyses during Period 2 will include geographic region and baseline weight category in the analysis models.

In general, when an MMRM is to be used for analyses, baseline value and baseline-by-visit interactions will be included as covariates; when an ANCOVA is to be used for analyses, baseline value will be included as a covariate.

Protocol Addendum RHCD(2), for the double-blind randomized withdrawal period (Period 4), subjects were re-randomized to ixekizumab according to their weight at the time of re-randomization. The stratification factor, weight at the time of re-randomization, will not be included in the analysis models.

6.3. Handling of Dropouts or Missing Data

The methods for imputation of missing data to be used in this study are in accordance with the precedent set in other Phase 3 Ps trials (Leonardi et al. 2008; Papp et al. 2008) and ixekizumab Phase 3 pivotal studies (RHAZ, RHBA, and RHBC).

6.3.1. Nonresponder Imputation (NRI)

Analysis of categorical efficacy and health-outcome variables will be assessed using a NRI method. Subjects will be considered nonresponders for the NRI analysis if they do not meet the clinical response criteria or have missing clinical response data at the analysis time point. Randomized patients without at least 1 postbaseline observation will also be defined as nonresponders for the NRI analysis.

6.3.2. Last Observation Carried Forward (LOCF)

An LOCF analysis will be performed on all continuous efficacy and health-outcome variables as a secondary analysis. For patients having missing data at the visit, the last nonmissing postbaseline observation before the missing data will be carried forward to the corresponding

time point for evaluation. Subjects who have a baseline and at least 1 postbaseline observation will be included for evaluation.

6.4. Multicenter Studies

This study will be conducted by multiple investigators at multiple sites internationally. Data from the sites are pooled within geographic region. Unless, otherwise, specified, geographic region will be included in the statistical analysis models. The co-primary endpoints at Week 12 will be summarized by center using descriptive statistics only.

6.5. Multiple Comparisons/Multiplicity

A multiple testing strategy for the primary and major secondary objectives will be implemented to control the family-wise type I error rate at a 2-sided α level of 0.05. The primary and key secondary comparisons will be tested by using the primary analysis method, Fisher's exact test, with an NRI missing-data imputation approach.

A gatekeeping approach will be used for multiple comparisons to control the family-wise error rate. To assess whether ixekizumab Q4W is superior to placebo, the following endpoints will be tested:

- Primary 1: Proportion of subjects achieving PASI 75 at Week 12
- Primary 2: Proportion of subjects achieving sPGA (0,1) at Week 12
- Secondary 1: Proportion of subjects achieving PASI 90 at Week 12
- Secondary 2: Proportion of subjects achieving sPGA (0) at Week 12
- Secondary 3: Proportion of subjects achieving PASI 100 at Week 12
- Secondary 4: Proportion of subjects achieving ≥4 point improvement for subjects who had a baseline Itch numeric rating scale (NRS) ≥4 at Week 12
- Secondary 5: Proportion of subjects achieving PASI 75 at Week 4
- Secondary 6: Proportion of subjects achieving sPGA (0,1) at Week 4

The Primary 1 will first be tested at 2-sided α=0.05. If successful, the test for Primary 2 will be performed at 2-sided α=0.05. Otherwise, the test will stop. If the Primary 2 endpoint is successful, the Secondary 1 endpoint will be tested. The test will continue to the last endpoint if all the prior tests are successful. If a test is not successful, all subsequent tests will not be tested.

6.6. Use of an "Efficacy Subset" of Patients

The PPS is defined above in Section 6.1.1 and is an efficacy subset of patients. The analysis of the co-primary endpoints will be repeated using the PPS.

6.7. Patient Disposition

Patient flow will be summarized from entered to randomized to completion, and analysis populations will be listed and summarized by treatment group.

Patient disposition from study will be listed and summarized with reasons for disposition for the ITT Population and the Follow-Up Population, respectively.

Patient disposition from study treatment will be listed and summarized for the ITT Population for the Double-Blind Treatment Period (Period 2) and the ITT Population of etanercept approved countries for the Double-Blind Treatment Period (Period 2) in Protocol Addendum RHCD(2) with reasons for disposition, which will be compared between and among treatment groups using Fisher's exact test.

Time to study treatment discontinuation due to any reason (in weeks) will be summarized by treatment group and graphically presented using Kaplan-Meier technique. The log-rank test will be used to compare time to study treatment discontinuation between treatment groups. Time to study treatment discontinuation will be calculated as:

$$\frac{Date\ of\ study\ treatment\ discontinuation - Date\ of\ first\ dose + 1}{7}$$

If the date of first dose is missing, the date of randomization will be used. Patients completing the study treatment will be censored at the date of completion.

Patient allocation by region, country, and center/site will be summarized with number of patients who entered the study, number of ITT patients for each dosing regimen, number of patients discontinued from study treatment, and number of patients discontinued from study.

6.8. Patient Characteristics

6.8.1. Demographics and Baseline Characteristics

Patient demographic variables and baseline characteristics will be summarized by treatment group and, overall, for the ITT Population and the ITT Population – etanercept-approved countries and the Double-Blind, Randomized Withdrawal Period Population. The continuous variables will be summarized using descriptive statistics, and the categorical variables will be summarized using frequency counts and percentages. The comparisons between treatment groups will be conducted using the Fisher's exact test for categorical data, and an analysis of variance model with treatment group as a factor for continuous data.

The following demographic variables and baseline characteristics will be summarized:

- Age (years)
- Age category: <12 years; and ≥12 years
- Gender
- Ethnicity
- Race
- Weight (kg): measured at Visit 2
- Weight Category: <25 kg; ≥25 to ≤50 kg; and >50 kg
- Height (cm): measured at Visit 1
- Body mass index (BMI) (kg/m^2): BMI will be calculated as:

$$BMI\ (kg/m^2) = \frac{Weight(kg)}{\left(Height(m)\right)^2}$$

- Habits (only for subjects ≥12 years old)

  - Caffeine consumption: never; current; former
  - Alcohol consumption: never; current; former
  - Tobacco consumption: never; current; former
- Country: Argentina, Canada, Czech Republic, France, Germany, Hungary, Mexico, Netherlands, Poland, Russia, Spain, United States
- Geographic region:
  - United States/Canada (United States, Canada)
  - European Union (Czech Republic, France, Germany, Hungary, Netherlands, Poland, Spain)
  - Rest of the world (Argentina, Mexico, Russia)
- Geographic region:
  - United States/Canada (United States, Canada)
  - Other
- Previous systemic therapy: never used; nonbiologic only; biologic only; biologic and nonbiologic.
  - Nonbiologics are defined as: methotrexate; cyclosporine; corticosteroids; acitretin; fumaric-acid derivatives; apremilast; or other nonbiologics
  - Biologics are defined as: efalizumab; ustekinumab; infliximab; etanercept; alefacept; adalimumab; golimumab; certolizumab pegol; secukinumab; or other biologics
- Tuberculosis (TB) exposure: positive; negative
- Age at Ps onset (in years)
- Duration of Ps (in years): will be calculated using the date of Ps onset (as recorded on the Prespecified Medical History - Psoriasis electronic case report form [eCRF] page) as follows:

$$Duration\ of\ psoriasis\ (years) = \frac{Date\ of\ informed\ consent - Date\ of\ psoriasis\ onset}{365.25}$$

- Age at psoriasis diagnosis (in years)
- Duration of psoriasis diagnosis (in years): will be calculated using the date of psoriasis diagnosis (as recorded on the Prespecified Medical History – Psoriasis eCRF page) as follows:

$$Duration\ of\ psoriasis\ diagnosis\ (years) = \frac{Date\ of\ Visit\ 2 - Date\ of\ psoriasis\ diagnosis}{365.25}$$

- Baseline sPGA
- Baseline sPGA category: 3; 4; and5
- Baseline sPGA category: 3; and combined 4 or 5
- Baseline PASI score
- Baseline PASI category: <20; and ≥20
- Baseline BSA (%)
- Baseline BSA category: <20%; and ≥20%
- Nail psoriasis: yes; and no

- Baseline Nail Psoriasis Severity Index (NAPSI) score
- Scalp psoriasis: yes; and no
- Baseline Psoriasis Severity Index (PSSI) score
- Palmoplantar psoriasis: yes; and no
- Baseline Palmoplantar Psoriasis Severity Index (PPASI) score
- Baseline Itch NRS score
- Baseline Itch NRS category: <4; and ≥4
- Baseline Children's Dermatology Life Quality Index (CDLQI) total score
- Baseline Dermatology Life Quality Index (DLQI) total score
- Patient's Global Assessment of Disease Severity (PatGA)
- PatGAcategory: 0; 1; 2; 3; 4; and 5
- Baseline Children's Depression Rating Scale, Revised (CDRS-R)
- Baseline CDRS-R category: ≤28; 29-39; and ≥40
- Baseline Columbia Suicide Severity Rating Scale (C-SSRS)
- Binary questions on psoriasis location
- Tanner Stage Scale

By-patient listings of demographic and baseline characteristics, respectively, for the ITT Population will be provided.

6.8.2. Historical Illnesses and Preexisting Conditions

Historical illnesses and preexisting conditions will be classified using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Historical illness/condition is defined as the condition/event recorded on the Pre-Existing Conditions and Medical History eCRF page or on the Prespecified Medical History eCRF page with an end date prior to the date of informed consent.

A preexisting condition is defined as the condition/event recorded on the Pre-Existing Conditions and Medical History eCRF page or on the Prespecified Medical History eCRF page with a start date prior to the date of informed consent, and no end date (that is, the event is ongoing) or an end date on or after the date of informed consent. Adverse events occurring prior to the date of first study injection will also be reported. Note that, if a preexisting condition worsens in severity on or after the date of informed consent, it will be recorded as an AE on Adverse Events eCRF page from the date of worsening onward.

The following summaries will be provided for both ITT Populations:

- The number and percentage of patients with historical illnesses by treatment group and overall, by System Organ Class (SOC) and preferred term (PT).
- The number and percentage of patients with preexisting conditions and adverse events occurring prior to the first dose, by treatment group and overall, by SOC and PT.
- The number and percentage of patients with prespecified medical history (hypertension; diabetes mellitus, Type I; diabetes mellitus, Type II; dyslipidemia; psoriatic arthritis;

inflammatory bowel disease [Crohn's disease and uncreative colitis]), by treatment group and overall.

For a condition/event that is gender-specific (as defined by MedDRA), the denominator and computation of the percentage will include only patients from the given gender.
The comparisons among treatment groups will be conducted using Fisher's exact test.

By-patient listings of historical illnesses and preexisting conditions, respectively, for the ITT Populations will be provided.

6.9. Treatment Compliance

By-patient listings of randomization schedules and study drug dispensed (include the clinical trial (CT) Lot number), respectively, for the ITT Populations will be provided.

Throughout treatment periods, randomized patients will record information in a Study Drug Administration Log (captured in the Exposure as Collected eCRF page), including the date, time, and anatomical location of administration of investigational product, syringe number, who administered the investigational product, and the reason if the investigational product was not fully administered.

Treatment compliance for each patient per period will be calculated as:

$$Treatment\ compliance\ (\%) = 100\ \times \frac{Total\ number\ of\ injections\ administered}{Total\ number\ of\ injections\ prescribed}$$

Clinical Protocol RHCD:

- For patients who complete Period 2 and receive ixekizumab 20 mg or 40 mg or placebo for ixekizumab 20 mg or 40 mg, the number of injections prescribed (that is, expected) during Period 2 will be equal to 3 (1 injection at Week 0 and 1 injection at Weeks 4 and 8).
  For patients who complete Period 2 and receive ixekizumab 80 mg or placebo for ixekizumab 80 mg, the number or injections prescribed during Period 2 will be equal to 4 (2 injections at Week 0 and 1 injection at Weeks 4 and 8).
- For patients who discontinue during Period 2, the number of injections prescribed during Period 2 can be derived from the IWRS study drug dispense dataset.

Protocol Addendum RHCD(2):

- The number of injections for ixekizumab group and placebo group are the same as in the main study ITT Population. For patients who complete Period 2 and receive etanercept, the number of injections prescribed during period 2 will be equal to 12 (1 injection every week from Week 0 to Week 11).
- For patients who discontinue during Period 2, the number of injections prescribed during Period 2 can be derived from the IWRS study drug dispense dataset.

A patient will be considered overall compliant with study treatment within each treatment period if he/she misses no more than 20% of the expected doses, does not miss 2 consecutive doses, and

does not overdose (that is, take more injections at the same time point than specified in the protocol).

Patient treatment compliance, by Period 2, will be summarized. The comparisons between treatment groups during Period 2 will be conducted using Fisher's exact test.

A by-patient listing of study treatment administration and compliance for the ITT Population will be provided.

6.10. Previous and Concomitant Therapy

Medication/therapy will be classified into Anatomical Therapeutic Chemical (ATC) drug classes using the latest version of the World Health Organization (WHO) Drug Dictionary.

A by-patient listing of previous and concomitant therapy, and a by-patient listing of previous Ps therapy for the ITT Population will be provided.

6.10.1. Previous Therapy

Previous therapy is defined as therapy that starts and ends prior to the date of first dose of study treatment in the Double-Blind Treatment Period (Period 2). If therapy start and/or end dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study treatment in Period 2. If there is clear evidence to suggest that the therapy stopped prior to the first dose of study treatment in Period 2, the therapy will be assumed to be previous dose only. The comparisons will be conducted using Fisher's exact test.

The following summaries will be provided for both ITT populations:

- Previous therapy (captured in the Prior Therapy: Psoriasis eCRF page and Concomitant Therapy eCRF page) by WHO ATC Level 4 and WHO PT.
- Previous Ps therapy captured in the Prior Therapy: Psoriasis eCRF page to be summarized according to type (topical prescription therapy, topical nonprescription therapy, nonbiologic systemic agent, biologic agent, nonbiologic nonsystemic agent, phototherapy) and therapy. The previous biologic agent will be further classified as tumor necrosis factor- (TNF-) α inhibitor (includes infliximab, etanercept, adalimumab, golimumab, certolizumab pegol), interleukin- (IL-) 12/23 inhibitor (includes ustekinumab), IL-17 inhibitor (includes secukinumab and brodalumab), and other (includes efalizumab, alefacept, or other biological agents).
- The number and percentage of patients with each reason for discontinuation of previous Ps therapy to be summarized by type and therapy.

6.10.2. Concomitant Therapy

Concomitant therapy is defined as the therapy that starts before, on, or after the first day of study treatment in the defined treatment period and before the last visit date in the treatment period, and continues into the treatment period, that is, either no end date (the therapy is ongoing) or an end date on or after the first day of study treatment in treatment period. Note, concomitant

therapy will belong to a treatment period if the therapy starts and ends on the exact same day as the first day of study treatment of the treatment period.

Concomitant therapy during period 2 will be summarized by both ITT populations. Concomitant therapy for Period 2 is defined as the therapy that starts before, on, or after the first day of study treatment of Period 2 and before the last visit date of Period 2, and continues into Period 2, that is, there is either no end date (the therapy is ongoing) or there is an end date on or after the first day of study treatment of Period 2. Note that concomitant therapy will belong to Period 2 if the therapy starts and ends on the exact same day as the first day of study treatment of Period 2.

Concomitant therapy during period 4 will be summarized by the Double-Blind Randomized Withdrawal Period Population. Concomitant therapy for Period 4 is defined as the therapy that starts before, on, or after the first day of study treatment of Period 4 and before the last visit date of Period 4, and continues into Period 4, that is, there is either no end date (the therapy is ongoing) or there is an end date on or after the first day of study treatment of Period 4. Note that concomitant therapy will belong to Period 4 if the therapy starts and ends on the exact same day as the first day of study treatment of Period 4.

The comparisons will be conducted using Fisher's exact test.

The following summaries will be provided:

- Concomitant therapy by WHO ATC Level 4 and WHO PT
- The number and percentage of patients taking concomitant therapy of a topical product to be summarized for topical and topical steroid therapies, respectively, by WHO ATC Level 4 and WHO PT. The definition of concomitant topical therapy can be found in Appendix 1. Please refer to I1F-MC-RHCD Clinical Protocol Section 7.7 for concomitant therapies permitted during the study.
- The number and percentage of patients who received premedication for allergic reaction/hypersensitivity captured in the Allergic/Hypersensitivity Reaction Follow-Up eCRF page.

If a partial or completely missing medication start date/time or end date/time is present, the following imputation rules will be utilized in the analysis:

- For the start date:
    - If year, month, and day are missing, then use the earlier of the patient's first visit date or the consent date.
    - If either month or month and day are missing, then use January 1.
    - If only day is missing, impute the first day of the month.
- For the start time:
    - Impute as 23:59
- For the end date:
    - If year, month, and day are missing, then use the patient's last visit date.
    - If either month or month and day are missing, then use December 31.
    - If only day is missing, then use the last day of the month.

  - The imputed date will not be beyond the patient's last visit date.
- For the end time:
  - Impute as 23:59.
- If there is any doubt, the medication will be flagged as concomitant.

6.11. Efficacy Analyses

Table RHCD.6.3 includes the description and derivation of the primary and secondary efficacy outcomes. Table RHCD.6.4 includes the description of primary and secondary efficacy analyses.

Table RHCD.6.3. Description and Derivation of Primary and Secondary Efficacy Outcomes

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
PASI	Psoriasis Area and Severity Index (PASI): combines assessments of the extent of body-surface involvement in 4 anatomical regions (head and neck, trunk, arms, and legs) and the severity of scaling (S), redness (R), and plaque induration/infiltration (thickness, T) in each region, yielding an overall score of 0 for no psoriasis to 72 for the most severe disease (Fredriksson and Pettersson 1978). Severity is rated for each index (R, S, T) on a 0-4 scale (0 for no involvement up to 4 for severe involvement): 0 = none 1 = slight 2 = mild 3 = moderate 4 = severe The body is divided into four anatomical regions comprising the head (h), upper limb (u), trunk (t), and lower limb (l). In each of these areas, the fraction of total body surface area affected is graded on a 0-6 scale (0 for no involvement up to 6 for 90% - 100% involvement): 0 = 0% (clear) 1 = >0% to <10% 2 = 10% to <30% 3 = 30% to <50% 4 = 50% to <70% 5 = 70% to <90% 6 = 90% to 100% The various body regions are weighted to	PASI score	The composite PASI score is calculated by multiplying the sum of the individual-severity scores for each area by the weighted area-of-involvement score for that respective area, and then summing the 4 resulting quantities as follows: PASI = 0.1(Rh + Th + Sh)Ah + 0.2(Ru + Tu + Su)Au + 0.3(Rt + Tt + St)At + 0.4(Rl + Tl + Sl)Al, where: Rh, Ru, Rt, Rl = redness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4 respectively; Th, Tu, Tt, Tl = thickness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4 respectively; Sh, Su, St, Sl = scaliness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4 respectively; Ah, Au, At, Al = numerical value translation of % area of psoriatic involvement score for the head, upper limb, trunk, and lower limb, respectively. PASI scores are treated as a continuous score, with 0.1 increments within these values.	If any individual score is missing, the PASI score will not be calculated, hence, missing.
		PASI change from baseline	Calculated as: observed PASI – baseline PASI	Missing if baseline or observed value is missing.
		PASI percent improvement from baseline	Calculated as: $Percent\ improvement\ from\ baseline = 100 \times \frac{Baseline\ PASI - Observed\ PASI}{Baseline\ PASI}$ If a patient has experienced an improvement, this measure will be positive. If a patient has experienced a worsening in the condition, this measure will be	Missing is baseline or observed value is missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	reflect their respective proportions of body surface area (BSA).		negative.	
		PASI 75 (co-primary)	A clinically meaningful response; at least a 75% improvement in PASI score from baseline.	Missing is baseline or observed value is missing
		PASI 90	Higher level of clearance; at least a 90% improvement in PASI score from baseline.	Missing is baseline or observed value is missing
		PASI 100	Complete resolution of plaque psoriasis; a 100% improvement in PASI score from baseline.	Missing is baseline or observed value is missing
sPGA	Static Physician Global Assessment (sPGA): the physician's global assessment of the patient's psoriasis lesions at a given time point (EMA 2004 [WWW]). Plaques are assessed for induration, erythema, and scaling, and an overall rating of psoriasis severity is given using the anchors of clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).	sPGA score	Range from 0 to 5: clear (0); minimal (1); mild (2); moderate (3); severe (4); or very severe (5).	Single item, missing if missing
		sPGA (0,1) (co-primary)	An sPGA assessed as either 0 or 1, which represents a clinically meaningful response of minimal plaque severity or complete resolution of plaque psoriasis.	Missing if sPGA is missing
		sPGA (0)	An sPGA assessed as 0, which represents a clinically important endpoint indicating complete resolution of plaque psoriasis.	Missing if sPGA is missing
BSA	Percentage of BSA: The investigator will evaluate the percentage involvement of psoriasis on each patient's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), in which 1% corresponds to the size of the patient's hand (including the palm, fingers, and thumb) (Van Voorhees et al. 2009).	BSA	Collected as a single scale as part of PASI electronic case report form (eCRF) page. Range from 0% to 100%.	Missing is baseline or observed value is missing
		BSA change from baseline	Calculated as: observed BSA – baseline BSA	Missing is baseline or observed value is missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
NAPSI	Nail Psoriasis Severity Index (NAPSI): will be used if the patient has nail psoriasis at baseline. The NAPSI is a numeric, reproducible, objective tool for evaluation of nail psoriasis. This scale is used to evaluate the severity of nail bed psoriasis and nail matrix psoriasis by area of involvement in the nail unit. In this study, both fingernail and toenail involvement will be assessed. The nail is divided with imaginary horizontal and longitudinal lines into quadrants. Each nail is given a score for nail bed psoriasis (0 to 4) and nail matrix psoriasis (0 to 4), depending on the presence (score of 1) or absence (score of 0) of any of the features of nail bed and nail matrix psoriasis in each quadrant: 0 = None 1 = present in one quadrant of nail 2 = present in two quadrants of nail 3 = present in three quadrants of nail 4 = present in four quadrants of nail	NAPSI score	The NAPSI score of a nail is the sum of scores in nail bed and nail matrix from each quadrant (maximum of 8). Each nail is evaluated, and the sum of all the fingernails and toenails is the total NAPSI score (range, 0 to 160), usually indicated as NAPSI score.	For each nail, if either bed or matrix score is missing or not done, the score for that nail is missing. If <50% of the nail scores from 20 nails are missing, the imputation will be performed by using the average score of the remaining nails. If ≥50% of the nail scores are missing, the NAPSI score will be left as missing.
		NAPSI score change from baseline	Calculated as: observed NAPSI – baseline NAPSI	Missing if baseline or observed value is missing
		NAPSI score = 0	A NAPSI response is defined as a NAPSI score of 0, which is also referred to as nail clearance.	Missing if NAPSI score is missing.
PSSI*	Psoriasis Scalp Severity Index (PSSI): will be used if the patient has scalp psoriasis at baseline. The scalp will be assessed for erythema (redness), induration (hardness), and desquamation (shedding of skin) and percentage of area affected as follows: Erythema, Induration and Desquamation: 0 = Absent	PSSI score	The PSSI score is a composite score derived from the sum of the scores for erythema, induration and desquamation multiplied by the score for the extent of scalp area involved (percent of scalp involved). The range is 0 to 72.	If any individual score is missing, the PSSI score will not be calculated, hence, missing.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	1 = Slight 2 = Moderate 3 = Severe 4 = Severest Possible Percent of Scalp Involved: 1 = <10% 2 = 10% – 29% 3 = 30% – 49% 4 = 50% – 69% 5 = 70% – 89% 6 = 90% – 100%	PSSI score change from baseline	Calculated as: observed PSSI – baseline PSSI	Missing if baseline or observed value is missing
		PSSI score = 0	A PSSI response is defined as a PSSI score of 0, which is also referred to as scalp clearance.	Missing if PSSI score is missing.
PPASI	Palmoplantar Psoriasis Area and Severity Index (PPASI): will be used if the patient has palmoplantar psoriasis at baseline. Both the palms and soles on each hand and foot will be individually assessed for erythema, induration, desquamation and percentage of area affected as follows: Erythema (E), Induration (I), and Desquamation (D): 0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very Severe Percent of Palm and Sole Area Covered: 0 = None 1 = <10% 2 = 10% – 29% 3 = 30% – 49% 4 = 50% – 69% 5 = 70% – 89%	PPASI score	The PPASI score is a composite score derived from the sum scores for erythema, induration, and desquamation multiplied by a score for the extent of palm and sole area involvement. The range is 0 to 72. PPASI = 0.2(Erp +Irp +Drp)Arp + 0.2(Elp +Ilp+Dlp)Alp + 0.3(Ers +Irs+Drs)Ars + 0.3(Els +Ils+Dls)Als, where: Erp, Elp, Ers, Els = Erythema score of plaques on the right palm (rp), left palm (lp), right sole (rs), left sole (ls), scored 0-4 respectively; Irp, Ilp, Irs, Ils = Induration score of plaques on the right palm (rp), left palm (lp), right sole (rs), left sole (ls), scored 0-4 respectively; Drp, Dlp, Drs, Dls = Desquamation score of plaques on the right palm (rp), left palm (lp), right sole (rs), left sole (ls), scored 0-4 respectively; Arp, Alp, Ars, Als = numerical value translation of % area covered for the right palm, left palm, right sole, and left sole, respectively.	If any individual score is missing, the PPASI score will not be calculated, hence, missing.
		PPASI change	Calculated as: observed PPASI – baseline PPASI	Missing if baseline or

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	6 = 90% – 100%	from baseline		observed value is missing
		PPASI percent improvement from baseline	Calculated as: $Percent\ improvement\ from\ baseline = 100 \times \frac{Baseline\ PPASI - Observed\ PPASI}{Baseline\ PPASI}$ If a patient has experienced an improvement, this measure will be positive. If a patient has experienced a worsening in the condition, this measure will be negative.	Missing is baseline or observed value is missing
		PPASI 50	At least a 50% improvement in PPASI score from baseline.	Missing is baseline or observed value is missing
		PPASI 75	At least a 75% improvement in PPASI score from baseline.	Missing is baseline or observed value is missing
		PPASI 100	A 100% improvement in PPASI score from baseline.	Missing is baseline or observed value is missing
Binary questions on psoriasis location	The presence of visible psoriasis on the following locations will be noted: 1. Face 2. Nail 3. Axilla 4. Genitals 5. Perianal region	Binary questions on psoriasis location	Binary responses (yes/no) will be noted to determine the presence of visible psoriasis on each of the 5 locations.	Missing if the response is missing

* A previous version of PSSI questionnaire was sent to the sites with percent of scalp involved range 1 to 6. Some sites still enter 0 to represent none scalp psoriasis involvement. The range of the total score is still 0 – 72, so that there is no impact on planned analyses.

Table RHCD.6.4. Description of Primary and Secondary Efficacy Analyses

Measure	Variable	Analysis (Method)	Population	Comparison/Time Point	Analysis Type
PASI	PASI 75 (co-primary)	Fisher's exact test with NRI (primary analysis) Logistic regression with NRI	ITT Population	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2.	Primary analysis is Fisher's exact test with NRI for ITT Population comparing ixekizumab and placebo at Week 12. Secondary analysis is logistic regression with NRI for ITT Population comparing ixekizumab and placebo at Week 12.
		Fisher's exact test with NRI Logistic regression with NRI	Per-Protocol Set	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2.	Additional analysis for co-primary outcomes.
	PASI 75	Fisher's exact test with NRI Logistic regression with NRI	ITT Population	Ixekizumab Q4W vs. placebo at Week 4.	Gated secondary analysis
			ITT Population - Etanercept-approved countries	All pairwise comparisons at Week 12 and all other postbaseline visits during Period 2.	Other secondary analysis
	PASI 90	Fisher's exact test with NRI Logistic regression with NRI	ITT Population	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2.	Gated secondary analysis comparing ixekizumab Q4W vs. Placebo at Week 12.
	PASI 100	Fisher's exact test with NRI Logistic regression with NRI	ITT Population	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2.	Gated secondary analysis comparing ixekizumab Q4W vs. Placebo at Week 12.
	PASI 50	Fisher's exact test with NRI Logistic regression with NRI	ITT Population	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2.	Other secondary analysis

Measure	Variable	Analysis (Method)	Population	Comparison/Time Point	Analysis Type
	Change from baseline, percent improvement	ANCOVA with LOCF; MMRM	ITT Population	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2.	Other secondary analysis
	PASI 75 PASI 90 PASI 100	Summarize	Ixekizumab Efficacy Primary Population	At all postbaseline visits during the Combined Treatment Periods (Periods 2, 3, and 4).	Other secondary analysis/ Exploratory analysis
			Ixekizumab Efficacy Secondary Population	At all postbaseline visits during the Combined Treatment Periods (Periods 3 and 4).	Exploratory analysis
		Fisher's exact test	Double-Blind, Randomized Withdrawal Population	Ixekizumab Q4W vs. placebo at all postbaseline visits during Period 4.	Other secondary analysis
sPGA	sPGA (0,1) (co-primary)	Fisher's exact test with NRI (primary analysis); Logistic regression with NRI	ITT Population	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2.	Primary analysis is Fisher's exact test with NRI for ITT Population comparing ixekizumab and placebo at Week 12. Secondary analysis is logistic regression with NRI for ITT Population comparing ixekizumab and placebo at Week 12.
		Fisher's exact test with NRI Logistic regression with NRI	Per-Protocol Set	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2.	Additional analysis for co-primary outcomes.
	sPGA (0,1)	Fisher's exact test with NRI Logistic regression with NRI	ITT Population	Ixekizumab Q4W vs. placebo at Week 4.	Gated secondary analysis
			ITT Population - Etanercept approved	Ixekizumab Q4W vs. etanercept at Week 12 and all	Other secondary analysis

Measure	Variable	Analysis (Method)	Population	Comparison/Time Point	Analysis Type
			countries	other postbaseline visits during Period 2.	
			Double-Blind, Randomized Withdrawal Period Population	Ixekizumab Q4W vs. placebo at Week 108 and all other postbaseline visits during Period 4.	Other secondary analysis
	sPGA (0)	Fisher's exact test with NRI Logistic regression with NRI	ITT Population	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2.	Gated secondary analysis
	sPGA (0,1) sPGA (0)	Fisher's exact test with NRI Logistic regression with NRI	ITT Population	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2.	Other secondary analysis
	sPGA (0,1) sPGA (0)	Summarize	Ixekizumab Efficacy Primary Population	At all postbaseline visits during the Combined Treatment Periods (Periods 2, 3, and 4).	Other secondary analysis/ Exploratory analysis
			Ixekizumab Efficacy Secondary Population	At all postbaseline visits during the Combined Treatment Periods (Periods 3 and 4)	Exploratory analysis
	Time to relapse to sPGA ≥2	Log-rank test Kaplan-Meier estimate	Double-Blind, Randomized Withdrawal Period Population	Ixekizumab Q4W vs. placebo during the Double-Blind Randomized Withdrawal Period.	Other secondary analysis
BSA	Change from baseline	ANCOVA with LOCF; MMRM	ITT Population	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2.	Other secondary analysis

Measure	Variable	Analysis (Method)	Population	Comparison/Time Point	Analysis Type
NAPSI	Change from baseline	ANCOVA with LOCF MMRM	ITT Population – patients with baseline nail involvement (NAPSI baseline score >0)	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2.	Other secondary analysis
	NAPSI score = 0	Fisher exact test with NRI Logistic regression with NRI	ITT Population – patients with baseline nail involvement (NAPSI baseline score >0)	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2.	Exploratory analysis
PSSI	Change from baseline	ANCOVA with LOCF; MMRM	ITT Population – patients with baseline scalp involvement (PSSI baseline score >0)	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2.	Other secondary analysis
	PSSI score = 0	Fisher's exact test with NRI Logistic regression with NRI	ITT Population – patients with baseline scalp involvement (PSSI baseline score >0)	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2.	Exploratory analysis
PPASI	Change from baseline	ANCOVA with LOCF; MMRM	ITT Population – patients with baseline palmoplantar involvement (PPASI baseline score >0)	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2.	Other secondary analysis
	PPASI 50 PPASI 75 PPASI 100	Fisher's exact test with NRI Logistic regression with NRI	ITT Population – patients with baseline palmoplantar involvement (PPASI baseline score >0)	Ixekizumab Q4W vs. placebo at Week 12 and at each postbaseline visit during Period 2.	Exploratory analysis
Binary questions on psoriasis location	Proportion of patients with no psoriasis presence on face	Fisher's exact test with NRI Logistic regression with NRI	ITT Population – patients with psoriasis presence on face at baseline	Ixekizumab Q4W vs. placebo at Week 12.	Other secondary analysis

Measure	Variable	Analysis (Method)	Population	Comparison/Time Point	Analysis Type
	Proportion of patients with no psoriasis presence on nail	Fisher's exact test with NRI Logistic regression with NRI	ITT Population – patients with psoriasis presence on nail at baseline	Ixekizumab Q4W vs. placebo at Week 12.	
	Proportion of patients with no psoriasis presence on axilla	Fisher's exact test with NRI Logistic regression with NRI	ITT Population – patients with psoriasis presence on axilla at baseline	Ixekizumab Q4W vs. placebo at Week 12.	
	Proportion of patients with no psoriasis presence on genital	Fisher's exact test with NRI Logistic regression with NRI	ITT Population – patients with psoriasis presence on genital at baseline	Ixekizumab Q4W vs. placebo at Week 12.	
	Proportion of patients with no psoriasis presence on perianal region	Fisher's exact test with NRI Logistic regression with NRI	ITT Population – patients with psoriasis presence on perianal region at baseline	Ixekizumab Q4W vs. placebo at Week 12.	

Abbreviations: ANCOVA = analysis of covariance; BSA = body surface area; ITT = intent-to-treat; LOCF = last observation carried forward; MMRM = mixed-effects model of repeated measures; NAPSI = Nail Psoriasis Severity Index; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; PASI 50/75/90 = at least a 50%/75%/90% improvement from baseline in PASI score; PASI 100 = a 100% improvement from baseline in PASI score; PPASI = Palmoplantar Psoriasis Area and Severity Index; PPASI 50/75 = at least a 50%/75% improvement from baseline in PPASI score; P)PASI 100 = a 100% improvement from baseline in PPASI score; PSSI = Psoriasis Scalp Severity Index; Q4W = every 4 weeks; sPGA = static Physician Global Assessment; vs. = versus.

6.11.1. Co-Primary Outcome and Primary Analysis Methodology

The co-primary outcomes are:

- Proportion of patients achieving PASI 75
- Proportion of patients achieving sPGA (0,1)

The primary analysis will be based on the ITT Population for the Double-Blind Treatment Period (Period 2) comparing ixekizumab versus placebo at Week 12. The primary analysis is Fisher's exact test. Missing data will be imputed using the NRI method. The secondary analyses for the primary efficacy measures will be conducted using a logistic regression with treatment group, region, baseline sPGA score (severity of the Ps), and baseline weight category (<25kg; ≥25 to ≤50 kg; or >50 kg) as factors. Missing data will be imputed using the NRI method.

6.11.2. Gated Secondary Efficacy Analyses

The gated secondary outcomes are:

- Proportion of patients achieving PASI 90 at Week 12
- Proportion of patients achieving an sPGA (0) at Week 12
- Proportion of patients achieving PASI 100 at Week 12
- Proportion of subjects achieving ≥4-point improvement for subjects who had a baseline Itch NRS ≥4 at Week 12
- Proportion of patients achieving PASI 75 at Week 4
- Proportion of patients achieving sPGA (0,1) at Week 4

The gated secondary analyses will be based on ITT Population for the Double-Blind Treatment Period (Period 2) comparing ixekizumab versus placebo. The analysis will be Fisher's exact test. Missing data will be imputed using the NRI method.

6.11.3. Additional Analyses of the Co-Primary Outcome

There will be no adjustment for multiple comparisons for additional analyses of the co-primary outcomes.

To support the primary efficacy analysis, the co-primary outcomes, PASI 75 and sPGA (0,1), will be analyzed based on the PPS Population for the Double-Blind Treatment Period (Period 2), comparing ixekizumab versus placebo at Week 12 using Fisher's exact test with NRI.

6.11.4. Other Secondary Efficacy Analyses

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

The other secondary efficacy variables include:

- PASI 50, PASI 90, PASI 100, PASI change from baseline percent improvement

- sPGA (0)
- NAPSI change from baseline
- PSSI change from baseline
- PPASI change from baseline

The other secondary analyses for the Double-Blind Treatment Period (Period 2) will be based on the ITT Population, except (refer to Table RHCD.6.4):

- NAPSI: based on ITT Population – patients with baseline nail involvement (NAPSI baseline score >0)
- PSSI: based on ITT Population – patients with baseline scalp involvement (PSSI baseline score >0)
- PPASI: based on ITT Population – patients with baseline palmoplantar involvement (PPASI baseline score >0)
- Binary questions on psoriasis locations

The other secondary analyses are detailed in Table RHCD.6.4. Comparisons of ixekizumab versus placebo at Week 12 and all other postbaseline visits will be provided.

Efficacy measures PASI 75, PASI 90, PASI 100, sPGA (0,1), and sPGA (0) at Week 24 and Week 48 will be summarized based on the ITT Population. The immunogenicity impact on efficacy is described in Section 6.14.11.2.2.

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The other secondary efficacy variables include:

- Period 2: ITT Population – Etanercept-Approved Countries
    - PASI50, PASI75, PASI90 and PASI100
    - sPGA (0,1) and sPGA (0)
- Double-Blind Randomized Withdrawal Period (Period 4): Randomized Withdrawal Population
    - Time to relapse to moderate severity (sPGA ≥2) during the Double-Blind, Randomized Withdrawal Period
    - sPGA(0,1) and sPGA (0)
    - PASI 50, PASI 75, PASI 90 and PASI 100

The other secondary analyses are detailed in Table RHCD.6.4. Analysis methods are detailed in Section 6.1.3.1.

6.12. Health-Outcome/Quality-of-Life Analyses

The health-outcome and quality-of-life (QOL) measures are Itch NRS, CDLQI/DLQI, and Patient's global assessment of disease severity. Table RHCD.6.5 and Table RHCD.6.6 include the description and derivation of the health-outcome and QOL measures. There will be no adjustment for multiple comparisons.

The analyses of health-outcome variables for Period 2 will be based on the ITT Population, except:

- Itch NRS ≥4 improvement from baseline: based on ITT Population - patients with baseline Itch NRS score ≥4

Table RHCD.6.6 provides the detailed analyses including analysis type, method and imputation, population, time point, and dosing regimen comparisons for health-outcome and QOL analyses.

Table RHCD.6.5. Description and Derivation of Health-Outcome and Quality-of-Life Measures

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
Itch NRS	Itch Numeric Rating Scale (NRS): is a single-item, patient-reported outcome (PRO) measure designed to capture information on the overall severity of a patient's itching due to his/her psoriatic skin condition by having the patient circle the integer that best describes the worst level of itching in the past 24 hours on an 11-point NRS anchored at 0 representing "no itching" and 10 representing "worst itch imaginable."	Itch NRS score	Range from 0 to 10.	Single item, missing if missing
		Itch NRS change from baseline	Calculated as: observed Itch NRS – baseline Itch NRS	Missing if baseline or observed value is missing
		Itch NRS ≥4 improvement from baseline	Reduced/decreased of ≥4 point from baseline	Missing if baseline or observed value is missing
		Itch NRS = 0	Defined as a postbaseline Itch NRS score of 0	Missing if Itch NRS score is missing
DLQI	Dermatology Life Quality Index (DLQI): is a validated, dermatology-specific, patient-reported measure that evaluates patient's health-related quality of life. This questionnaire has 10 items that are grouped in 6 domains, including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall period of this scale is over the "last week." Response categories and corresponding scores are: Very much = 3 A lot = 2 A little = 1 Not at all = 0 Not relevant = 0	DLQI symptoms and feelings domain	Sum of responses of questions #1 and #2: #1. How itchy, sore, painful or stinging has your skin been? #2. How embarrassed or self-conscious have you been because of your skin?	If one question in a domain is missing, that domain is missing.
		DLQI daily activities domain	Sum of responses of questions #3 and #4: #3. How much has your skin interfered with you going shopping or looking after your home or garden? #4. How much has your skin influenced the clothes you wear?	If one question in a domain is missing, that domain is missing.
		DLQI leisure domain	Sum of responses of questions #5 and #6: #5. How much has your skin affected any social or leisure activities? #6. How much has your skin make it difficult for you to do any sport?	If one question in a domain is missing, that domain is missing.
		DLQI work and school domain	Sum of responses of questions question #7A and #7B: #7A. Has your skin prevented you from working or studying? #7B. If No: how much has your skin been	If the answer to question #7A is missing, this domain is missing. If #7A is No, and #7B is missing, this domain is missing.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
			a problem at work or studying?	
		DLQI personal and relationships domain	Sum of responses of questions #8 and #9: #8. How much has your skin created problems with your partner or any of your close friends or relatives? #9. How much has your skin caused any sexual difficulties?	If 1 question in a domain is missing, that domain is missing.
		DLQI treatment	Response of question #10: #10. How much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	If 1 question in a domain is missing, that domain is missing.
		DLQI total score	A DLQI total score is calculated by summing all 10 question responses, and has a range of 0 to 30 (less to more impairment) (Finlay and Khan 1994; Basra et al. 2008).	If 2 or more questions are missing, the total score is missing. Note: #7B could be a valid missing while #7A is not "No." That is, #7 should be considered as 1 question.
		DLQI (0,1)	A DLQI (0,1) response is defined as a postbaseline DLQI total score of 0 or 1. A DLQI total score of 0 to 1 is considered as having no effect on a patient's health-related quality of life (HRQoL) (Khilji et al. 2002; Hongbo et al. 2005).	Missing if DLQI total score is missing
CDLQI	Children's Dermatology Life Quality Index (CDLQI): is designed for use in children (subjects form age 4 to age 16 years) (Lewis-Jones and Finlay 1995; Waters et al. 2010; Salek et al. 2013). It consists of 10 items, of which there are 6 headings, including symptoms and feelings, leisure, school or holidays, personal relationships, sleep, and treatment. The recall period of this scale is	CDLQI symptoms and feelings domain	Sum of responses of questions #1 and #2: #1. How itchy, "scratchy," sore, or painful has your skin been? #2. How embarrassed or self-conscious, have you been because of your skin?	If 1 question in a domain is missing, that domain is missing.
		CDLQI leisure	Sum of responses of questions #4, #5, and #6: #4. How much have you changed or worn different or special clothes/shoes because	If 1 question in a domain is missing, that domain is missing.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	over the "last week." Response categories and corresponding scores are: 0-1 = no effect on child's life 2-6 = small effect 7-12 = moderate effect 13-18 = very large effect 19-30 = extremely large effect		of your skin? #5. How much has your skin trouble affected going out, playing, or doing hobbies? #6. How much have you avoided swimming or other sports because of your skin trouble?	
		CDLQI school or holidays	Response of question #7A or #7B: #7A. If school time, how much did your skin problem affect your school work? #7B. If holiday time, how much has your skin problem interfered with your enjoyment of the holiday?	If 1 question in a domain is missing, that domain is missing. If both parts of Question 7 are answered, the higher of the 2 scores should be counted.
		CDLQI personal relationships	Sum of responses of questions #3 and #8: #3. How much has your skin affected your friendships? #8. How much trouble have you had because of your skin with other people calling you names, teasing, bullying, asking questions, or avoiding you?	If 1 question in a domain is missing, that domain is missing.
		CDLQI sleep	Response of question #9: #9. How much has your sleep been affected by your skin problem?	If 1 question in a domain is missing, that domain is missing.
		CDLQI treatment	Response of question #10: #10. How much of a problem has the treatment for your skin been?	If 1 question in a domain is missing, that domain is missing.
		CDLQI total score	A CDLQI total score is calculated by summing all 10 question responses, and has a range of 0 to 30 (less to more impairment) (Lewis-Jones and Finlay 1995; Basra et al. 2008).	If 2 or more questions are missing, the total score is missing.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
		CDLQI (0,1)	A CDLQI (0,1) response is defined as a postbaseline CDLQI total score of 0 or 1.	Missing if CDLQI total score is missing
Patient's Global Assessment of Disease Severity	Patient's Global Assessment of Disease Severity (PatGA): is a subject-administered single-item scale on which subjects are asked to rank by circling a number on a 0 to 5 numerical rating scale (NRS) the severity of their psoriasis today from 0 (clear) = no psoriasis to 5 (severe) = the worst their psoriasis has ever been.	PatGA (0,1)	A PatGA (0,1) response is defined as a postbaseline PatGA score of 0 or 1.	Missing if the item is missing
		Change from baseline	Calculated as: observed PatGA – baseline PatGA	Missing if baseline or observed value is missing

Table RHCD.6.6. Description of Health-Outcomes and Quality-of-Life Analyses

Measure	Variable	Analysis (Method)	Population	Comparison/Time Point
Itch NRS	Itch NRS ≥4 improvement from baseline (Gated secondary)	Fisher's exact test with NRI Logistic regression with NRI	ITT Population – patients with baseline value ≥4	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2
	Change from baseline	MMRM	ITT Population	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2
		ANCOVA with LOCF	ITT Population	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2
CDLQI/DLQI	CDLQI/DLQI (0,1)	Fisher's exact test with NRI Logistic regression with NRI	ITT Population	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2
PatGA	PatGA (0,1)	Fisher's exact test with NRI Logistic regression with NRI	ITT Population	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2
	Change from baseline	ANCOVA with LOCF	ITT Population	Ixekizumab Q4W vs. placebo at Week 12 and all other postbaseline visits during Period 2

Abbreviations: ANCOVA = analysis of covariance; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; ITT = intent-to-treat; LOCF = last observation carried forward; MMRM = mixed-effects model of repeated measures; NRI = nonresponder imputation; NRS = Numeric Rating Scale; PatGA = Patient's Global Assessment of Disease Severity; Q4W = every 4 weeks; vs. = versus.

6.13. Pharmacokinetic/Pharmacodynamic Methods

More details of the pharmacokinetic/pharmacodynamic (PK/PD) analyses can be found in a separate PK/PD analysis plan.

Briefly, observed ixekizumab serum trough concentrations will be summarized by time point across the study. The PK parameters of ixekizumab in pediatric subjects will be determined using population PK methods. The exposure-response relationship will be investigated between steady-state trough concentrations of ixekizumab and clinically important efficacy measures (for example, sPGA and PASI endpoints) at Week 12 using graphical methods and, if appropriate, modeling methods. If applicable, the potential impact of immunogenicity on ixekizumab exposure and/or exposure or efficacy responses may be evaluated by graphical assessments, as appropriate, to compare drug exposure or efficacy responses between antidrug antibody- (ADA-) negative and ADA-positive subjects at corresponding visits, or before and after ADA development for subjects who developed ADA. Both treatment-emergent only and all ADA-positive/negative subjects may be explored. A similar approach may be taken if subjects become neutralizing antibody positive.

Additional analyses may be performed upon receipt of the data. The data from this study may be combined with data from previous adult studies, if needed, for model development.

6.14. Safety Analyses

Safety will be assessed by summarizing and analyzing AEs, laboratory analytes, including neutrophil counts and immunogenicity; vital signs, CDRS, and C-SSRS. The duration of dosing exposure will also be summarized. Immunization history will be summarized at baseline, and any unexpected outcomes or effects related to standard-of-care vaccination will be summarized.

For Period 2 in Main Protocol RHCD, the safety data will be summarized and analyzed for the safety population with treatment comparisons of ixekizumab versus placebo. This population will be abbreviated as “P2 Main Study Safety Population.”

For Period 2 in Protocol Addendum RHCD(2), the select safety data will be summarized and analyzed for the safety population etanercept-approved countries with all pairwise comparisons. This population will be abbreviated as “P2 Addendum Safety Population.”

For Period 4 in Protocol Addendum RHCD(2), the select safety data will be summarized and analyzed for the Double-Blind, Randomized Withdrawal Period Population with treatment comparisons of ixekizumab versus placebo. This population will be abbreviated as “P4 Randomized Withdrawal Population.”

For all ixekizumab treatment periods combined (Period 2, 3, and 4), the safety data will be summarized to all ixekizumab population. This population will be abbreviated as “All Ixekizumab Safety Population.”

For Period 5, safety data will be summarized using Follow-Up Population.

6.14.1. Extent of Exposure

Duration of exposure to study drug will be summarized by treatment group using descriptive statistics, the summary will also include the total exposure in patient years, mean, and median total dose. Exposure of the following safety population will be summarized:

- P2 Main Study Safety Population
- P2 Addendum Safety Population
- P4 Randomized Withdrawal Population
- All Ixekizumab Safety Population

The duration of exposure will be calculated as:

- $Duration\ of\ exposure\ (days) =$
  $Date\ of\ last\ visit\ (scheduled\ or\ unscheduled)\ in$ the $treatment\ period\ -$
  $Date\ of\ first\ dose\ in\ the\ treatment\ period\ + 1$

- Total exposure in patient years will be calculated as:

  $$Total\ exposure\ in\ patient\ years = \frac{Sum\ of\ duration\ (days)\ of\ exposures\ for\ all\ patients\ in\ treatment\ group}{365.25}$$

- Total dose (in mg) is calculated by the summation of dose for each active injection taken during the treatment period. Dose for placebo injection will be 0.

For P2 Main Study and P2 Addendum Safety Populations, the number and percentage of patients in each of the following categories will be included in the summaries:

- >0, ≥7 days, ≥14 days, ≥30 days, ≥60 days, ≥84 days, and ≥90 days. Note that patients may be included in more than 1 category.
- >0 to <7 days, ≥7 to <14 days, ≥14 to <30 days, ≥30 to <60 days, ≥60 to <84 days, ≥84 to <90 days, and ≥90 days.

For P4 Randomized Withdrawal Population, the number and percentage of patients in each of the following categories will be included in the summaries:

- >0, ≥7 days, ≥14 days, ≥30 days, ≥60 days, ≥84 days, ≥90 days, ≥120 days, ≥183 days, and ≥365 days. Note that patients may be included in more than 1 category.
- >0 to <7 days, ≥7 to <14 days, ≥14 to <30 days, ≥30 to <60 days, ≥60 to <84 days, ≥84 to <90 days, ≥90 to <120 days, ≥120 to <183 days, ≥183 to <365 days, and ≥365 days

For the All Ixekizumab Safety Population, duration of exposure for each uninterrupted ixekizumab treatment period will be calculated as:

$$Duration\ of\ ixekizumab\ exposure\ (days) = Date\ of\ last\ visit\ of\ ixekizumab\ treatment\ period - Date\ of\ first\ dose\ of\ ixekizumab\ treatment\ period + 1$$

If a patient had more than 1 uninterrupted ixekizumab treatment periods, patients who re-randomized to placebo during the Double-Blind, Randomized Withdrawal Period (Period 4) and relapsed, the duration of total ixekizumab exposure is the sum of durations of both uninterrupted ixekizumab exposure.

The number and percentage of patients in each of the following categories will be included in the summaries for the All Ixekizumab Safety Population:

- >0, ≥7 days, ≥14 days, ≥30 days, ≥60 days, ≥84 days, ≥90 days, ≥120 days, ≥183 days, ≥365 days, ≥548 days, and ≥730 days. Note that patients may be included in more than 1 category.
- >0 to <7 days, ≥7 to <14 days, ≥14 to <30 days, ≥30 to <60 days, ≥60 to <84 days, ≥84 to <90 days, ≥90 to <120 days, ≥120 to <183 days, ≥183 to <365 days, ≥365 days to <548 days, ≥548 days to <730 days, and ≥730 days.

6.14.2. Adverse Events

Adverse events will be classified based upon the latest version of the MedDRA. Adverse events will be recorded at every study visit. Any condition starting on or after the date of informed consent will be considered an AE. Any preexisting condition which worsens in severity on or after the date of informed consent will be considered and recorded as an AE on the Adverse Event (AE) eCRF page from the date of worsening onward.

A treatment-emergent adverse event (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 defined treatment period. Both the date/time of the event and the date/time of the dose (that is, injection) are considered when determining TEAEs. Treatment-emergent AEs will be assigned to the study period to which it is considered treatment-emergent:

- The MedDRA lowest level term (LLT) will be used when classifying AEs as treatment-emergent.
- The maximum severity recorded for each LLT prior to the first dose date/time in the treatment period will be used as the pre-treatment severity for that LLT. If an event during the baseline period has missing severity, and the event persists during the treatment period, then it will be considered as treatment-emergent, regardless of the postbaseline level of severity. Events with a missing severity during the treatment period will be considered treatment-emergent.
- AEs with a particular LLT will be classified as treatment-emergent if they first start on or after the first dose date/time in the treatment period (that is, a patient has no preexisting conditions with that LLT), or if the severity is greater than the pre-treatment severity for that LLT. If a partial AE start date/time is present, the date/time will be compared as far as possible to the treatment start date/time in order to determine whether the event is treatment-emergent. If there is any doubt, the event will be flagged as treatment-emergent.

A follow-up-emergent adverse event (FEAE) is defined as an event that first occurred or worsened in severity after the date of Visit 31 (that is, Week 108) or the ETV:

- The MedDRA LLT will be used when classifying AEs as follow-up-emergent.
- For AEs that are ongoing at the date of Visit 31 or ETV, the maximum severity recorded for each LLT on or prior to the date of Visit 31 or ETV will be used as the follow-up baseline severity for that LLT.

If a partial or completely missing AE start date/time or end date/time is present the following imputation rules will be utilized in the analysis:

- For the start date:
  - If year, month, and day are missing, then use the earlier of the patient's first visit date or the consent date.
  - If either month or month and day are missing, then use January 1.
  - If only day is missing, impute the first day of the month.
- For the start time:
  - Impute as 23:59
- For the end date:
  - If year, month, and day are missing, then use the patient's last visit date in the follow-up period.
  - If either month or month and day are missing, then use December 31.
  - If only day is missing, then use the last day of the month.
  - The imputed date will not be beyond the patient's last visit date in the follow-up period.
- For the end time:
  - Impute as 23:59.
- If there is any doubt, the event will be flagged as treatment-emergent or follow-up-emergent, according the corresponding study period. If a follow-up-emergent event was already counted as treatment-emergent during the prior treatment period, it will not be counted as a follow-up-emergent event.

Adverse events and TEAEs will be summarized for the following study periods and analysis populations; treatment comparisons between treatment groups will be conducted using a Fisher's exact test.

The following summaries/analyses will be performed for P2 Main Study Safety Population and All Ixekizumab Safety Population:

- An overall summary of AEs, including the number and percentage of patients who experienced TEAE, TEAE by maximum severity, death, serious adverse event (SAE), TEAE possibly related to study treatment, discontinuations from the treatment due to an AE, and TEAEs of special interest.
- TEAE by SOC and PT.
- TEAE by maximum severity, SOC, and PT.

The following summaries/analyses will be performed for P2 Addendum Safety Population and P4 Randomized Withdrawal Population:

- An overall summary of AEs, including the number and percentage of patients who experienced TEAE, TEAE by maximum severity, death, SAE, TEAE possibly related to study treatment, discontinuations from the treatment due to an AE, and TEAEs of special interest.
- TEAE by SOC and PT.

Follow-up emergent adverse events will be summarized for the Follow-Up Population for Period 5:

- FEAE by SOC and PT.

In general, for all AE-related summaries, the number and percentage of patients experiencing the events will be presented by treatment group. In general, events will be ordered by decreasing frequency in the total ixekizumab group, followed in the order of ixekizumab Q4W, etanercept, and placebo (when applicable) group, within SOC and/or PT for sorting. For events that are gender-specific (as defined by MedDRA), the denominator and computation of the percentage will include only patients from the given gender.

A by-patient listing of all AEs will be provided.

6.14.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

By-patient listings of deaths, SAEs, and AEs leading to discontinuation will be provided, respectively.

All deaths will be included, regardless of the investigator's or the Sponsor's judgment about causality, including:

- any deaths occurring during participation in the study in the database for which data are being presented
- any deaths occurring after a patient leaves (is discontinued from or completed) the study in the database for which data are being presented if the death is:
    - the result of a process initiated during the study, regardless of when it actually occurred
    - occurs during the Period 5 after discontinuation of study drug

An SAE is any AE that results in one of the following outcomes: death, life-threatening, initial or prolonged hospitalization, disability or permanent damage, congenital anomaly or birth defect, or any other serious/important medical events.

The following summary tables (including treatment group comparison for Period 2) will be provided for P2 Main Study Safety Population and All Ixekizumab Safety Population:

- SAEs by SOC and PT
- AEs that lead to treatment discontinuation (including death) by SOC and PT

The following summary tables (including treatment group comparisons for Period 2 and Period 4) will be provided P2 Addendum Safety Population and P4 Randomized Withdrawal Population:

- SAEs by SOC and PT

6.14.3.1. Special Safety Topics including Adverse Events of Special Interest

Safety information on special topics including AEs of special interest (AESIs) will be presented by treatment group for P2 Main Study Safety Population and All Ixekizumab Safety Population.

Table RHCD.6.7 provides the definitions/derivations and analyses methods (including analyses, summaries and by-patient listings) of special safety topics including AESIs.

Potential AESIs will be identified by a standardized MedDRA query (SMQ) or a Lilly-defined MedDRA PT listing. Preferred terms within an SMQ will be classified as broad and narrow. In the Lilly-defined MedDRA PT listings, Lilly has provided the broad and narrow classification. The Lilly-defined broad terms are for a more sensitive search of potential events of interest, and the Lilly-defined narrow terms are for a more specific search. Therefore, the summaries will include the classifications of broad term (same as pooling narrow and broad terms together) and narrow term.

In the event that the listing of terms or analysis changes for a special safety topic, it will be documented in the most current program safety analysis plan (PSAP) which will supersede this document; it will not warrant an amendment to the individual study SAP.

Fisher's exact tests will be used to compare the treatment groups.

In general, AESI summary will not be provided for Follow-Up Population during Period 5 except for cytopenia and hepatic laboratory tests.

Table RHCD.6.7. Definitions and Analyses of Special Safety Topics including Adverse Events of Special Interest

Special Safety Topic	Definition/Derivation	Analysis/Summary/Listing
Hepatic	Hepatic AE analysis will include events that are potentially drug-related hepatic disorders by using the MedDRA PTs contained in any of the following SMQs: • Broad and narrow terms in the Liver related investigations, signs and symptoms (20000008) • Broad and narrow terms in the Cholestasis and jaundice of hepatic origin (20000009) • Broad and narrow terms in the Hepatitis, non-infectious (20000010) • Broad and narrow terms in the Hepatic failure, fibrosis and cirrhosis and other liver damage (20000013) • Narrow terms in the Liver-related coagulation and bleeding disturbances (20000015)	P2 Main Study Safety Population **(Fisher's exact test)** and All Ixekizumab Safety Population **(Summary)**: TEAE by PT within SMQ or sub-SMQ **Listing:** TEAE (display in Spotfire)
	Elevations in hepatic laboratory tests (ALT, AST, ALP, total bilirubin) using Performing Laboratory Reference Ranges are defined as: • Include scheduled visits, unscheduled visits, and repeat measurements. • ALT or AST: maximum postbaseline measurement ≥3 times (3×), 5 times (5×), 10 times (10×), and 20 times (20×) the Performing Lab ULN for all patients with a postbaseline value. o The analysis of 3× ULN will contain 4 subsets: patients whose nonmissing maximum baseline value is ≤1× ULN, patients whose maximum baseline is >1× ULN but <3× ULN, patients whose maximum baseline value is ≥3× ULN, and patients whose baseline values are missing. o The analysis of 5× ULN will contain 5 subsets: patients whose nonmissing maximum baseline value is ≤ to 1× ULN, patients whose maximum baseline is >1× ULN but <3× ULN, patients whose maximum baseline is ≥3× ULN but <5× ULN, patients whose maximum baseline value is ≥5× ULN, and patients whose baseline values are missing. o The analysis of 10× ULN will contain 6 subsets: patients whose nonmissing maximum baseline value is ≤1× ULN, patients whose maximum baseline is >1× ULN but <3× ULN, patients whose maximum baseline is ≥3× ULN but <5× ULN, patients whose maximum baseline is ≥5× ULN but <10× ULN, patients whose maximum baseline value is ≥10× ULN, and patients whose baseline values are missing. o The analysis of 20× ULN will contain 7 subsets: patients whose nonmissing maximum baseline value is ≤1× ULN, patients whose maximum baseline is >1× ULN but <3× ULN, patients whose maximum baseline is ≥3× ULN but <5× ULN, patients whose maximum baseline is ≥5× ULN but <10× ULN, patients whose maximum baseline is ≥10× ULN but <20× ULN, patients whose maximum baseline value is ≥20× ULN, and patients whose baseline values are missing. • Total bilirubin: The number and percentages of patients with a total bilirubin measurement ≥1.5×, and	**Listing:** Elevations in hepatic laboratory tests (display in Spotfire)

Special Safety Topic	Definition/Derivation	Analysis/Summary/Listing
	≥2×) the Performing Lab ULN during the treatment period will be summarized for all patients with a postbaseline value. o The analysis of 1.5× ULN will contain 4 subsets: patients whose nonmissing maximum baseline value is ≤1× ULN, patients whose maximum baseline is >1× ULN but <1.5× ULN, patients whose maximum baseline value is ≥1.5× ULN, and patients whose baseline values are missing. o The analysis of 2× ULN will contain 5 subsets: patients whose nonmissing maximum baseline value is ≤1× ULN, patients whose maximum baseline is >1× ULN but <1.5× ULN, patients whose maximum baseline is ≥1.5× ULN but <2× ULN, patients whose maximum baseline value is ≥2× ULN, and patients whose baseline values are missing. • ALP: The number and percentages of patients with an ALP measurement >1.5× the Performing Lab ULN during the treatment period will be summarized for all patients with a postbaseline value, and divided into 4 subsets: patients whose nonmissing maximum baseline value is ≤1× ULN, patients whose maximum baseline is >1× ULN but ≤1.5× ULN, patients whose maximum baseline value is >1.5× ULN, and patients whose baseline values are missing. • The number and percentages of patients meeting the following elevated hepatic criteria: maximum ALT ≥3× ULN and maximum total bilirubin ≥2× ULN during the treatment period will be summarized.	
	Shift for ALT, AST, and total bilirubin from maximum baseline to maximum postbaseline will be produced with the requirements using Performing Lab Reference Ranges: • Include scheduled visits, unscheduled visits, and repeat measurements. • Use the maximum nonmissing value in the baseline period. • Use the maximum nonmissing postbaseline value within each study period. • Categories are: o ALT: ≤1× ULN, >1 to <3× ULN, ≥3 to <5× ULN, ≥5 to <10× ULN, ≥10 to <20× ULN, and ≥20× ULN o AST: ≤1× ULN, >1 to <3× ULN, ≥3 to <5× ULN, ≥5 to <10× ULN, ≥10× to <20× ULN and ≥20× ULN o Total bilirubin: ≤1× ULN, >1 to <1.5× ULN, ≥1.5 to <2× ULN, ≥2× ULN o ALP: ≤1× ULN, >1 to ≤1.5× ULN, >1.5× ULN • With additional categories: o Decreased: postbaseline category < baseline category o Increased: postbaseline category > baseline category o Same: postbaseline category = baseline category	
	Elevated hepatic criteria: maximum ALT ≥3× ULN, maximum total bilirubin ≥2× ULN.	

Special Safety Topic	Definition/Derivation	Analysis/Summary/Listing
	Listing of patients who meet any of the following criteria: • Elevated hepatic criteria: defined as maximum ALT ≥3× ULN, maximum total bilirubin ≥2× ULN • An ALT or AST ≥3× ULN • An ALP ≥1.5× ULN • A total bilirubin ≥2× ULN The listing will include: patient demographics, concomitant medications, ALT/AST/ALP/total bilirubin/GGT by visit, treatment start and stop dates, and reason for treatment discontinuation	
	Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot: use maximum ALT measurement and maximum total bilirubin measurement with patients having at least 1 postbaseline ALT and total bilirubin, which contributes 1 point to the plot. The measurements do not need to be taken at the same blood draw.	P2 Main Study Safety Population and All Ixekizumab Safety Population: eDISH plot (display in Spotfire)
Cytopenias	Cytopenias are defined using the PTs from the following 2 sub-SMQs of the Haematopoietic cytopenias SMQ (20000027) as defined in MedDRA version: • Broad and narrow terms in the Haematopoietic leukopenia (20000030) • Broad and narrow terms in the Haematopoietic thrombocytopenia (20000031)	P2 Main Study Safety Population **(Fisher's exact test)** and All Ixekizumab Safety Population **(Summary)**: TEAE by PT within sub-SMQ **Period 5 (Summary)**: FEAE by PT within sub-SMQ **Listing:** TEAE (display in Spotfire)
Infections	Infections are events including all infections (defined using all the MedDRA PTs from the Infections and infestations SOC), serious infections, potential opportunistic infections, and infections resulting in anti-infective medication administration (i.e., antibacterial, antiviral, antifungals, antiparasitic treatment.). The relationship between TEAEs-infections and other clinical, laboratory, and hematology parameters will be examined using Spotfire tool.	P2 Main Study Safety Population **(Fisher's exact test)** and All Ixekizumab Safety Population **(Summary)**: TEAE by PT* SAE by PT* DCAE by PT* * Included in overall TEAE tables.

Special Safety Topic	Definition/Derivation	Analysis/Summary/Listing
		Listing: TEAE (display in Spotfire)
	Anti-infective medications are defined in Appendix 2 including antibiotics, antifungals, antivirals, or antiprotozoals.	
	The opportunistic infections (OI) are defined in Appendix 3. This list contain PTs as contained within Categories (narrow or broad) from the Infections and Infestations SOC and from the Investigations SOC which can assist in identifying potential OIs. The narrow terms are considered opportunistic infections unless medical review determines that the reported term is not consistent with the patient's clinical history/presentation/course. Medical review of broad terms is needed for final determination of patients meeting the program definition ofOIs. The number and percentage of patients with TEAEs that represent potential OIs and as potential OIs will be summarized by treatment group using MedDRA PT nested within categories. Events will be ordered by decreasing frequency in the ixekizumab group (or combined ixekizumab group in the event of multiple cohorts/doses) nested within categories.	P2 Main Study Safety Population **(Fisher's exact test)** and All Ixekizumab Safety Population **(Summary)**: TEAE of OIs **Listing:** TEAE of OIs (display in Spotfire)
	The duration of each common TEAE PT of Infections and narrow terms for Opportunistic infections is defined as: Duration of treatment-emergent AE Infections (in weeks) = (End date of AE – Start date of AE + 1) / 7. Patients who do not have the PT will not be included in the analysis. If the TEAE has not ended by the date of completion from the study, or date of early discontinuation, it will be censored as of that date. If a patient has multiple episodes of the same TEAE, the episode with the greatest severity will be used for the duration of event calculation. If a patient has multiple episodes of the same TEAE with the same severity, the episode with the longest duration will be used for the duration of event calculation.	P2 Main Study Safety Population and All Ixekizumab Safety Population **(Summary)**: Duration of Common TEAE – Infections (display in Spotfire)
Allergic Reactions/ Hypersensitiv-ities	Allergic reactions/hypersensitivity events will be categorized as either anaphylaxis or nonanaphylaxis events (these will refer to events that are not localized to the site of injection) and summarized separately. Allergic Reactions/Hypersensitivity Events, Anaphylaxis: Anaphylaxis has been broadly defined as "a serious allergic reaction that is rapid in onset and may cause death" (Sampson et al. 2006). Identification of cases of potential anaphylaxis from the clinical trial data involves 2 screening criteria:	P2 Main Study Safety Population **(Fisher's exact test)** and All Ixekizumab Safety Population **(Summary)**:

Special Safety Topic	Definition/Derivation	Analysis/Summary/Listing
	1) Designed to specifically identify cases (following Criterion 1) based on narrow terms from the MedDRA SMQ for anaphylactic reaction (20000021). Criterion 1 for anaphylaxis is defined by the presence of a TEAE based on the following MedDRA PTs from the anaphylactic reaction SMQ: • Anaphylactic reaction • Anaphylactic shock • Anaphylactoid reaction • Anaphylactoid shock • Kounis Syndrome • Type 1 hypersensitivity 2) To identify possible cases, following Criterion 2 as defined by Sampson et al. (2006). Criterion 2 for anaphylaxis requires having TEAEs from 2 or more of 4 categories of AEs as described by Sampson et al. (2006). Occurrence of these events should be nearly coincident; based on recording of events or CRFs. All qualifying events must be within 1 day of study drug injection. The 4 categories to be considered in Criterion 2 are: • Category A: Involvement of the skin-mucosal tissue • Category B: Respiratory compromise • Category C: Reduced blood pressure or associated symptoms • Category D: Persistent gastrointestinal symptoms The specific MedDRA PTs covered by each of these Criterion 2 categories are shown in Appendix 4. Summaries of Criterion 2 anaphylactic TEAEs will be provided by the specific combination of categories as follows: • AB: events based on meeting Category A and Category B (but no other category) • AC: events based on meeting Category A and Category C (but no other category) • AD: events based on meeting Category A and Category D (but no other category) • BC: events based on meeting Category B and Category C (but no other category) • BD: events based on meeting Category B and Category D (but no other category) • CD: events based on meeting Category C and Category D (but no other category) • ABC: events based on meeting Category A, Category B and Category C (but no other category) • ABD: events based on meeting Category A, Category B and Category D (but no other category) • ACD: events based on meeting Category A, Category C and Category D (but no other category) • BCD: events based on meeting Category B, Category C and Category D (but no other category) • ABCD: events based on meeting each of the 4 Criterion 2 categories. Summaries of treatment-emergent anaphylactic AEs will be provided for patients meeting each of the 2 criteria and for patients who meet either criteria, overall. Separate summaries will be provided for TEAEs	TEAE by PT within Category, SAE by PT within Category, AE leading to treatment discontinuation by PT within Category. **Listing:** TEAE (display in Spotfire)

Special Safety Topic	Definition/Derivation	Analysis/Summary/Listing
	by maximum severity, SAEs, and AEs resulting in study drug discontinuation. Severity of treatment-emergent Criterion 2 anaphylactic AEs will be based on the maximum severity of the specific events met by the patient. Maximum severity of an (overall) treatment-emergent anaphylactic AE will be based on the maximum severity within Criterion 1 and/or Criterion 2. Allergic Reactions/Hypersensitivity Events, Nonanaphylaxis: TEAEs of allergic reaction/hypersensitivity categorized as nonanaphylaxis events are defined by the narrow terms within Hypersensitivity SMQ (20000214) excluding the PTs noted in Appendix 5 and excluding the anaphylactic events as defined above.	
Injection Site Reactions	Injection site reaction is defined using the PTs from the MedDRA HLT of Injection site reactions as defined by MedDRA, excluding the following 10 PTs: 1) Embolia cutis medicamentosa 2) Injection site joint discomfort 3) Injection site joint effusion 4) Injection site joint redness 5) Injection site joint infection 6) Injection site joint inflammation 7) Injection site joint movement impairment 8) Injection site joint pain 9) Injection site joint swelling 10) Injection site joint warmth. Patients with TEAE of injection site reactions will be categorized into 3 groups: patients with 1 TEAE of injection site reaction event, patients with 2 or 3 events, and patients with ≥4 events. Redness (Scored 0-4) • [0] Subject's normal skin color, no increased redness • [1] Noticeable, but very mild redness • [2] Clearly red • [3] Bright red • [4] Dark with some scar formation Swelling (Scored 0-4 after running a finger over injected area) • [0] No bump • [1] Barely noticeable • [2] Clear bump but very thin • [3] Clear bump 1-mm thick • [4] Clear bump 2-mm thick or more	P2 Main Study Safety Population **(Fisher's exact test)** and All Ixekizumab Safety Population **(Summary)**: TEAE by PT within HLT, SAE by PT within HLT (display in Spotfire), AE leading to treatment discontinuation by PT within HLT (display in Spotfire) **Listing:** TEAE (display in Spotfire)

Special Safety Topic	Definition/Derivation	Analysis/Summary/Listing
	Pain (including burning) (Scored 0-3) • [1] Mild • [2] Moderate • [3] Severe	
Malignancies	Malignancy is defined using PTs from the Malignant or unspecified tumors SMQ as defined in MedDRA (SMQ: 20000091, which includes the sub-SMQs: [1] 20000194 [Malignant tumours], including sub-SMQs of 20000227 [Haematological malignant tumours] and 20000228 [Non-haematological malignant tumours]; [2] 20000195 [Tumours of unspecified malignancy], including sub-SMQs of 20000229 [Haematological tumours of unspecified malignancy] and 20000230 [Non-haematological tumours of unspecified malignancy]. Events will be summarized by the following categories: • Nonmelanoma Skin Cancer (NMSC) o Basal Cell Carcinoma, PTs include: ▪ Basal cell carcinoma ▪ Basosquamous carcinoma ▪ Basosquamous carcinoma of skin o Squamous Cell Carcinoma, PTs include: ▪ Squamous cell carcinoma of skin ▪ Bowen's disease ▪ Lip squamous cell carcinoma ▪ Skin squamous cell carcinoma metastatic ▪ Keratoacanthoma • Malignancies excluding NMSC: all PTs in the Malignant or unspecified tumors SMQ excluding the 8 defined NMSC PTs.	P2 Main Study Safety Population **(Fisher's exact test)** and All Ixekizumab Safety Population **(Summary):** TEAE by PT within category **Listing:** TEAE (display in Spotfire)
Depressions	Depression and suicide/self-injury is defined using the PTs from the Depression and suicide/self-injury SMQ as specified in MedDRA (SMQ: 20000035, which includes the sub-SMQs: 20000037 [Suicide/self-injury] and 20000167 [Depression (excl suicide and self-injury)]).	P2 Main Study Safety Population **(Fisher's exact test)** and All Ixekizumab Safety Population **(Summary)**: TEAE by PT within SMQ and sub-SMQ **Listing:** TEAE (display in Spotfire)
Inflammatory Bowel Disease	Inflammatory Bowel Disease (IBD) will be identified using the following subcategory and MedDRA PTs. The narrow terms are considered IBD. Medical reviews of patients identified with broad terms are needed	P2 Main Study Safety Population **(Fisher's exact**

Special Safety Topic	Definition/Derivation	Analysis/Summary/Listing
(IBD)	for final determination of patients with IBD. IBD Specific Terms (Narrow terms) • Inflammatory Bowel Disease: Inflammatory bowel disease • Crohn's Disease: Crohn's disease • Ulcerative Colitis: Acute haemorrhagic ulcerative colitis; Colitis ulcerative; Proctitis ulcerative IBD Non-Specific Terms: The PTs in this category are listed in Appendix 6.	**test)** and All Ixekizumab Safety Population **(Summary)**: IBD confirmed by adjudication (included in AE overview) **Listing**: TEAE (display in Spotfire)
Interstitial Lung Disease (ILD)	ILD is defined using the following terms: • Narrow terms in the Interstitial lung disease SMQ (20000042) • Additional 6 PTs from Eosinophilic pneumonia SMQ (20000157): o Angiolymphoid hyperplasia with eosinophilia (Narrow) o Eosinophilic bronchitis (Narrow) o Hypereosinophilic syndrome (Narrow) o Loeffler's syndrome (Narrow) o Pulmonary eosinophilia (Narrow) o Pulmonary vasculitis (Narrow)	**Listing**: TEAE (display in Spotfire)

Abbreviations: AE = adverse event; AESI = adverse event of special interest; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DCAE = adverse event leading to discontinuation; eCRF = electronic case report form; FEAE = follow-up emergent adverse event; GGT = gamma-glutamyltransferase; HLT = high-level term; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; SMQ = standardized MedDRA query; SOC = System Organ Class; TB = tuberculosis; TEAE = treatment emergent adverse event; ULN = upper limit of normal.

6.14.4. Clinical Laboratory Evaluation

Clinical laboratory assessments include hematology, serum chemistry, urinalysis, and safety-related immune markers, such as neutrophil counts.

Laboratory test observed values at each visit (starting at baseline) and change from baseline to each scheduled visit, respectively, will be displayed in box plots for patients in the P2 of the Main Study Safety Population who have both a baseline and at least 1 postbaseline result. These box plots will be used to evaluate trends over time and to assess a potential impact of outliers on central tendency summaries.

- The scheduled visits/measurements will be included. The unscheduled visits and the repeat measurements will be excluded.
- The displays with both SI and conventional units will be provided, when different.
- The following summary statistics will be included as a table below the box plot: number of patients with a baseline and at least 1 postbaseline result, mean, SD, minimum, Q1, median, Q3, and maximum.
- Data will be summarized based on original scale.
- On the box plots of the laboratory test observed values, the lines of the reference ranges/limits (by using the large clinical trial population-based reference limits, that is, Lilly reference ranges) will be added. In cases where limits vary across age and gender, the lowest of the high limits and the highest of the low limits will be used.

The number and percentage of patients with a treatment-emergent or follow-up emergent abnormal high or low for laboratory tests will be summarized by treatment group for each safety population. The comparisons between treatment groups will be conducted using Fisher's exact test.

- All scheduled, unscheduled and repeated measurements will be included.
- In general, performing lab reference ranges will be used to define the low and high limits. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and alkaline phosphatase (ALP) will not be included in the treatment-emergent abnormal high or low summary as a separate analysis addressing the risk of liver injury is described in Table RHCD.6.7.
- Note that the ranges are defined by a lower limit of normal (LLN) and an upper limit of normal (ULN). A result that is greater than or equal to the LLN and less than or equal to the ULN is considered to be within the normal ranges.
- For categorical laboratory tests:
    - Treatment-emergent abnormal value is defined as a change from normal at all baseline visits to abnormal at any time postbaseline during the treatment period.
    - Follow-up emergent abnormal result is defined as a change from normal at baseline to abnormal at any time during the follow-up period.

- For continuous laboratory tests:
    - Treatment-emergent high value is defined as a change from a value less than or equal to the ULN at all baseline visits to a value greater than the ULN at any time postbaseline during the treatment period.
    - Treatment-emergent low value is defined as a change from a value greater than or equal to the LLN at all baseline visits to a value less than the LLN at any time postbaseline during the treatment period.
    - Follow-up emergent high value is defined as a change from a value less than or equal to the ULN at baseline to a value greater than the ULN at any time postbaseline during the follow-up period.
    - Follow-up emergent low value is defined as a change from a value greater than or equal to the LLN at baseline to a value less than the LLN at any time postbaseline during the follow-up period.

6.14.4.1. Leukocytes (White Blood Cells [WBCs]) and Platelets

Further analyses will be conducted for total leukocytes, neutrophils, platelets, lymphocytes, monocytes, eosinophils, and basophils. Neutrophils will include both segmented neutrophils and absolute neutrophils (derived by adding segmented neutrophils and band neutrophil).
The segmented neutrophils and absolute neutrophils will be summarized using the same categories.

Shift table will be produced showing the number and percentage of patients shifting from baseline to a minimum postbaseline result in each relevant category by treatment groups P2 Main Study Safety Population, All Ixekizumab Safety Population, and Follow-Up Safety Population:

- Scheduled visits, unscheduled visits, and repeat measurements will be included.
- Baseline is defined as the minimum result during the defined baseline period or baseline.
- Use the minimum nonmissing postbaseline value within each study period.
- The parameters and categories are:
    - Leukocytes: $\geq$1× LLN, < LLN to $\geq$3.0× 10^9/L, <3.0× 10^9/L to $\geq$2.0× 10^9/L, <2.0× 10^9/L to $\geq$1.0× 10^9/L, and <1.0× 10^9/L
    - Neutrophils: segmented neutrophils and absolute neutrophils; $\geq$1× LLN, < LLN to $\geq$1.5× 10^9/L, <1.5× 10^9/L to $\geq$1.0× 10^9/L, <1.0× 10^9/L to $\geq$0.5× 10^9/L, and <0.5× 10^9/L
    - Platelets: $\geq$1 × LLN, < LLN to $\geq$75.0 × 10^9/L, <75.0 × 10^9/L to $\geq$50.0 × 10^9/L, <50.0 × 10^9/L to $\geq$25.0 × 10^9/L, and <25.0 × 10^9/L
    - Lymphocytes: $\geq$1× LLN, < LLN to $\geq$0.8× 10^9/L, <0.8× 10^9/L to $\geq$0.5× 10^9/L, <0.5× 10^9/L to $\geq$0.2× 10^9/L, and <0.2× 10^9/L
- The LLNs are defined by as follow:
    - Leukocytes: LLN = 4.0×10^9/L
    - Neutrophils: LLN = 2.0×10^9/L
    - Lymphocytes: LLN = 1.1×10^9/L
    - Platelets: LLN = 150×10^9/L
- With additional categories:

- Decreased; postbaseline category < baseline category
- Increased; postbaseline category > baseline category
- Same; postbaseline category = baseline category.

The change from minimum baseline to minimum postbaseline result for each of these leukocytes and platelets will be summarized graphically using a box plot for P2 Main Study Safety Population.

6.14.4.2. Neutrophil Follow-Up

Neutrophil counts will be followed throughout the study. Patients will continue in Period 5 until their neutrophil counts have recovered.

The neutrophil follow-up analysis will be conducted on the Neutrophil Follow-Up Population defined as patients who have an absolute neutrophil count <1500 cells/μL (SI units: $<1.5\times 10^9$/L) at the last scheduled visit or early termination visit prior to entering the Post-Treatment Follow-Up Period (Period 5) and less than the patient's baseline absolute neutrophil count (that is, prior to first injection at Week 0). These patients are monitored during the Period 5 until neutrophil recovery.

Neutrophil clinical recovery is defined as an absolute neutrophil count ≥1500 cells/μL (SI units: $\geq 1.5\times 10^9$/L) or greater than or equal to a patient's minimum absolute neutrophil count prior to first study drug injection at Week 0.

If a patient's neutrophil count has not recovered, within 12 weeks after entering the follow-up period (Visit 802), the patient will return for Visit 803 (12 weeks after Visit 802). Additional visits may be required for appropriate patient management depending upon the degree of neutropenia. If at Visit 802, a patient's has met the criteria for neutrophil recovery, the patient's participation in the study will be considered complete, unless the investigator deems additional follow-up may be necessary.

The number and percentage of patients achieving neutrophil clinical recovery will be presented by dosing regimen and week interval for Neutrophil Follow-Up Population for Post-Treatment Follow-Up Period (Period 5). The number and percentage of patients with an absolute neutrophil cell count that is at least 25%, 50%, 75%, or 100% of the patient's baseline absolute neutrophil count (that is, prior to first injection at Week 0), irrespective of absolute neutrophil minimum, will be included in the summary.

6.14.5. Vital Signs and Other Physical Findings

Analyses will be conducted on vital signs and physical characteristics including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse (bpm), weight (kg), BMI (kg/m^2), and by-patient listing of vital signs and physical characteristics will be provided.

For vital signs and physical characteristics, the observed values at each visit (starting at baseline) and change from baseline to each scheduled visit, respectively, will be displayed in box plots for patients in P2 Main Study Safety Population who have both a baseline and at least 1 postbaseline result. These box plots will be used to evaluate trends over time and to assess a potential impact of outliers on central tendency summaries.

- The scheduled visits/measurements will be included. The unscheduled visits and the repeat measurements will be excluded.
- The following summary statistics will be included as a table below the box plot: number of patients with a baseline and at least 1 postbaseline result, mean, SD, minimum, Q1, median, Q3, and maximum.
- Data will be summarized based on original scale.

To assess the effect of administration of study drug on vital signs (blood pressures and pulse rate) among patients, at Weeks 0 and 12, vital signs will be measured before the first injection and 1 hour after the injection. The box plots will be produced for predose and postdose vital signs at Week 0 (Visit 2) and Week 12 (Visit 7).

The number and percentage of patients with treatment-emergent high blood pressure and pulse at any time for P2 Main Study Safety Population and All Ixekizumab Safety Population will be summarized. The comparisons between treatment groups will be conducted using Fisher's exact test.

- Table RHCD.6.8 and Table RHCD.6.9 define the limits of each category that are specified as treatment-emergent.
- All postbaseline scheduled, unscheduled and repeated measurements will be included.
- For treatment-emergent high blood pressure:
    - A treatment-emergent prehypertension is defined as a change from a value less than the low limit of prehypertension at all baseline visits to a value that is within the limits of prehypertension at any time postbaseline during the treatment period.
    - A treatment-emergent stage 1 hypertension is defined as a change from a value less than the low limit of stage 1 hypertension at all baseline visits to a value that is within the limits of stage 1 hypertension at any time postbaseline during the treatment period.
    - A treatment-emergent stage 2 hypertension is defined as a change from a value less than the low limit of stage 2 hypertension at all baseline visits to a value that is greater than or equal to the limits of stage 2 hypertension at any time postbaseline during the treatment period.
- Treatment-emergent high or low value in pulse rate:
    - A treatment-emergent high value is defined as a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time postbaseline during the treatment period.
    - Treatment-emergent low value is defined as a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time postbaseline during the treatment period.

Table RHCD.6.8. Blood Pressure Levels for Children by Age and Gender (Median Height)

		Boy		Girl	
Age (Year)	Hypertension Stage	Systolic BP (mmHg) (supine or sitting – forearm at heart level)	Diastolic BP (mmHg) (supine or sitting – forearm at heart level)	Systolic BP (mmHg) (supine or sitting – forearm at heart level)	Diastolic BP (mmHg) (supine or sitting – forearm at heart level)
6	Prehypertension	≥110 and <114	≥70 and <74	≥108 and <111	≥70 and <74
	Stage 1	≥114 and <126	≥74 and <87	≥111 and <124	≥74 and <86
	Stage 2	≥126	≥87	≥124	≥86
7	Prehypertension	≥111 and <115	≥72 and <76	≥109 and <113	≥71 and <75
	Stage 1	≥115 and <127	≥76 and <89	≥113 and <125	≥75 and <87
	Stage 2	≥127	≥89	≥125	≥87
8	Prehypertension	≥112 and <116	≥73 and <78	≥111 and <115	≥72 and <76
	Stage 1	≥116 and <128	≥78 and <91	≥115 and <127	≥76 and <88
	Stage 2	≥128	≥91	≥127	≥88
9	Prehypertension	≥114 and <118	≥75 and <79	≥113 and <117	≥73 and <77
	Stage 1	≥118 and <130	≥79 and <92	≥117 and <129	≥77 and <89
	Stage 2	≥130	≥92	≥129	≥89
10	Prehypertension	≥115 and <119	≥75 and <80	≥115 and <119	≥74 and <78
	Stage 1	≥119 and <132	≥80 and <93	≥119 and <131	≥78 and <91
	Stage 2	≥132	≥93	≥131	≥91
11	Prehypertension	≥117 and <121	≥76 and <80	≥117 and <121	≥75 and <79
	Stage 1	≥121 and <134	≥80 and <93	≥121 and <133	≥79 and <92
	Stage 2	≥134	≥93	≥133	≥92
12	Prehypertension	≥120 and <123	≥76 and <81	≥119 and <123	≥76 and <80
	Stage 1	≥123 and <136	≥81 and <94	≥123 and <135	≥80 and <93
	Stage 2	≥136	≥94	≥135	≥93
13	Prehypertension	≥120 and <126	≥77 and <81	≥120 and <124	≥77 and <81
	Stage 1	≥126 and <138	≥81 and <94	≥124 and <137	≥81 and <94
	Stage 2	≥138	≥94	≥137	≥94
14	Prehypertension	≥120 and <128	≥78 and <82	≥120 and <126	≥78 and <82
	Stage 1	≥128 and <141	≥82 and <95	≥126 and <138	≥82 and <95
	Stage 2	≥141	≥95	≥138	≥95
15	Prehypertension	≥120 and <131	≥79 and <83	≥120 and <127	≥79 and <83
	Stage 1	≥131 and <143	≥83 and <96	≥127 and <139	≥83 and <96
	Stage 2	≥143	≥96	≥139	≥96
16	Prehypertension	≥120 and <134	≥80 and <84	≥120 and <128	≥80 and <84
	Stage 1	≥134 and <146	≥84 and <97	≥128 and <140	≥84 and <96
	Stage 2	≥146	≥97	≥140	≥96
17	Prehypertension	≥120 and <136	≥80 and <87	≥120 and <129	≥80 and <84
	Stage 1	≥136 and <148	≥87 and <99	≥129 and <141	≥84 and <96
	Stage 2	≥148	≥99	≥141	≥96

Abbreviations: BP = blood pressure; mmHg = millimeters of mercury.
Source: [NIH] The Fourth report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Revised May 2005

Table RHCD.6.9. Categorical Criteria for Abnormal Treatment-Emergent Pulse Rate in Children and Adolescents Requiring Evaluation and Potential Intervention by a Health Care Professional

Parameter	Age (year)	Low	High
Pulse (bpm) [a]	6 - 9	<60	>150
	10 - 11	<60	>140
	12 - 14	<50	>120
	15 - 17	<50	>100

Abbreviations: bpm = beats per minute.
Source: See the Selected Reference Limits for Pulse/Heart Rate, Arterial Blood Pressure [Including Orthostasis], and Electrocardiogram Numerical Parameters for Use in Analyses of Phase 2-4 Clinical Trials guidance, located on the CV SAC Collaboration site.
[a] Baseline abnormal values are defined by the value presented.

6.14.6. Standardized Growth

Weight, height, and BMI data will be merged to the Centers for Disease Control and Prevention (CDC) standard growth data (released in 2000) by age and gender in order to compare patients' growth with the standard. Z-score and standardized percentile of weight, height, and BMI at each visit will be calculated and compared to the 2000 CDC growth charts.

The z-score and percentile calculations are based on algorithms and data provided by the National Center for Health Statistics. The details are provided in the CDC website (https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm).

The following summaries will be provided for All Ixekizumab Safety Population:

- Baseline, endpoint and mean change of actual measure, z-score and standardized percentile of weight, height, and BMI will be summarized by month of ixekizumab exposure..
- Patient's mean weight, height, and BMI standardized percentile will be plotted versus ixekizumab exposure time.

By-patient listings of actual measures, z-scores, standardized percentiles in weight height, BMI for each visit will be provided.

6.14.7. Children's Depression Rating Scale, Revised (CDRS-R)

The Children's Depression Rating Scale–Revised (CDRS-R) (Poznanski and Mokros 1996) is the most widely used rating scale for assessing severity of depression and change in depressive symptoms for clinical research studies in children and adolescents with depression.
The CDRS-R was originally developed as a rating scale for children aged 6 to 12 years. It is a 17-item scale, with items ranging from 1 to 5 or 1 to 7 (the total score is the sum of the 17 items

and ranges from 17-113, with higher scores indicating more depressive symptoms) and is rated by a clinician via interviews with the child and parent or legal guardian. A score of ≥40 is indicative of depression, whereas, a score ≤28 is often used to define remission (minimal or no symptoms) (Mayes et al. 2010).

Change from baseline to each postbaseline visits in CDRS-R total score will be analyzed using MMRM methods for P2 Main Study Safety Population.

A shift table will be produced showing the number and percentage of patients shifting from maximum baseline score to a maximum postbaseline score in categories of ≤28, >28 and<40, and ≥40 for P2 Main Study Safety Population and All Ixekizumab Safety Population.

By-patient listing of CDRS-R data will be provided.

6.14.8. Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) is an assessment tool that evaluates suicidal ideation and behavior. Information on the C-SSRS scale can be found through the following link: http://www.cssrs.columbia.edu.

Specifically, the following outcomes are C-SSRS categories and have binary responses (yes/no). The categories have been re-ordered from the actual scale to facilitate the definitions of the composite and comparative endpoints, and to enable clarity in the presentation of the results.

Category 1 – Wish to be Dead
Category 2 – Non-specific Active Suicidal Thoughts
Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5 – Active Suicidal Ideation with Specific Plan and Intent
Category 6 – Preparatory Acts or Behavior
Category 7 – Aborted Attempt
Category 8 – Interrupted Attempt
Category 9 – Actual Attempt (non-fatal)
Category 10 – Completed Suicide

Self-injurious behavior without suicidal intent is also a C-SSRS outcome (although not suicide-related) and has a binary response (yes/no).

Composite endpoints based on the above categories are defined below.

- **Suicidal ideation:** A "yes" answer at any time during treatment to any 1 of the 5 suicidal ideation questions (Categories 1-5) on the C-SSRS.
- **Suicidal behavior:** A "yes" answer at any time during treatment to any 1 of the 5 suicidal behavior questions (Categories 6-10) on the C-SSRS.
- **Suicidal ideation or behavior:** A "yes" answer at any time during treatment to any 1 of the 10 suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

The Self-Harm Supplement Form is a 1-question form that is completed, at any visit, including baseline visit, that asks for the number of suicidal behaviors, possible suicidal behaviors, 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.

Given that few or no suicidal ideation or behaviors are anticipated, C-SSRS will be listed by patient and visit. Only patients that show suicidal ideation/behavior or self-injurious behavior without suicidal intent will be displayed (that is, if a patient's answers are all "no" for the C-SSRS, then that patient will not be displayed). However, if a patient reported any suicidal ideation/ behavior or self-injurious behavior without suicidal intent at any time point, then all his/her ideation and behavior will be displayed, even if not positive. Note that missing data should not been imputed.

The Self-Harm data will be listed by patient and visit if number of events on Self-Harm Supplement Form is not zero in the eCRF Self Harm Questionnaire Supplement.

6.14.9. Tanner Stage Scale

The Tanner Stage Scales are a series of line drawings that are designed to aid the investigator in appropriately assessing the sexual maturity of the subject. Data gathered will be assessed to determine that no pubertal disruption has occurred during the study. Although the line drawings were originally intended for child self-assessment, evidence suggests that pubertal assessment by the child or the parents/legal guardian is not a reliable measure of exact pubertal staging, and should be augmented by a physical examination (Rasmussen et al. 2015). The drawings will be used by the dermatologist investigator as an aid.

Shift table will be produced showing the number and percentage of patients shifting from the highest stage score at baseline to the highest postbaseline stage score by gender for each scale item for All Ixekizumab Safety Population.

A by-patient listing of Tanner stage data will be provided.

6.14.10. Immunization

A by-patient listing of all immunization data will be provided. The listing will include any TEAEs occurring within 30 days after the vaccinations.

6.14.11. Immunogenicity

6.14.11.1. Definitions and Terms

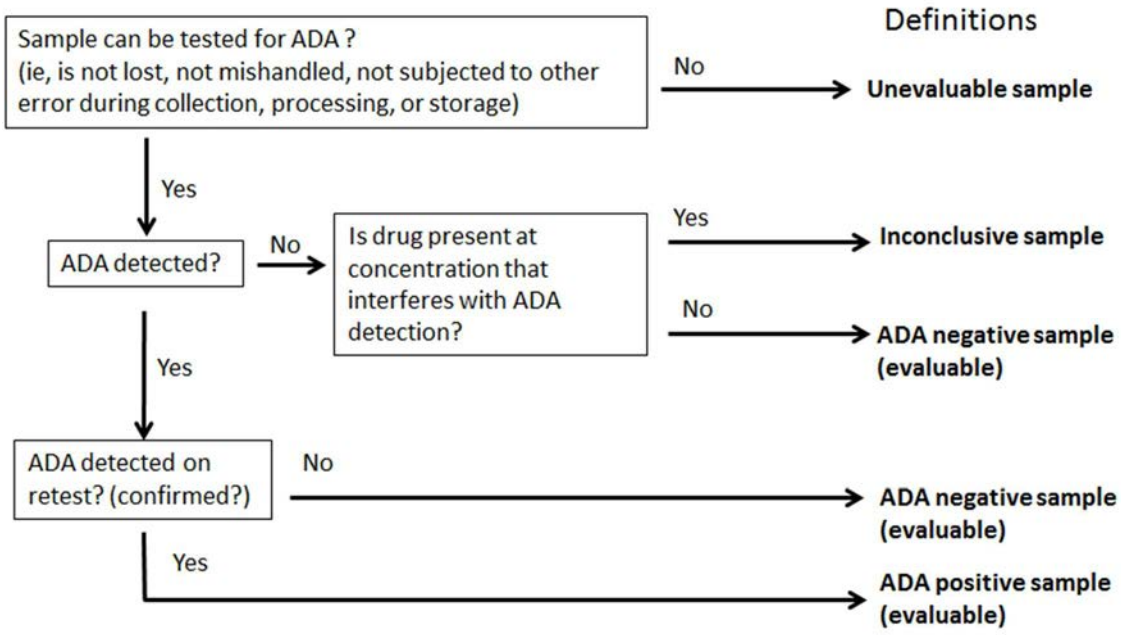
The following sample- and patient-related definitions and parameters will be used to describe the immunogenicity data.

6.14.11.1.1. Sample Category Definitions

Samples are classified into the following categories:

- **Unevaluable sample:** Sample could not be tested for ADA due to sample loss, mishandling, or errors in collection, processing, storage, and so on.
- **Anti-drug antibody (ADA) Positive sample:** The presences of ADA is detected and confirmed. The samples are reported as positive. If the sample is positive, a titer value is reported.
- **Neutralizing anti-drug antibody (NAb) Positive sample:** NAb are reported as detected.
- **Anti-drug antibody (ADA) Negative sample:** The presence of ADA is not detected and the assay drug tolerance level is not exceeded.
- **NAb Negative sample:** The presence of NAb is not detected and the assay drug tolerance level is not exceeded.
- **Inconclusive sample:** ADA/NAb is not detected in a sample, but the drug is present in the same sample at a level that can cause interference in the ADA/NAb detection method. The negative ADA/NAb result cannot be confirmed, and the sample was considered inconclusive.
    - Confirmation of a negative ADA result was based on expected ixekizumab concentrations based on PK modeling.
    - Confirmation of negative NAb results was based on ixekizumab concentrations.

Figure RHCD.6.1 illustrates the relationship of some of the above terms.



Abbreviation: ADA = anti-drug antibody.

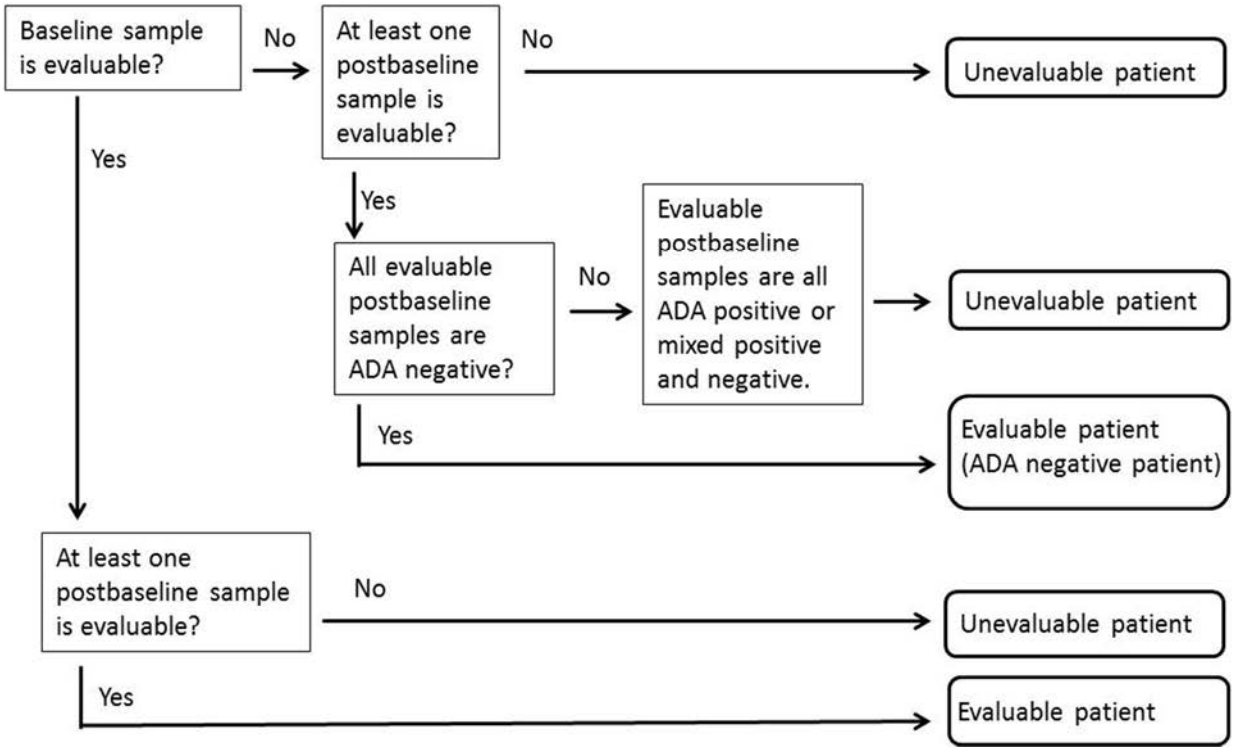
Figure RHCD.6.1. Sample definitions.

6.14.11.1.2. Patient Category Definitions

The following categories are applied to patients, based on the classification of their samples:

- **Unevaluable patient:** a) a patient with no evaluable baseline sample and/or no evaluable postbaseline samples; b) a patient with an evaluable baseline sample, but no evaluable postbaseline sample; c) a patient with no evaluable baseline sample, but whose evaluable postbaseline values are all ADA-positive or a mix of positive and negative. Note: If all postbaseline samples are negative, the patient is considered "evaluable" and will be classified as ADA-negative.
- **Evaluable patient:** a) Patient with an evaluable baseline sample and at least 1 evaluable postbaseline sample (that is, sample after administration of study drug); b) patient with no evaluable baseline sample whose evaluable postbaseline samples are all ADA negative.

Figure RHCD.6.2 illustrates the relationship of the above terms.



Abbreviation: ADA = anti-drug antibody.

Figure RHCD.6.2. Patient categories (evaluable/unevaluable) based on sample status at baseline and postbaseline.

6.14.11.1.3. Definitions for Clinical Interpretation of Assay Results

- **Baseline:** For immunogenicity analyses during Period 2, baseline is the last nonmissing observation on, or prior to, the date of the first injection of study treatment of ixekizumab (Week 0). Unless, otherwise, specified, the baseline for Overall Ixekizumab Treatment Period (Period 2, 3, and 4 combined) is defined as the last nonmissing observation on, or prior to, the date of first injection of ixekizumab. For patients originally randomized to ixekizumab during Period 2, baseline is the last nonmissing observation on, or prior to, the date of the first injection of study treatment for Period 2 (Week 0). For patients who are not originally randomized to ixekizumab in Period 2, baseline is the last nonmissing observation on, or prior to, the date of the first injection of ixekizumab (see Table RHCD.6.10 for further details).

Table RHCD.6.10. Baseline Definition for Immunogenicity Analyses for Overall Ixekizumab Treatment Period

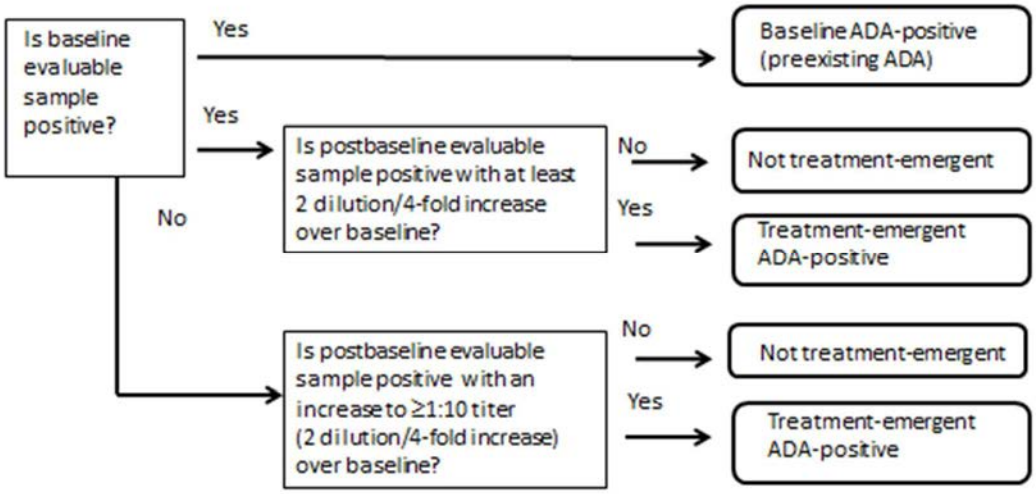
Treatment Assignment for Double-Blind Treatment Period (Period 2)	Treatment Assignment for Maintenance Period (Period 3) and Extension Period (Period 4) or Period 3 Only (Protocol Addendum RHCD[2])	Treatment Assignment for 48-Week Double-Blind, Randomized Withdrawal Period (Protocol Addendum RHCD[2] Period 4)	Baseline for Overall Ixekizumab Treatment Period Analysis[a]
Ixekizumab	Ixekizumab	NA	Week 0
Placebo	Ixekizumab	NA	Week 12
Ixekizumab	Ixekizumab	Ixekizumab	Week 0
Ixekizumab	Ixekizumab	Placebo	Week 0
Etanercept	Ixekizumab	Ixekizumab	Week 20
Etanercept	Ixekizumab	Placebo	Week 20
Placebo	Ixekizumab	Ixekizumab	Week 12
Placebo	Ixekizumab	Placebo	Week 12

Abbreviations: NA = not applicable.

[a] Last non-missing observation on, or prior to, the date of the first injection of study treatment at the defined week.

- **Baseline ADA-positive (preexisting antibody):** ADA detected in a sample collected at baseline.
- **Baseline ADA-negative:** ADA is not detected in a sample collected at baseline.
- **Treatment-emergent-(TE-) ADA positive:** a) a patient with a ≥4-fold increase over a positive baseline antibody titer (Tier 3); or b) for a negative baseline titer, a patient with an increase from the baseline to a level of ≥1:10.
- **TE-ADA inconclusive:** A patient without a TE-ADA positive sample and with at least 1 sample for which drug levels may interfere with the ADA assay.
- **TE-ADA negative:** A patient who is evaluable for TE-ADA and is not either TE-ADA positive or TE-ADA inconclusive.

Figure RHCD.6.3 illustrates the relationship of some of these terms.



Abbreviation: ADA = anti-drug antibody.

Figure RHCD.6.3. Relationship of terms for clinical interpretation of assay results for evaluable patients.

- **Incidence of TE-ADA:** Patients with TE-ADA as a proportion of the evaluable patient population during the treatment period. This excludes unevaluable patients.
- **Follow-up-emergent ADA:** ADA is first detected during the follow-up period, after study drug administration is discontinued. This category includes patients negative at baseline who increased to ≥1:10 titer (4-fold increase/ 2 dilutions) after baseline in the follow-up period or patients ADA positive at baseline and increased at least 4-fold (2 dilutions) over baseline for the first time in the follow-up period.
- **Incidence of follow-up emergent ADA:** Patients with follow-up-emergent ADA as a proportion of the follow-up evaluable patient population. This excludes unevaluable patients.

All ADA positive samples will be evaluated for NAb. Definitions for NAb patient status will be defined as follows:

- **NAb-positive:** A patient where a NAb positive result is detected for ≥1 TE-ADA positive samples.
- **NAb-inconclusive:** A patient without a NAb positive sample and with at least 1 sample for which drug levels may interfere with the NAb assay.
- **NAb-negative:** A patient who is evaluable for NAb and is not either NAb positive or NAb inconclusive.

A flow chart that reflects the connection between the analytical test results and the clinical interpretation based on the definitions is shown in Figure RHCD.6.4.

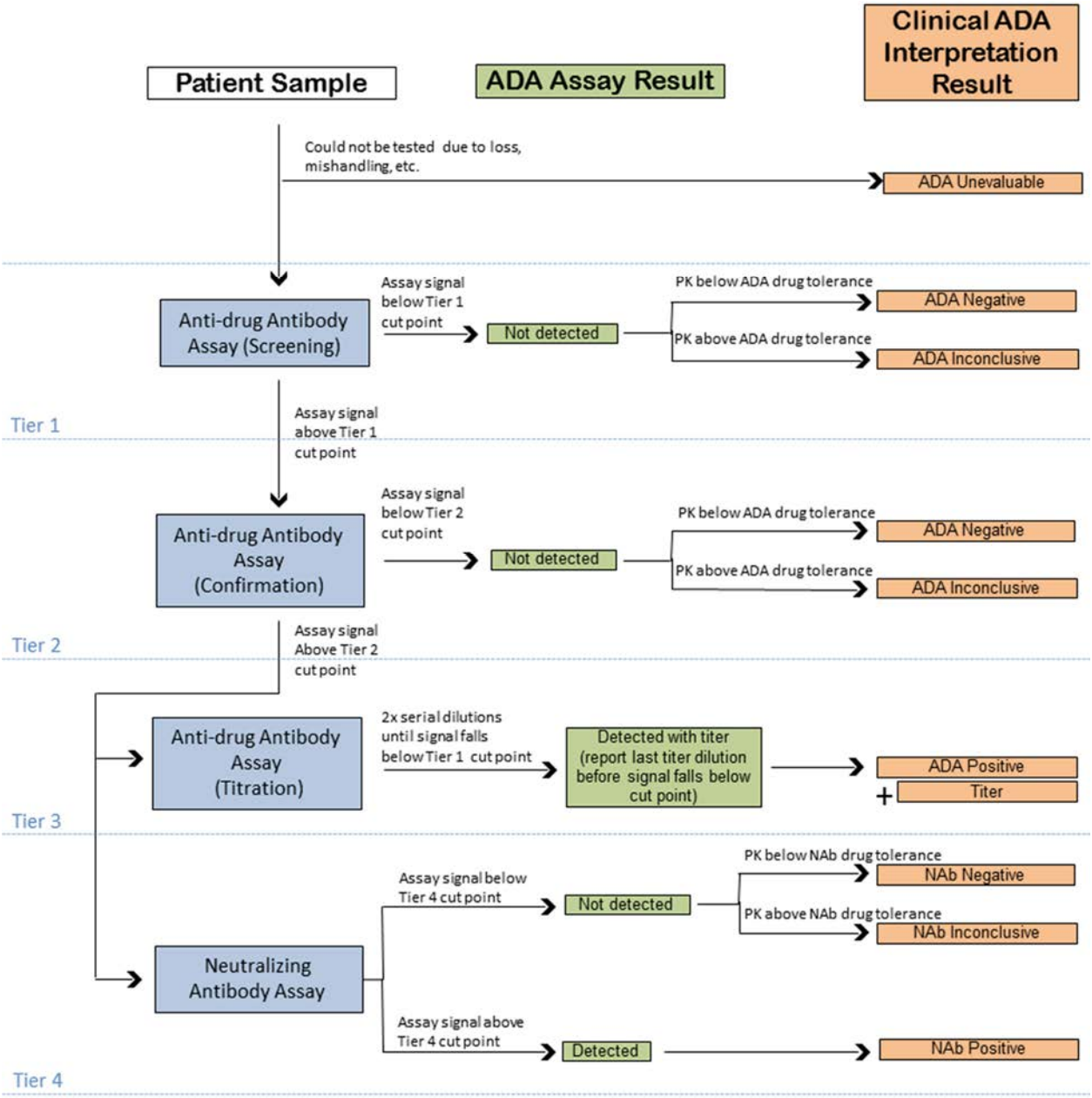


Figure RHCD.6.4. Flow chart of ADA assessment with clinical interpretation of the various result possibilities.

6.14.11.2. Immunogenicity Analyses

Immunogenicity evaluable patients will be identified as TE-ADA positive, TE-ADA negative, or TE-ADA inconclusive, according to the definitions provided in Section 6.14.11.1.2 and further grouped into TE-ADA status groups and time-varying TE-ADA status groups:

TE-ADA Status Groups:

- TE-ADA status (positive, negative, or inconclusive)
- NAb status (positive, negative, or inconclusive) for TE-ADA positive patients
- TE-ADA titer groups for TE-ADA positive patients:
  - Low Titer: TE-ADA titer value (LOCF) <1:160
  - Moderate Titer: TE-ADA titer value (LOCF) ≥1:160 and <1:1280
  - High Titer: TE-ADA titer value (LOCF) ≥1:1280

Time-Varying TE-ADA Status Groups:

Individual ADA samples will be ascribed into 3 different dichotomous variables as explained in Table RHCD.6.11. Each variable has possible values of a "greater-TE-ADA status" or a "lesser-TE-ADA status," in the sense that the level of TE-ADA detected in the greater-TE-ADA category is higher than in the lesser-TE-ADA category.

Table RHCD.6.11. TE-ADA Status Dichotomous Variables for AE Analysis

TE-ADA Status Dichotomous Variable	Greater-TE-ADA Status	Lesser-TE-ADA Status
TE-ADA positive	TE-ADA positive	not TE-ADA positive
TE-ADA moderate-to-high	TE-ADA positive with moderate titer or high titer	not TE-ADA positive, or TE-ADA positive with low titer
TE-ADA high status	TE-ADA positive with high titer	not TE-ADA positive, or TE-ADA positive with low or moderate titer

Abbreviations: TE-ADA = treatment-emergent antidrug antibodies/

Note: for purpose of this analysis, TE-ADA Inconclusive is taken to be "not TE-ADA positive." A TE-ADA low is defined as a TE-ADA positive with a titer value <1:160; a TE-ADA moderate is defined as a TE-ADA positive with a titer value ≥1:160 and <1:1280; and a TE-ADA high is defined as a TE-ADA positive with a titer value ≥1:1280.

For each TE-ADA status dichotomous variable, a time-varying TE-ADA status will be computed. At time *t*, the TE-ADA status is taken to be the highest of the TE-ADA values bracketing time *t*. More formally, the TE-ADA status at time *t* is given by the greater of: (a) the TE-ADA status at the most-recent postbaseline measurement prior to *t*; and (b) the TE-ADA status at the first TE-ADA postbaseline measurement at or after time *t*. In this computation, "greater" is given by the greater-TE-ADA status of Table RHCD.6.11. If there is no value satisfying criterion (a), then the value (b) is used. Similarly, if there is no value (b), then the value (a) is used.

For each TE-ADA status dichotomous variable, patients will be categorized according to whether they were: (1) always in lesser-TE-ADA status postbaseline; or (2) at some point postbaseline, were in greater-TE-ADA status.

6.14.11.2.1. Analyses of Characteristics of ADA Immune Response

The analyses of ADA effects will be conducted on all evaluable patients within the defined Safety Population for Period 2, All Ixekizumab Population for Combined Treatment Period (Period 2, 3, and 4 combined), and Follow-Up Population for Period 5.

The overall frequency and percentage (incidence) of patients will be summarized for the TE-ADA status groups and the time-varying TE-ADA status groups. Scheduled visits, unscheduled visits, and repeat measurements will be included.

The time to the development of TE-ADAs (TE-ADA positive, low titer, moderate titer, high titer, and NAb positive) will be calculated as follows:

Time to development of TE-ADAs/NAb (in weeks) = (Date of development of TE-ADAs/NAb – Date of first injection of study treatment + 1) / 7.

If a patient has not developed TE-ADAs/NAbs, he/she will be censored at the date of the last immunogenicity assessment. If a patient does not have any postbaseline assessments for immunogenicity, he/she will be censored at the date of randomization.

Descriptive statistics, including 25th percentile, 50th percentile (median), 75th percentile, and corresponding 95% CIs, as well as probability of TE-ADA/NAb positive by endpoint summarized by treatment group, will also be provided if sufficient data is present. A Kaplan-Meier plot of the time to development of treatment-emergent ADA/NAb will be presented by treatment group, also if sufficient data is present. Caution should be exercised in the interpretation of time-to-event analyses and related statistics, given the limited sampling scheme for immunogenicity testing.

For each TE-ADA status dichotomous variable (as defined in Table RHCD.6.11), summaries will be provided of the total postbaseline time in the greater-TE-ADA status for patients who were at some point postbaseline in the greater-TE-ADA status group. Postbaseline time in greater-TE-ADA status for each patient will be aggregated.

A by-patient listing to include treatment, visit date, visit, ADA result, TE-ADA result, NAb result, ADA titer value, ixekizumab concentration, and ADA and NAb inconclusive results will also be provided, for patients with any one sample of ADA (or NAb) positive or inconclusive.

6.14.11.2.2. Analyses of Treatment-Emergent ADA Effects on Efficacy

Efficacy analyses for Period 2 will be conducted on all evaluable patients within the ITT Population.

Analyses will be performed to examine how patient TE-ADA effects PASI 75 and sPGA(0,1) response rates at week 12 with NRI by the TE-ADA status groups as described in Section 6.14.11.1.2.

A logistic regression model with treatment group, TE-ADA status and the interaction of treatment group-by-TE-ADA status included as factors will be used to test the interaction of treatment group -by-TE-ADA status for ITT Population during Period 2. The p-value associated

with the interaction term will be used to assess if the treatment groups effect is consistent across TE-ADA status groups. When the interaction term is statistically significant, the association between responder status and treatment groups depends, in some manner, on the status. The interaction will be tested at the 10% significance level. Treatment group differences will be evaluated within each TE-ADA subgroup using Fisher's exact test, regardless of whether the interaction is statistically significant.

6.14.11.2.3. Analyses of Treatment-Emergent ADA on Specific Adverse Events

The analyses of TE-ADA effects on safety will be conducted on all evaluable patients within the defined Safety Population for Period 2 and All Ixekizumab Population for combined Periods 2, 3, and 4.

Adverse events of special interest of allergic reaction/hypersensitivity (anaphylaxis and nonanaphylaxis) and of injection-site reactions will be included in an assessment of AE to TE-ADA over time. See Section 6.14.3.1 for the definitions of the AESIs. Timing of an AE will be taken to be the reported AE start date.

For each TE-ADA status dichotomous variable (as defined in Table RHCD.6.11), patients will be categorized according to whether they were: (1) always in lesser-TE-ADA status postbaseline; or (2) at some point postbaseline, were in greater-TE-ADA status. For each AESI, within the time-varying TE-ADA status groups, a summary will be provided of the number of patients who had no event, events only while in lesser-TE-ADA status for group (1), or – for group (2) – at least 1 event while in greater-TE-ADA status.

Additionally, summaries will be provided of the total number of AESI events (with unique start dates) by time-varying TE-ADA status groups at the event date. The summaries will aggregate time respectively in greater-TE-ADA status and in lesser-TE-ADA status, along with the event rates (rates per 100 patient-years) relative to those aggregate times.

By-patient listings will be provided of patients with TE-ADA who experience a treatment-emergent allergic reaction/hypersensitivity reaction or an injection site reaction.

6.15. Subgroup Analyses

6.15.1. Efficacy Subgroup Analyses

Subgroup analysis will be conducted for the co-primary endpoints of proportion of patients achieving PASI 75 and sPGA (0,1) response using the ITT Population for Period 2.

Subgroups to be evaluated may include gender, age, weight, ethnicity, region, geographic region, baseline disease severity, duration of disease, previous nonbiologic systemic therapy, and previous biologic therapy.

A logistic regression model with treatment, subgroup, and interaction of subgroup-by-treatment included as factors will be used. The subgroup-by-treatment interaction will be tested at the significance level of 0.10. Treatment group differences will be evaluated within each category of the subgroup using the Fisher's exact test, regardless of whether the interaction is statistically

significant. Missing data will be imputed using NRI. If any group within the subgroup is <10% of the Total ITT Population, only summaries of the efficacy data will be provided (that is, no inferential testing).

The following subgroups will be analyzed:

- Patient Demographics Subgroups:
    - Gender
    - Age Group (years): <12; and ≥12
    - Weight Category: <25 kg; ≥25 to ≤50 kg; and >50 kg (only summary statistics)
    - Ethnicity
- Geographic Region Subgroups:
    - Geographic Region: North America; Europe Union; and Rest of the World
- Baseline Severity of Disease Subgroups:
    - Baseline PASI category: <20; and ≥20
    - Baseline sPGA category: 3; 4; and 5
    - Baseline sPGA category: 3; and combined 4 or 5
    - Baseline BSA category: <20%; and ≥20%
- Previous Psoriasis Therapy Subgroups:
    - Previous Nonbiologic Systemic Therapy (methotrexate, cyclosporine, retinoids, corticosteroid, fumaric acid derivatives, apremilast, psoralen and ultraviolet A [PUVA]): never used; and ever used
    - Previous Biologic Systemic Therapy: never used; and ever used
- Other Patient Characteristics Subgroups:
    - Duration of Disease (in years): >0.5 and <=1; >1 and <=1.5; >1.5 and <=2; and >2

Additional subgroup analyses on efficacy may be performed, as deemed appropriate and necessary.

6.15.2. Safety Subgroup Analyses

Safety subgroup analysis for common TEAEs and AESI of infections and injection site reactions will be summarized for P2 Main Study Safety Population. The common TEAEs will be presented by decreasing frequency of PT within SOC. The infections and injection site reactions will be presented by decreasing frequency of PT

A logistic regression model with treatment, subgroup, and the interaction of subgroup-by-treatment included as factors will be used. The subgroup-by- treatment interaction will be tested at the significance level of 0.10. The response variable will be each AE. Treatment group differences will be evaluated within each category of the subgroup using Fisher's exact test, regardless of whether the interaction is statistically significant. If any group within the subgroup is <10% of the total population, only the descriptive statistics will be provided for that subgroup (that is, no inferential testing).

The following subgroups will be analyzed:

- Weight Category: <25 kg; ≥25 to ≤50 kg; and >50 kg
- Geographic Region: North America; Europe Union; and Rest of the World

Additional subgroup analyses on safety may be performed, as deemed appropriate and necessary.

6.16. Protocol Deviations

Protocol deviations will be identified throughout the study. Important protocol deviations are defined as those deviations from the protocol likely to have a significant impact on the completeness, accuracy, and/or reliability of the study data, or that may significantly affect subject's rights, safety, or well-being.

The major protocol deviations, which are the subset of the important protocol deviations, are the protocol deviations that might have impact on the efficacy and/or safety results. The impact of major protocol deviations on the efficacy results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis population, both by including and excluding the data potentially affected by major protocol deviations. As specified in Section 6.1.1, the PPS Population is defined as all randomized patients who do not have major protocol deviations.

Table RHCD.6.12 includes the categories and subcategories of important protocol deviations, whether or not these deviations are major protocol violations, the action to be taken regarding the exclusion of patients from PPS, the source of the deviation identified, and the statistical programming guidance for the clinical study report (CSR).

The number and percentage of patients having important protocol deviation(s) will be summarized within category and subcategory of deviations by treatment group for the ITT Population for the Double-Blind Treatment Period (Period 2).

A by-patient listing of important protocol deviations will be provided.

Table RHCD.6.12. Identification and Action of Important Protocol Deviations

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]	Statistical Programming Guidance for Clinical Study Report
Category: Eligibility			
Subcategory: Inclusion/Exclusion			
[1] No confirmed diagnosis of moderate-to-severe plaque-type Ps for at least 6 months prior to Visit 2	Excluded from PPS	Monitor and Stats	Either from monitor's list, or, if date of diagnosis of Ps is missing or less than 6 months prior to Visit 2.
[2] PASI score <12 or sPGA <3 or BSA involvement <10% at Visit 1 or Visit 2	Excluded from PPS	Monitor and Stats	Either from monitor's list, or, If PASI score <12 or sPGA <3 or BSA involvement <10% or any missing at Visit 1 or Visit 2.
[3] Not a candidate for phototherapy or systemic therapy	Excluded from PPS	Monitor	From monitor's list.
[4] Age <6 years or ≥18 years	Excluded from PPS	Monitor	From monitor's list.
[5] Improper informed consent	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or, if patient informed consent date is after Visit 1 date.
[6] Immunizations are not up to date in agreement with current immunization guidelines	Excluded from PPS	Monitor	From monitor's list.
[7] Have pustular, erythrodermic, and/or guttate forms of Ps	Excluded from PPS	Monitor	From monitor's list.
[8] With drug-induced Ps	Excluded from PPS	Monitor	From monitor's list.
[9] Have clinical and/or laboratory evidence of untreated latent or active TB	Excluded from PPS	Monitor and Stats	From monitor's list, or If a PPD skin test response of ≥5 mm in duration, or a "positive" for the QuantiFERON-TB® Gold test or T-SPOT.TB test.

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]	Statistical Programming Guidance for Clinical Study Report
[10] Have evidence of or test positive for hepatitis B virus (HBV)	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or, if test positive for HBV at Visit 1 by testing: 1) positive for hepatitis B surface antigen (HBsAg+); or 2) positive for anti-hepatitis B core antibody (HBcAb+) and are HBV deoxyribonucleic acid (DNA) positive. Note: Subjects who are HBcAb+ and HBV DNA negative may be enrolled in the study. Subjects who meet these criteria at screening will be identified by the central laboratory and monitored during the study.
[11] Have evidence of or test positive for hepatitis C virus (HCV)	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or, if test positive for HCV at Visit 1 by testing: 1) positive for hepatitis C antibody (anti-HCVAb); and 2) positive via a confirmatory test for HCV.
[13] Have any varicella-zoster virus infection within 12 weeks of Visit 2	Do not exclude from PPS	Monitor	From monitor's list.
[22] Presence of significant uncontrolled neuropsychiatric disorder, or have had a recent past history of a suicide attempt, or marked a yes to C-SSRS question 4 or 5 on ideation or yes to suicide behaviors	Do not exclude from PPS	Monitor	From monitor's list
[24] Have not had any immunizations, or are not up to date on immunizations recommended by country specific Pediatric guidance	Do not exclude from PPS	Monitor	From monitor's list.
[29] At Visit 1, have a neutrophil count <1500 cells/μL (<1.50×10^9/μL or <1.50 GI/L), a lymphocyte count <800 cells/μL (<0.80×10^9/μL or <0.80 GI/L), a platelet count <100,000 cells/μL (<100×10^9/μL or <100 GI/L)	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or, If have a neutrophil count <1500 cells/μL (<$1.50x10^9$/μL or <1.50 GI/L, a lymphocyte count <800 cells/μL (<$0.80x10^9$/μL or <0.80 GI/L), a platelet count <100,000 cells/μL (<$100x10^9$/μL or <100 GI/L) or missing at Visit 1.
[32] Previously treated with etanercept	Excluded from PPS	Monitor and Stats	Either from monitor's list, or, If have etanercept in the CRFs "*Prior Therapy: Psoriasis*".

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]	Statistical Programming Guidance for Clinical Study Report
[33] Have used any therapeutic agent targeted at reducing interleukin-17 (IL-17)	Excluded from PPS	Monitor	From monitor's list.
[35] Had a live vaccination within 12 weeks prior to Visit 2, or intend to have a live vaccination during the course of the study or within 12 weeks of completing treatment in this study, or have participated in a vaccine clinical study within 12 weeks prior to Visit 2	Do not exclude from PPS	Monitor	From monitor's list.
Category: Study Procedures			
Subcategory: Violation of Discontinuation Criteria			
[D1] ALT or AST >8× ULN	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or, if a patient still receives study treatment after 10 days with confirmed ALT or AST >8× ULN (defined as a test of 8× ULN and a retest within 10 days still >8 × ULN; if not retest, use the test as the confirmed).
[D2] ALT or AST >5× ULN for more than 2 weeks	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or, if a patient still receives study treatment after 24 days with confirmed ALT or AST >5× ULN (defined as a test of 5× ULN and a retest within 14 days still >5× ULN; if not retest, use the test as the confirmed).
[D3] ALT or AST >3× ULN and TBL >2 × ULN or prothrombin time >1.5 time ULN	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or, if a patient still receives study treatment after 10 days with confirmed ALT or AST >3× ULN and TBL >2× ULN or prothrombin time >1.5× ULN (defined as a test of 3× ULN and 2× ULN or 1.5× ULN and a retest within 10 days still >3× ULN and 2× ULN or 1.5× ULN; if not retest, use the test as the confirmed).
[D4] ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or, If a patient still receives study treatment after 10 days with confirmed ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) (defined as a test of 3× ULN and a retest within 10 days still >3× ULN; if not retest, use the test as the confirmed).

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]	Statistical Programming Guidance for Clinical Study Report
[D5] ALP >3× ULN	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or, If a patient still receives study treatment after 10 days with confirmed ALP >3× ULN (defined as a test of 3× ULN and a retest within 10 days still >3× ULN; if not retest, use the test as the confirmed).
[D6] ALP >2.5× ULN and TBL >2× ULN	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or, If a patient still receives study treatment after 10 days with confirmed ALP >2.5× ULN and TBL >2× ULN (defined as a test of 3× ULN and 2× ULN and a retest within 10 days still >3× ULN and 2× ULN; if not retest, use the test as the confirmed).
[D7] ALP >2.5× ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or, If a patient still receives study treatment after 10 days with confirmed ALP >2.5× ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) (defined as a test of 2.5× ULN and a retest within 10 days still >2.5× ULN; if not retest, use the test as the confirmed).
[D8] Neutrophil counts <500 cells/μL, or ≥500 and <1000 cells/μL based on 2 test results, or ≥1000 and <1500 cells/μL based on 3 test results and a concurrent infection	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or, If a patient still receives study treatment after 10 days with confirmed segmented neutrophil counts <500 cells/μL (defined as a test of <500 cells/μL and a retest within 10 days still <500 cells/μL; if no retest, use the test as the confirmed).
[D9] Total WBC count <2000 cells/μL	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or, If a patient still receives study treatment after 10 days with confirmed total WBC count <2000 cells/ μL (defined as a test of <2000 cells/μL and a retest within 10 days still <2000 cells/μL; if no retest, use the test as the confirmed)
[D10] Lymphocyte count <200 cells/μL	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or, If a patient still receives study treatment after 10 days with confirmed lymphocyte count <200 cells/μL (defined as a test of <200 cells/μL and a retest within 10 days still <200 cells/μL; if no retest, use the test as the confirmed).

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]	Statistical Programming Guidance for Clinical Study Report
[D11] Platelet count <50,000 cells/μL	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or, If a patient still receives study treatment after 10 days with confirmed platelet count <50,000 cells/μL (defined as a test of <50,000 cells/μL and a retest within 10 days still <50,000 cells/μL; if no retest, use the test as the confirmed).
[D12] Subject BP readings are greater than 95th percentile at 3 consecutive study visits	Do not exclude from PPS	Monitor	From monitor's list.
[D13] A severe AE or an SAE, or a clinically significant change in a laboratory value	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or, If patient still receives study treatment on the same day or after the date with an AE or SAE.
[D14] Clinically significant systemic hypersensitivity reaction that does not respond to treatment	Do not exclude from PPS	Monitor	From monitor's list.
[D15] Patient became pregnant	Do not exclude from PPS	Monitor	From monitor's list.
[D16] Patient developed a malignancy (more than 2 nonmelanoma skin cancers)	Do not exclude from PPS	Monitor	From monitor's list.
[D17] Patient has a positive TB test using PPD or QuantiFERON®-TB Gold	Do not exclude from PPS	Monitor	From monitor's list.
[D18] Change in disease phenotype	Excluded from PPS	Monitor	From monitor's list.
[D19] Patient requires treatment with another therapeutic agent that has been demonstrated to be effective for the treatment of Ps	Excluded from PPS	Monitor	From monitor's list.
[D20] Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study	Excluded from PPS	Monitor	From monitor's list.
[D21] The investigator or attending physician decides that the patient should be withdrawn from the study treatment	Do not exclude from PPS	Monitor	From monitor's list.

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]	Statistical Programming Guidance for Clinical Study Report
[D22] The patient (or guardian) requests to be withdrawn from the study treatment	Do not exclude from PPS	Monitor	From monitor's list.
[D23] The patient, at any time during the study, scores ≥5 for Item 13 on the CDRS-R. Or	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or, score ≥5 to Item 13 (Suicidal Ideation) of CDRS-R.
[D24] Develops active suicidal ideation with some intent to act with or without a specific plan	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or, yes to question 4 or 5 on the "Suicidal Ideation" Portion of C-SSRS.
[D25] Develops suicide-related behaviors as recorded on C-SSRS	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or, yes to question "suicidal behavior" on the "Suicidal Behavior" Portion of C-SSRS.
[D26] It is recommended that the subject be assessed by an appropriately trained professional to assist in deciding whether the subject is to be discontinued from the study	Do not exclude from PPS	Monitor	From monitor's list.
[D27] Investigator or Lilly stopped the patient participation	Do not exclude from PPS	Monitor	From monitor's list.
Category: Study Procedures			
Subcategory: Excluded Con-meds	Excluded from PPS	Monitor and Stats	Either from monitor's list, or If patient takes prohibited concomitant medication. Note: Prohibited concomitant medication will be provided by medical in a separate file.
Subcategory: Other			
Missing CDRS-R total score: missing baseline or any scheduled visit prior to discontinuation visit	Do not exclude from PPS	Stats	If missing CDRS-R total score baseline or any scheduled visit prior to discontinuation visit.
Missing C-SSRS: missing baseline or any scheduled visit prior to discontinuation visit	Do not exclude from PPS	Stats	If missing C-SSRS baseline or any scheduled visit prior to discontinuation visit. C-SSRS is missing if the whole questionnaire is missing.

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]	Statistical Programming Guidance for Clinical Study Report
Missing sPGA: not having Week 12 measurement for patients who have completed Week 12	Do not exclude from PPS. Note: such patients will be treated as nonresponders at Week 12	Stats	If not having Week 12 sPGA measurement for patient who have completed week 12.
Missing PASI: not having Week 12 measurement for patients who have completed Week 12	Do not exclude from PPS. Note: such patients will be treated as nonresponders at Week 12	Stats	If not having Week 12 PASI measurement for patient who have completed week 12.
Had unqualified site personnel perform clinical safety and/or efficacy assessments	Do not exclude from PPS	Monitor	From monitor's list.
Missing parents/other adult to respond CDRS-R scale at any visit	Do not exclude from PPS	Monitor	From monitor's list.
Missing or Unqualified blinded assessor	Do not exclude from PPS	Monitor	From monitor's list.
Category: Investigational Product			
Subcategory: Treatment Assignment/Randomization Error			
Took incorrect study medication	Do not exclude from PPS. Analyze "As randomized" or "As assigned."	Stats	If IWRS study drug dispense data not match with the treatment label identifier on the Exposure as Collected eCRF page.
Moderate-to-severe patients from etanercept approved countries randomized as severe	Do not exclude from PPS	Monitor and Stats	Either from monitor's list, or If patient with PASI <20 and sPGA <4 at baseline received etanercept in P2.

Important Protocol Deviation Category/Subcategory/Study Specific	Action for PPS Analysis	Source to Identify Protocol Deviation[a]	Statistical Programming Guidance for Clinical Study Report
Subcategory: Compliance	Excluded from PPS	Stats	If non-compliant with study medication regimen or over-dose during the treatment period. Note: Non-compliance with therapy is defined to be missing more than 20% of expected doses and missing 2 or more consecutive doses; over-dose is defined as to take more injections at the same time point than specified in the protocol.
Subcategory: Patient took medication not fit for use	Do not excluded from PPS	Monitor	From monitor's list.
Subcategory: Other			
Randomized but did not take any study medication	Excluded from PPS	Stats	If a patient is randomized but does not take any study medication.
Overdose/ Underdose in terms of actual volume of IP	Excluded from PPS	Monitor	From monitor's list.
Category: Safety			
Subcategory: SAEs			
Failure to report within 24 hours of the PI aware	Do not Excluded from PPS	Monitor	From monitor's list.
Category: Informed Consent			
Subcategory: Informed Consent not Obtained/Missing/Late	Excluded from PPS	Monitor and Stats	Either from monitor's list, or, if patient informed consent date is after Visit 1 date or missing informed consent.
Subcategory: Improper Informed Consent	Do not Excluded from PPS	Monitor	From monitor's list.
Category: Administrative/Oversight			
Subcategory: Reg/Ethic Approvals	Excluded from PPS	Monitor	From monitor's list.
Subcategory: Other			
Enrolled in a site with significant GCP noncompliance issue	Excluded from PPS	Monitor	From monitor's list.

Abbreviations: AE = adverse event; BCG = Bacille de Calmette et Guérin; BSA = body surface area; CDRS-R = Children's Depression Rating Scale–Revised; Con-Meds = concomitant medications; C-SSRS = Columbia–Suicide Severity Rating Scale; DV = protocol deviations; eCRF = electronic case report form; GCP = good clinical practice; IgG = immunoglobulin G; IL = interleukin; ITT = intent-to-treat; IV = intravenous; IWRS = interactive web-response system; PASI = Psoriasis Area and Severity Index; PPD = purified protein derivative; PPS = per protocol set; Ps = psoriasis; PsA = psoriatic arthritis; Reg = regulatory; SAE = serious adverse event; sPGA = static Physician Global Assessment; stats = statistics; TB = tuberculosis; TBL = total bilirubin.

[a] The term "Monitor" indicates the protocol deviation will be identified by site monitors and entered into monitor's list using a spreadsheet. The spreadsheet will be exported as Study Data Tabulation Model (SDTM) DV domain.
The term "Stats" indicates the protocol deviation will be programmed based on data in clinical database by statistical programmers with the statistical programming guidance provided as the last column. The detailed programming specification will be documented in Analysis Data Model (ADaM) specification.
The terms "Monitor and Stats" indicates the protocol deviation will be a combination of monitor's list (SDTM.DV domain) and statistical programming from clinical database, the deviation will show if either source identifies.

6.17. Interim Analyses and Data Monitoring

Two planned interim analyses will be conducted with an conditional third dependent upon enrollment.

A staggered approach to enrollment by weight group will be used so that a minimum of 15 subjects >12 years and >50 kg will be enrolled and safety evaluated for the initial 12 weeks of dosing before opening enrollment in the middle weight group (25 to 50 kg).
When approximately 15 subjects have enrolled in the middle weight group and completed up to Week 12, an analysis of all available PK data will be conducted to confirm that exposures are within the range expected. All safety data from these subjects will also be analyzed at this time in addition to select efficacy data. Doses for the remaining subjects in the study will be confirmed, based on these analyses. Once confirmed, all weight groups will be open for enrollment of the remaining subjects needed to complete the study.

The first interim analysis will be conducted after approximately 15 subjects in the 25- to 50-kg weight group have completed to Week 12. Pharmacokinetic, safety, and efficacy data on all subjects will be evaluated during this interim. The analysis will include all data available at this time – that is, it will include data from subjects in both weight groups who have enrolled at the time of the interim. The analysis of the data will be conducted by statisticians and PK/PD scientists external to the study team (statistical assessment center). The statistical assessment center will provide the analyses to a data monitoring committee (DMC) consisting of members external to Lilly. The DMC will recommend whether changes to weight-based dosing are necessary, based on the analysis. This committee will consist of 2 physicians external to Lilly, a pediatrician and a dermatologist, a statistician external to Lilly, and an nonvoting PK/PD member internal to Lilly, but external to the study team. No member of the DMC may have contact with study sites. Only the DMC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their subjects.

Study sites will receive information about interim results ONLY if they need to know for the safety of their subjects.

The second interim database lock and unblinding will occur and the analysis will be performed at the time (that is, a cutoff date) the last subject completes Study Period 2 (Week 12) or ETV. This interim database lock will include all data collected by the cutoff date including follow-up data from subjects that have begun Periods 3, 4, or 5. Because the study will still be ongoing at the time of this database lock, the analysis will be referred to as an interim analysis. This interim analysis includes the final analysis for the Double-Blind Treatment Period (Period 2) of the study; therefore, there is no alpha adjustment due to this interim analysis. The DMC is not needed for this interim analysis.

Additional analyses and snapshots of study data may be performed during and/or after completion of Period 3 and/or Period 4 to fulfill the need for regulatory interactions or publication purposes.

Enrollment of each geographic region will be closely monitored. If 120 subjects from the United States and Canada complete the 12-week Double-Blind Randomized Period, and if other regions are behind in reaching their enrollment goal, an additional interim analysis may be conducted to include only the subjects from the United States and Canada to meet the US submission timeline. The DMC is not needed for this interim analysis. The analysis specified in this SAP for Period 2 will be conducted using the ITT Population and Safety Population subsetting on subjects from the United States and Canada and removing the term "region" from the analysis models. There will be no alpha adjustment applied as this will be considered the primary analysis for some regulatory agencies. The details will be documented in the unblinding plan.

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

6.18. Planned Exploratory Analyses

The following analyses will be conducted for exploratory purposes and are not intended to be included in the CSR.

6.18.1. Psychometric Analyses of the Itch NRS

Following the examination of the distributional characteristics of measures, the following psychometric properties of the instruments will be evaluated: test-retest reliability; convergent validity; known-groups validity; and sensitivity to change (responsiveness) using anchor- and distribution-based methods.

6.18.1.1. Descriptive Statistics

Descriptive statistics (sample size, mean, standard deviation [SD], minimum, median, maximum, and % missing) will be calculated for the Itch NRS, including scores from Baseline to Week 12. The frequency distributions for Itch NRS responses will be calculated at Baseline and Week 12. Floor and ceiling effects will be evaluated at Baseline. A cut-off of >25% will be used to indicate floor/ceiling effects (McHorney et al. 1994).

6.18.1.2. Test-Retest Reliability

Test-retest reliability has been emphasized by the Food and Drug Administration (FDA) as an important aspect of reliability in the FDA Patient-Reported outcome (PRO) Guidance (FDA 2009). Test-retest reliability reflects the ability of the instrument to give reproducible results when the clinical state is stable and indicates the degree to which a measure produces consistent results over several administrations. Test-retest reliability will be assessed using intra-class correlations coefficients (ICCs) and paired sample t-tests among stable patients only. The ICC will be used to assess the association between Itch NRS at Week 0 and Week 1 in the subsample of placebo arm patients with the same rating on the sPGA at Week 0 and Week 1.

Intra-class correlations coefficients range from 0 to 1.0, with higher scores indicating a more stable instrument. The hypothesis is that there will be no significant differences in scale scores when there is no change in disease status. An ICC of $\geq$0.70 will be considered substantial agreement (Nunnally and Bernstein 1994).

6.18.1.3. Construct Validity

6.18.1.3.1. Convergent and Discriminant Validity

Construct validity is the degree to which a measure is related to other measures or constructed in a manner that is consistent with theory. *Convergent validity* involves demonstrating that different measures of the same concept substantially correlate, while *discriminant validity* demonstrates that concepts that are supposed to be unrelated are, in fact, unrelated.

Convergent validity will be assessed by Pearson correlations and Spearman rank-based correlation coefficient at baseline and at Week 12 between scores of the Itch NRS and other assessments, including PASI, sPGA, PatGA, DLQI (assessed in patients aged >16 years), and CDLQI (assessed in patients aged 6-16 years).

Cohen's conventions will be used to interpret the absolute value of the correlation results, where a correlation >0.5 is large, 0.3 to ≤0.5 is moderate, 0.1 to <0.3 is small, and <0.1 is insubstantial (Cohen 1988). It is hypothesized that small-to-moderate correlations at baseline and moderate-to-large (≥0.30) correlations at Week 12 are expected between the Itch NRS and PASI, sPGA, PatGA, and DLQI / CDLQI total scores.

Additionally, convergent and discriminant validity will be assessed by Pearson correlation and Spearman rank-based correlation at baseline and at Week 12 between scores of the Itch NRS and the DLQI / CDLQI 6 domains: Symptoms and Feelings, Daily Activities, Leisure, Work and School, Personal Relationships, and Treatment (note the CDLQI domains are Symptoms and Feelings, Sleep, Leisure, School or Holidays, Personal Relationships, and Treatment). It is hypothesized that the Itch NRS will correlate higher with the DLQI / CDLQI Symptoms and Feelings domain than with the other 5 DLQI domains.

6.18.1.3.2. Known-Groups Validity

Known-group validity is the extent to which scores from an instrument are different for groups of participants that differ on a relevant clinical or other indicator. Determining known-group validity involves evaluating an instrument in relation to clinical measures of disease status (Stewart et al. 1992; Hays and Revicki 2005). Known-groups validity of the Itch NRS will be evaluated using analysis of covariance to distinguish the Itch NRS scores between subgroups defined on the basis of sPGA score at baseline: sPGA score of 3; or combined 4 and 5. Patients with more severe plaques are hypothesized to report significantly greater itching severity.

6.18.1.4. Responsiveness

Responsiveness will be evaluated by correlating calculated changes from baseline in scores on the Itch NRS with changes in PASI, sPGA, and PatGA scores at 12 weeks. Moderate-to-large correlations are hypothesized based on Cohen's conventions. Additionally, responsiveness will be evaluated using 1-way ANCOVA, adjusted for Itch NRS baseline score, for overall and independent-sample t-tests for paired comparisons with Scheffe's correction-based post-hoc tests in distinguishing between subgroups, defined on the basis of the following:

1) PASI scores at Week 12: (1) PASI improved ≥75%; (2) PASI improved ≥50% to <75%; and (3) PASI got worse or improved <50%

2) sPGA scores at Week 12: sPGA score of 0 or 1 to those subjects with sPGA score >1
3) PatGA scores at Week 12: PatGA no change, improved, or worsened

It is hypothesized that an overall statistically significant difference will be observed ($p<.05$) with at least 1 statistically significant subgroup comparison (for example, PASI improved ≥75% vs. PASI got worse or improved <50%).

The above responsiveness analysis will be repeated using an ANOVA model (without Itch NRS baseline score) as a sensitivity analysis.

6.18.1.5. Clinical Significance (Minimal Within-Patient Change)

To aid in the interpretation of the Itch NRS results we will propose a range of thresholds that will contain minimal within-patient change (MWPC) in scores in the target patient population for FDA review. FDA is interested in what constitutes a meaningful within-patient change in scores from the ***patient perspective,*** i.e. individual patient level (FDA 2018). A number of analytic methods will be used to assess the MWPC of the Itch NRS. The results of these analyses can be used to guide score interpretation. Both anchor-based methods and distribution-based methods will be used for evaluating MWPC. However, anchor-based methods are preferred by the FDA for interpretation of PRO scores (FDA 2009), and will be considered the primary analysis. Distribution-based methods will be considered supportive and secondary (Revicki et al. 2008).

6.18.1.5.1. Anchor-Based Method

The following analyses will be conducted to confirm the a priori defined Itch NRS ≥4-point reduction from baseline response criterion. The MWPC threshold for Itch NRS improvement will be derived by using the primary anchor variable of sPGA status at Week 12. As a secondary anchor, the PatGA will be used. The mean and median Itch NRS score improvement will be derived for patients meeting the anchor definitions for meaningful improvement.

The anchor-based analyses are as follows:

1) Determining the associations between sPGA and Itch NRS; and PatGA and Itch NRS. This will be assessed by Pearson and Spearman correlations at baseline and change from baseline to Week 12. Note these associations will be assessed in previously described convergent validity and responsiveness analyses.
2) Categorizing the primary anchor variable, the sPGA change (baseline to Week 12) as:
    - ≥2 point improvement and sPGA = 0,1
    - ≥2 point improvement and sPGA = 2,3
    - 1 point improvement
    - no change
    - ≥1 point worsening of sPGA
3) Categorizing the secondary anchor variable, the PatGA (baseline to Week 12) as:
    - ≥2 point improvement
    - 1 point improvement
    - no change
    - 1 point worsening

- ≥2 point worsening

If sample size in any above category <10 then it will be combined with adjacent category

6.18.1.5.2. Distribution-Based Methods

Distribution-based methods will provide supportive evidence for the MWPC, secondary to the anchor-based methods..

6.18.1.5.2.1. Standard Error of Measurement

Standard error of measurement has been proposed as a useful distribution-based statistic for evaluating clinically meaningful change in health-related quality of life (HRQL) measures (Wyrwich et al. 1999a; Wyrwich et al. 1999b). The SEM describes the error associated with the measure, and is estimated by the Baseline SD of the measure multiplied by the square root of 1 minus its reliability coefficient (ICC from the test-retest assessment). Previous research suggests that 1 SEM is roughly associated with a clinically important difference for PRO measures (Wyrwich et al. 1999a, Guyatt et al. 2002). Other research suggests changes (or differences) of 0.20 to 0.30 effect size may be indicative of a minimal important difference (Osoba and King 2005; Revicki et al. 2008).

An alternative distribution-based approach consists of calculating a 0.5 SD of the scales of interest at Baseline. It has been suggested that one-half of an SD of a measure represents a clinically meaningful change, while a change corresponding to 0.2 of an SD of measure is a small effect (Norman and Streiner 2003). The 0.5 SD estimate can be considered to provide an upper boundary for what would constitute a meaningful change, while 0.2 provides a lower boundary (Revicki et al. 2008). Given that a clinically important change is of interest, a 0.5 SD will be used, with a 0.2 SD calculated to provide reference for range.

The number and percentage of patients meeting the various RDs derived from anchor- and distribution-based methods for each measure will also be calculated.

Using the results from both the anchor- and distribution-based approaches, triangulation across possible thresholds indicating a minimal, but meaningful change will be considered.

6.18.1.5.2.2. Empirical Cumulative Distribution Functions

As a complement to the confirmation of the MWPC, empirical cumulative distribution function (eCDF) curves will be calculated for the Itch NRS. The eCDF is a continuous (both positive and negative) presentation of the Itch NRS change from basline score at Week 12 on the X-axis and a cumulative proportion of patients with that level of score change on the Y-axis. The eCDF curve will be plotted for each anchor category. The meaningful-within patient threshold of the itch NRS should be considered by the eCDF of the anchor category where patients have experienced a meaningful improvement by definition of the anchor measure.

6.18.1.5.2.3. Probability Density Functions

To aid in the interpretation of the eCDF analyses, probability density function (PDF) curves will be estimated using kernel density estimation of change in the Itch NRS to Week 12 by change in

anchor category. The PDF will present the same data as the eCDF but with probability density on the Y axis.

6.19. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and "other" AEs are summarized by treatment group and by MedDRA PT.

- An AE is considered "serious" whether or not it is a TEAE.
- An AE is considered in the "other" category if it is both a TEAE and is not serious. For each SAE and "other" AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced
- Consistent with www.ClinicalTrials.gov requirements, "other" AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

7. Unblinding Plan

Refer to a separate blinding and unblinding plan.

8. References

Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol*. 2008;159(5):997-1035.

[CDC] Centers for Disease Control and Prevention resources page. National Center for Health Statistics. Data table of weight-for-age charts. Available at: http://www.cdc.gov/growthcharts/html_charts/wtage.htm. Accessed October 20, 2016.

Cohen, J. Statistical power analysis for the behavioral sciences (2nd ed.) Hillsdale, NJ: Erlbaum; 1988.

Columbia University Medical Center. Columbia‑Suicide Severity Rating Scale (C-SSRS) web site. Available at: http://www.cssrs.columbia.edu. Accessed January 13, 2016.

DeVellis RF. Scale Development: Theory and Applications. Newbury Park, CA, USA: Sage, 1991.

Diggle PJ, Liang KY, Zeger SL. Analysis of longitudinal data. Oxford: Clarendon Press; 1994.

[EMA] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. November 18, 2004; CHMP/EWP/2454/02 corr. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003329.pdf. Accessed October 19, 2016.

[FDA] Food and Drug Administration. Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims. *Fed Regist*. 2009;74(235):65132-65133.

[FDA] Food and Drug Administration. PATIENT-FOCUSED DRUG DEVELOPMENT GUIDANCE PUBLIC WORKSHOP: Methods to Identify What is Important to Patients & Select, Develop or Modify Fit-for-Purpose Clinical Outcomes Assessments. Workshop date: October 15-16 2018.

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19(3):210-216.

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

Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, Reich K, Amato D, Ball SG, Braun DK, Cameron GS, Erickson J, Konrad RJ, Muram TM, Nickoloff BJ, Osuntokun OO, Secrest RJ, Zhao F, Mallbris L, Leonardi CL; UNCOVER-1 Study Group; UNCOVER-2 Study Group; UNCOVER-3 Study Group. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med.* 2016;375(4):345-356.

Griffiths CE, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, Cameron GS, Erickson J, Zhang L, Secrest RJ, Ball S, Braun DK, Osuntokun OO, Heffernan MP, Nickoloff BJ, Papp K; UNCOVER-2 and UNCOVER-3 investigators. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet*. 2015;386(9993):541-551.

Guyatt GH, Osoba D, Wu AW, et al. Methods to explain the clinical significance of health status measures. Paper presented at: Mayo Clinic Proceedings; 2002.

Hays RD, Revicki D. Reliability and validity (including responsiveness). In: Fayers P, Hays RD, eds. Assessing Quality of Life in Clinical Trials: Methods and Practice. 2nd ed. New York, NY: Oxford University Press; 2005:25-39.

Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? *J Invest Dermatol.* 2005;125(4):659-664.

Khilji FA, Gonzalez M, Finlay AY. Clinical meaning of change in Dermatology Life Quality Index scores. *Br J Dermatol*. 2002;147(suppl 62):50.

Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, Li S, Dooley LT, Gordon KB; PHOENIX 1 study investigators. Efficacy and safety of ustekinumab, a human interleukin- 12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet.* 2008;371(9625):1665-1674. [Erratum appears in Lancet. 2008;371(9627):1838].

Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *Br J Dermatol.* 1995;132(6):942-949.

Mayes TL, Bernstein IH, Haley CL, Kennard BD, Emslie GJ. Psychometric properties of the Children's Depression Rating Scale-Revised in adolescents. *J Child Adolesc Psychopharmacol.* 2010;20(6):513-516.

McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Medical care.* Jan 1994;32(1):40-66.

[NIH] National Institutes of Health. The Fourth Report on The Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Revised May 2005. Available at: https://www.nhlbi.nih.gov/files/docs/resources/heart/hbp_ped.pdf. Accessed Mar 20, 2017.

Norman GR, Streiner DL. *PDQ statistics.* Vol 1: PMPH-USA; 2003.

Nunnally JC, Bernstein I. *Psychometric theory.* 3 ed. New York,: McGraw-Hill; 1994.

Osoba D, King M. Meaningful differences. *Assessing quality of life in clinical trials.* 2005;2:243-257.

Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, Guzzo C, Hsu M-C, Wang Y, Li S, Dooley LT, Reich K. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet.* 2008;371(9625):1675-1684

Poznanski EO, Mokros HB. Children's depression rating scale, revised (CDRS-R). Los Angeles: Western Psychological Services; 1996.

Rasmussen AR, Wohlfahrt-Veje C, Tefre de Renzy-Martin K, Hagen CP, Tinggaard J, Mouritsen A, Mieritz MG, Main KM. Validity of self-assessment of pubertal maturation. *Pediatrics.* 2015;135(1):86-93.

Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *J. Clin. Epidemiol*. 2008;61(2):102-109.

Salek MS, Jung S, Brincat-Ruffini LA, MacFarlane L, Lewis-Jones MS, Basra MK, Finlay AY. Clinical experience and psychometric properties of the Children's Dermatology Life Quality Index (CDLQI), 1995-2012. *Br J Dermatol.* 2013;169(4):734-759.

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, Brown SG, Camargo CA Jr, Cydulka R, Galli SJ, Gidudu J, Gruchalla RS, Harlor AD Jr, Hepner DL, Lewis LM, Lieberman PL, Metcalfe DD, O'Connor R, Muraro A, Rudman A, Schmitt C, Scherrer D, Simons FE, Thomas S, Wood JP, Decker WW. Second symposium on the definition and management of anaphylaxis: Summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391–397.

Schisterman EF, Perkins NJ, Liu A, Bondell H. Optimal cut-point and its corresponding Youden Index to discriminate individuals using pooled blood samples. *Epidemiology*. 2005;16(1):73-81.

Stewart A, Hays R, Ware J. Methods of validating MOS health measures. In: Stewart A, Ware J, eds. Measuring Functioning and Well-being: The Medical Outcomes Study Approach. Durham, NC: Duke University Press; 1992:25-39.

Van Voorhees A, Feldman SR, Koo JYM, Lebwohl MG, Menter A. The psoriasis and psoriatic arthritis pocket guide. National Psoriasis Foundation. 2009. Available at: https://www.psoriasis.org/sites/default/files/accessing-health-care/FY10_Pocket_Guide_WEB.pdf. Accessed November 18, 2016.

Waters A, Sandhu D, Beattie P, Ezughah F, Lewis-Jones S. Severity stratification of Children's Dermatology Life Quality Index (CDLQI) scores [abstract]. *Br J Dermatol.* 2010;163(Suppl 1):121.

Wyrwich KW, Nienaber NA, Tierney WM,Wolinksy FD. Linking clinical relevance and statistical significance in evaluating intra-individual changes in health-related quality of life. *Med Care.* 1999a;37(5):469-478.

Wyrwich KW, Tierney WM, Wolinsky FD. Further evidence supporting an SEM-based criterion for identifying meaningful intra-individual changes in health-related quality of life. *J Clin Epidemiol*. 1999b;52(9):861-873.

9. Appendices

Appendix 1. Concomitant Topical Therapy Definition

This appendix provides the instruction to derive flags for patients who took concomitant topical therapy or concomitant topical steroid therapy for ixekizumab psoriasis and psoriatic arthritis studies.

- **Concomitant Topical Therapy** – defined as patients who took concomitant medications which met all the following conditions:
    1) Route = topical
    2) Indication for use = primary study condition
    3) ATC codes (defined in the table below):
       D07-- (level 2, include all sub-levels), A11CC, D05AC, D05BB, L04AD, D02AF, D05AA,
       D02A- (Level 3, include all sub-levels), D05AX, V90

- **Concomitant Topical Steroid Therapy** – defined as patients who took concomitant medications which met all the following conditions:
    1) Route = topical
    2) Indication for use = primary study condition
    3) ATC code: D07-- (level 2, include all sub-levels)

Reference Table: List of Topical Treatments that are Prescribed/Administered for Psoriasis or Psoriatic Arthritis Patients with Appropriate ATC Code

Topical Treatments	ATC Code
Topical corticosteroids: These powerful anti-inflammatory drugs are the most frequently prescribed medications for treating mild-to-moderate psoriasis. They slow cell turnover by suppressing the immune system, which reduces inflammation and relieves associated itching. Topical corticosteroids range in strength from mild to very strong. Low-potency corticosteroid ointments are usually recommended for sensitive areas, such as your face or skinfolds, and for treating widespread patches of damaged skin. Your doctor may prescribe stronger corticosteroid ointment for small areas of your skin, for persistent plaques on your hands or feet, or when other treatments have failed. Medicated foams and scalp solutions are available to treat psoriasis patches on the scalp. Long-term use or overuse of strong corticosteroids can cause thinning of the skin and resistance to the treatment's benefits. To minimize side effects and to increase effectiveness, topical corticosteroids are generally used on active outbreaks until they are under control.	D07-- (Level 2)
Vitamin D analogs: These synthetic forms of vitamin D slow down the growth of skin cells. Calcipotriene (Dovonex) is a prescription cream or solution containing a vitamin D analog that may be used alone to treat mild-to-moderate psoriasis or in combination with other topical medications or phototherapy. This treatment can irritate the skin. Calcitriol (Rocaltrol) is expensive, but may be equally effective and possibly less irritating than calcipotriene.	A11CC
Anthralin: This medication is believed to normalize DNA activity in skin cells. Anthralin (Dritho-Scalp) can also remove scale, making the skin smoother. However, anthralin can irritate skin, and it stains virtually anything it touches, including skin, clothing, countertops, and bedding. For that reason, doctors often recommend short-contact treatment – allowing the cream to stay on your skin for a brief time before washing it off. Anthralin is sometimes used in combination with ultraviolet light.	D05AC
Topical retinoids: These are commonly used to treat acne and sun-damaged skin, but tazarotene (Tazorac, Avage) was developed specifically for the treatment of psoriasis. Like other vitamin A derivatives, it normalizes DNA activity in skin cells and may decrease inflammation. The most common side effect is skin irritation. It may also increase sensitivity to sunlight, so sunscreen should be applied while using the medication. Although the risk of birth defects is far lower for topical retinoids than for oral retinoids, your doctor needs to know if you are pregnant or intend to become pregnant if you are using tazarotene.	D05BB
Calcineurin inhibitors: Currently, calcineurin inhibitors – tacrolimus (Prograf) and pimecrolimus (Elidel) – are approved only for the treatment of atopic dermatitis, but studies have shown them to be effective, at times, in the treatment of psoriasis. Calcineurin inhibitors are thought to disrupt the activation of T cells, which in turn reduces inflammation and plaque buildup. The most common side effect is skin irritation. Calcineurin inhibitors are not recommended for long-term or continuous use because of a potential increased risk of skin cancer and lymphoma. Calcineurin inhibitors are used only with your doctor's input and approval. They may be especially helpful in areas of thin skin, such as around the eyes, where steroid creams or retinoids are too irritating or may cause harmful effects.	L04AD
Salicylic acid: Available over-the-counter (nonprescription) and by prescription, salicylic acid promotes sloughing of dead skin cells, and reduces scaling. Sometimes it is combined with other medications, such as topical corticosteroids or coal tar, to increase its effectiveness. Salicylic acid is available in medicated shampoos and scalp solutions to treat scalp psoriasis.	D02AF
Coal tar: A thick, black byproduct of the manufacture of petroleum products and coal, coal tar is probably the oldest treatment for psoriasis. It reduces scaling, itching, and inflammation. Exactly how it works is not known. Coal tar has few known side effects, but it is messy, stains clothing and bedding, and has a strong odor. Coal tar is available in over-the-counter shampoos, creams, and oils. It is also available in higher concentrations by prescription.	D05AA

Topical Treatments	ATC Code
Moisturizers: By themselves, moisturizing creams will not heal psoriasis, but they can reduce itching and scaling and can help combat the dryness that results from other therapies. Moisturizers in an ointment base are usually more effective than are lighter creams and lotions.	D02A- (Level 3)
Calcipotriene	D05AX
Tazarotene	D05AX
Herbal and traditional preparations	V90

Note: ATC = WHOCC Anatomical Therapeutic Chemical classification system; WHOCC = World Health Organization Collaborating Centre for Drug Statistics Methodology.

Appendix 2. Anti-infective Treatments and Anatomical Therapeutic Chemical (ATC) Code List

ATC Code	ATC Level	ATC Description (Based on ATC Dictionary 18JAN2016)
A01AB	4	ANTIINFECTIVES AND ANTISEPTICS FOR LOCAL ORAL TREA
A02BD	4	COMBINATIONS FOR ERADICATION OF HELICOBACTER PYLOR
A07A	3	INTESTINAL ANTIINFECTIVES
A07AA	4	ANTIBIOTICS
A07AB	4	SULFONAMIDES
A07AC	4	IMIDAZOLE DERIVATIVES
A07AX	4	OTHER INTESTINAL ANTIINFECTIVES
B05CA	4	ANTIINFECTIVES
C05AB	4	ANTIBIOTICS
D01	2	ANTIFUNGALS FOR DERMATOLOGICAL USE
D01A	3	ANTIFUNGALS FOR TOPICAL USE
D01AA	4	ANTIBIOTICS
D01AC	4	IMIDAZOLE AND TRIAZOLE DERIVATIVES
D01AE	4	OTHER ANTIFUNGALS FOR TOPICAL USE
D01B	3	ANTIFUNGALS FOR SYSTEMIC USE
D01BA	4	ANTIFUNGALS FOR SYSTEMIC USE
D06	2	ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGIC
D06A	3	ANTIBIOTICS FOR TOPICAL USE
D06AA	4	TETRACYCLINE AND DERIVATIVES
D06AX	4	OTHER ANTIBIOTICS FOR TOPICAL USE
D06B	3	CHEMOTHERAPEUTICS FOR TOPICAL USE
D06BA	4	SULFONAMIDES
D06BB	4	ANTIVIRALS
D06BX	4	OTHER CHEMOTHERAPEUTICS
D06C	3	ANTIBIOTICS AND CHEMOTHERAPEUTICS, COMBINATIONS
D07C	3	CORTICOSTEROIDS, COMBINATIONS WITH ANTIBIOTICS
D07CA	4	CORTICOSTEROIDS, WEAK, COMBINATIONS WITH ANTIBIOTICS
D07CB	4	CORTICOSTEROIDS, MODERATELY POTENT, COMBINATIONS WITH ANTIBIOTICS
D07CC	4	CORTICOSTEROIDS, POTENT, COMBINATIONS WITH ANTIBIOTICS
D07CD	4	CORTICOSTEROIDS, VERY POTENT, COMBINATIONS WITH ANTIBIOTICS
D09AA	4	MEDICATED DRESSINGS WITH ANTIINFECTIVES
D10AF	4	ANTIINFECTIVES FOR TREATMENT OF ACNE
G01AA	4	ANTIBIOTICS
G01AC	4	QUINOLINE DERIVATIVES
G01AE	4	SULFONAMIDES
G01AF	4	IMIDAZOLE DERIVATIVES
G01AG	4	TRIAZOLE DERIVATIVES
G01AX	4	OTHER ANTIINFECTIVES AND ANTISEPTICS
G01BA	4	ANTIBIOTICS AND CORTICOSTEROIDS

ATC Code	ATC Level	ATC Description (Based on ATC Dictionary 18JAN2016)
G01BC	4	QUINOLINE DERIVATIVES AND CORTICOSTEROIDS
G01BE	4	SULFONAMIDES AND CORTICOSTEROIDS
G01BF	4	IMIDAZOLE DERIVATIVES AND CORTICOSTEROIDS
G04AB	4	QUINOLONE DERIVATIVES (EXCL. J01M)
G04AC	4	NITROFURAN DERIVATIVES
G04AG	4	OTHER URINARY ANTISEPTICS AND ANTIINFECT
G04AH	4	SULFONAMIDES IN COMBINATION WITH OTHER DRUGS
G04AK	4	URINARY ANTISEPT&ANTIINF, COMB EXCL SULFONAMIDES
J01	2	ANTIBACTERIALS FOR SYSTEMIC USE
J01A	3	TETRACYCLINES
J01AA	4	TETRACYCLINES
J01B	3	AMPHENICOLS
J01BA	4	AMPHENICOLS
J01C	3	BETA-LACTAM ANTIBACTERIALS, PENICILLINS
J01CA	4	PENICILLINS WITH EXTENDED SPECTRUM
J01CE	4	BETA-LACTAMASE SENSITIVE PENICILLINS
J01CF	4	BETA-LACTAMASE RESISTANT PENICILLINS
J01CG	4	BETA-LACTAMASE INHIBITORS
J01CR	4	COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE
J01D	3	OTHER BETA-LACTAM ANTIBACTERIALS
J01DA	4	CEPHALOSPORINS AND RELATED SUBSTANCES
J01DB	4	FIRST-GENERATION CEPHALOSPORINS
J01DC	4	SECOND-GENERATION CEPHALOSPORINS
J01DD	4	THIRD-GENERATION CEPHALOSPORINS
J01DE	4	FOURTH-GENERATION CEPHALOSPORINS
J01DF	4	MONOBACTAMS
J01DH	4	CARBAPENEMS
J01DI	4	OTHER CEPHALOSPORINS
J01E	3	SULFONAMIDES AND TRIMETHOPRIM
J01EA	4	TRIMETHOPRIM AND DERIVATIVES
J01EB	4	SHORT-ACTING SULFONAMIDES
J01EC	4	INTERMEDIATE-ACTING SULFONAMIDES
J01ED	4	LONG-ACTING SULFONAMIDES
J01EE	4	COMBINATIONS OF SULFONAMIDES AND TRIMETHOPRIM, INC
J01F	3	MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS
J01FA	4	MACROLIDES
J01FF	4	LINCOSAMIDES
J01FG	4	STREPTOGRAMINS
J01G	3	AMINOGLYCOSIDE ANTIBACTERIALS
J01GA	4	STREPTOMYCINS
J01GB	4	OTHER AMINOGLYCOSIDES
J01M	3	QUINOLONE ANTIBACTERIALS
J01MA	4	FLUOROQUINOLONES
J01MB	4	OTHER QUINOLONES
J01R	3	COMBINATIONS OF ANTIBACTERIALS
J01RA	4	COMBINATIONS OF ANTIBACTERIALS

ATC Code	ATC Level	ATC Description (Based on ATC Dictionary 18JAN2016)
J01WA	4	HERBAL ANTIBACTERIALS FOR SYSTEMIC USE
J01WB	4	HERBAL URINARY ANTISEPTICS AND ANTIINFECTIVES
J01X	3	OTHER ANTIBACTERIALS
J01XA	4	GLYCOPEPTIDE ANTIBACTERIALS
J01XB	4	POLYMYXINS
J01XC	4	STEROID ANTIBACTERIALS
J01XD	4	IMIDAZOLE DERIVATIVES
J01XE	4	NITROFURAN DERIVATIVES
J01XX	4	OTHER ANTIBACTERIALS
J02	2	ANTIMYCOTICS FOR SYSTEMIC USE
J02A	3	ANTIMYCOTICS FOR SYSTEMIC USE
J02AA	4	ANTIBIOTICS
J02AB	4	IMIDAZOLE DERIVATIVES
J02AC	4	TRIAZOLE DERIVATIVES
J02AX	4	OTHER ANTIMYCOTICS FOR SYSTEMIC USE
J04AA	4	AMINOSALICYLIC ACID AND DERIVATIVES
J04AB	4	ANTIBIOTICS
J04AC	4	HYDRAZIDES
J04AK	4	OTHER DRUGS FOR TREATMENT OF TUBERCULOSIS
J04AM	4	COMBINATIONS OF DRUGS FOR TREATMENT OF TUBERCULOSI
J04B	3	DRUGS FOR TREATMENT OF LEPRA
J04BA	4	DRUGS FOR TREATMENT OF LEPRA
J05	2	ANTIVIRALS FOR SYSTEMIC USE
J05A	3	DIRECT ACTING ANTIVIRALS
J05AA	4	THIOSEMICARBAZONES
J05AB	4	NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRI
J05AC	4	CYCLIC AMINES
J05AD	4	PHOSPHONIC ACID DERIVATIVES
J05AE	4	PROTEASE INHIBITORS
J05AF	4	NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE IN
J05AG	4	NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS
J05AH	4	NEURAMINIDASE INHIBITORS
J05AR	4	ANTIVIRALS FOR TREATMENT OF HIV INFECTIONS, COMBIN
J05AX	4	OTHER ANTIVIRALS
P01A	3	AGENTS AGAINST AMOEBIASIS AND OTHER PROTOZOAL DISE
P01AA	4	HYDROXYQUINOLINE DERIVATIVES
P01AB	4	NITROIMIDAZOLE DERIVATIVES
P01AC	4	DICHLOROACETAMIDE DERIVATIVES
P01AR	4	ARSENIC COMPOUNDS
P01AX	4	OTHER AGENTS AGAINST AMOEBIASIS AND OTHER PROTOZOA
P01BA	4	AMINOQUINOLINES
P01BC	4	METHANOLQUINOLINES
P01BD	4	DIAMINOPYRIMIDINES
P01BE	4	ARTEMISININ AND DERIVATIVES, PLAIN
P01BF	4	ARTEMISININ AND DERIVATIVES, COMBINATIONS
P01BX	4	OTHER ANTIMALARIALS

ATC Code	ATC Level	ATC Description (Based on ATC Dictionary 18JAN2016)
P01C	3	AGENTS AGAINST LEISHMANIASIS AND TRYPANOSOMIASIS
P01CA	4	NITROIMIDAZOLE DERIVATIVES
P01CB	4	ANTIMONY COMPOUNDS
P01CC	4	NITROFURAN DERIVATIVES
P01CD	4	ARSENIC COMPOUNDS
P01CX	4	OTHER AGENTS AGAINST LEISHMANIASIS AND TRYPANOSOMI
P02	2	ANTHELMINTICS
P02B	3	ANTITREMATODALS
P02BA	4	QUINOLINE DERIVATIVES AND RELATED SUBSTANCES
P02BB	4	ORGANOPHOSPHOROUS COMPOUNDS
P02BX	4	OTHER ANTITREMATODAL AGENTS
P02C	3	ANTINEMATODAL AGENTS
P02CA	4	BENZIMIDAZOLE DERIVATIVES
P02CB	4	PIPERAZINE AND DERIVATIVES
P02CC	4	TETRAHYDROPYRIMIDINE DERIVATIVES
P02CE	4	IMIDAZOTHIAZOLE DERIVATIVES
P02CF	4	AVERMECTINES
P02CX	4	OTHER ANTINEMATODALS
P02D	3	ANTICESTODALS
P02DA	4	SALICYLIC ACID DERIVATIVES
P02DW	4	HERBAL ANTICESTODALS
P02DX	4	OTHER ANTICESTODALS
P02WA	4	HERBAL ANTHELMINTICS
P03A	3	ECTOPARASITICIDES, INCL. SCABICIDES
P03AA	4	SULFUR CONTAINING PRODUCTS
P03AB	4	CHLORINE CONTAINING PRODUCTS
P03AC	4	PYRETHRINES, INCL. SYNTHETIC COMPOUNDS
P03AX	4	OTHER ECTOPARASITICIDES, INCL. SCABICIDES
P03BA	4	PYRETHRINES
R02AB	4	ANTIBIOTICS
S01A	3	ANTIINFECTIVES
S01AA	4	ANTIBIOTICS
S01AB	4	SULFONAMIDES
S01AD	4	ANTIVIRALS
S01AE	4	FLUOROQUINOLONES
S01AX	4	OTHER ANTIINFECTIVES
S01C	3	ANTIINFLAMMATORY AGENTS AND ANTIINFECTIVES IN COMB
S01CA	4	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION
S01CB	4	CORTICOSTEROIDS/ANTIINFECTIVES/MYDRIATICS IN COMBI
S01CC	4	ANTIINFLAMMATORY AGENTS, NON-STEROIDS AND ANTIINFECTIVES
S02A	3	ANTIINFECTIVES
S02AA	4	ANTIINFECTIVES
S02C	3	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION
S02CA	4	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION
S03A	3	ANTIINFECTIVES
S03AA	4	ANTIINFECTIVES

ATC Code	ATC Level	ATC Description (Based on ATC Dictionary 18JAN2016)
S03C	3	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION
S03CA	4	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION

Abbreviation: ATC = WHOCC Anatomical Therapeutic Chemical classification system; INCL. = including; WHOCC = World Health Organization Collaborating Centre for Drug Statistics Methodology.

Appendix 3. Lilly-Defined MedDRA V21.0 Preferred Terms for Opportunistic Infections (OIs)

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
Pneumocystis jirovecii (II)	Pneumocystis jirovecii infection Pneumocystis jirovecii pneumonia	Narrow
	Blood beta-D-glucan Blood beta-D-glucan abnormal Blood beta-D-glucan increased Gomori methenamine silver stain Carbon monoxide diffusing capacity decreased Carbon monoxide diffusing capacity Pneumocystis test positive	Broad
Human Polyomavirus Infection including BK virus disease and PVAN (V), and Progressive Multifocal Leukoencephalopathy (IV)	BK virus infection Human polyomavirus infection JC virus granule cell neuronopathy JC virus infection Polyomavirus-associated nephropathy Progressive multifocal leukoencephalopathy	Narrow
	Anti-JC virus antibody index JC polyomavirus test JC virus test JC virus test positive Polyomavirus test Polyomavirus test positive	Broad
Cytomegalovirus disease (V)	Cytomegalovirus chorioretinitis Cytomegalovirus colitis Cytomegalovirus duodenitis Cytomegalovirus enteritis Cytomegalovirus enterocolitis Cytomegalovirus gastritis Cytomegalovirus gastroenteritis Cytomegalovirus gastrointestinal infection Cytomegalovirus gastrointestinal ulcer Cytomegalovirus hepatitis Cytomegalovirus infection Cytomegalovirus mononucleosis Cytomegalovirus mucocutaneous ulcer Cytomegalovirus myelomeningoradiculitis Cytomegalovirus myocarditis Cytomegalovirus oesophagitis Cytomegalovirus pancreatitis Cytomegalovirus pericarditis	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	Cytomegalovirus syndrome Cytomegalovirus urinary tract infection Cytomegalovirus viraemia Disseminated cytomegaloviral infection Encephalitis cytomegalovirus Pneumonia cytomegaloviral	
	Cytomegalovirus test Cytomegalovirus test positive	Broad
Post-transplant lymphoproliferative disorder (EBV) (V)	Epstein-Barr virus associated lymphoma Epstein-Barr virus associated lymphoproliferative disorder Epstein Barr virus positive mucocutaneous ulcer Post transplant lymphoproliferative disorder	Narrow
	Epstein-Barr viraemia Epstein-Barr virus infection Lymphoproliferative disorder Lymphoproliferative disorder in remission Oral hairy leukoplakia	Broad
Bartonellosis (disseminated disease only) (V)	Bacillary angiomatosis Peliosis hepatis Splenic peliosis Systemic bartonellosis Trench fever	Narrow
	Bartonella test Bartonella test positive Bartonellosis Cat scratch disease	Broad
Blastomycosis (IV)	Blastomycosis Epididymitis blastomyces Osteomyelitis blastomyces Pneumonia blastomyces	Narrow
	NA	Broad
Toxoplasmosis (myocarditis, pneumonitis, or characteristic retinochoroiditis only) (IV)	Cerebral toxoplasmosis Eye infection toxoplasmal Hepatitis toxoplasmal Meningitis toxoplasmal Myocarditis toxoplasmal Pneumonia toxoplasmal	Narrow
	Toxoplasma serology Toxoplasma serology positive Toxoplasmosis	Broad
Coccidioidomycosis (II)	Coccidioides encephalitis Coccidioidomycosis Cutaneous coccidioidomycosis	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	Meningitis coccidioides	
	NA	Broad
Histoplasmosis (II)	Acute pulmonary histoplasmosis Chronic pulmonary histoplasmosis Endocarditis histoplasma Histoplasmosis Histoplasmosis cutaneous Histoplasmosis disseminated Meningitis histoplasma Pericarditis histoplasma Retinitis histoplasma	Narrow
	Presumed ocular histoplasmosis syndrome	Broad
Aspergillosis (invasive disease only) (II)	Aspergillosis oral Cerebral aspergillosis Meningitis aspergillus Oro-pharyngeal aspergillosis	Narrow
	Aspergillus infection Aspergillus test Aspergillus test positive Bronchopulmonary aspergillosis Sinusitis aspergillus	Broad
Candidiasis (invasive disease or oral) (II)	Candida endophthalmitis Candida osteomyelitis Candida pneumonia Candida retinitis Candida sepsis Cerebral candidiasis Endocarditis candida Fungal oesophagitis Gastrointestinal candidiasis Hepatic candidiasis Hepatosplenic candidiasis Meningitis candida Oesophageal candidiasis Oropharyngeal candidiasis Peritoneal candidiasis Splenic candidiasis Systemic candida	Narrow
	Bladder candidiasis Candida infection Candida test Candida test positive Mucocutaneous candidiasis Oral candidiasis Oral fungal infection Respiratory moniliasis	Broad

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
Cryptococcosis (II)	Cryptococcal cutaneous infection Cryptococcal fungaemia Cryptococcosis Disseminated cryptococcosis Gastroenteritis cryptococcal Meningitis cryptococcal Neurocryptococcosis Osseous cryptococcosis Pneumonia cryptococcal	Narrow
	Cryptococcus test Cryptococcus test positive	Broad
Other invasive fungi: Mucormycosis (zygomycosis), *Rhizopus*, *Mucor*, and *Lichtheimia*, *Scedosporum/ Pseudallescheria boydii*, *Fusarium* (II)	Allescheriosis Fusarium infection Mucormycosis Scedosporium infection Phaeohyphomycosis Phaeohyphomycotic brain abscess Pseudallescheria infection Pseudallescheria sepsis	Narrow
	See "Non-specific terms" below	Broad
Legionellosis (II)	Legionella infection Pneumonia legionella Pontiac fever	Narrow
	Legionella test Legionella test positive	Broad
Listeria monocytogenes (invasive disease only) (II)	Listeria encephalitis Listeria sepsis Meningitis listeria	Narrow
	Listeria test Listeria test positive Listeraemia Listeriosis	Broad
Tuberculosis (I)	Adrenal gland tuberculosis Bone tuberculosis Choroid tubercles Conjunctivitis tuberculous Cutaneous tuberculosis Disseminated Bacillus Calmette-Guerin infection Disseminated tuberculosis Ear tuberculosis Epididymitis tuberculous	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	Extrapulmonary tuberculosis Immune reconstitution inflammatory syndrome associated tuberculosis Intestinal tuberculosis Joint tuberculosis Lymph node tuberculosis Male genital tract tuberculosis Meningitis tuberculous Oesophageal tuberculosis Oral tuberculosis Pericarditis tuberculous Peritoneal tuberculosis Prostatitis tuberculous Pulmonary tuberculoma Pulmonary tuberculosis Renal tuberculosis Salpingitis tuberculous Silico tuberculosis Spleen tuberculosis Thyroid tuberculosis Tuberculid Tuberculoma of central nervous system Tuberculosis Tuberculosis bladder Tuberculosis gastrointestinal Tuberculosis liver Tuberculosis of central nervous system Tuberculosis of eye Tuberculosis of genitourinary system Tuberculosis of intrathoracic lymph nodes Tuberculosis of peripheral lymph nodes Tuberculosis ureter Tuberculous abscess central nervous system Tuberculous endometritis Tuberculous laryngitis Tuberculous pleurisy Tuberculous tenosynovitis	
	Interferon gamma release assay Interferon gamma release assay positive Mycobacterium tuberculosis complex test Mycobacterium tuberculosis complex test positive Tuberculin test Tuberculin test false negative Tuberculin test positive	Broad
Nocardiosis (II)	Cutaneous nocardiosis	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	Nocardia sepsis Nocardiosis Pulmonary nocardiosis	
	Nocardia test positive	Broad
Nontuberculous *Mycobacterium* disease (II)	Atypical mycobacterial infection Atypical mycobacterial lower respiratory tract infection Atypical mycobacterial lymphadenitis Atypical mycobacterial pneumonia Atypical mycobacterium pericarditis Borderline leprosy Bovine tuberculosis Indeterminate leprosy Leprosy Lepromatous leprosy Mycobacterial infection Mycobacterial peritonitis Mycobacterium abscessus infection Mycobacterium avium complex immune restoration disease Mycobacterium avium complex infection Mycobacterium chelonae infection Mycobacterium fortuitum infection Mycobacterium kansasii infection Mycobacterium marinum infection Mycobacterium ulcerans infection Superinfection mycobacterial Tuberculoid leprosy Type 1 lepra reaction Type 2 lepra reaction	Narrow
	Atypical mycobacterium test positive Mycobacterial disease carrier Mycobacterium leprae test positive Mycobacterium test Mycobacterium test positive	Broad
Salmonellosis (invasive disease only) (II)	Aortitis salmonella Arthritis salmonella Meningitis salmonella Osteomyelitis salmonella Paratyphoid fever Pneumonia salmonella Salmonella bacteraemia Salmonella sepsis Typhoid fever	Narrow
	Salmonella test positive Salmonellosis	Broad

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
HBV reactivation (IV)	Hepatitis B reactivation	Narrow
	Asymptomatic viral hepatitis Chronic hepatitis B HBV-DNA polymerase increased Hepatitis B Hepatitis B antigen Hepatitis B antigen positive Hepatitis B core antigen Hepatitis B core antigen positive Hepatitis B DNA assay Hepatitis B DNA assay positive Hepatitis B DNA increased Hepatitis B e antigen Hepatitis B e antigen positive Hepatitis B surface antigen Hepatitis B surface antigen positive Hepatitis B virus test Hepatitis B virus test positive Hepatitis infectious Hepatitis post transfusion Hepatitis viral Withdrawal hepatitis	Broad
Herpes simplex (invasive disease only) (IV)	Colitis herpes Gastritis herpes Herpes oesophagitis Herpes sepsis Herpes simplex colitis Herpes simplex encephalitis Herpes simplex gastritis Herpes simplex hepatitis Herpes simplex meningitis Herpes simplex meningoencephalitis Herpes simplex meningomyelitis Herpes simplex necrotising retinopathy Herpes simplex oesophagitis Herpes simplex pneumonia Herpes simplex sepsis Herpes simplex viraemia Herpes simplex visceral Meningitis herpes Meningoencephalitis herpetic Meningomyelitis herpes Pneumonia herpes viral	Narrow
	Eczema herpeticum Herpes ophthalmic Herpes simplex	Broad

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	Herpes simplex DNA test positive Herpes virus infection Herpes virus test abnormal Herpes simplex virus test positive Ophthalmic herpes simplex	
Herpes zoster (any form) (II)	Disseminated varicella zoster vaccine virus infection Encephalitis post varicella Genital herpes zoster Herpes zoster Herpes zoster cutaneous disseminated Herpes zoster disseminated Herpes zoster infection neurological Herpes zoster meningitis Herpes zoster meningoencephalitis Herpes zoster meningomyelitis Herpes zoster necrotising retinopathy Herpes zoster oticus Herpes zoster pharyngitis Necrotising herpetic retinopathy Ophthalmic herpes zoster	Narrow
	Varicella zoster virus infection Varicella virus test Varicella virus test positive	Broad
Stronglyoides (hyperinfection syndrome and disseminated forms only) (IV)	Strongyloidiasis	Narrow
	NA	Broad
Paracoccidioides infections (V)	Paracoccidioides infection Pulmonary paracoccidioidomycosis	Narrow
	NA	Broad
Penicillium marneffei (V)	Penicilliosis	Narrow
	Penicillium test positive	Broad
Sporothrix schenckii (V)	Cutaneous sporotrichosis Pulmonary sporotrichosis Sporotrichosis	Narrow
	NA	Broad
Cryptosporidium species (chronic disease only) (IV)	Biliary tract infection cryptosporidial	Narrow
	Cryptosporidiosis infection Gastroenteritis cryptosporidial	Broad
Microsporidiosis (IV)	Microsporidia infection	Narrow
	NA	Broad
Leishmaniasis (Visceral only) (IV)	Visceral leishmaniasis	Narrow
	Leishmaniasis	Broad
Trypanosoma cruzi infection (Chagas' Disease) (progression of chronic and disseminated disease	Chagas' cardiomyopathy Meningitis trypanosomal	Narrow
	American trypanosomiasis	Broad

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
only) (V)	Trypanosomiasis Trypanosoma serology positive	
Campylobacteriosis (invasive disease only) (V)	Campylobacter sepsis	Narrow
	Campylobacter infection Campylobacter test positive	Broad
Shigellosis (invasive disease only) (V)	Shigella sepsis	Narrow
	Shigella infection Shigella test positive	Broad
Vibriosis (invasive disease due to *V. vulfnificus*) (V)	NA	Narrow
	Vibrio test positive Vibrio vulnificus infection	Broad
HCV progression (V)	NA	Narrow
	Chronic hepatitis C Hepatitis C Hepatitis C RNA Hepatitis C RNA increased Hepatitis C RNA fluctuation Hepatitis C RNA positive Hepatitis C virus test Hepatitis C virus test positive	Broad
Non-specific terms	NA	Narrow
	Abscess fungal Alternaria infection Arthritis fungal Biliary tract infection fungal Central nervous system fungal infection Cerebral fungal infection Encephalitis fungal Erythema induratum Eye infection fungal Fungaemia Fungal abscess central nervous system Fungal endocarditis Fungal labyrinthitis Fungal peritonitis Fungal pharyngitis Fungal retinitis Fungal sepsis Hepatic infection fungal Meningitis fungal Mycotic endophthalmitis Myocarditis mycotic Oropharyngitis fungal Osteomyelitis fungal Otitis media fungal Pancreatitis fungal	Broad

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	Parasitic lung infection Parasitic pneumonia Pericarditis fungal Phaehyphomycosis Pneumonia fungal Pulmonary mycosis Pulmonary trichosporonosis Sinusitis fungal Splenic infection fungal Systemic mycosis	

Abbreviations: EBV = Epstein-Barr virus; HBV = hepatitis B virus; HCV = hepatitis C virus; NA = not applicable; PVAN = polyomavirus-associated nephropathy.

Appendix 4. MedDRA Preferred Terms for each Category Associated with Criterion 2 for Anaphylactic Allergic Reactions/Hypersensitivity Events

Preferred Terms (MedDRA Version 21.0)	
Category A: Involvement of the Skin/Mucosal Tissue	
Administration site hypersensitivity	Localised oedema
Administration site rash	Mouth swelling
Administration site urticarial	Nasal obstruction
Allergic oedema	Nodular rash
Allergic otitis externa	Ocular hyperaemia
Angioedema	Oedema
Circumoral oedema	Oedema mouth
Drug eruption	Oedema mucosal
Erythema	Orbital oedema
Eye allergy	Palatal oedema
Eye oedema	Palatal swelling
Eye pruritus	Perineal rash
Eye swelling	Periorbital oedema
Eyelid oedema	Pruritus
Face oedema	Pruritus allergic
Flushing	Pruritus generalised
Generalised erythema	Rash
Gingival oedema	Rash erythematous
Gingival swelling	Rash generalised
Idiopathic urticaria	Rash pruritic
Injection site dermatitis	Skin oedema
Injection site hypersensitivity	Skin swelling
Injection site rash	Swelling
Injection site urticaria	Swelling face
Injection site vasculitis	Swollen tongue
Lip oedema	Tongue oedema
Lip swelling	Urticaria
	Urticaria papular
Category B: Respiratory Compromise	
Acute respiratory failure	Laryngotracheal oedema
Allergic cough	Oropharyngeal spasm
Allergic pharyngitis	Oropharyngeal swelling
Asthma	Pharyngeal oedema
Asthmatic crisis	Respiratory arrest
Bronchial hyperreactivity	Respiratory distress
Bronchial oedema	Respiratory failure
Bronchospasm	Respiratory tract oedema
Cardio-respiratory distress	Reversible airways obstruction
Chest discomfort	Sensation of foreign body
Choking	Sneezing

Preferred Terms (MedDRA Version 21.0)	
Choking sensation	Spasmodic dysphonia
Cough	Status asthmaticus
Cyanosis	Stridor
Dyspnoea	Tachypnea
Epiglottic oedema	Throat tightness
Hyperventilation	Tracheal obstruction
Hypoxia	Tracheal oedema
Laryngeal dyspnoea	Upper airway obstruction
Laryngeal obstruction	Wheezing
Laryngeal oedema	
Laryngitis allergic	
Laryngospasm	
Category C: Reduced Blood Pressure or Associated Symptoms	
Blood pressure decreased	Hypoperfusion
Blood pressure diastolic decreased	Hypotension
Blood pressure systolic decreased	Hypovolaemic shock
Cardiac arrest	Incontinence
Cardiopulmonary failure	Mean arterial pressure decreased
Cardio-respiratory arrest	Peripheral circulatory failure
Cardiovascular insufficiency	Presyncope
Circulatory collapse	Shock
Diastolic hypotension	Shock symptom
Distributive shock	Syncope
Dizziness	Urinary Incontinence
Category D: Persistent Gastrointestinal Symptoms	
Abdominal discomfort	Gastrointestinal pain
Abdominal pain	Intestinal angioedema
Abdominal pain lower	Nausea
Abdominal pain upper	Retching
Diarrhoea	Visceral pain
Epigastric discomfort	Vomiting
Gastrointestinal oedema	

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities.

Appendix 5. Allergic Reactions/Hypersensitivity MedDRA Preferred Term List

Allergic reactions/hypersensitivities will be defined using the following MedDRA Preferred Terms as defined in MedDRA:

- Broad and narrow terms in the Anaphylactic reaction SMQ (20000021)
- Broad and narrow terms in the Angioedema SMQ (20000024)
- Broad and narrow terms in the Severe cutaneous adverse reactions SMQ (20000020)
- Broad and narrow terms in the Hypersensitivity SMQ (20000214), excluding the preferred terms as noted below.

Preferred Terms (MedDRA v.21.0) from Hypersensitivity SMQ Excluded from Analysis	
Administration site dermatitis	Injection site rash
Administration site eczema	Injection site recall reaction
Administration site rash	Injection site urticaria
Administration site recall reaction	Injection site vasculitis
Allergic otitis externa	Instillation site hypersensitivity
Allergic otitis media	Instillation site rash
Allergic sinusitis	Instillation site urticaria
Allergic transfusion reaction	Iodine allergy
Allergy alert test positive	Mast cell degranulation present
Allergy test positive	Medical device site dermatitis
Allergy to surgical sutures	Medical device site eczema
Allergy to vaccine	Medical device site hypersensitivity
Anaphylactic transfusion reaction	Medical device site rash
Antiallergic therapy	Medical device site recall reaction
Application site dermatitis	Medical device site urticaria
Application site eczema	Nodular rash
Application site hypersensitivity	Pathergy reaction
Application site rash	Radioallergosorbent test positive
Application site recall reaction	Reaction to azo-dyes
Application site urticaria	Reaction to colouring
Application site vasculitis	Shock
Arthritis allergic	Shock symptom
Aspirin-exacerbated respiratory disease	Skin test positive
Asthma-chronic obstructive pulmonary disease overlap syndrome	Solvent sensitivity
	Stoma site hypersensitivity
Blepharitis allergic	Stoma site rash
Blood immunoglobulin E abnormal	Urticaria contact
Blood immunoglobulin E increased	Urticarial vasculitis
Bromoderma	Vaccination site dermatitis
Catheter site dermatitis	Vaccination site exfoliation
Catheter site eczema	Vaccination site eczema
Catheter site hypersensitivity	Vaccination site hypersensitivity
Catheter site rash	Vaccination site rash

Preferred Terms (MedDRA v.21.0) from Hypersensitivity SMQ Excluded from Analysis	
Catheter site urticaria	Vaccination site recall reaction
Catheter site vasculitis	Vaccination site urticaria
Chronic eosinophilic rhinosinusitis	Vaccination site vasculitis
Chronic hyperplastic eosinophilic sinusitis	Vaccination site vesicles
Circulatory collapse	Vessel puncture site rash
Conjunctivitis allergic	Vessel puncture site vesicles
Contact stomatitis	Vulvovaginal rash
Complement factor decreased	Acute respiratory failure
Complement factor increased	Allergy to chemicals
Complement factor C1 decreased	Allergy to fermented products
Complement factor C1 increased	Anti-insulin antibody increased
Complement factor C2 decreased	Anti-insulin antibody positive
Complement factor C2 increased	Anti-insulin receptor antibody increased
Complement factor C3 decreased	Anti-insulin receptor antibody positive
Complement factor C3 increased	Blood immunoglobulin A abnormal
Complement factor C4 decreased	Blood immunoglobulin A increased
Complement factor C4 increased	Blood immunoglobulin D increased
Complement fixation abnormal	Blood immunoglobulin G abnormal
Complement fixation test positive	Blood immunoglobulin G increased
Contrast media allergy	Blood immunoglobulin M abnormal
Contrast media reaction	Blood immunoglobulin M increased
Dennie-Morgan fold	Immune complex level increased
Dermatitis acneiform	Immunoglobulins abnormal
Dermatitis contact	Immunoglobulins increased
Dermatitis herpetiformis	Immunology test abnormal
Dermatitis infected	Haemolytic transfusion reaction
Device allergy	Infantile asthma
Dialysis membrane reaction	Fixed eruption
Distributive shock	Rhinitis perennial
Drug cross-reactivity	Seasonal allergy
Drug provocation test	
Eczema infantile	
Eczema vaccinatum	
First use syndrome	
Fixed drug eruption	
Giant papillary conjunctivitis	
Heparin-induced thrombocytopenia	
Hereditary angioedema	
Implant site dermatitis	
Implant site hypersensitivity	
Implant site rash	
Implant site urticaria	
Immune-mediated adverse reaction	
Incision site dermatitis	
Incision site rash	
Infusion site dermatitis	
Infusion site eczema	
Infusion site hypersensitivity	

Preferred Terms (MedDRA v.21.0) from Hypersensitivity SMQ Excluded from Analysis	
Infusion site rash	
Infusion site recall reaction	
Infusion site urticaria	
Infusion site vasculitis	
Injection site dermatitis	
Injection site eczema	
Injection site hypersensitivity	

Appendix 6. Lilly-Defined MedDRA V21.0 Preferred Terms for Inflammatory Bowel Disease (IBD)

Condition	Preferred Term (MedDRA version 21.0)	Lilly-Defined Classification
Inflammatory bowel disease	Inflammatory bowel disease	Narrow
Crohn's disease	Crohn's disease	Narrow
Ulcerative colitis	Acute haemorrhagic ulcerative colitis	Narrow
	Colitis ulcerative	Narrow
	Proctitis ulcerative	Narrow
Non-specific terms	Abscess intestinal	Broad
	Anal abscess	Broad
	Anal fistula	Broad
	Anal fistula excision	Broad
	Anal fistula infection	Broad
	Anovulvar fistula	Broad
	Aorto-duodenal fistula	Broad
	Colitis	Broad
	Colon fistula repair	Broad
	Colonic fistula	Broad
	Diverticular fistula	Broad
	Duodenal fistula	Broad
	Enterocolitis haemorrhagic	Broad
	Enterocolonic fistula	Broad
	Enterocutaneous fistula	Broad
	Enterovesical fistula	Broad
	Gastrointestinal fistula	Broad
	Gastrointestinal fistula repair	Broad
	Fistula of small intestine	Broad
	Intestinal fistula	Broad
	Intestinal fistula infection	Broad
	Intestinal fistula repair	Broad
	Jejunal fistula	Broad
	Large intestinal ulcer perforation	Broad
	Rectal fistula repair	Broad
	Faecal calprotectin abnormal	Broad
	Faecal calprotectin increased	Broad
	Proctitis haemorrhagic	Broad
	Pseudopolyposis	Broad
	Rectoprostatic fistula	Broad
	Rectourethral fistula	Broad

Leo Document ID = 49b21032-dd6b-42de-b571-d08947d59dd4

Approver: PPD
Approval Date & Time: 26-Jun-2019 15:54:01 GMT
Signature meaning: Approved