I1F-MC-RHCD(2.1) Clinical Protocol Addendum

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.

NCT03073200

Approval Date: 20-Jul-2017

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

Ixekizumab (LY2439821)

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

Eli Lilly and Company
Indianapolis, Indiana USA 46285

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

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

Approval Date: 20-Jul-2017 GMT

2. Table of Contents

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

Section **Page**

List of Attachments

Attachment **Page**

3. Rationale for Addendum

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

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

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

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

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

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

4. Protocol Additions

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

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

4. Objectives and Endpoints

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

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

5.1. Overall Design

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

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

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

7.1. Treatments Administered

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

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

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

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

Table RHCD.3 shows the etanercept treatment regimen.

Table RHCD.3. Etanercept Treatment Regimen

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

7.1.1. Packaging and Labeling

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

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

7.2. Method of Treatment Assignment

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

7.3. Blinding

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

7.5. Preparation/Handling/Storage/Accountability

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

7.6. Treatment Compliance

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

10.3.1. General Statistical Considerations

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

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

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

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

Further details will be described in the SAP.

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

4. Objectives and Endpoints

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

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

5.1. Overall Design

- **Period 4:**

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

  OR

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

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

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

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

7.2. Method of Treatment Assignment

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

7.3. Blinding

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

10.3.1. General Statistical Considerations

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

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

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

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

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

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

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

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

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

Further details will be described in the SAP.

5. References

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

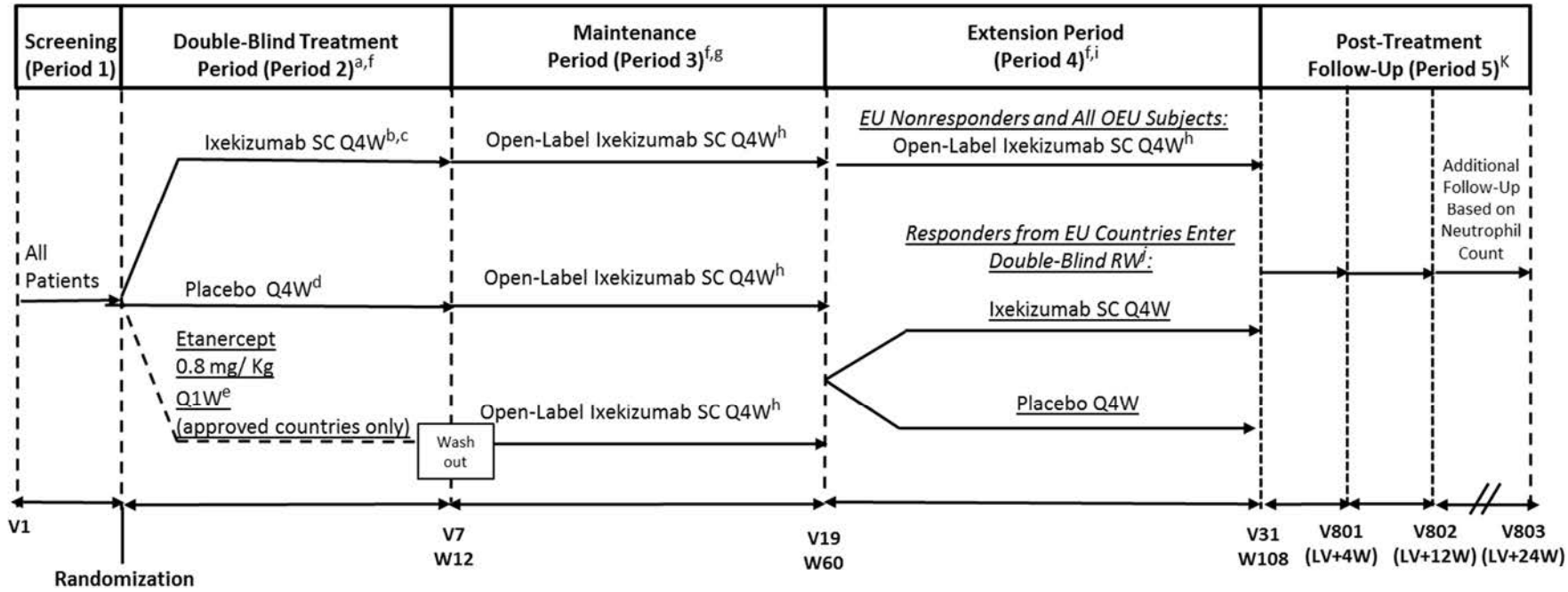
[v] This visit will only occur if a subject's neutrophil counts have not returned to the defined criteria.

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

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

Attachment 2. Protocol Addendum RHCD(2.1) Study Design

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



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

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

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

Protocol Addendum RHCD(2) Study Design

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

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

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

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

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

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

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

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

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

Revised Protocol Addendum

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

Attachment 2: Protocol Addendum RHCD(2.1) Study Design

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

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

Leo Document ID = b88f7f39-71e3-431d-a8f5-bfd9b5dfd793

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

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