Supplementary Online Content

Paller AS, Seyger MMB, Magariños GA, et al; for the IXORA-PEDS Investigators. Long-term efficacy and safety of up to 108 weeks of ixekizumab in pediatric patients with moderate to severe plaque psoriasis: the IXORA-PEDS randomized clinical trial. *JAMA Dermatology.* Published online April 13, 2022. doi:10.1001/jamadermatol.2022.0655

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Patients and Methods

Inclusion Criteria

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

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 a 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
4) Male and female patients from 6 to <18 years of age at time of randomization
    a. Male patients agree to use a reliable method of birth control during the study
    b. Female patients:
        i. Patients of childbearing age or childbearing potential who are sexually active who test negative for pregnancy must be counselled 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.
    c. 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:
        i. Male or female condom with spermicide
        ii. Cap, diaphragm, or sponge with spermicide
    d. Highly effective methods of contraception (use 1 form):
        i. Combined oral contraceptive pill and mini-pill
        ii. NuvaRing®
        iii. Implantable contraceptives
        iv. Injectable contraceptives (such as Depo-Provera®)
        v. Intrauterine device (such as Mirena® and ParaGard®)
        vi. Contraceptive patch—ONLY women <198 pounds or 90 kg
        vii. Abstinence from sex
        viii. Vasectomy—for men in clinical studies
    e. Effective methods of contraception (use 2 forms combined):
        i. Male condom with spermicide
        ii. Female condom with spermicide
        iii. Diaphragm with spermicide
        iv. Cervical sponge
        v. Cervical cap with spermicide
    f. Females who are not of childbearing potential include those who have undergone or who have:
        i. Female sterilization
        ii. Hysterectomy
        iii. Menopause
        iv. 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 paediatric authorities (e.g., the American Academy of Pediatrics). Note, patients who are not up to date or have never been immunized are not to be enrolled in the trial.

Exclusion Criteria

Patients were excluded from study enrolment if they met any of the following criteria at screening:

1) Have pustular, erythrodermic, and/or guttate forms of plaque psoriasis
2) Patients with drug-induced plaque psoriasis (e.g., a new onset of plaque psoriasis or an exacerbation of plaque psoriasis from beta-blockers, calcium channel blockers, or lithium)
3) Have clinical and/or laboratory evidence of untreated latent or active tuberculosis
4) 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: Patients who are HBcAb+ and HBV DNA negative may be enrolled in the study. Patients who meet these criteria at screening will be identified by the central laboratory and monitored during the study)
5) 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)
6) 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
7) Have or had a herpes zoster or any other clinically apparent varicella-zoster virus infection within 12 weeks of baseline (Week 0; Visit 2)
8) 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 patient if participating in the study; these patients may be rescreened (1 time) 4 or more weeks after documented resolution of symptoms
9) Have sepsis or risk of sepsis
10) Have a body temperature ≥38°C (100·5°F) at baseline (Week 0; Visit 2); these patients may be rescreened (1 time) ≥4 weeks after documented resolution of elevated temperature
11) Patients 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)
12) Patients 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
13) 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)
14) 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 patient

15) 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 patient if participating in the study or of interfering with the interpretation of data
16) Presence of significant uncontrolled neuropsychiatric disorder that, in the opinion of the investigator, poses an unacceptable risk to the patient 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 Columbia-Suicide Severity Rating Scale question 4 or 5 on ideation or yes to suicide behaviours
17) 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 patient
18) Have not had any immunizations, or are not up to date on immunizations recommended by country specific paediatric guidance
19) Females of childbearing potential, who are sexually active and not on either 1 highly effective form of contraception or 2 effective forms of contraception
20) Females of childbearing potential, who are pregnant or intending to become pregnant or are breastfeeding
21) Have any other condition or laboratory values that, in the opinion of the investigator, preclude the patient from following and completing the protocol
22) Have evidence of precocious puberty at the time of study enrolment
23) At screening, have a neutrophil count <1500 cells/µL (<1·50 x 10^3/µL or <1·50 GI/L), a lymphocyte count <800 cells/µL (<0·80 x 10^3/µL or <0·80 GI/L), or a platelet count <100,000 cells/µL (<100 x 10^3/µL or <100 GI/L)
24) At screening, have alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2·5 times the upper limit of normal. (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)
25) At screening, have a total white blood cell (WBC) count <3000 cells/µL (<3·00 x 10^3/µL or <3·00 GI/L), haemoglobin <8·5 g/dL (85·0 g/L) for male patients, and haemoglobin <8·0 g/dL (80 g/L) for female patients
26) Patients previously treated with etanercept
27) Have used any therapeutic agent targeted at reducing interleukin-17
28) Have received other therapies within the specified time frames prior to screening (see below):
    a. Adalimumab and infliximab 60 days, abatacept 90 days, anakinra 7 days, or any other biologic disease-modifying antirheumatic drug 5 half-lives
    b. Systemic therapy for plaque psoriasis and psoriatic arthritis (other than above, e.g., methotrexate, cyclosporine) or phototherapy (e.g., photochemotherapy [psoralen plus ultraviolet A]) in the previous 4 weeks
    c. Any investigational drugs in the previous 4 weeks or 5 half-lives, whichever is longer
    d. Ultraviolet-A therapy, ultraviolet-B therapy, and topical treatments (except on face, scalp, and genital area during screening) in the previous 4 weeks

29) 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 paediatric governance bodies non-live 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)
30) Are not up to date on all vaccinations according to country-specific guidance provided by paediatric governing bodies (e.g., the American Academy of Pediatrics), or have not had any vaccinations.
31) 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
32) 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
33) 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
34) Have previously completed or withdrawn from this study or any other study investigating ixekizumab
35) 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

eAppendix 2. Study Design, Patients, and Methods

Study design

Patients outside the EU who completed the open-label maintenance period, and patients from EU countries who did not meet response criteria at Week 60 (sPGA [0,1]), entered the extension period (Weeks 60 to 108) during which they continued treatment with open-label IXE Q4W. IXE dose was adjusted during the open-label maintenance period and the extension period if a patient changed weight categories.

Patients from countries in the EU who met response criteria at Week 60 (sPGA [0,1]) entered a double-blind randomized withdrawal period and were re-randomized 1:1 to IXE Q4W (dosing according to weight category at the time of re-randomization) or to placebo. Upon disease relapse (sPGA≥2), these patients received weight-based dosing of IXE Q4W.

Patients who either completed the last treatment period visit (Week 108) or who discontinued from the study after receiving at least one dose of study drug entered a 24-week post-treatment follow-up period for safety monitoring. Study visits and assessments occurred at screening, Weeks 0 (baseline), 1, 4, and 6, and every 4 weeks from Weeks 8 to 108.

Enrolment for IXORA-PEDS occurred between April 17, 2017 and November 13, 2018. Recruitment occurred at 68 sites in 13 countries in Europe, South America, and North America. Assignment to treatment groups was determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS was used to assign cartons containing double-blind study drug to each patient. Site personnel confirmed they had located the correct carton by entering a confirmation number into the IWRS. The syringes and contents containing ixekizumab or placebo were visibly indistinguishable from each other.

A staggered approach to enrolment by weight group was implemented for subjects 12 years of age or older and >50 kg initially enrolling in the study. If no safety concern was identified after an initial safety analysis of the first 12 weeks of treatment in the first 15 patients >50 kg, enrolment proceeded with patients in the 25-kg to 50-kg group. Once data were obtained to Week 12 for approximately 15 patients in the 25-kg to 50-kg group, an interim analysis of pharmacokinetics, safety, and efficacy data in all subjects in the study at that point was performed to confirm doses for the remaining subjects in the study. Once confirmed, enrolment was open for all weight groups. A data monitoring committee monitored the safety, efficacy, and pharmacokinetics of ixekizumab in the IXORA-PEDS study to advise on the continuing safety and appropriateness of the weight-based dosing regimens in paediatric patients and to confirm the continuing validity and scientific merit of the study.

Randomization was stratified by region (United States/Canada, European countries, and the rest of the world) and by etanercept approval status (patients with severe paediatric psoriasis [PASI ≥20 or sPGA ≥4] in countries where etanercept is approved for severe paediatric psoriasis or all other patients, including those with moderate paediatric psoriasis [PASI ≥12 and <20 and sPGA=3] in countries where etanercept is approved for severe paediatric psoriasis and patients with moderate-to-severe psoriasis in countries were etanercept is not approved for severe paediatric psoriasis).

Ixekizumab and placebo were supplied as an injectable solution in 1-mL, single-dose, prefilled syringes with study-specific labels. Each syringe of ixekizumab was designed to deliver 80 mg ixekizumab. For patients requiring lower doses of ixekizumab or placebo, the dose was prepared by injecting the contents 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). Etanercept was supplied in two presentations to be administered based on patient weight: a powder in a single-dose vial containing

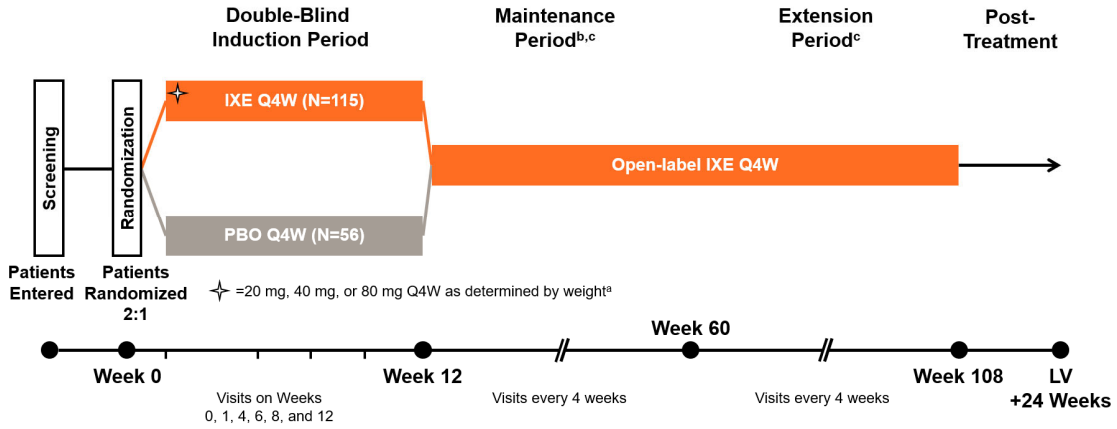
25 mg etanercept and diluent for reconstitution or a solution in a single-dose, prefilled syringe designed to deliver 50 mg of etanercept.

Study site personnel who prepared study drug were considered to be unblinded. However, study site personnel who administered ixekizumab or placebo to patients, as well as personnel who conducted efficacy assessments, were blinded.

Blood samples were collected for testing of anti-drug antibodies at baseline, every 4 weeks through Week 12, and at Weeks 36, 64, and 108. Samples were also collected, when possible, for any event judged to be a potential systemic allergic/hypersensitivity reaction. Anti-drug antibodies were assessed using a validated assay designed to perform in the presence of ixekizumab. Anti-drug antibodies were identified using an Enzyme-Linked Immunosorbent Assay-based affinity capture elution assay (sensitivity: 4.6 ng/mL, drug tolerance: 480.5 µg/mL).[1] Antibodies were also characterized for their ability to neutralize the activity of ixekizumab. Neutralizing Anti-drug antibodies were characterised using a direct competition immunoassay on a MesoScale Discovery platform (MesoScale Discovery, Rockville, MD) with an assay sensitivity of 253.4 ng/mL and drug tolerance of 1.1 µg/mL.

Supplementary Methods

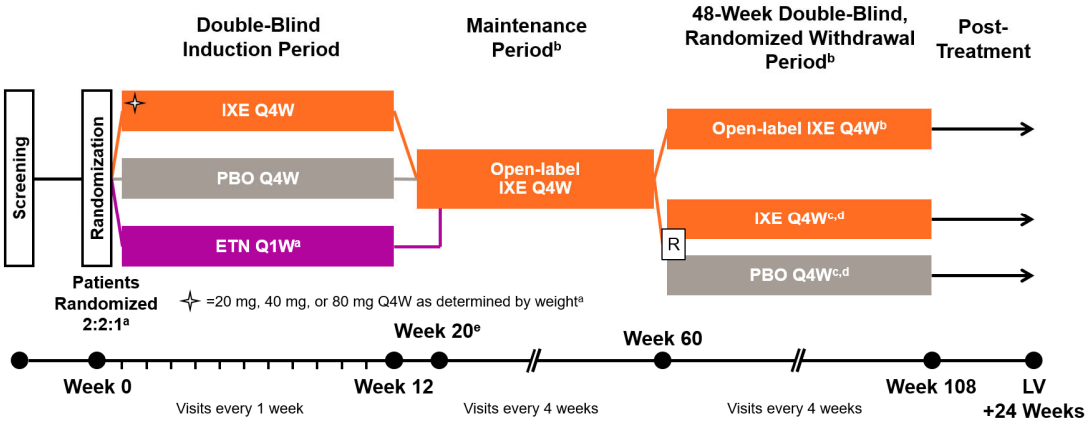
eFigure 1. Primary Study Design: IXORA-PEDS [Aged 6 to <18 Years]



Weight Group	Dosing Regimen
>50 kg	160mg at Wk0 and 80mg IXE Q4W thereafter
25-50 kg	80mg at Wk0 and 40mg IXE Q4W thereafter
<25 kg	40mg at Wk0 and 20mg IXE Q4W thereafter

[a]Proposed dosing regimens based on patient weight categories: >50 kg (IXE starting dose of 160 mg [Week 0] and 80 mg Q4W thereafter); ≥25 to ≤50 kg (IXE starting dose of 80 mg [Week 0] and 40 mg Q4W thereafter); <25 kg (IXE starting dose of 40 mg [Week 0] and 20 mg Q4W thereafter). [b]Subjects randomized to IXE during the double-blind induction period received 1 injection of IXE and 1 injection of PBO at Week 12. Subjects randomized to PBO during the double-blind induction period received IXE at doses of 20, 40, or 80 mg (with a starting dose of 40, 80, or 160 mg, respectively) based on weight (see footnote 'a'). All subjects received 2 injections of IXE at Week 12 and 1 injection of IXE Q4W at Week 16 and thereafter. [c]IXE dose was adjusted during the open-label maintenance period and extension periods if a patient changed weight categories. Paller AS, et al. *Br J Dermatol.* 2020;183:231-241.

eFigure 2. EU Protocol Addendum: IXORA-PEDS [Aged 6 to <18 Years]



[a]Subjects with severe disease (PASI ≥20 and sPGA ≥4) from countries where etanercept is approved for the treatment of severe pediatric psoriasis only were randomized to either ixekizumab, open-label etanercept (assessor-blinded reference arm), or placebo in a 2:2:1 ratio; all subjects from countries where etanercept is not approved for the treatment of pediatric psoriasis and also subjects with moderate disease (12 ≤PASI <20 and sPGA=3) in countries where etanercept is approved for the treatment of pediatric psoriasis were randomized to either ixekizumab or placebo in a 2:1 ratio. [b]Non-EU countries and all non-responders. [c]PBO (N=33); IXE Q4W (N=34).[2] [d]Randomized withdrawal in EU countries only. [e]Patients who were administered ETN during the Induction Period did not receive IXE until Week 20 to allow for an 8-week washout.

1. Paller AS, et al. *Br J Dermatol.* 2020;183:231-241.

eAppendix 3. List of All Study Endpoints in IXORA-PEDS

Co-primary objectives:

1) To assess whether ixekizumab Q4W is superior to placebo at Week 12 in the treatment of paediatric patients (children and adolescents) with moderate-to-severe plaque psoriasis as measured by PASI 75 and by sPGA (0,1):
    a. Proportion of patients achieving PASI 75 at Week 12
    b. Proportion of patients achieving sPGA (0,1) at Week 12

Gated secondary objectives:

1) To assess whether ixekizumab Q4W is superior to placebo as measured by the following endpoints:
    a. Proportion of patients achieving PASI 90 at Week 12
    b. Proportion of patients achieving sPGA (0) at Week 12
    c. Proportion of patients achieving PASI 100 at Week 12
    d. Improvement ≥4 for patients who had a baseline Itch NRS score ≥4 at Week 12
    e. Proportion of patients achieving PASI 75 at Week 4
    f. Proportion of patients achieving sPGA (0,1) at Week 4

Other secondary objectives:

1) To assess whether ixekizumab Q4W is superior to placebo as measured by the following endpoints assessed at Week 12 and at each post-baseline visit during the Double-Blind Treatment Period:
    a. Proportion of patients achieving PASI 50, PASI 75, PASI 90, and PASI 100
    b. Proportion of patients achieving sPGA (0,1) and sPGA (0)
    c. Change from baseline in itching severity (Itch NRS) score
    d. CDLQI/DLQI (0,1)
    e. Change from baseline in NAPSI, PSSI, and/or PPASI score in case of nail, scalp, or hand/feet involvement
2) To summarize the efficacy of ixekizumab Q4W at Week 24, Week 48, Week 60 and Week 108 as measured by the following endpoints:
    a. Proportion of patients achieving PASI 75 at Weeks 24, 48, 60 and 108
    b. Proportion of patients achieving sPGA (0,1) at Weeks 24, 48, 60 and 108
    c. Proportion of patients achieving PASI 90 at Weeks 24, 48, 60 and 108
    d. Proportion of patients achieving sPGA (0) at Weeks 24, 48, 60 and 108
    e. Proportion of patients achieving PASI 100 at Weeks 24, 48, 60 and 108
3) To evaluate the potential development of anti-ixekizumab antibodies and its impact on patient efficacy of ixekizumab:
    a. PASI 75 and sPGA (0,1) at Week 12 correlated with treatment-emergent anti-drug antibody titre (low, moderate, and high) and by neutralizing antibody status
4) To measure ixekizumab exposure and characterize the pharmacokinetics of ixekizumab in paediatric patients:
    a. Serum trough concentrations of ixekizumab
5) To assess the relationship between exposure and efficacy and exposure and immunogenicity:
    a. Model parameters for the exposure-response relationship between ixekizumab serum trough concentrations and efficacy endpoints (for example, sPGA, PASI) at Week 12
    b. Serum trough concentrations for ixekizumab antibody titre subgroups
6) To assess the safety of ixekizumab:
    a. To evaluate the safety of ixekizumab, including but not limited to: infections; injection-site reactions; B-, T-, and NK-cell levels; WBC count; red blood cell count;

and laboratory values (haematology and chemistry [including ALT and AST]) during the course of the study

7) To demonstrate normal growth and pubertal progression in children treated with ixekizumab during the course of the study:
    a. Weight, height, and body mass index data will be merged to the Centers for Disease Control and Prevention standard growth data by age and gender to compare patients' growth with normal values
    b. Shift table for Tanner stage from maximum baseline to maximum postbaseline by gender
8) To evaluate the genital involvement of the patients per the questionnaire Binary Questions on Psoriasis Location
    a. Proportion of patients achieving no psoriasis presence in each psoriasis location
9) To evaluate the patient's global assessment of disease severity:
    a. Proportion of patients achieving patient's global assessment of disease severity 0 or 1
10) To evaluate the effect of ixekizumab on maintenance of efficacy and health outcomes during the open-label maintenance period and the extension period:
    a. Proportion of patients achieving PASI 90
    b. Proportion of patients achieving sPGA (0)
    c. Proportion of patients achieving PASI 100
    d. Proportion of patients achieving PASI 75
    e. Proportion of patients achieving sPGA (0,1)
    f. Improvement ≥4 for patients who had a baseline Itch NRS score ≥4

Other secondary objectives from the EU protocol addendum:

1) To compare the efficacy of ixekizumab Q4W and etanercept at Week 12 as measured by PASI 75 and by sPGA (0,1) in countries where etanercept is approved
    a. Proportion of patients achieving PASI 75 at Week 12
    b. Proportion of patients achieving sPGA (0,1) at Week 12
2) To assess whether ixekizumab Q4W is superior to placebo for EU patients during the Double-Blind Randomized Withdrawal Period
    a. Time to relapse to moderate severity (sPGA ≥2) during the Double-Blind, Randomized Withdrawal Period
    b. Proportion of patients achieving sPGA (0,1) at Week 108

eAppendix 4. Description of Efficacy Outcomes

PASI

The PASI is an accepted primary efficacy measurement for this phase of development of plaque psoriasis treatments.[2] The PASI combines assessments of the extent of body-surface involvement in four 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 psoriasis to 72 for the most severe disease.[3] 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 psoriasis (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.[4]

sPGA

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

NAPSI

If the subject had fingernail/toenail plaque psoriasis at baseline, the NAPSI was used. The NAPSI is a numeric, reproducible, objective tool for evaluation of fingernail/toenail plaque psoriasis. This scale is used to evaluate the severity of fingernail/toenail bed plaque psoriasis matrix plaque psoriasis by area of involvement in the fingernail/toenail unit. In this study, both fingernail and toenail involvement were 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 psoriasis (0 to 4) and nail matrix plaque psoriasis (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 psoriasis 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).

PSSI

If the subject had scalp plaque psoriasis at baseline, the Psoriasis Scalp Severity Index (PSSI) was 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).

PPASI

If the subject had palmoplantar plaque psoriasis at baseline, the Palmoplantar Psoriasis Severity index (PPASI) was 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).

BSA

The investigator evaluated the percentage involvement of plaque psoriasis on each subject's body surface area 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).[5]

Binary Questions for Psoriasis Location

The binary questions for psoriasis location define specific locations of plaque psoriasis. This assessment was used as a secondary endpoint and is especially helpful to delineate the presence of psoriasis on the face and in the genital area.

Itch NRS

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 psoriasis is indicated by circling the number that best describes the worst level of itching in the past 24 hours.

DLQI

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.[6] The Dermatology Life Quality Index (DLQI) was completed by subjects aged 17 years and older.

CDLQI

The Children's Dermatology Life Quality Index (CDLQI) questionnaire is designed for use in children (subjects from 4 to 16 years of age).[7-9] 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.[6] The Children's Dermatology Life Quality Index (CDLQI) questionnaire was completed by subjects aged 6 to 16 years of age. The sites used the appropriate version according to the age and transitioned from CDLQI to DLQI when the subject turn 17 years old, with the exception during the double-blind treatment period (induction).

PatGA

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 psoriasis "today" from 0 (clear) = no plaque psoriasis to 5 (severe) = the worst their plaque psoriasis has ever been.

PASI, sPGA, and BSA assessments were conducted at screening visits, baseline visits (Week 0), and post-baseline visits occurring at Weeks 1, 4, 6, 8, 12, and every 4 weeks from Week 16 to 108. Itch NRS was assessed at baseline visits (Week 0) and at post-baseline visits occurring at Weeks 1, 4, 8, 12, and every 12 weeks from Week 24 to 108. NAPSI, PSSI, PPASI, DLQI, CDLQI, PatGA, and the binary questions for psoriasis location were assessed at baseline (Week 0), and at post-baseline visits occurring at Weeks 4, 8, 12, and every 12 weeks from Week 24 to 108.

Additional details regarding safety outcomes

Adverse events were classified based upon the latest version of the Medical Dictionary for Regulatory Activities. Any condition starting on, or any pre-existing condition which worsened in severity on or after the date of informed consent was considered an adverse event. Treatment-emergent adverse events were defined as events that first occurred or worsened in severity after baseline and on or prior to the date of the last visit. Serious adverse events were any adverse event that resulted in death, hospitalization, a life-threatening experience, persistent or significant disability or incapacity, congenital anomaly or birth defect, or that was considered significant by the investigator for any other reason. Adverse events of special interest for ixekizumab in the paediatric population are cytopenia, liver biochemical test changes or enzyme elevations, infection, immunogenicity, injection-site reactions, allergic reactions/hypersensitivity, malignancies, depression, inflammatory bowel disease, or interstitial lung disease.

Events of suspected inflammatory bowel disease, as identified by events possibly indicative of ulcerative colitis or Crohn's disease, were adjudicated by an external clinical events committee composed of gastroenterologists with expertise in inflammatory bowel disease. The role of the clinical events committee was to adjudicate defined clinical events in a blinded, consistent, and unbiased manner throughout the study and to ensure that all reported events were evaluated uniformly by a single group.

Statistical Analyses

A sample size of 165 patients (N=110 for IXE and N=55 for placebo) was determined to provide >99% power to test the superiority of IXE to placebo for PASI 75 and for sPGA (0,1) at Week 12, based on the 2-sided Fisher's exact test at a significance level of 0·05. Power calculations used assumptions of 80% response for IXE and 10% response for placebo for both PASI 75 and sPGA (0,1) based on efficacy data from IXE clinical studies in adult subjects with moderate-to severe psoriasis.[10, 11]

Approximately 75 subjects with severe psoriasis from etanercept-approved countries were planned to be randomized to ixekizumab (30 subjects), etanercept (30 subjects), and placebo (15 subjects) in a 2:2:1 ratio during the double-blind treatment period, which was determined to have approximately 85% power to test the superiority of ixekizumab to etanercept for sPGA (0,1) and at least a 75% improvement from baseline in PASI score (PASI 75) at Week 12, based on the 2-sided Fisher's exact test at significance level of 0·05. The study was determined to have approximately 45% power to test the superiority of etanercept to placebo for PASI 75 at Week 12, based on the 2-sided Fisher's exact test at significance level of 0·05. The following assumptions were used for the power calculations for both sPGA (0,1) and PASI 75 response rates, based on efficacy data from ixekizumab clinical studies in adult subjects with moderate-to-severe psoriasis: 80% responders for ixekizumab, 40% responders for etanercept, and 10% for placebo.[10, 11]

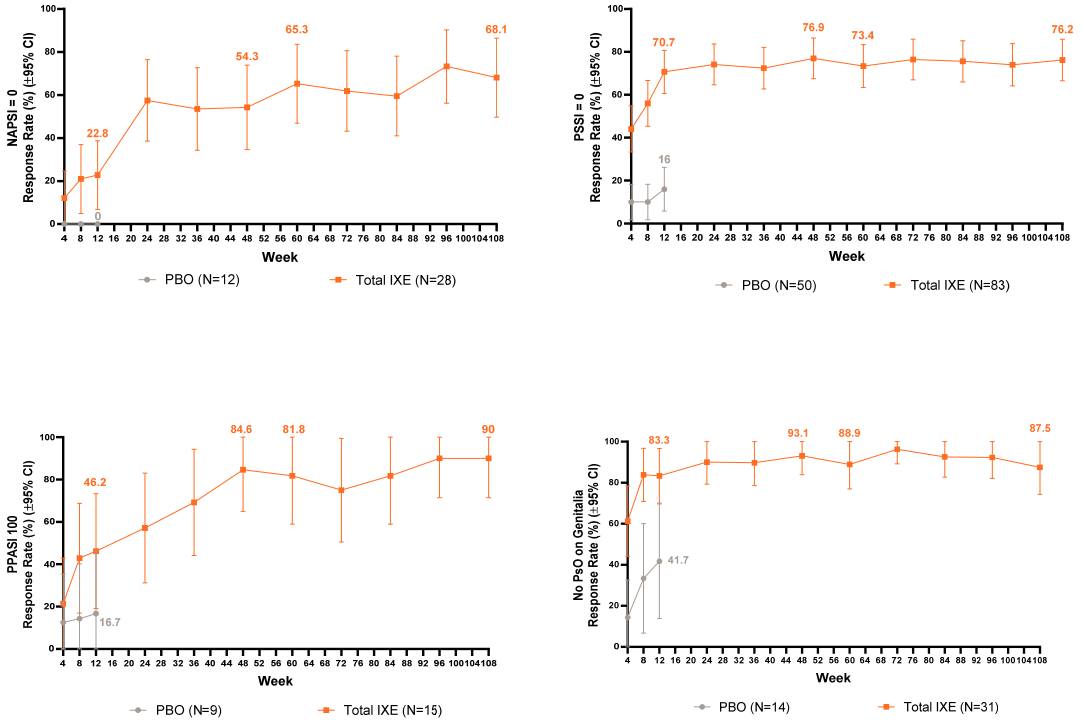
Statistical analyses were performed using SAS Version 9·2 or higher. Nonresponder imputation was used for missing data for categorical outcomes. Subjects were considered nonresponders if they did not meet the clinical response criteria or had missing clinical response data at the analysis time point. Randomized patients without at least one postbaseline observation were also defined as nonresponders.

For analyses of anti-drug antibodies, evaluable patients were those with an evaluable baseline sample and at least one evaluable postbaseline sample or, for patients with no evaluable baseline sample, those who's evaluable postbaseline samples were all anti-drug antibody negative. Treatment-emergent anti-drug antibodies were defined as a 4-fold or 2-dilution increase in titer over the pretreatment baseline titer or, if baseline titer was negative, an increase in titer to ≥1:10.

B. SUPPLEMENTARY RESULTS

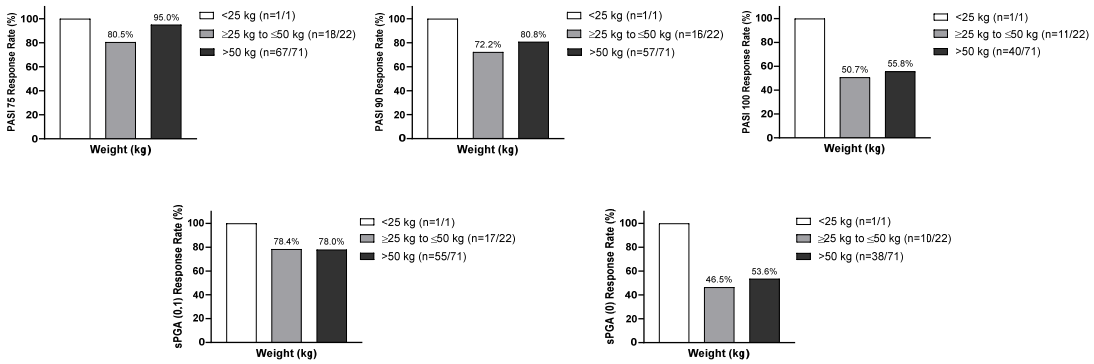
eFigure 3. Challenging Body Areas: Proportion of Patients Achieving NAPSI=0, PSSI=0, PPASI 100 and no PsO on Genitalia at 108 Weeks

Population is defined as all subjects randomized to ixekizumab at Week 0 (Visit 2) and who received ixekizumab throughout their study participations NAPSI and PSSI data are mNRI for the IXE arm and NRI for the PBO arm; PPASI and PsO on genitalia data are observed. Abbreviations: IXE, ixekizumab, N, Number of total responders, NAPSI, Nail Area Psoriasis Severity Index, PSSI, Psoriasis Scalp Severity Index, PPASI, Palmoplantar Psoriasis Area and Severity Index.



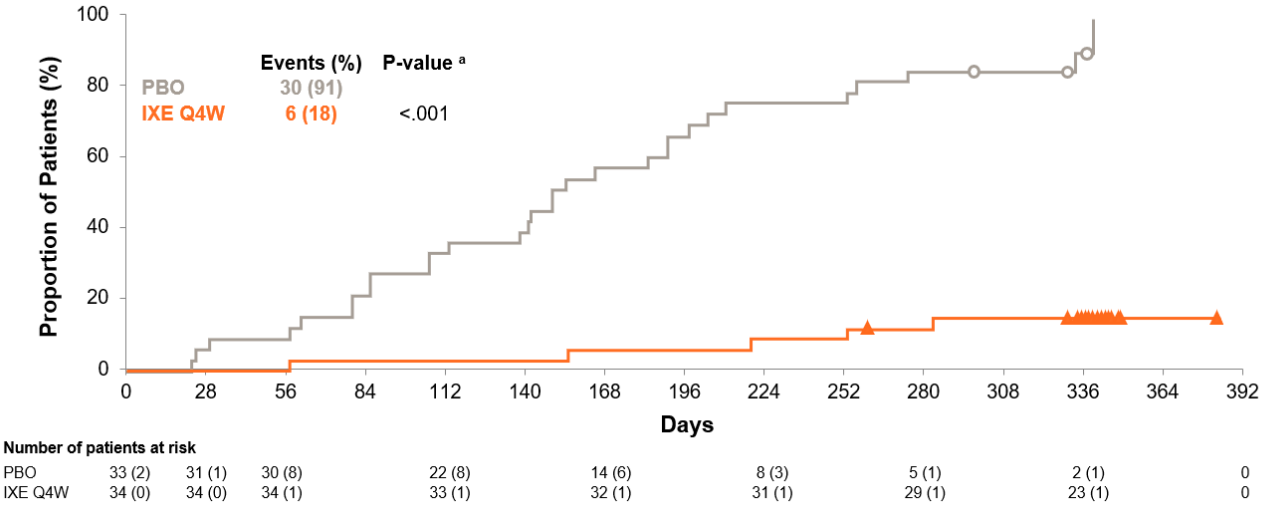
eFigure 4. PASI and sPGA Responses at Week 108 by Weight Category (mNRI)

Population is defined as all subjects randomized to ixekizumab at Week 0 (Visit 2) and who received ixekizumab throughout their study participations. Unless otherwise specified, values are presented as number of responders (%). Abbreviations: IXE, ixekizumab; mNRI, modified non-responder imputation; PASI, Psoriasis Area and Severity Index; Q4W, every 4 weeks; sPGA, static Physician's Global Assessment



eFigure 5. Time to Relapse to sPGA≥2

Randomized Withdrawal Period Population, EU Protocol Addendum. [a]unadjusted log-rank teat. Percentage is calculated by n/N*100%. Note: The time to first clinical relapse is calculated as: (date of first sPGA >=2 during Period 4 - date of Week 60 rerandomization + 1). If a patient has not experienced relapse by completion or early discontinuation of Period 4, the patient is censored at the date of their last visit during period 4. Abbreviations: IXEQ4W, ixekizumab Q4W; PBO, Placebo; N, number of patients in the analysis population; n, number of patients in the specified category.



eTable 1. Infections

Preferred term	n (%)
Infections and infestations	*145 (74.0)*
Nasopharyngitis	43 (21.9)
Upper respiratory tract infection	41 (20.9)
Pharyngitis	22 (11.2)
Tonsillitis	19 (9.7)
Conjunctivitis	16 (8.2)
Impetigo	13 (6.6)
Influenza	13 (6.6)
Viral upper respiratory tract infection	13 (6.6)
Pharyngitis streptococcal	12 (6.1)
Gastroenteritis	10 (5.1)
Viral infection	10 (5.1)
Folliculitis	9 (4.6)
Urinary tract infection	9 (4.6)
Pharyngotonsillitis	8 (4.1)
Ear infection	7 (3.6)
Hordeolum	7 (3.6)
Oral herpes	7 (3.6)
Otitis externa	7 (3.6)
Gastroenteritis viral	6 (3.1)
Otitis media	6 (3.1)
Bronchitis	5 (2.6)
Rhinitis	5 (2.6)
Staphylococcal infection	5 (2.6)
Respiratory tract infection	4 (2.0)
Sinusitis	4 (2.0)
Skin infection	4 (2.0)
Acrodermatitis	3 (1.5)
Molluscum contagiosum	3 (1.5)
Bacterial infection	2 (1.0)
Conjunctivitis viral	2 (1.0)
Cystitis	2 (1.0)
Furuncle	2 (1.0)
Lice infestation	2 (1.0)
Otitis media acute	2 (1.0)
Pneumonia mycoplasmal	2 (1.0)
Respiratory tract infection viral	2 (1.0)
Skin bacterial infection	2 (1.0)
Viral pharyngitis	2 (1.0)
Vaginal infection*[a]	1 (0.9)
Vulvitis*[a]	1 (0.9)
Acute sinusitis	1 (0.5)
Blastocystis infection	1 (0.5)

Boston exanthema	1 (0.5)
Chronic tonsillitis	1 (0.5)
Conjunctivitis bacterial	1 (0.5)
Croup infectious	1 (0.5)
Ear lobe infection	1 (0.5)
Eyelid infection	1 (0.5)
Fungal infection	1 (0.5)
Gastrointestinal infection	1 (0.5)
Genital herpes	1 (0.5)
Genital infection bacterial	1 (0.5)
Herpes simplex	1 (0.5)
Kidney infection	1 (0.5)
Laryngitis	1 (0.5)
Localized infection	1 (0.5)
Lower respiratory tract infection	1 (0.5)
Mucosal infection	1 (0.5)
Onychomycosis	1 (0.5)
Paronychia	1 (0.5)
Parotitis	1 (0.5)
Pertussis	1 (0.5)
Pneumonia	1 (0.5)
Pseudomonas infection	1 (0.5)
Scarlet fever	1 (0.5)
Sialoadenitis	1 (0.5)
Staphylococcal skin infection	1 (0.5)
Subcutaneous abscess	1 (0.5)
Tinea cruris	1 (0.5)
Tinea infection	1 (0.5)
Tinea pedis	1 (0.5)
Varicella zoster virus infection	1 (0.5)
Viral rash	1 (0.5)

*a=denominator adjusted because this is a gender-specific event for females: N=115 (Total IXE). N=number of subjects in the specified category.

eTable 2. Serious Adverse Events

All IXE Safety Population[a] (N=196), n (%)			
15 patients (7.7%) with ≥1 SAEs			
Crohn's disease	2 (1.0)	Inflammatory Bowel Disease[b]	1 (0.5)
Dehydration	2 (1.0)	Vomiting	1 (0.5)
Splenic rupture	2 (1.0)	Furuncle	1 (0.5)
Pregnancy	1 (0.9)	Otitis media acute	1 (0.5)
Ovarian cyst rupture	1 (0.9)	Tonsilitis	1 (0.5)
Accidental overdose	1 (0.5)	Pyrexia	1 (0.5)
Ankle fracture	1 (0.5)	Glucose tolerance decreased	1 (0.5)
Postoperative ileus	1 (0.5)	Astrocytoma	1 (0.5)
Rib fracture	1 (0.5)	Epilepsy	1 (0.5)
Road Traffic Accident	1 (0.5)	Renal hematoma	1 (0.5)
Diarrhea	1 (0.5)	Pneumothorax	1 (0.5)

[a]Population is defined as all subjects randomized to ixekizumab at Week 0 (Visit 2) and who received ixekizumab throughout their study participations. [b]No new cases of IBD occurred in the extension period. Abbreviations: IXE,ixekizumab; SAE, serious adverse events; N, number of total responders.

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