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ORIGINAL ARTICLE

Population pharmacokinetic and exposure–efficacy analysis of ixekizumab in paediatric patients with moderate-to-severe plaque psoriasis (IXORA-PEDS)

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Aims: Ixekizumab is a high-affinity monoclonal antibody that selectively targets interleukin-17A used in the treatment of adult and paediatric patients with moderate-to-severe psoriasis. This analysis evaluated the pharmacokinetics (PK) of ixekizumab and the exposure–efficacy relationship in paediatric patients aged 6 to <18 years with psoriasis.

Methods: Population PK and exposure–efficacy models were developed. The models used data from paediatric patients with psoriasis participating in the Phase 3 IXORA-PEDS trial in which patients were dosed according to weight categories. The exposure–efficacy model is a Psoriasis Area and Severity Index (PASI) time course model using data up to Week 12, a co-primary efficacy endpoint.

Results: A 2-compartment population PK model describes the PK of ixekizumab in paediatric patients with the effect of body weight incorporated on clearance and volume terms using an allometric relationship. The weight category-based dosing ensured that ixekizumab mean trough serum concentrations in paediatric patients with psoriasis (3.20–3.33 μg/mL) were within the range of concentrations observed in adult patients with psoriasis (mean [standard deviation]: 3.48 [2.16] μg/mL) administered an efficacious dosing regimen. The observed PASI response rates at Week 12 in paediatric patients (91.9/81.8/52.5% for PASI75/90/100) are well predicted by the final exposure–efficacy model and response rates are similar or higher than those achieved in adults (86.2/66.6/35.0% for PASI75/90/100).

Conclusion: This analysis is the first to describe the PK and exposure–efficacy relationship of ixekizumab in paediatric patients with psoriasis. The analyses support the selection of the weight category-based ixekizumab dosing regimens approved for use in paediatric patients with psoriasis.

The authors confirm that the Principal Investigator for this paper is Marieke Seyger and that she had direct clinical responsibility for patients in the Phase 3 study IXORA-PEDS. This disclosure analyses data obtained in that study.

KEYWORDS
ixekizumab, paediatric, pharmacokinetics, pharmacokinetics-pharmacodynamics, population pharmacokinetics, psoriasis

1 | INTRODUCTION

Psoriasis is a common chronic inflammatory skin disease characterised by red, thick, scaly plaques that affects areas such as the elbows, scalp, knees, back, hands and feet. The prevalence estimates for paediatric psoriasis are up to 1.37% and about 1/3 of adult patients with psoriasis report the onset of the disease during childhood.[1,2] Paediatric psoriasis can be associated with comorbidities that are similar to those for adult psoriasis. These include psoriatic arthritis, obesity, diabetes, Crohn's disease, depression and anxiety.[3] Paediatric psoriasis often reduces the quality of life and can have a negative impact on psychological well-being.[4,5]

Ixekizumab (IXE) is a high-affinity monoclonal antibody that selectively targets **interleukin (IL)-17A**, a proinflammatory cytokine that is increased in psoriasis and key to its pathogenesis.[6] The efficacy and safety of IXE in adult patients with psoriasis was established in the UNCOVER studies.[7–10] In addition, the pharmacokinetics (PK) of IXE from a combined analysis of adult patients with psoriasis or psoriatic arthritis has previously been reported. IXE concentrations in adults were described by a 2-compartment linear population PK (PopPK) model with maximum concentrations achieved within 4 and 7 days after subcutaneous administration, a volume of distribution at steady state (V_{ss}) of approximately 6 L, clearance (CL) of 0.0147 L/h and a terminal half-life ($t_{1/2}$) of around 12 days. IXE CL and V_{ss} increase as body weight increases and this relationship was described using an allometric relationship with estimated exponents.[11] The exposure–efficacy relationship, using either Psoriasis Area and Severity Index (PASI) or static Physician's Global Assessment (sPGA) as the efficacy endpoint, has been established at the time of the primary endpoint (after 12 weeks of treatment initiation) and over time.[12,13] The PASI and sPGA are the accepted primary efficacy endpoints for evaluating treatments for extensive psoriasis.[14] Treatment-emergent antidrug antibodies (TE-ADAs) occurred in 17.4% of adult patients with psoriasis and, for most patients, had a negligible impact on IXE serum concentrations and efficacy.[15] IXE was approved in 2016 by the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA) for the treatment of adults with moderate-to-severe psoriasis. Based on results from the UNCOVER studies, the approved dose for adult psoriasis in the USA, European Union (EU), Japan and other areas is 160 mg (2 80-mg subcutaneous injections) at Week 0 followed by 80 mg every 2 weeks at Weeks 2–12, then 80 mg every 4 weeks (Q4W).

IXE was then evaluated in a global, Phase 3 study in paediatric patients aged 6 to <18 years with moderate-to-severe psoriasis (IXORA-PEDS). The results for the efficacy and safety up to 48 weeks of IXE administered to at least 100 paediatric patients with moderate-to-severe psoriasis in the IXORA-PEDS study have recently been published.[16] IXE showed superior efficacy *vs.* placebo in the treatment of moderate-to-severe psoriasis in this paediatric population and the safety profile was overall consistent with that observed in adults.[16] Based on results from the IXORA-PEDS study, IXE was approved in 2020 by the FDA and EMA for the treatment of paediatric patients with moderate-to-severe psoriasis, and the approved dose in the USA and EU is weight-based. IXE is administered every 4 weeks with a 20-mg dose if body weight <25 kg (only in USA), 40-mg dose if body weight ≥25 and ≤50 kg, or an 80-mg dose if body weight >50 kg, after an initial dose of 40 (only in USA), 80 or 160 mg, respectively.

The main goals of the analyses described herein were to characterise the PK of IXE, to define the relationship between IXE exposure and efficacy (PASI), and to evaluate the appropriateness of the weight-based IXE dosing regimens that were used in paediatric patients with moderate-to-severe psoriasis in the IXORA-PEDS trial.

What is already known about this subject

- Ixekizumab is a treatment approved for adult and paediatric patients with moderate-to-severe plaque psoriasis with an established efficacy and safety profile.
- The pharmacokinetics and exposure–efficacy relationship for ixekizumab using the Psoriasis Area and Severity Index (PASI) or static Physician's Global Assessment is established in adult patients with psoriasis.

What this study adds

- The pharmacokinetics and exposure–PASI relationship for ixekizumab in paediatric patients aged 6 to <18 years with psoriasis in the IXORA-PEDS study were characterised.
- The weight-based dosing regimens evaluated in the IXORA-PEDS study are efficacious and achieve similar targeted concentrations as were observed in adult patients with psoriasis using efficacious dosing regimens.

2 | METHODS

2.1 | Study design and patient population

Data included in these analyses were obtained from the IXORA-PEDS study (ClinicalTrials.gov: NCT03073200). The details of the study design have been described previously.[16] Briefly, IXORA-PEDS is a Phase 3, 108-week, multicentre, double-blind, randomised, placebo-controlled study in patients aged 6 to <18 years with moderate-to-severe plaque psoriasis (PASI score ≥12, sPGA ≥3 and body surface area ≥10% at screening and baseline). During the double-blind period, patients were randomised 2:1 to weight-based dosing of subcutaneous IXE Q4W ($n = 115$) or placebo ($n = 56$) up to Week 12, followed by an open-label IXE Q4W maintenance period for 48 weeks and an open-label IXE Q4W extension period for 48 weeks. The percentage of participants with a ≥75% improvement in PASI (PASI75) and the percentage of participants with a sPGA of 0 or 1 at Week 12 were the co-primary efficacy endpoints. An EU protocol addendum included an etanercept reference arm for paediatric patients with severe psoriasis (PASI score ≥20 or sPGA ≥4).

Patients were candidates for phototherapy or systemic therapy, or their psoriasis was not adequately controlled by topical therapies. The full list of inclusion and exclusion criteria is in the supporting information of the IXORA-PEDS publication.[16]

IXORA-PEDS was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study was approved by the ethical review board at each participating site. A parent or legal guardian provided written informed consent and the patient provided written assent before conducting study assessments, examinations or procedures.

Weight-based dosing regimens of IXE were selected based on simulations from adult PopPK and exposure–efficacy models that were used to simulate the expected PK and efficacy responses across a range of ages and weights in paediatric patients.[11,12] The doses were selected to target exposures in paediatric patients to be within the range of exposures observed in the Phase 3 adult studies with the 80-mg every 2 weeks and 80-mg every 4 weeks dosing regimens, both of which had a positive benefit/risk ratio.[12] Figure S1 shows the expected PK data in paediatric patients with psoriasis using the final adult PopPK model (based on combined data in psoriasis and psoriatic arthritis patients) and the good agreement with the observed PK data. Different doses and dosing frequencies were evaluated, as well as different body weight categories, using the Centers for Disease Control and Prevention current growth charts.[17]

Based on the above, the dosing regimens of IXE that were later approved by the US FDA (specified in the introduction) were selected for evaluation in the IXORA-PEDS study. All IXE doses were administered by study site personnel at each participating site.

2.2 | Efficacy assessments

The PASI response at Weeks 1, 4, 6, 8 and 12 was evaluated in the exposure–efficacy analyses. The PASI is a measure of the average redness, thickness and scaliness of the lesions weighted by the area of involvement. Severity is rated for each index (redness, scaliness and thickness) on a 0–4 scale (0 = no involvement, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe involvement). The body is divided into 4 areas comprising the head, upper extremities, trunk and lower extremities. In each of these areas, the fraction of total surface area affected is graded on a 0 (for no involvement) to 6 (for 90–100% involvement) scale. The various body regions are weighted to reflect their respective proportion of body surface area. The PASI yields an overall score of 0 for no psoriasis to 72 for the most severe disease. The percent improvement in PASI scores from baseline was computed as follows:

$$\text{Percent improvement from baseline} = 100 \times (\text{Baseline PASI} - \text{Observed PASI})/\text{Baseline PASI}.$$

A clinically meaningful response is a PASI75, which represents at least a 75% reduction (improvement) from the baseline PASI score. Similarly, the categorical variables PASI90 and PASI100 refer to patients with improvements of ≥90% and 100% (complete resolution of plaque psoriasis) from the baseline PASI score, respectively.

The other co-primary endpoint was the sPGA, which is the physician's determination of the patient's psoriatic lesions overall at a given time point. Lesions are categorised by descriptions of induration, erythema and scaling, in which the extend of the lesion is taken into account. For the analysis of responses, the patient's psoriasis is assessed as clear (0), minimal (1), mild (2), moderate (3), severe (4) or very severe (5). Response to treatment at Week 12 is defined as a sPGA score of 0 or 1, whereas nonresponse is a score >1. The sPGA relationship to IXE trough concentrations was determined at Week 12 but results from that analysis are not presented herein.

2.3 | PK assessments

The PopPK analysis included data from a database lock, in which all patients completed the Week 12 visit or had discontinued study drug early and a minimum of 100 patients were treated with IXE for at least 1 year. All PK samples that were available at the time of the primary database lock were included in the PopPK analysis. Blood samples for PK analysis were collected in paediatric patients at Weeks 0 (prior to the first dose), 4, 8, 12, 36, 64 and 108, just prior to dosing, designed as trough samples. Two additional PK samples were collected at Weeks 1 and 9 at the time of the approximate maximum concentration after the first and third doses, respectively, for 12 patients who participated in the PK addendum and received IXE. IXE serum concentrations were determined using a validated enzyme-linked immunosorbent assay with a limit range of quantification of 6.30–400 ng/mL. Samples above this range were diluted to yield results within the calibrated range. The interassay accuracy (% relative error) during validation ranged from −1.00 to 1.60%. The interassay precision (% coefficient of variation [CV]) during validation ranged from 4.07 to 12.0%. IXE serum concentration measurements that were below the quantitation limit (BQL) were excluded from the analysis.

2.4 | Antidrug antibody assessments

Samples for immunogenicity testing were time matched to PK samples to determine the presence/absence of antidrug antibodies (ADAs), incidence of TE-ADAs, ADA titre and neutralising antibody (NAb) status. Immunogenicity was assessed using a validated assay designed to perform in the presence of IXE. Antibodies were further characterised and/or evaluated for their ability to neutralise the activity of IXE. Treatment-emergent immunogenicity was defined as any occurrence of a 4-fold or 2-dilution increase in titre over the pretreatment baseline titre. In the case of a negative result at baseline, treatment-emergent immunogenicity was defined as an increase in titre to ≥1:10.

2.5 | PopPK data analysis

PopPK analyses were performed using nonlinear mixed effects modelling (NONMEM 7.4.2). The first-order conditional estimation with epsilon-eta interaction method was used.[18] Analyses were conducted in accordance with the tenets contained in the most recent US FDA Guidance for Industry on Population Pharmacokinetics.[19]

The base structural PopPK model in paediatric patients with psoriasis was based on the final PopPK models in adult patients with psoriasis and psoriatic arthritis.[11] It is a 2-compartment linear model parameterised in terms of first-order CL, volume of distribution of the central compartment (V_2), volume of distribution of the peripheral compartment (V_3), intercompartmental clearance (Q) and absolute bioavailability (F).[11] Since IXE was administered only as a subcutaneous injection in the IXORA-PEDS study, the F in the model was fixed to the F from the adult PopPK model. The PopPK model development for paediatric patients with psoriasis followed a 2-stage approach. First, covariates that had previously been found to be significant and retained in the final adult PopPK model in patients with psoriasis or psoriatic arthritis were evaluated in the base paediatric model (specifically baseline body weight on CL, V_2, V_3 and Q, site of injection on F, and immunogenicity effects on CL) and were only retained in the base paediatric PopPK model if the effects remained significant. In the second step, additional covariates specific to the IXORA-PEDS study were evaluated using stepwise covariate modelling implemented in Perl-Speaks NONMEM (PsN 4.2.0).[20] These included age, race, sex, baseline PASI and sPGA, and geographic region. Covariate–parameter relationships were investigated using a forward inclusion process followed by a backward elimination process. The criterion for forward inclusion and backward deletion of covariates was a *P*-value ≤.001 corresponding to a change in the objective function value (OFV) of 10.828. Covariates were retained in the final model based on several factors, as well as OFV, such as convergence of the estimation and covariance routines, reasonable parameter and error estimates based upon the known PK, good precision of the parameter and error estimates (low percentage relative standard error) and clinical relevance.

The final PopPK model was evaluated through visual predictive checks (VPC) and bootstrap methods.[21] The VPC ensures that the model maintains fidelity with the data used to develop it and entailed the simulation of 500 datasets. Simulated and observed data distributions were compared by calculating the median, 5th and 95th percentiles. A bootstrap analysis was conducted to assess the precision of the parameter estimates of the final model. The bootstrap was carried out by sampling from the analysis dataset with replacement, to produce resampled datasets with the same number of patients. A total of 1000 bootstrap datasets were created and the model was fit to each. The 95% confidence intervals for each parameter were calculated using the 2.5th and 97.5th percentile values from the distribution of bootstrap parameter values.

Missing values of independent variables, such as patient characteristic data, were imputed within a patient using the last observation carried forward method, except for site of injection where the most common site of injection of each patient was used as the imputed value. For IXE serum concentration (dependent variable), records in the NONMEM dataset containing missing dates, times, or dose amounts essential to PK or exposure–efficacy analysis were excluded from the analysis. Actual IXE doses were used in the analyses.

2.6 | Exposure–efficacy relationship

A longitudinal exposure–efficacy model for PASI response rates was used to evaluate the relationship between drug concentrations and efficacy response over time. The Laplacian estimation method (NONMEM 7.4.2) was used for the analysis. An ordered categorical model was used to describe the drug effect on efficacy response. Several model structures were explored including a latent variable to describe the drug effect and several drug effect models were also explored, including sigmoidal models. A separate latent variable structure was also explored to describe the placebo effect, ensuring that placebo and drug effects may be described by different pathways and mechanisms of action if necessary.

During the course of model building, different data transformations were evaluated, including modelling of the raw PASI data as well as the PASI75/90/100 responder rates. The efficacy in a large proportion of patients that has reached complete resolution of the disease, that is, complete plaque clearance, is represented by a PASI score of zero. The large quantity of zeros in the dataset when using the actual PASI scores was problematic analytically, as the data were not normally distributed, and these bounded outcomes of zero were poorly predicted by the model unless a minimal arbitrary threshold was set just above zero. Transforming the data to ordered categories (PASI75/90/100), indicating different levels of clinical improvement, helped to normalise the distribution. The transformation of the raw PASI scores also enabled a more accurate prediction of the clinical responses outcomes of interest i.e., the PASI75, PASI90 and, in particular, the PASI100 response rates. Lastly, PASI50 was included to stabilise the model and PASI<50 was included as the fifth outcome when response was not achieved.

Observed data for PASI response were used over time from baseline (Week 0) up to Week 12, as this was the time of the co-primary efficacy endpoint in the IXORA-PEDS study and efficacy data up to Week 12 was collected from all participants at the time of the

database lock. As PASI75/90/100 indicate different levels of disease improvement using the same scale, they may be combined into 1 unique ordered categorical dependent variable (DV). A PASI50 (PASI improvements ≥50% from baseline) response rate was also incorporated in the analysis. Therefore, the PASI response was categorised into 5 ordered outcomes: DV = 0, if not achieving PASI50; DV = 1, if achieving PASI50 but not PASI75; DV = 2, if achieving PASI75 but not PASI90; DV = 3 if achieving PASI90 but not PASI100; DV = 4, if achieving PASI100.

Sequential exposure–efficacy modelling was performed wherein the *posthoc* PK parameters derived from the final PopPK model were used as the PK input for patients who received IXE, and for patients randomised to placebo, the typical population PK parameter values were assigned.

In the ordered categorical model developed to determine the probability of a patient to be responder to PASI50/75/90/100, the complete logit function to attain each PASI response category (PASI50/75/90/100) is described below:

$$LGE_1 = B_1 + RESP1 + PLA$$

$$LGE_2 = B_1 - B_2 + RESP1 + PLA$$

$$LGE_3 = B_1 - B_2 - B_3 + RESP1 + PLA$$

$$LGE_4 = B_1 - B_2 - B_3 - B_4 + RESP1 + PLA$$

where LGE_1, LGE_2, LGE_3 and LGE_4 are the logits for DV ≥ 1 (PASI100/90/75/50), for DV ≥ 2 (PASI100/90/75), for DV ≥ 3 (PASI100/90) and for DV = 4 (PASI100), respectively. B_1, B_2, B_3 and B_4 correspond to the baseline values used for the calculation of the logits: DV ≥ 1 (PASI100/90/75/50), DV ≥ 2 (PASI100/90/75), DV ≥ 3 (PASI100/90) and DV = 4 (PASI100). B_1 may be any value $(-\infty, +\infty)$ and B_2, B_3 and B_4 are a positive value. RESP1 and PLA represent drug effect and placebo effect, respectively.

Then, the probability of a particular response status was calculated as shown below:

$PGE_i = EXP(LGE_i)/(1 + EXP[LGE_i])$; i = 1,2,3,4.

where PGE_i are the probability of i = 1 DV ≥ 1 (PASI100/90/75/50), i = 2 DV ≥ 2 (PASI100/90/75), i = 3 DV ≥ 3 (PASI100/90) and i = 4 DV = 4 (PASI100). The probabilities of PASI responses are then calculated as follows:

$$P_0 = 1 - PGE_1$$

$$P_1 = PGE_1 - PGE_2$$

$$P_2 = PGE_2 - PGE_3$$

$$P_3 = PGE_3 - PGE_4$$

$$P_4 = PGE_4$$

where P_0, P_1, P_2, P_3 and P_4 are the probabilities of not achieving PASI50, achieving PASI50 but not achieving PASI75, achieving PASI75 but not achieving PASI90, achieving PASI90 but not achieving PASI100, and achieving PASI100, respectively.

The effects of the following patient factors were evaluated using the stepwise covariate modelling procedure implemented in Perl-Speaks NONMEM (PsN 4.2.0) in the exposure–efficacy model: age, baseline body weight, sex, baseline PASI or sPGA score, palmoplantar/nail/scalp psoriasis involvement, immunogenicity status, prior psoriasis treatment, or geographic region. All factors were tested on each parameter (B_1, RESP1 and PLA), except immunogenicity status, which was not tested on B_1 and geographic region that was not tested on RESP1. Criteria for retention of covariate effects in the final model followed the same principles as the PopPK model. The final exposure–efficacy model was evaluated through VPC and bootstrap methods similar to the evaluations described above for the PopPK model, with the exception that for the bootstrap analysis for the exposure–efficacy model, 500 datasets were created.

Missing values of patient characteristic data were treated as for the PopPK analyses above. Missing PASI data were treated as missing and no imputation was carried out.

3 | RESULTS

3.1 | PopPK

A total of 558 measurable IXE serum concentration measurements were available from 184 patients, including patients randomised to IXE at Week 0 (n = 114) and patients randomised to placebo or etanercept at Week 0 who then received IXE during the open-label maintenance period, which commenced after the Week 12 visit (n = 70). Four IXE serum concentration samples were BQL, all of which were at time points up to Week 12 and were excluded from the PopPK analysis. Continuous and categorical baseline characteristics for these patients are summarised in Table 1. Out of the 184 patients, 135 patients (73.4%) had a body weight above 50 kg (median weight 65.2 kg), 45 patients (24.5%) between 25 and 50 kg (median weight 40 kg), and 4 patients (2.2%) below 25 kg (median weight 21.7 kg). The overall age of these patients ranged from 6 to 17 years and the median age by weight category was 15, 10 and 7 years in the >50-kg, 25–50-kg and <25-kg weight groups, respectively. The majority of patients were white (81.5%) and approximately half were female (56.5%).

There were 330 (59.1%) IXE serum concentrations at time points up to Week 12 and 228 (40.9%) samples at time points after Week 12, all of which were included in the PopPK analysis. Figure 1 displays the observed mean IXE concentration profile *vs*. time by weight-based dosing regimen groups up to Week 12. Mean trough concentrations at predicted steady state (Weeks 8 and 12) were consistent over time and across weight groups within the range of 3.20–3.33 μg/mL for the 25–50-kg and >50-kg groups. Insufficient PK data were available

TABLE 1 Baseline demographics and disease characteristics of paediatric patients with moderate-to-severe plaque psoriasis included in the final population pharmacokinetic dataset, grouped by body weight

Baseline covariate	<25 kg (*n* = 4)	25–50 kg (*n* = 45)	>50 kg (*n* = 135)	Overall (*n* = 184)
Age (y)[a]	7.25 ± 1.26 (6–9)	10.4 ± 2.84 (6–17)	14.8 ± 1.93 (9–17)	13.6 ± 3.04 (6–17)
Body weight (kg)[a]	21.9 ± 0.520 (21.5–22.6)	37.7 ± 8.10 (25.0–50)	71.3 ± 19.5 (50.1–136)	62.0 ± 23.2 (21.5–136)
BMI (kg/m^2)[a]	15.0 ± 0.608 (14.3–15.7)	18.8 ± 2.33 (13.5–23.4)	25.7 ± 6.13 (17.5–49.8)	23.8 ± 6.28 (13.5–49.8)
Sex—female (%)	75.0	60.0	54.8	56.5
Baseline PASI[a]	20.8 ± 8.53 (13.6–33.1)	21.1 ± 9.41 (12.0–47.8)	19.9 ± 7.15 (12.0–49.2)	20.2 ± 7.76 (12.0–49.2)
Baseline sPGA[b]	4 (4–4)	4 (3–5)	4 (3–5)	4 (3–5)
Baseline sPGA = 3 (%)	0	44.4	48.1	46.2
Baseline sPGA = 4 (%)	100	48.9	45.2	47.3
Baseline sPGA = 5 (%)	0	6.67	6.67	6.52
Race (%):				
White	75	75.6	83.7	81.5
Black or African American	0	2.22	3.70	3.26
Asian	0	6.67	2.22	3.26
American Indian or Alaska native	25	2.22	0.741	1.63
Other	0	8.89	7.41	7.61
Missing	0	4.44	2.22	2.72
Site of SC injection (%):				
Abdomen	24.3	27.9	28.9	28.6
Arm	70.3	55.4	57.2	57.0
Thigh	5.41	16.7	13.8	14.4
Geographic region (%):				
US	25	35.6	38.5	37.5
Europe	25	40.0	42.2	41.3
Rest of world	50	24.4	19.3	21.2

BMI, body mass index; *n*, total number of patients included in the pharmacokinetic analysis; PASI, Psoriasis Area Severity Index; SC, subcutaneous; sPGA, static Physician's Global Assessment.
[a]Mean ± standard deviation (range).
[b]Median (range).

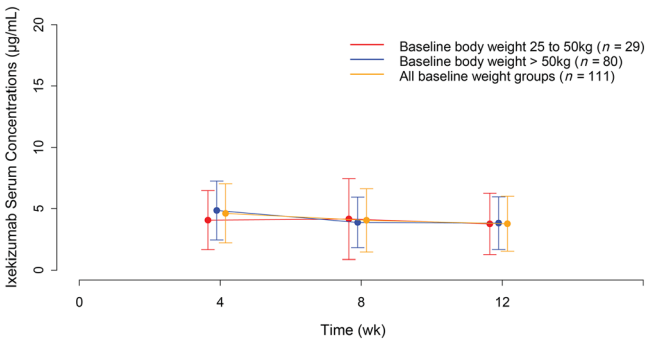

FIGURE 1 Mean (standard deviation) ixekizumab serum concentrations *vs*. time from Week 0 to 12 of the double-blinded dosing period grouped by weight category and overall for paediatric patients randomised to ixekizumab every 4 weeks at Week 0. Mean data for patients <25 kg are not plotted as there were only 2 patients with pharmacokinetic data in the Week 0–12 period but they are included in all baseline weigh group. All samples were designed to be trough samples. Only samples that met predefined trough criteria were included in the summary statistical calculation. If concentrations were reported as below the quantitation limit, they were set to a nominal value of lower than the lower limit of the assay (0.0063 µg/mL) and included in the summary statistical calculation for the purpose of plotting the data

for the <25-kg weight group to summarise the data up to Week 12, as only 2 patients <25 kg were assigned to IXE during the double-blind period. The individual IXE concentration data *vs.* time up to Week 108, including all available data at the time of the database lock from the ongoing periods beyond the double-blind period, are shown in Figure S2. Concentrations overlapped substantially between weight groups across time points up to Week 108.

The parameter estimates of the final paediatric PopPK model are presented in Table 2, and the goodness-of-fit diagnostic plots are included in Figure S3. The effects of body weight on CL, Q, V_2 and V_3, and ADA titre on CL are the covariates that were significant and retained in the final paediatric PopPK model. Briefly, the final model successfully described the available IXE PK data in paediatric patients with psoriasis, as indicated by the consistency between observed and predicted IXE concentrations and by the randomness of residual error distribution (Figure S3). All parameters were well estimated, with percentage relative standard error at or below 33%, for fixed and random effects. Epsilon-shrinkage was <13% indicating no significant overfitting of the data. Eta-shrinkage was <7% for CL indicating that the individual estimates of this parameter were informative. A VPC was conducted using the final PopPK model (Figure 2). The results indicate that the model predicts the observed drug concentrations well.

Figure 3A shows a plot of model-predicted Week 12 trough IXE concentrations *vs.* body weight for each individual patient included in the analysis. Trough concentrations in paediatric patients decrease as body weight increases in the >50-kg weight category. At weights <70 kg, the relationship between concentration and body weight was relatively flat as a result of doses being administered based on body weight categories for these lower weight patients. Despite trough concentrations decreasing for some patients in the >50-kg weight category, they remained within the 90% range of the observed adult trough concentrations using the Q4W dosing regimen in the pivotal Phase 3 UNCOVER studies,[12] shown by the grey shaded area in Figure 3A. Also shown in Figure 3B are the individual model-predicted trough concentrations by age. Age was not found to be a significant covariate in the final model, and this plot showed that paediatric patients aged from 6 to 17 years had exposure in a similar range to the adult patients in the UNCOVER studies[12] using the weight category-based dosing regimens.

Across all IXE dosing regimen groups over the period up to Week 108, the majority of samples (85.8%, 471 of a total of 549 immunogenicity-evaluable samples in 184 patients) were ADA negative and 14.2% (78 samples in 49 patients) were identified as TE-ADA positive. Four of these TE-ADA-positive samples were associated with IXE serum concentration reported as BQL, as mentioned above. Maximum postbaseline titres in the TE-ADA-positive samples ranged from 1:10 to 1:2560. Approximately half (52.6%) of TE-ADA-positive samples were classified as low titre (<1:160), 38.5% as moderate titre (≥1:160 to

TABLE 2 Parameter estimates from the final population pharmacokinetic model in paediatric patients with psoriasis (base and final models are the same)

Parameter	Population estimate (95% CI, %SEE)[a]	Interindividual variability (95% CI, %SEE)[a,b]
Rate of absorption		
Ka (h^{-1})	0.00801 (0.00446–0.0201, 29.3)	---
Clearance		
CL (L/h)	0.0120 (0.0107–0.0131, 3.94)	28.4% (23.7%–33.2%, 14.5)
Covariate ADA titre on CL	0.0292 (0.0130–0.0499, 32.3)	---
Q (L/h)	0.0119 (0.00249–0.0208, 27.6)	---
Covariate weight on CL and Q	0.989 (0.827–1.17, 8.43)	---
Volume of distribution		
V_2 (L)	2.72 (1.16–5.36, 31.8)	---
V_3 (L)	2.11 (0.638–2.93, 17.6)	---
Covariate weight on V_2 and V_3	0.998 (0.753–1.27, 11.8)	
Bioavailability		
F1	0.72 (FIXED)[c]	---
Residual error (proportional)	27.7% (23.2%–31.9%, 7.62)	

The table provides the population estimate. To obtain individual CL, Q, V_2 and V_3 estimates, the following equations were used:
$CL_{individual} = CL^*(weight/58.6)^{0.989}*(1 + 0.0292*LOG_e[ADA\ titre])$.
$Q_{individual} = Q^*(weight/58.6)^{0.989}$.
$V_{2,individual} = V_2^*(weight/58.6)^{0.998}$; $V_{3,individual} = V_3^*(weight/58.6)^{0.998}$.

ADA, antidrug antibody; CI, confidence interval; CL, clearance; F1, bioavailability; Ka, absorption rate constant; Q, inter-compartmental clearance; SEE, standard error of the estimate; V_2, volume of distribution of the central compartment; V_3, volume of distribution of the peripheral compartment.
[a]The CI was estimated using bootstrap.
[b]Interindividual variability (IIV) was calculated using the following equation for log-normal distributions of the random effects for CL:
[a]$\%IIV = 100 \times \sqrt{(e^{OMEGA_N} - 1)}$, where $OMEGA_N$ is the variance of the CL parameter.
[c]Bioavailability was fixed to the mean value from the existing adult model (F = 0.72) as the same formulation was utilised in all studies.

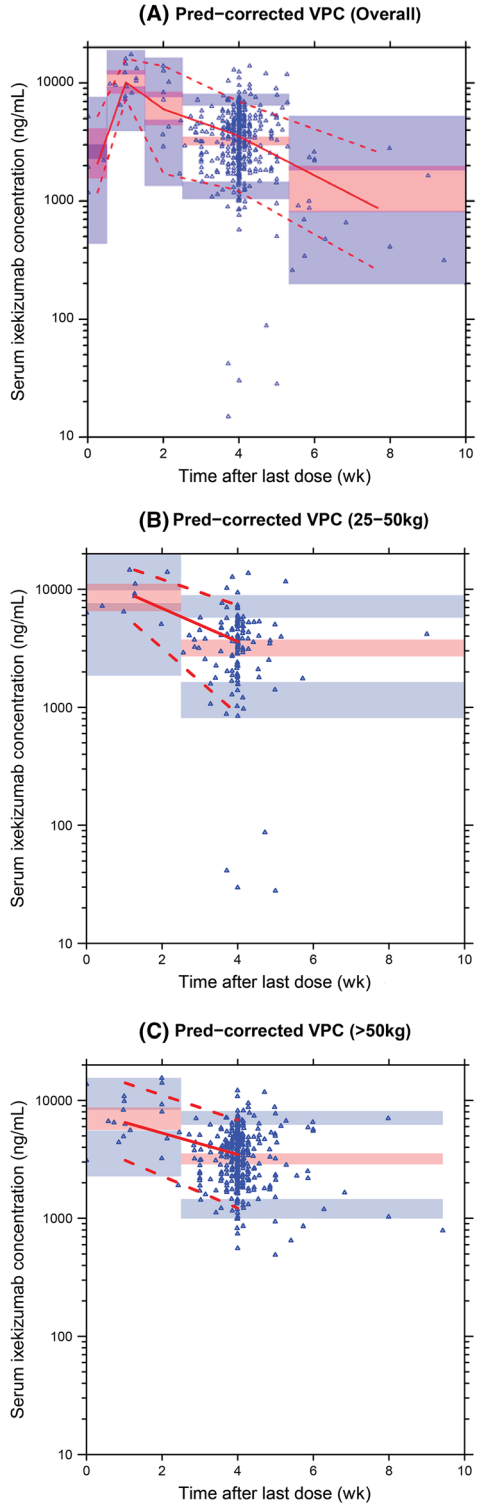

FIGURE 2 Pred-corrected visual predictive check (VPC) of the final population pharmacokinetic model in paediatric patients with psoriasis: overall (A) and stratified by weight category (25–50 kg, B; and >50 kg, C). There are insufficient data to plot the <25-kg weight group. The blue triangles are observations. The solid red line depicts the median of the observed data, and the red dashed lines represent the 5th and 95th percentiles of the observed data. The pink shaded area defines the 95% confidence interval around the median of the simulated data. The blue shaded areas are the model-predicted 95% confidence intervals of 5th and 95th percentiles of the simulated data

<1:1280) and 9.0% as high titre (≥1:1280). Seven samples were detected as NAb positive, all of which were reported in the initial period up to Week 12, of which 6 were high titre and 1 was a moderate titre. The majority of TE-ADA-positive samples were associated with IXE concentrations overlapping those associated with ADA-negative samples. However, a few samples were NAb positive ($n = 6$ associated with measurable IXE serum concentrations) and were associated with IXE concentrations that were at the low end or below the range of concentrations associated with ADA-negative samples and correspond to the cluster of data points below 100 ng/mL in Figure 2A. ADA titre was significant on CL but NAb status was not significant on CL in this analysis, whereas both factors were significant in the adult PopPK model. It is likely that both covariate effects were not required in the IXORA-PEDS analysis, because only 6 measurable IXE serum concentration samples were NAb positive and 5 of the 6 were also high titre and, therefore, inclusion of ADA titre was sufficient to describe the impact of immunogenicity in this dataset. Based on the PopPK parameter estimates shown in Table 2, the model predicts that high, moderate, or low ADA titre within the ranges ≥1:1280, ≥1:160 to <1:1280 or <1:160, respectively, would be associated with a predicted increase in CL of approximately 20.9–22.9%, 14.8–18.9% or 4.70–12.8%, respectively, compared to CL in ADA-negative patients.

Finally, Figure 4 shows a summary of observed IXE trough concentrations at Week 12 achieved in the 3 weight groups of paediatric patients with psoriasis enrolled in the IXORA-PEDS study compared with adult psoriasis data with the 80-mg Q4W dosing regimen from the pivotal Phase 3 UNCOVER studies.[12] The box plots overlap substantially for the 25–50-kg and >50-kg paediatric and the adult groups.

3.2 | Exposure–efficacy relationship: PASI time course model

The dataset includes all observed PASI response data up to and including Week 12 (842 PASI observations from 171 patients, 115 on IXE and 56 on placebo).

A simple slope parameterisation of the model was sufficient to describe both the drug and placebo effects in this paediatric population across the exposure range achieved. The drug effect was best described by a slope function using log-transformed IXE concentrations predicted by the PopPK model as the exposure input:

$$E_{drug} = SLP * LOG_e\,(Conc[t] + 1)$$

where E_{drug} refers to the drug effect, SLP is the slope parameter, LOG_e is the natural logarithm and Conc(t) is the predicted IXE concentration for each patient at any time t. The placebo effect was best described by a time-dependent slope function:

$$E_{pla} = SLPLA * LOG_e(t + 1)$$

where E_{pla} refers to the placebo effect, SLPLA is the slope parameter and t is any time. Table 3 displays the parameter estimates from the

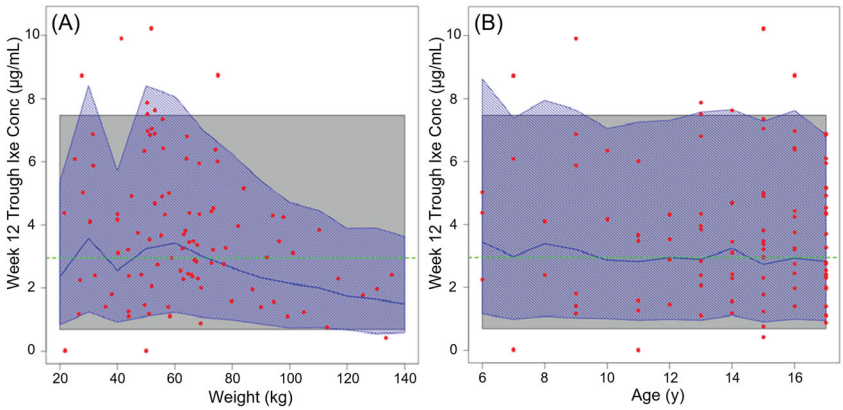

FIGURE 3 Model-predicted ixekizumab trough concentrations (Trough Ixe Conc) by body weight (A) and age (B) of paediatric patients compared with adult patients with psoriasis. The data points represent model-predicted concentrations from individual paediatric patients. The blue line is the median simulated paediatric trough concentration, and the blue shaded area encompasses 90% of the simulated paediatric patients. The green dashed line is the median observed adult trough concentrations, and the horizontal grey band encompasses 90% of the observed adult patients receiving 80 mg every 4 weeks from 3 Phase 3 studies (UNCOVER-1, UNCOVER-2 and UNCOVER-3).[12]

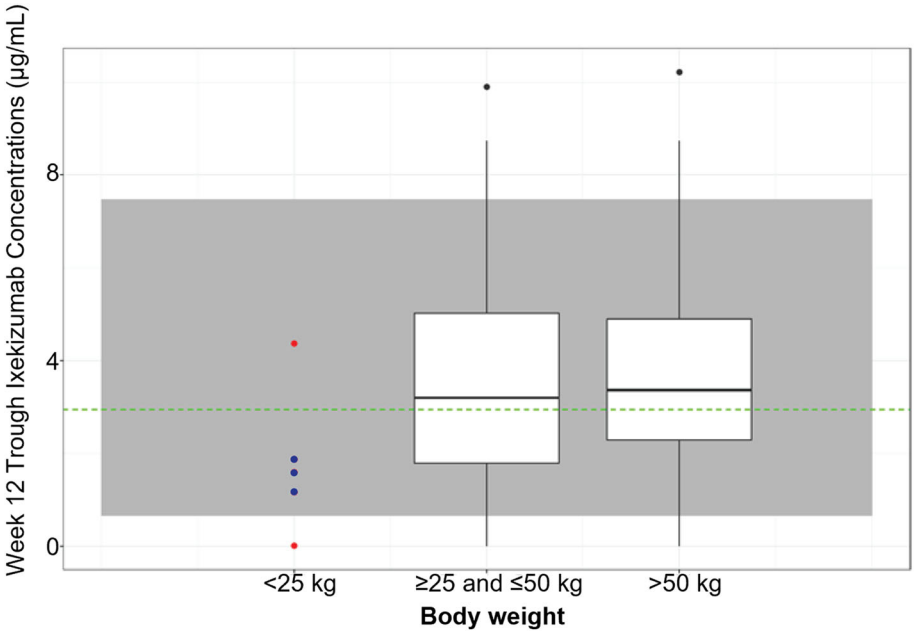

FIGURE 4 Comparison of observed ixekizumab trough concentrations by weight groups for paediatric patients *vs*. adult patients with psoriasis. Solid grey band represents the 5th and 95th percentiles of the observed Week 12 adult Q4W data from 3 Phase 3 studies (UNCOVER-1, UNCOVER-2 and UNCOVER-3),[12] the green dashed line represents median adult Q4W concentration, and the box plots represent observed paediatric data. Forty-5 patients in the 25- to 50-kg group and 127 patients in the >50-kg group had PK samples at Week 12. As only 2 patients in the <25-kg group had PK samples at Week 12 (red data points), additional trough PK samples beyond Week 12 were included (blue data points) to give a total of 5 PK samples from 4 patients. PK, pharmacokinetics; Q4W, every 4 weeks

final PASI time course model. These were estimated with good precision. A VPC was performed to evaluate the adequacy of the selected final model and is shown in Figure 5. The model was generally able to predict well the proportion of paediatric patients on either IXE or placebo who achieved different levels of PASI response from Week 0 to 12 (Figure 5).

The only covariate effect that was retained in the final model was the involvement of palmoplantar psoriasis. This was a significant covariate effect on the baseline disease state (B1) using a linear relationship in which patients with palmoplantar psoriasis at baseline had higher disease activity compared to patients without palmoplantar psoriasis. Figure S4 displays simulations evaluating the impact of the presence/absence of palmoplantar psoriasis on PASI response rates. Patients with palmoplantar involvement had more severe disease initially. In addition, response rates increased mostly in parallel for those with or without palmoplantar psoriasis except PASI100 responses, for which palmoplantar involvement appeared to respond more slowly during the 12-week period, as shown by their shallower response curve. It should be noted that the 90% confidence interval for the patients with palmoplantar involvement is large due to the relatively small number of patients in this group (14%). In general, the predicted data agreed well with the observed data and patients with or without palmoplantar psoriasis achieved high levels of response.

Finally, Figure 6 shows the comparison of observed mean PASI responses at the median IXE trough concentration at Week 12 in each weight category of paediatric patients compared with model-predicted PASI response–concentration curves in adult patients with psoriasis. It shows high response rates in both populations with the

TABLE 3 Parameter estimates from the final population ixekizumab PASI time course exposure–efficacy model

Parameter	Population estimate (%RSE)	95% CI from bootstrap
B_1	−5.80 (9.57)	−7.01, −4.88
B_2	0.935 (11.0)	0.742, 1.17
B_3	0.973 (10.8)	0.794, 1.19
B_4	1.13 (12.0)	0.868, 1.43
SLP	0.394 (11.8)	0.315, 0.496
SLPLA	2.30 (7.48)	2.02, 2.67
PPP effect on B1[a]	−0.865 (38.0)	−1.67, −0.234

B1, Baseline disease state; B_1, Base value for PASI50 (DV ≥ 1); B_2, Base value for PASI75 (DV ≥ 2); B_3, Base value for PASI90 (DV ≥ 3); B_4, Base value for PASI100 (DV = 4); CI, confidence interval; DV, dependent variable; PASI, Psoriasis Area and Severity Index; PASI50/75/90/100 at least 50%/75%/90%/100% improvement from baseline in PASI score; %RSE, relative standard error; PPP, palmoplantar psoriasis; SLP, slope parameter for drug effect; SLPLA, parameter for maximum placebo effect.
[a]PPP effect on B1 = −0.865 + B1.

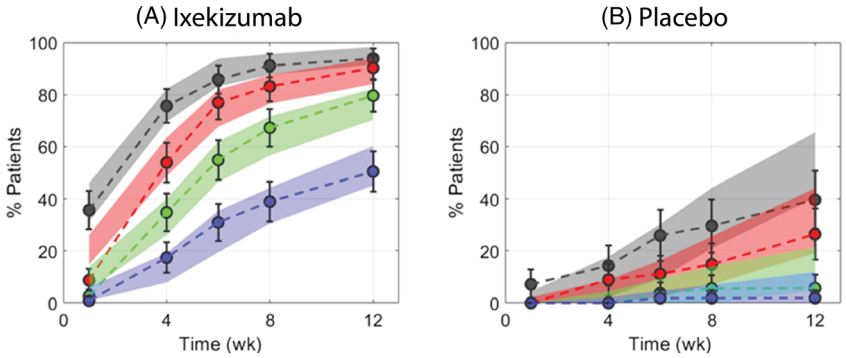

FIGURE 5 Visual predictive check from the final PASI time course exposure–efficacy model. Dashed lines represent the observed average percentage of paediatric patients achieving PASI50 (grey), PASI75 (red), PASI90 (green) and PASI100 (blue) by time for ixekizumab Q4W-treated (A) and placebo-treated (B) patients. The symbols represent the observed response and 90% CI. The shaded area is the predicted 90% CI from the model. CI, confidence interval; PASI, Psoriasis Area and Severity Index; PASI50/75/90/100, at least 50%/75%/90%/100% improvement from baseline in PASI score; Q4W, every 4 weeks

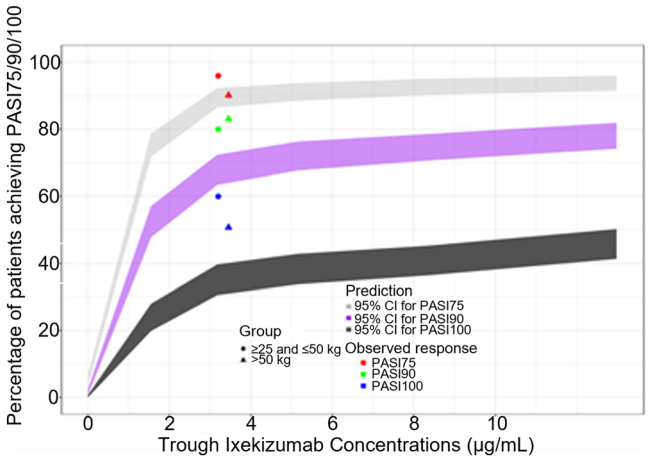

FIGURE 6 Comparison of Week 12 model-predicted efficacy response rates in adult patients with psoriasis with observed response rates at Week 12 in paediatric patients with psoriasis. The colour shaded curves represent the 95% CI of PASI75/90/100 responses predicted from the adult exposure–efficacy model. The position of the observed data points on the y-axis is the observed percentage of paediatric patients achieving a PASI75/90/100 response and the position of the observed data points on the x-axis occurs at the median observed exposure from the model for that weight group. Adult data are published elsewhere.[12] CI, confidence interval; PASI, Psoriasis Area and Severity Index; PASI75/90/100, at least 75%/90%/100% improvement from baseline in PASI score

response rates being as good as if not better at the median concentration in the paediatric dose groups compared with the adult response rates. The adult PASI-concentration data are from the UNCOVER studies and were published elsewhere.[12] In addition, the observed PASI response rates at Week 12 in paediatric compared with adult patients with psoriasis are shown in Table S1 and also show high and consistent response rates across groups. Thus, the response rates are as good as, if not better, for paediatric patients with psoriasis in the IXORA-PEDS study than for adult patients with psoriasis from the UNCOVER studies, using the 80-mg Q4W regimen.

4 | DISCUSSION

This is the first report of the PK and exposure–efficacy relationship of IXE in a paediatric population with moderate-to-severe plaque psoriasis. A PopPK model and an exposure–efficacy model were developed using data from patients aged 6 to <18 years who participated in the IXORA-PEDS study.

The final PopPK model in paediatric patients with moderate-to-severe plaque psoriasis is the same structural 2-compartment model with linear elimination that was previously developed in adult patients with psoriasis and psoriatic arthritis with concomitant psoriasis.[11] Of the covariates that were significant in the adult PopPK models, weight on CL, Q, V_2 and V_3 and immunogenicity on CL were also significant in the paediatric PopPK model. Results from the PK analysis in paediatric patients with psoriasis are comparable to reported results from this prior adult PopPK analysis. When CL and V_{ss} estimates are normalised for a 70-kg individual to allow comparison across the population, the mean estimate is 0.0144 L/h and 5.77 L for CL and V_{ss}, respectively, in paediatric patients, compared to 0.0123 L/h and 5.05 L, respectively, in adult patients. The estimated mean half-life was 12 days in each population.[11] It should be noted that the baseline body weight was used in this paediatric PopPK analysis since the majority of the PK data were collected in the first 12-week period of the study, at which time the mean percent change from baseline in body weight was 1.6%. Over the 108-week period of the study, 23% of patients had a ≥ ±10% change in body weight that was not taken into account in the model. This is expected to have minimal impact on the analyses and interpretation of the results.

The observed and model-predicted IXE exposures in paediatric patients with psoriasis across weight groups are within a similar range to the observed IXE trough concentrations achieved with the 80-mg Q4W dosing regimen in adult patients with psoriasis (mean [standard deviation] 3.48 [2.16] μg/mL; Figures 3A and 4). In addition, the overall impact of body weight on IXE serum concentrations is similar in paediatric and adult populations in that higher body weight is associated with lower IXE concentrations. The findings from this analysis indicate that the weight category-based dosing regimens used in IXORA-PEDS study are able to achieve similar efficacious concentrations as observed in adult patients with psoriasis. These weight category-based dosing regimens were approved by the US FDA for the treatment of paediatric patients with moderate-to-severe psoriasis. The dosing regimens for patients weighing 25–50 and >50 kg were also approved by the EMA, whereas the <25-kg dose was not approved due to the small number of patients in this category in the IXORA-PEDS study.[11]

All patients in the IXORA-PEDS study had PK samples to include in the PopPK model with many being trough samples (taken at the end of a dosing interval). Twelve patients who participated in the PK addendum also had samples taken approximately 1 week after the first and third doses (at approximate maximum concentration). Collectively, these PK samples enabled estimation of all parameters in the PopPK model with good precision, so the IXORA-PEDS dataset could be analysed independently without the adult PK data. Data in the absorption phase were somewhat limited in this analysis, potentially explaining why the site of injection, which was a significant covariate in the adult PopPK models, was not found to be significant in the paediatric PopPK model.

Limited PK data from only 2 patients were available for the <25-kg paediatric group up to Week 12 but are consistent with the above conclusions. There were 3 more trough samples in 3 patients who received IXE after Week 12, during the open-label maintenance period, included in the popPK analysis; these trough samples were also consistent with observed adult targeted efficacious exposures.

A relationship between IXE exposure and the time course of PASI response was established in paediatric patients in the IXORA-PEDS study. The model is able to describe well the time course of the response, with good agreement between observed and predicted responses, and was able to describe the rapid onset of efficacy observed after the initiation of dosing (Figure 5). This relationship between concentration and PASI response was quantified and comparable in both paediatric and adult patients with moderate-to-severe psoriasis (Figure 6). These findings support that the dosing regimens by weight category evaluated in the IXORA-PEDS study were effective.

The analysis presented herein is focused on 1 of the 2 co-primary endpoints, the PASI score. A static time point exposure–efficacy model was also developed using Week 12 IXE concentration and sPGA response data,[11] the other co-primary endpoint. These data were also well predicted using a static exposure–efficacy model but since the modelling approach was different to the PASI time course model and space is limited here, we focused on the PASI model as being a representative efficacy endpoint for IXE.

As noted with the PK data, efficacy data were limited for the <25-kg paediatric group, although both patients in this weight category assigned to IXE at Week 0 did achieve clinically meaningful response at Week 12. Also as noted earlier, trough concentrations started to decrease as weight increased for paediatric patients >70 kg dosed with 80 mg Q4W in the >50-kg weight category (Figure 3A). Concentrations, however, remained in the range observed in adult patients dosed with 80 mg Q4W and there was no reduction in efficacy in this group of patients. Taking the response rates in the 10 patients in the IXORA-PEDS analysis dataset who weighed >100 kg, 8, 7 and 4 of these 10 patients achieved PASI75/90/100

responses, respectively. These rates are within the range of the overall paediatric and adult population response rates observed in Figure 6 and Table S1.[13]

This exposure–efficacy analysis was conducted at the time of the primary database lock of the study, when all patients had completed the Week 12 visit, thus this was the timeframe over which the PASI time course model was developed and inferences about the exposure–efficacy cannot be made to address the longer-term durability of the response. However, in the main publication for this study, a subsequent analysis of longer-term data demonstrated that a sustained or improved response was observed up to Week 48 in the IXORA-PEDS study.[16]

PopPK and exposure–efficacy models have previously been shown to be successful in predicting the PK as well as the categorical clinical endpoints of other biologic drugs, such as **ustekinumab** (an **IL-12** and **IL-23** antagonist approved for paediatric psoriasis), in paediatric patients with psoriasis.[22] In the analyses presented herein, PopPK and exposure–efficacy models were developed that adequately describe the PK of IXE and the relationship between IXE concentrations and PASI response rates in paediatric patients aged 6 to <18 years with psoriasis. IXE doses in the IXORA-PEDS study were selected based on simulations from the adult psoriasis models. These doses were shown to be appropriate and result in the desired exposure and provide high levels of efficacy in the IXORA-PEDS study.

4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in https://www.guidetopharmacology.org/, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019).[23]

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CONTRIBUTORS

K.J. and L.C. contributed to the study design, data analysis and data interpretation. N.V.M. and C.P. contributed to data analysis and data interpretation. C.R.C. contributed to the conduct of the study and data interpretation. A.S.P. contributed to the study design, conduct of the study, data acquisition and data interpretation. P.L. contributed to data interpretation. M.M.B.S. and K.P. contributed to the conduct of the study, data acquisition and data interpretation. All authors participated in the critical revision of the manuscript and approved this manuscript to be submitted for publication.

COMPETING INTERESTS

K.J., L.C., C.P. and C.R.C. are employees and shareholders of Eli Lilly and Company. N.V.M. was an employee and shareholder of Eli Lilly and Company. A.S.P. has been an investigator for AbbVie, Eli Lilly and Company, Janssen, and UCB; and has been a consultant with honoraria from AbbVie, Almirall, Anaptysbio, Eli Lilly and Company, Exicure, Galderma, Janssen, LEO Pharma, Novartis, Pfizer, and UCB. P.L. has served as a consultant, speaker, investigator, or advisory board member for AbbVie, Amgen, Bausch, Celgene, Dermira, Eli Lilly and Company, Janssen, LEO Pharma, Novartis, Pfizer, Sanofi, Sun Pharma, and Valeant. M.M.B.S. has received grants from or has been involved in clinical trials with AbbVie, Amgen, Celgene, Eli Lilly and Company, Janssen, LEO Pharma, and Pfizer; and has served as a consultant for AbbVie, Eli Lilly and Company, Janssen, LEO Pharma, Novartis, Pfizer, and UCB; fees were paid directly to the institution. K.P. has received honoraria, grants and/or research funding as a speaker, investigator, advisory board member, data safety monitoring board member, and/or consultant for AbbVie, Akros, Amgen, Anacor, Arcutis, Astellas Pharma US, Avillion, Bausch Health, Baxalta, Boehringer Ingelheim, Bristol Myers Squibb, Can-Fite Biopharma, Celgene Corporation, Coherus, Dermavant, Dermira, Dice Pharmaceuticals, Dow Pharmaceuticals, Eli Lilly and Company, Evelo, Galapagos, Galderma, Genentech, Gilead, GlaxoSmithKline, Incyte, Janssen, Kyowa Hakko Kirin Pharma, LEO Pharma, MedImmune, Meiji Seika Pharma, Merck (MSD), Merck Serono, Mitsubishi Pharma, Moberg Pharma, Novartis, Pfizer, PRCL Research, Regeneron, Roche Laboratories, Sanofi Genzyme, Sun Pharma, Takeda Pharmaceuticals, and UCB.

DATA AVAILABILITY STATEMENT

Lilly provides access to all individual participant data collected during the trial, after anonymisation, with the exception of PK or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after a receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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