I1F-MC-RHCD(b) Clinical Protocol

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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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.

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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[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
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

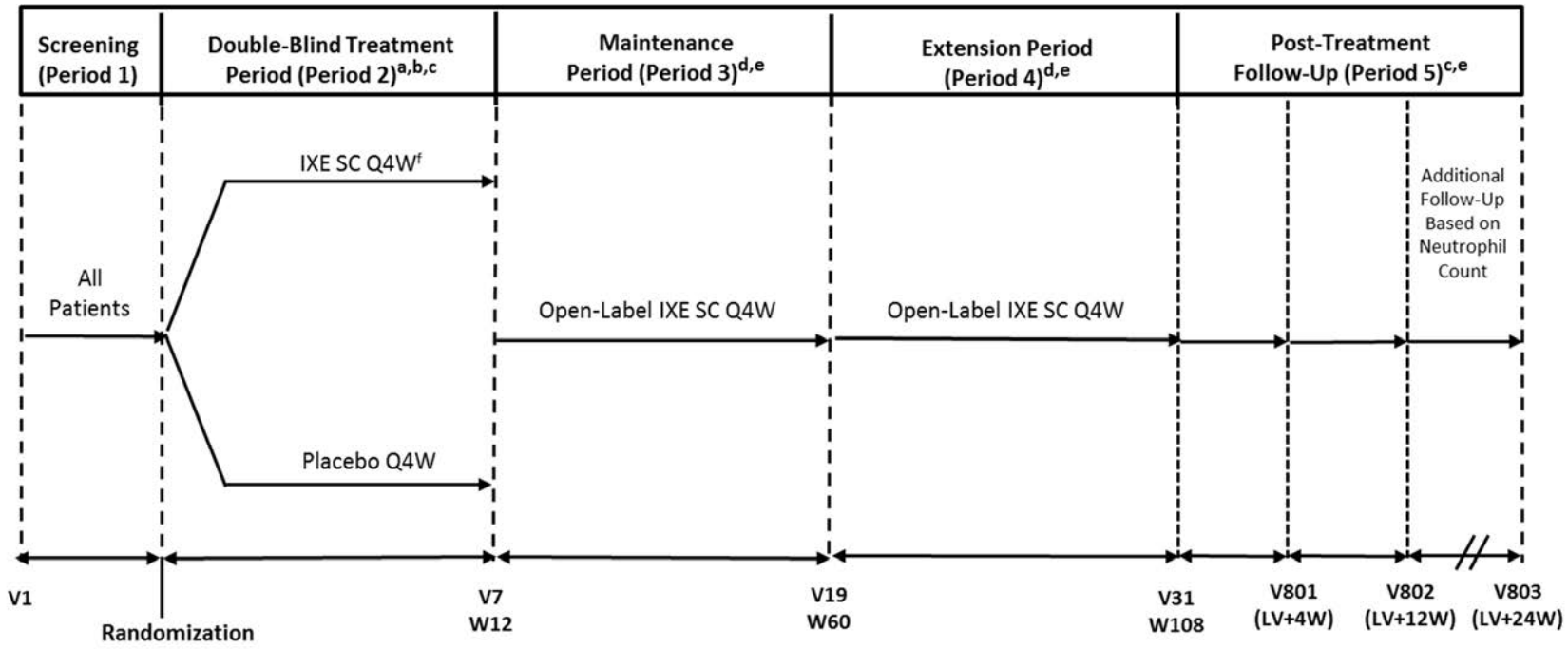
5.1. Overall Design

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 ≥ 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.

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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[m,o]	X						
Read PPD[m,o]	X						
Chest x-ray[o,p]	X						
Bone age imaging[q]		X					
ECG[r,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[u] [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[~~qs~~]			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[~~tt~~ 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[qi]		X			X			X			X			X
Urine pregnancy test[r 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[s u,t v]						X								
PK sample[tt–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)~~[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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