28 May 2020
EMA/366227/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Taltz

International non-proprietary name: ixekizumab

Procedure No. EMEA/H/C/003943/II/0031

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Term	Definition
ADA	antidrug antibodies
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
ANOVA	analysis of variance
axSpA	axial spondyloarthritis
BSA	body surface area
CD	Crohn's disease
CDLQI	Children's Dermatology Life Quality Index
CDRS	Children's Depression Rating Scale
CHMP	Committee for Medicinal Products for Human use
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
DLQI	Dermatology Life Quality Index
EMEA	European Medicines Agency
EU	European Union
FOIA	Freedom of Information Act
GCP	good clinical practice
HRQoL	health-related quality of life
IBD	inflammatory bowel disease
ICH	International Conference on Harmonisation
IL	interleukin
ISR	injection-site reaction
ITT	intent-to-treat
JIA	juvenile idiopathic arthritis
Lilly	Eli Lilly and Company
LSM	least squares mean

Term	Definition
MedDRA	**Med**ical **D**ictionary for **R**egulatory **A**ctivities: a standard coding terminology for adverse events used globally in compliance with International Conference for Harmonisation (ICH) guidelines.
NAb	**neutralising antibodies**
NAPSI	**Nail Psoriasis Severity Index**
nr-axSpA	nonradiographic axial spondyloarthritis
NRI	nonresponder imputation
NRS	numeric rating scale
PASI	Psoriasis Area and Severity Index
PASI 50	at least a 50% improvement from baseline in PASI score
PASI 75	at least a 75% improvement from baseline in PASI score
PASI 90	at least a 90% improvement from baseline in PASI score
PASI 100	a 100% improvement from baseline in PASI score
PatGA	Patient's Global Assessment of disease severity
PD	pharmacodynamic(s)
PDCO	Paediatric Committee
PI	prediction interval
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
PPASI	Palmoplantar Psoriasis Severity Index
PPASI 50	at least 50% from baseline improvement rate in PPSI
PPS	per-protocol set
PRAC	Pharmacovigilance Risk Assessment Committee
Ps	psoriasis
PsA	psoriatic arthritis
PSSI	Psoriasis Scalp Severity Index
PY	patient-year(s)
Q1W	every 1 week
Q2W	every 2 weeks
Q4W	every 4 weeks

Term	Definition
r-axSpA	radiographic axial spondyloarthritis
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SE	standard error
SmPC	Summary of Product Characteristics
sPGA	static Physician's Global Assessment
$t_{1/2}$	elimination half-life
TE-ADA	treatment-emergent antidrug antibodies
TEAE	treatment-emergent adverse event
TNF-α	tumour necrosis factor alpha
US	United States
USPI	United States Prescribing Information
V_{ss}	volume of distribution at steady state

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 15 October 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of Indication to include the treatment of moderate to severe plaque psoriasis in children from the age of 6 years and adolescents who are candidates for systemic therapy for Taltz; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated with new safety and efficacy information. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. The RMP version 7.1 has also been submitted.

The variation requested amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0351/2018 the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0351/2018 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Peter Kiely

Timetable	Actual dates
Submission date	15 October 2019
Start of procedure:	2 November 2019
CHMP Rapporteur Assessment Report	20 December 2019
CHMP Co-Rapporteur Assessment Report	20 December 2019
PRAC Rapporteur Assessment Report	3 January 2020
PRAC members comments	8 January 2020
Updated PRAC Rapporteur Assessment Report	9 January 2020
PRAC Outcome	16 January 2020
CHMP members comments	20 January 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	24 January 2020
Request for supplementary information (RSI)	30 January 2020
PRAC Rapporteur Assessment Report	6 April 2020
PRAC members comments	7 April 2020
Updated PRAC Rapporteur Assessment Report	8 April 2020
CHMP Rapporteur Assessment Report	15 April 2020
PRAC Outcome	17 April 2020
CHMP members comments	20 April 2020
Updated CHMP Rapporteur Assessment Report	23 April 2020
2nd Request for supplementary information (RSI)	30 April 2020
Rapporteur's preliminary assessment report circulated on:	13 May 2020
CHMP members comments	18 May 2020
Updated CHMP Rapporteur Assessment Report	N/A
CHMP opinion:	28 May 2020

2. Scientific discussion

2.1. Introduction

Taltz contains the recombinant humanised monoclonal antibody ixekizumab that binds with high affinity (< 3 pM) and specificity to interleukin 17A (both IL-17A and IL-17A/F). Taltz is approved for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy and also for the tretament of active psoriatic arthritis in adults.

The variation application sought initially to extend the indication in plaque psoriasis to include also *treatment of moderate to severe plaque psoriasis in children from the age of 6 years and adolescents who are candidates for systemic therapy*.

The associated posology is a starting dose and a recommended dose every 4 weeks thereafter based on patient's body weight, as follows:

- greater than 50kg: starting dose of 160mg, followed by 80mg Q4W

- 25 to 50kg: starting dose of 80mg, followed by 40mg Q4W

- less than 25kg: starting dose of 40mg, followed by 20mg Q4W

In October 2010, the MAH submitted the first proposal for a paediatric investigation plan (PIP) to the Paediatric Committee (PDCO) to investigate the safety and efficacy of ixekizumab in paediatric patients with juvenile idiopathic arthritis (JIA) and paediatric patients with plaque psoriasis (Ps). In May 2012, PIP EMEA-001050-PIP01-10 was agreed, covering the conditions of JIA in children from the age of 1 year and Ps in children from the age of 6 years. The PIP contained pharmaceutical, pre-clinical and clinical obligations. The PIP was split in October 2018, with EMEA-001050-PIP01-10-M04, covering only the condition of paediatric Ps. 'Study 6' of this PIP (Lilly study acronym I1F-MC-RHCD) is the only clinical study.

No scientific advice has been provided for the paediatric psoriasis development.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

The two non-clinical studies performed in agreement with the paediatric investigation plan (PIP) and included in the present Type II variation application; *A Repeat-Dose Fertility Study in Cynomolgus Monkeys Given LY2439821 by Subcutaneous Injection Once Weekly for 3 Months* (Study 20003965) performed in 2011 and *An Assessment of LY2439821 on Pre- and Postnatal Development When Administered by Subcutaneous Injection Once Weekly to Pregnant Cynomolgus Monkeys* (Study 20018253) performed in 2014, were also included in the original MAA for Ixekizumab submitted in 2015.

These two non-clinical study reports submitted with this application have been assessed previously.

2.2.1. Ecotoxicity/environmental risk assessment

Ixekizumab is a monoclonal anti-human Interleukin-17A antibody and therefore in accordance with the CHMP guideline on the environmental risk assessment (EMEA/CHMP/SWP/4447/00) is exempt of the need for an environmental risk assessment (ERA). No additional ERA is thus needed for this Type II variation in accordance with the applicable guideline.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trial was performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1 Summary of the Pivotal Phase 3 Study Supporting the Paediatric Psoriasis Indication

Study	Description	N	Treatment	Primary Endpoint
I1F-MC-RHCD	Efficacy and safety in paediatric patients with moderate-to-severe psoriasis.	201	Double-Blind Treatment Period (Period 2): Placebo Q4W,[a,b] or Etanercept 0.8 mg/kg Q1W,[c] or Ixekizumab[a,b,d] *Patients >50 kg:* 160 mg at Week 0, and 80 mg at Weeks 4, 8, and 12 *Patients 25-50 kg:* 80 mg at Week 0, and 40 mg at Weeks 4, 8, and 12 *Patients <25 kg:* 40 mg at Week 0, and 20 mg at Weeks 4, 8, and 12 Maintenance Period (Period 3), and Extension Period or Randomised Withdrawal Period (Period 4): Placebo Q4W[e] Ixekizumab[e,f] *Patients >50 kg:* 80 mg Q4W *Patients 25-50 kg:* 40 mg Q4W *Patients <25 kg:* 20 mg Q4W	Proportion of patients achieving PASI 75 at Week 12 Proportion of patients achieving sPGA (0,1) at Week 12

Abbreviations: EU = European Union; N = number of patients in intent-to-treat population; PASI 75 = at least a 75% improvement from baseline in Psoriasis Area and Severity Index score; PK = pharmacokinetic(s); Q1W = every week; Q4W = every 4 weeks; SC = subcutaneous; sPGA = static Physicians Global Assessment.

Summary of the Pivotal Phase 3 Study Supporting the Paediatric Psoriasis Indication

a Patients were randomised to either ixekizumab or placebo in a 2:1 ratio.

b Patients receiving ixekizumab 20 mg or 40 mg received 1 SC injection of ixekizumab at Week 0 (Visit 2) and 1 SC injection of ixekizumab Q4W at Weeks 4 and 8.

Patients receiving ixekizumab 80 mg received 2 SC injections of ixekizumab at Week 0 (Visit 2) and 1 SC injection of ixekizumab Q4W at Weeks 4 and 8.

Patients receiving placebo for ixekizumab 20 mg or 40 mg received 1 SC injection of placebo at Week 0 (Visit 2) and 1 SC injection of placebo Q4W at Weeks 4 and 8.

Patients receiving placebo for ixekizumab 80 mg received 2 SC injections of placebo at Week 0 (Visit 2) and 1 SC injection of placebo Q4W at Weeks 4 and 8.

c In countries where etanercept was approved for severe paediatric psoriasis treatment only (emerging markets and European countries), patients were randomised in a 2:2:1 ratio to ixekizumab, etanercept (an open-label reference arm), or placebo until approximately 75 patients with severe psoriasis from etanercept-approved countries were randomised to ixekizumab (30 patients), etanercept (30 patients), and placebo (15 patients). This study involves a comparison of ixekizumab administered by subcutaneous (SC) injection with placebo and with etanercept (as a reference arm). Placebo was not given to match etanercept.

d At Visit 2, randomisation occurred based on the following weight groups:

1) <25 kg: randomisation to ixekizumab 20 mg, receiving a starting dose of 40 mg;
2) 25 kg to 50 kg: randomisation to ixekizumab 40 mg, receiving a starting dose of 80 mg; and
3) >50 kg: randomisation to 80 mg, receiving a starting dose of 160 mg.

A staggered approach to enrolment by weight group was implemented with patients 12 years of age or older and >50 kg enrolling initially to 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, patients started to enrol in the 25- to 50-kg group. Once data were obtained to Week 12 for approximately 15 patients in the 25- to 50-kg group, an interim analysis of PK, safety, and efficacy data in all patients in the study at that point was performed to confirm doses for the remaining patients in the study. Once confirmed, all weight groups were open for enrolment.

e A 48-Week double-blind, Randomised Withdrawal Period will occur from Week 60 (Visit 19) to Week 108 (Visit 31) for subjects in the EU who meet the response criterion at Week 60 (defined as sPGA 0,1). Subjects will be rerandomised to ixekizumab or placebo (1:1 ratio). Patients who are rerandomised to ixekizumab will receive ixekizumab 20, 40, or 80 mg every 4 weeks (Q4W) according to their weight at the time of rerandomisation. Upon disease relapse to Ps (sPGA ≥2), subjects will receive ixekizumab 20, 40, or 80 mg Q4W according to their weight
f Patients randomised to ixekizumab during Period 2, Induction received 1 SC injection of ixekizumab and 1 SC injection of placebo at Week 12.
Patients randomised to the placebo group during Period 2, Induction were assigned to receive ixekizumab at doses of 20, 40, or 80 mg based on weight: patients assigned to 20 mg received a starting dose of 40 mg; patients assigned to 40 mg received a starting dose of 80 mg; and patients assigned to 80 mg received a starting dose of 160 mg.
Patients randomised to etanercept during Period 2 received ixekizumab at doses of 20, 40, or 80 mg according to their weight after an etanercept 8-week washout period was complete. The etanercept washout period was from Week 12 through Week 20
All patients received 2 SC injections of ixekizumab at Week 12 and 1 SC injection of ixekizumab Q4W at Week 16 and thereafter. Treatment with ixekizumab was weight-based. If a patient changed weight category during the study after completing the double-blind treatment period (induction), the dose was to be adjusted accordingly.

2.3.2. Pharmacokinetics

Efficacy, safety, and PK data from the Phase 2 and Phase 3 programs in adults with plaque Ps have been used to guide the dose and dosing regimen for investigation in paediatric patients with plaque Ps. The recommended dosing regimens were selected so that predicted exposures in paediatric patients are within the range of exposures evaluated in adult patients at doses and dosing frequencies that had a positive benefit/risk profile.

A Phase 3 pivotal study (RHCD) supporting the paediatric psoriasis indication was conducted where subjects aged 6-17 years received placebo (n=56) or ixekizumab (n=115) according to the recommended posology for 12 weeks during period 2. In period 3 and 4, subjects who received placebo were also switched to ixekizumab recommended dosing regimen. Study RHCD also included an active-controlled (etanercept) reference arm in period 2, who switched to treatment with ixekizumab after an 8-week (Week 12 through Week 20 washout period). Population PK and exposure–response modelling was conducted using serum drug concentration data from the pivotal Phase 3 clinical study (RHCD) in paediatric patients with Ps.

Demographics, sampling and treatment regimens

Table 2 shows the demographics at study entry for patients in Study RHCD and **Table 3** shows the treatment regimens.

Table 2: Demographics at Study Entry for Patients in Study RHCD Included in the Pharmacokinetic Analysis by Baseline Weight Categories at Randomisation Stratified per Treatment Group and Weight

Baseline Covariate	PBO <25	PBO 25–50 kg	PBO >50 kg	ETN <25	ETN 25–50 kg	ETN >50 kg	IXE <25 kg	IXE 25–50 kg	IXE >50 kg	Overall
Age (range), years[a]	9	10 (6–14)	14 (10–17)	7	12 (9–13)	16 (11–	6.5 (6–7)	9 (6–17)	15 (9–17)	14 (6–17)
Body weight (range), kg[a]	21.5	41.9	61.8	22.6	34.3	63	21.6	38	67.7	58.6
BMI (range), kg/m^{2a}	14.7	20.3	23.4	15.7	15.8	22.5	14.7	18.5	25	22.7
Female (%)	100.0	66.7	62.2		25.0	53.3	100.0	62.1	51.8	56.5
Male (%)		33.3	37.8	100.0	75.0	46.7		37.9	48.2	43.5
Baseline PASI[a], (range)	17.1	16	16.4	13.6	24.4	27.4	26.3	18.6	17	18.1
Baseline sPGA[a], (range)	4	4 (3–5)	3 (3–5)	4 (4–4)	4 (4–4)	4 (4–5)	4 (4–4)	3 (3–5)	3 (3–5)	4 (3–5)
Race (%)										
White	100.0	75	78.4	–	75.0	93.3	100.0	75.9	84.3	81.5
Black or African American	–	–	8.1	–	–	–	–	3.5	2.4	3.3
Asian	–	16.7	–	–	–	–	–	3.5	3.6	3.3
American Indian/ Alaska	–	–	–	100.0	–	–	–	3.5	1.2	1.6
Other	–	–	8.1	–	–	6.7	–	13.8	7.2	7.6
Missing	–	8.3	5.4	–	25.0	–	–	–	1.2	2.7
Site of SC injection (%):										
Abdomen	–	30.1	20.0	100.0	24.1	44.3	18.2	27.2	30.6	28.6
Arm	100.0	56.6	63.1	–	51.7	27.2	72.7	55.1	58.2	57.0
Thigh	–	13.3	16.8	–	24.1	28.5	9.1	17.7	11.1	14.4
Geographic Region (%)										
US	–	50.0	40.5	–	–	–	50.0	34.5	44.6	37.5
Europe	–	33.3	40.5	–	50.0	80.0	50.0	41.4	36.1	41.3
Rest of World	100	16.7	18.9	100	50.0	20.0	–	24.1	19.3	21.2

Abbreviations: BMI = body mass index; N = total number of patients included in the pharmacokinetic analysis; PASI = Psoriasis Area Severity Index; RHCD = Study I1F-MC-RHCD; SC = subcutaneous; sPGA = static Physician's Global Assessment.
[a] Median (range).

Biological Sampling and Clinical Data Collections

Concentrations at Weeks 1 and 9 are non-troughs; all other time points are Ctrough. Blood sample collection for PK measurements is scheduled at the following time points during the 108-week study,

- Weeks 0, 4, 8, 12, 36, 64, and 108, prior to dosing and
- 12 weeks after the last study visit.
- Samples are time matched to samples for immunogenicity testing.

Two additional PK samples (collection time at approximately maximum concentration after the first and third doses [Weeks 1 and 9, respectively]) are obtained for patients who participate in Addendum (1). An estimated 24 additional paediatric patients will participate in Addendum (1),

- 12 patients in the higher weight group, >50 kg

- 12 patients in the middle weight group, 25 to 50 kg

Clinical data are collected via electronic case report form. The schedule of study procedures and data collection are specified in the study protocol.

Table 3: Treatment regimens

	Period 2			Period 3 and Period 4
Regimen	Dose Week 0	Dose Week 4 and Week 8	Dose Week 12	Dose Week 16 through Week 104
Ixekizumab >50 kg	160 mg (administered as two 80-mg SC injections)	80-mg Q4W SC injection	80-mg SC injection + a placebo injection at Week 12	80-mg Q4W SC injection
Ixekizumab 25-50 kg	80-mg SC injection	40-mg Q4W SC injection	40-mg SC injection + a placebo injection at Week 12	40-mg Q4W SC injection
Ixekizumab <25 kg	40-mg SC injection	20-mg Q4W SC injection	20-mg SC injection + a placebo injection at Week 12	20-mg Q4W SC injection
Etanercept All weight groups	0.8 mg/kg, not exceeding 50 mg per dose		No injections because of the washout period	Ixekizumab Q4W SC per weight group[a] OR matching placebo[b]
Placebo >50 kg	Placebo for ixekizumab 160 mg (administered as 2 placebo SC injections)	Placebo for ixekizumab 80-mg Q4W SC injection	Starting ixekizumab dose: 160-mg (administered as two 80-mg SC injections)	80-mg Q4W SC injection
Placebo 25-50 kg	Placebo for ixekizumab 80-mg SC injection	Placebo for ixekizumab 40-mg Q4W SC injection	Starting ixekizumab dose: 80-mg (administered as two 40-mg SC injections)	40-mg Q4W SC injection
Placebo <25 kg	Placebo for ixekizumab 40-mg SC injection	Placebo for ixekizumab 20-mg Q4W SC injection	Starting ixekizumab dose: 40-mg (administered as two 20-mg SC injections)	20-mg Q4W SC injection

Abbreviations: EU = European Union; Q4W = every 4 weeks; SC = subcutaneous; sPGA = static Physicians Global Assessment.

[a] From Week 20.

[b] From Week 60, for patients for patients from the EU who meet response criteria (sPGA 0,1) and are randomised to placebo.

Bioanalytical methods

Ixekizumab in human serum samples

Serum samples collected in clinical studies were analysed for ixekizumab concentrations using a validated enzyme-linked immunosorbent assay method. The bioanalytical method was originally developed and validated at ALTA Analytical Laboratory (subsequently renamed Intertek Pharmaceutical Services), San Diego, CA, and was re-developed and validated at ICON Laboratory Services, Inc., Whitesboro, NY. Details on the Intertek validation were provided in the application for psoriasis.

Table 4:Summary of method validation for determination of ixekizumab in human serum by ELISA (report 184959))

Method validation report:	184959, Method Validation Report, Determination of LY2439821 in Human Serum by ELISA
Method validation lab job #:	184959
Method report	M08.LY2439821.huse.1
Matrix:	Human serum
Analyte(s):	LY2439821
Capture molecule:	LSN2815254
Minimum Required Dilution:	5-fold
Secondary Antibody:	Mouse anti-human IgG4 HRP
Validation range:	Calibration range is 3.20 ng/mL to 800 ng/mL in 100% matrix. The 3.20 ng/mL and 800 ng/mL calibrators are anchor points. Lower limit of quantitation = 6.30 ng/mL in 100% matrix ; Upper limit of quantitation = 400 ng/mL in 100% matrix. Samples above the limit of quantitation were diluted and reanalysed to yield results within the calibrated range.
Validated Dilution Limit	20,000-fold overall (includes MRD)
Validation inter-assay accuracy and precision:	-1.00% - 1.60% accuracy; 4.07% - 12.0% precision. Inter-run accuracy should not deviate by more than ± 20.0% of the nominal value (± 25.0% at the LLOQ and ULOQ) and the inter-run precision should not deviate by more than 20.0% (25.0% at the LLOQ and ULOQ).
Validation intra-assay accuracy and precision:	1.15% - 8.93% accuracy; 1.48% - 2.78% precision. The intra-run accuracy should not deviate by more than ± 20.0% of the nominal value (± 25.0% at the LLOQ and ULOQ) and the intra-run precision should not deviate by more than 20.0% (25.0% at the LLOQ and ULOQ).
Stability:	Long term stability storage period is 1095 days in human serum at approximately -70ºC. Benchtop stability is 25 hours at ambient temperature and 6 cycle freeze (approximately -70ºC) / thaw stability has been validated in human serum.
Incurred Sample Reproducibility Evaluation	Incurred Sample Reproducibility was not evaluated in this study.

Immunogenicity Assay Methods

Immunogenicity-evaluable patients were grouped into TE-ADA (treatment-emergent antidrug antibodies) status groups and time-varying TE-ADA status groups. An immunogenicity evaluable patient is defined as

1. a patient with an evaluable baseline sample and at least 1 evaluable postbaseline sample (that is, sample after administration of study drug).
2. patient with no evaluable baseline sample whose evaluable postbaseline samples are all ADA negative.

TE-ADA Status Groups:

- TE-ADA status (positive, negative, or inconclusive)
- NAb status (positive, negative, or inconclusive) for TE-ADA-positive patients
- TE-ADA titer groups for TE-ADA-positive patients:

- Low Titer: TE-ADA titer value (LOCF) <1:160
- Moderate Titer: TE-ADA titer value (LOCF) ≥1:160 and <1:1280
- High Titer: TE-ADA titer value (LOCF) ≥1:1280

Time-Varying TE-ADA Status Groups:

Individual ADA samples were ascribed into 3 different dichotomous variables as explained in **Table 5**. Each variable has possible values of a "greater-TE-ADA status" or a "lesser-TE-ADA status," in the sense that the level of TE-ADA detected in the greater-TE-ADA category is higher than in the lesser-TE-ADA category.

Table 5: TE-ADA Status Dichotomous Variables for AE Analysis

TE-ADA Status Dichotomous Variable	Greater-TE-ADA Status	Lesser-TE-ADA Status
TE-ADA positive	TE-ADA positive	not TE-ADA positive
TE-ADA moderate to high	TE-ADA positive with moderate titer or high titer	not TE-ADA positive nor TE-ADA positive with low titer
TE-ADA high status	TE-ADA positive with high titer	not TE-ADA positive nor TE-ADA positive with low or moderate titer

Abbreviations: AE = adverse event; TE-ADA = treatment-emergent anti-drug antibody.

Note: For purpose of this analysis, TE-ADA Inconclusive is taken to be "not TE-ADA positive." A TE-ADA low is defined as a TE-ADA positive with a titer value <1:160; a TE-ADA moderate is defined as a TE-ADA positive with a titer value ≥1:160 and <1:1280; and a TE-ADA high is defined as a TE-ADA positive with a titer value ≥1:1280.

All ADA-positive samples were evaluated for NAb. Definitions for NAb patient status are defined as follows:

- NAb-positive: A patient where a NAb-positive result is detected for ≥1 TE-ADA positive samples.
- NAb-inconclusive: A patient without a NAb-positive sample and with at least 1 sample for which drug levels may interfere with the NAb assay.
- NAb-negative: A patient who is evaluable for NAb and is neither NAb positive nor NAb inconclusive.

Observed Concentrations

Table 6 shows the number of post-dose concentration-time data records available for Week 0 through Week 12, at time points after Week 12 by weight group and overall. In Study RHCD, a total of 562 post-dose concentrations from 184 patients are available up to and including Week 108 at the time of the database lock. Ixekizumab concentration data after Week 12 include data from patients at Week 0 assigned to ixekizumab, and patients at Week 0 assigned to placebo or etanercept and were subsequently assigned to ixekizumab in Period 3 onwards.

Table 6: Number of Post-dose Ixekizumab Concentration-Time Samples

	Samples in Patients by Weight Group, n (N)			
	<25 kg	25-50 kg	>50 kg	Overall
From Week 0 to 12	5 (2)	90 (29)	239 (80)	334 (111)
Time Points after Week 12	3 (3)	51 (40)	174 (127)	228 (170)

Abbreviations: N = number of patients; n = number of samples.

There are 4 (0.712% of total post-dose samples) post-dose concentrations that are below the quantifiable lower limit of the assay (BQL), all of which are at time points up to Week 12. Across the weight groups randomized to ixekizumab at Week 0, 105 samples taken prior to the first dose of ixekizumab are excluded from the analyses and all samples are BQL except for one. All samples for patients randomized to placebo or etanercept in the Week 0 to 12 period are also excluded. No PK observations are excluded based on classification as outliers.

The majority of samples are designed to be trough (taken at time points at the end of a dosing interval, immediately before the next dose). Concentrations at Weeks 1 and 9 are non-troughs. Samples collected outside a window of ±7 days from the scheduled time of last dose as these are not considered to represent a trough concentration and will introduce inaccuracy into the data. Only PK samples meeting trough criteria are included in plots/analyses.

Samples that do not meet trough criteria (N=71 [12.6%]) are excluded,

- 35 (49.3%) at time points up to and including Week 12
- 36 (50.7%) at time points after Week 12.

The variability tended to be higher for the reported trough concentrations in the 25- to 50-kg weight group compared to the >50-kg weight group (%CVs of 190% and 73% at Weeks 8 and 12 compared to 65% and 71%, respectively). Six of the 29 patients dosed in the 25- to 50-kg body weight group received at 1 or more visits a lower or higher dose than what the patients should have received. There are a few very low concentrations reported in the 25- to 50-kg weight group associated with high titer and NAb-positive samples that will have also contributed to the variability. Insufficient PK data are available for the <25-kg weight group to summarize the data up to Week 12 as only 2 patients are assigned to ixekizumab during the double-blind period. One of these 2 patients inadvertently received 80 mg at Week 4 instead of 20 mg resulting in a high Week 8 concentration (12.3 µg/mL). The second patient had no Week 8 concentration reported and the patient's Week 12 trough concentration was 0.009 µg/mL. This sample was associated with a TE-ADA-positive immunogenicity sample with a high titer that was also detected as NAb positive at Week 12.

Table 7: Summary (Geometric Mean [%CV]) of Ixekizumab Serum Concentrations (µg/mL) Versus Protocol Time by Weight Category Group and Overall during Week 0 to 12 of the Double-Blind Treatment Dosing Period (Period 2)

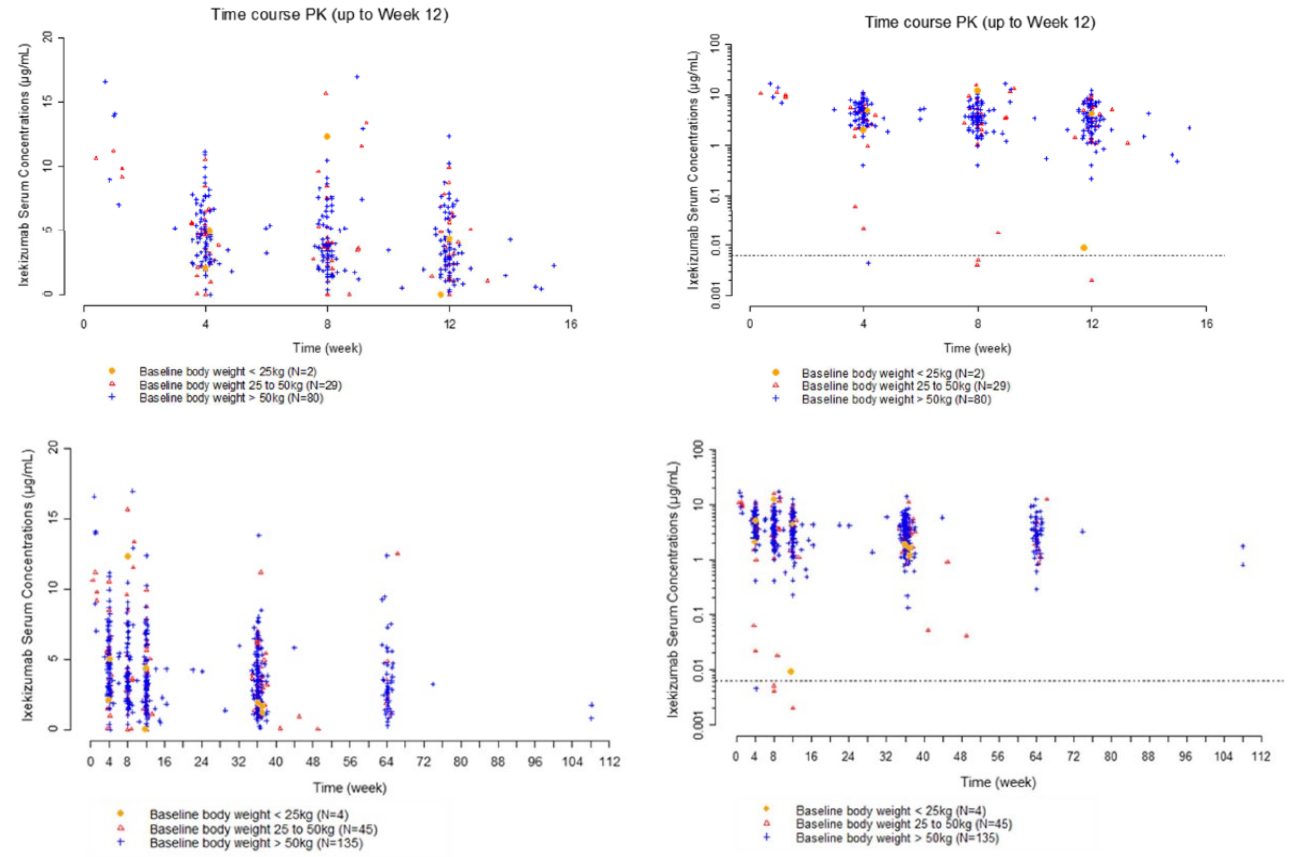
Treatment Group	Double-Blind Treatment Dosing Period (Period 2)		
	Week 4	Week 8	Week 12
<25-kg Group (N=2)	2.09, 4.99a	12.3[a,b]	0.009, 4.37[a]
25- to 50-kg Group (N=29)	2.75 (224)	3.21 (190)	3.23 (73)
>50-kg Group (N=80)	4.32 (61)	3.33 (65)	3.20 (71)
Overall – All patients (N=111)	3.79 (105)	3.35 (96)	3.03 (106)

Abbreviations: %CV = percent coefficient of variation; N = total number of patients per dosing regimen group.
Note: Data are presented as geometric mean and %CV. Only samples that were taken within ±7 days of the scheduled time from last dose were considered to represent a trough concentration and were included in the summary. The number of samples may have differed by protocol time point. Data that were below the quantifiable lower limit of the assay (0.0063 µg/mL) were excluded from the calculation of summary statistics.

[a] Due to small numbers, individual data are shown for the <25-kg weight group as insufficient samples are available to calculate summary statistics.

[b] Patient received 80 mg at Week 4 instead of 20 mg, which was the assigned dose for their weight category.

Figure 1:Scatterplot of ixekizumab serum concentration versus time data from Weeks 0 to 12 (top 2 plots) and Week 0 to 108 (bottom 2 plots) of the study in patients randomized to ixekizumab at Week 0 by Weight Category Group (linear scale – left panel; log scale – right panel).



Abbreviations: N = number of patients; PK = pharmacokinetics; Q4W = every 4 weeks. Notes: Data that are below the quantifiable lower limit of the assay (0.0063 µg/mL) were set to a randomly assigned nominal value lower than the lower limit of the assay for the purposes of plotting the data. The dotted horizontal line represents the lower limit of the assay.

Population pharmacokinetics

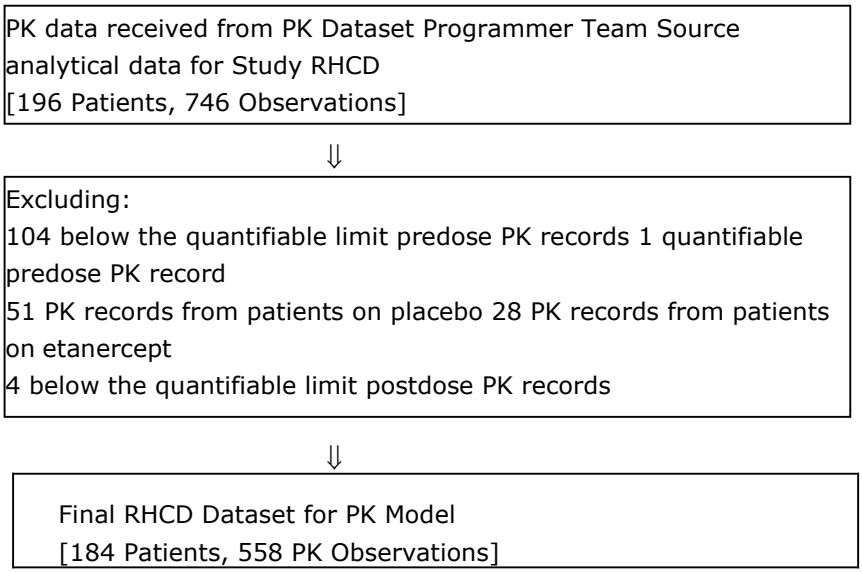
Population PK and exposure–response modelling was conducted using serum drug concentration data from the pivotal Phase 3 clinical study (RHCD) in paediatric patients with Ps. All available PK data up to 28 June 2019 were included in the population PK dataset and descriptive summaries of PK data and PK/treatment-emergent (TE)-ADA assessments. Data from Period 2 (double-blind treatment phase) up to Week 12 are included for the exposure-efficacy and exposure-safety analyses.

The PK/PD analysis plan aimed to address the following Study RHCD secondary objectives in paediatric patients with moderate-to-severe plaque Ps

- to measure ixekizumab exposure,
- to characterize the PK of ixekizumab, and
- to assess the relationship between exposure and efficacy, exposure and safety, and exposure and immunogenicity.

Number of patients removed from the PopPK/PD analyses in paediatric patients with psoriasis is presented in **Figure 2**. Four PK samples (0.712% of post-dose concentrations) were below quantification limit.

Figure 2:Data disposition: data included in the PK analysis.



Abbreviations: PK = pharmacokinetic; RHCD = Study I1F-MC-RHCD.

Base PK model

A priori, the existing PK models based on adult Ps and adult Ps/PsA data are expected to describe the ixekizumab PK from the present study in paediatric patients with Ps. The adult structural model is a 2-compartment linear model parameterized in terms of first-order clearance (CL), V2, V3, intercompartmental clearance (Q), and absolute bioavailability (F). Inter-individual variability is estimated for F, CL, and V2, and residual error is determined using a proportional error model. The same model is applied, and parameters re-estimated with the RHCD dataset. The same covariates that are retained in the final Ps and Ps/PsA PK models are evaluated (weight on clearance and volume terms, ADA titer and NAb status on clearance, and site of injection on bioavailability) and are retained only in the base PK model in paediatric patients with Ps if the effects remain significant. Once a structural and statistical model is established, the effect of additional patient factors is assessed for their clinical relevance on the disposition of ixekizumab (**Table 8**). Potentially significant covariate relationships are identified as those that, when added to the base model individually, result in a decrease in the objective function of ≥10.828 points ($p \leq 0.001$ for the change of 1 degree of freedom). Stepwise covariate modelling (SCM) is implemented using Perl-Speaks NONMEM (PsN 4.2.0) for covariate selection. The final backward model from the SCM process after any additional model refinement is considered the final model.

Table 8:Patient Factors Assessed in the Population Pharmacokinetic Analysis

Covariate	Type	Parameters Tested
Covariates Retained from Adult Ps and Ps/PsA PK Final Models		
Body weight	Continuous/Categorical	Q, CL, V_2, V_3
Injection site (thigh, abdomen, arm, buttock)	Categorical	F
ADA titer	Continuous/Categorical	CL
Neutralizing antibody status (Yes/No)	Categorical	CL
Covariates to Be Evaluated Specific to Study RHCD		
Age	Continuous	CL, V_2, V_3, KA
Sex	Categorical	CL, V_2, V_3, KA
Body mass index (BMI)	Continuous	CL, V_2, V_3, KA, F
Race	Categorical	CL
Baseline disease status: sPGA or PASI	Continuous/Categorical	CL
Geographical Region (US/EU/RoW)	Categorical	CL, V_2, V_3, KA, F

Abbreviations: ADA = antidrug antibody; CL = clearance; EU = Europe; F = bioavailability; KA = absorption rate constant; PASI = Psoriasis Area Severity Index; PK = pharmacokinetics; Ps = psoriasis; PsA = psoriatic arthritis; Q = intercompartmental clearance; RoW = Rest of World; sPGA = static Physician's Global Assessment; US = United States; V_2 = volume of distribution for central compartment; V_3 = volume of distribution for peripheral compartment.

Results: Base Model

The following modifications are made during the analysis of PK data in paediatric patients with Ps:

- The typical value of bioavailability is fixed to the mean value across the Ps and PsA Phase 3 trials from the existing Ps/PsA model (F = 0.72) as the same formulation is utilized in Study RHCD. No bioavailability parameter could be estimated as SC administration is used in this study.
- Inter-individual variability is not supported on F and V2 and the estimates tend toward zero.
- Covariance between CL and V2 or V3 are not supported by the data.

The final base model contains an IIV parameter with a log-normal distribution on CL only. The same covariates that were retained in the final adult Ps and Ps/PsA PK models are evaluated (i.e., weight on clearance and volume terms, ADA titer and NAb status on clearance, and site of injection on bioavailability). The results are as follows:

- The effect of body weight on clearance, described using an allometric relationship with an estimated exponent, is significant and is retained in the paediatric model. Inclusion of weight on CL and Q together results in a drop in OFV of 82.7 points, reduces IIV on CL from 44.8% to 34.7% (estimated with a low %RSE.
- With weight on CL already in the model, inclusion of weight on V2 and V3 together is incorporated (also using an allometric relationship with an estimated exponent) and results in a further drop in OFV of 29.0 points, estimated with low %RSE.
- Models where the allometric exponents are fixed are also evaluated. 1 model where the exponents are fixed to 0.75 and 1 on CL and V terms, respectively, and 1 model where the exponents are fixed to 0.85 and 1 for CL and V terms, respectively. Both the estimated and fixed exponent models converge successfully and have changes in OFV of a similar magnitude and effects are well estimated with low %RSE. As the data support estimation of the exponents, the model with estimated exponents is chosen (**Table 9**).

Table 9:Comparison of Pharmacokinetic Parameters in the Different Models

Parameter Description	Final Model (%SEE)[a]	Fixed Model 1 (%SEE)[a]	Fixed Model 2 (%SEE)[a]
Rate of Absorption			
Parameter for Ka (hr^{-1})	0.00801 (29.3)	0.00618 (22.3)	0.00715 (25.3)
Clearance			
Parameter for CL (L/hr)	0.0120 (3.94)	0.0120 (3.90)	0.0120 (3.85)
Titer effect on CL[b]	0.0292 (32.3)	0.0292 (34.3)	0.0291 (33.5)
Parameter for Q (L/hr)	0.0119 (27.6)	0.0112 (24.0)	0.0118 (25.5)
Weight effect on CL and Q[b,c]	0.989 (8.43)	0.75 (FIXED)	0.85 (FIXED)
Volume of Distribution			
Parameter for V_2 (L)	2.72 (31.8)	2.07 (30.6)	2.42 (31.5)
Parameter for V_3 (L)	2.11 (17.6)	2.36 (9.83)	2.24 (13.4)
Weight effect on V_2 and V_3	0.998 (11.8)	1 (FIXED)	1 (FIXED)
Bioavailability			
Parameter for F1	0.72 (FIXED)[e]	0.72 (FIXED)[e]	0.72 (FIXED)[e]
Residual Error (Proportional)			
	27.7% (7.62)	27.7% (7.69)	27.7% (7.65)

Abbreviations: ADA = antidrug antibody; CL = clearance; F1 = bioavailability; Fixed Model 1 = weight exponents were fixed to 0.75 and 1 on clearance and volume of distribution terms; Fixed Model 2 = weight exponents were fixed to 0.85 and 1 for clearance and volume of distribution terms; IV = intravenous; Ka = absorption rate constant; LOGe = natural logarithm; Ps = plaque psoriasis; PsA = psoriatic arthritis; Q = inter-compartmental clearance; SEE = standard error of the estimate; V2 = volume of distribution of the central compartment; V3 = volume of distribution of the peripheral compartment.

[a] All 3 models have the same structure and the only difference is in weight exponents.

[b] The table provides the population estimate. To obtain individual clearance estimates, use the following equation: $CL_{individual} = CL*(bodyweight/58.6)^{THETA1}*(1+THETA2*LOG_e[ADA\ titer])$ where THETA1 is the weight effect on CL and Q and THETA2 is the titer effect on CL in each model.

[c] $Q_{individual} = Q * (bodyweight/58.6)^{THETA1}$

[d] $V_{2,individual} = V_2*(bodyweight/58.6)^{THETA3}$, $V_{3,individual} = V_3*(bodyweight/58.6)^{THETA3}$ where THETA3 is the weight effect on V_2 and V_3 in each model.

[e] Bioavailability was fixed to the mean value across the Ps and PsA Phase 3 trials from the existing Ps/PsA model (F = 0.72) as the same formulation was utilized in all studies and no IV data are included in the RHCD analysis.

- Immunogenicity is evaluated using titer, TE-ADA status, or NAb status. The change in OFV is significant when either log titer or NAb status is included on clearance and the effects are well estimated with low %RSE. As 5 of the 6 NAb-positive samples associated with measurable concentrations are also high titer (i.e. high titre and NAb-positive is correlated. Note: 1 NAb-positive sample is BQL and is not included in the population PK analysis), and only 1.28% of immunogenicity-evaluable samples are NAb positive (7 of 549 samples), log titer is retained in the final base model to evaluate the impact of immunogenicity to CL.
- For site of injection, 28.6% of injections associated with doses included in this analysis are administered via the abdomen, 57.0% via the arm, and 14.4% via the thigh. In paediatric patients with Ps, site of injection is not significant and thus, is not retained in the final base model.

No additional covariates were found to be significant. Therefore, no additional covariates are retained in the final model. Epsilon-shrinkage is less than 13% indicating no significant overfitting of the data. Eta-shrinkage is less than 7% for CL indicating that the individual estimates of this parameter are informative.

Table 10:Pharmacokinetic Parameters in the Population Model in Paediatric Patients with Ps (Base and Final Models are the Same)

Parameter Description	Population Estimate (95% CI, %SEE)[a]	Inter-Individual Variability (95% CI, %SEE)[a,b]
Rate of Absorption		
Parameter for Ka (hr^{-1})	0.00801 (0.00446 – 0.0201, 29.3)	---
Clearance		
Parameter for CL (L/hr)	0.0120 (0.0107 – 0.0131, 3.94)	28.4% (23.7% - 33.2%, 14.5)
Titer effect on CL[c]	0.0292 (0.0130 – 0.0499, 32.3)	---
Parameter for Q (L/hr)	0.0119 (0.00249 – 0.0208, 27.6)	---
Weight effect on CL and Q[c,d]	0.989 (0.827 – 1.17, 8.43)	---
Volume of Distribution		
Parameter for V_2 (L)	2.72 (1.16 – 5.36, 31.8)	---
Parameter for V_3 (L)	2.11 (0.638 – 2.93, 17.6)	---
Weight effect on V_2 and V_3[e]	0.998 (0.753 – 1.27, 11.8)	
Bioavailability		
Parameter for F1	0.72 (FIXED)[f]	---
Residual Error (proportional)	27.7% (23.2% - 31.9%, 7.62)	

Abbreviations: ADA = antidrug antibody; CI = confidence interval; CL = clearance; F1 = bioavailability; IV = intravenous; Ka = absorption rate constant; LOG_e = natural logarithm; Ps = plaque psoriasis; PsA = psoriatic arthritis; 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.
Note: The final population model is the same as the base population model.

[a] The CI was estimated using bootstrap.

[b] Inter-individual variability (IIV) was calculated using the following equation for log-normal distributions of the random effects for CL: $\%IIV = 100 \times \sqrt{(e^{OMEGA_N} - 1)}$, where $OMEGA_N$ is the variance of the CL parameter.

[c] The table provides the population estimate. To obtain individual clearance estimates, use the following equation: $CL_{individual} = CL*(bodyweight/58.6)^{0.989}*(1+0.0292*LOG_e[ADA\ titer])$.

[d] $Q_{individual} = Q*(bodyweight/58.6)^{0.989}$

[e] $V_{2,individual} = V_2*(bodyweight/58.6)^{0.998}$, $V_{3,individual} = V_3*(bodyweight/58.6)^{0.998}$

[f] Bioavailability was fixed to the mean value across the Ps and PsA Phase 3 trials from the existing Ps/PsA model (F = 0.72) as the same formulation was utilized in all studies and no IV data are included in the RHCD analysis.

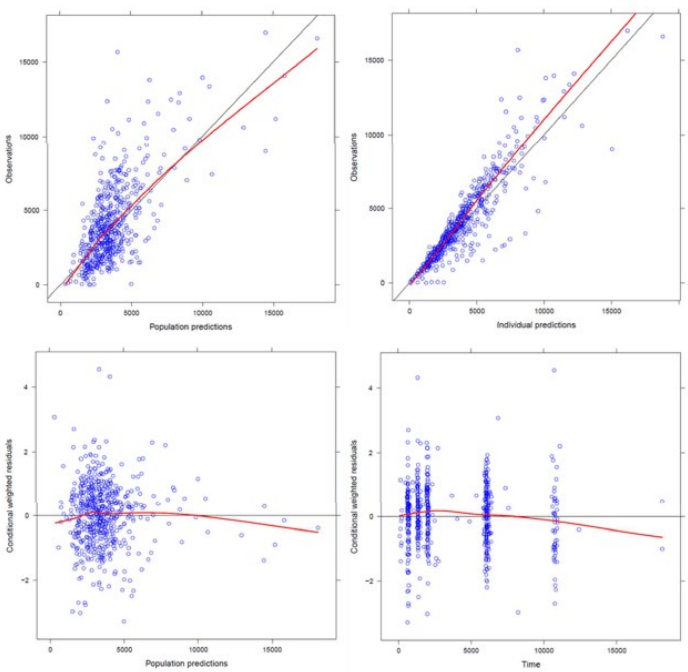
Table 11:Comparison of Model-Estimated Ixekizumab Pharmacokinetic Parameters between Pediatric patients with Ps and Adult Patients with Psoriasis, Psoriatic Arthritis, Nonradiographic, and Radiographic Axial Spondyloarthritis[a]

PK Parameter	Pediatric Ps PK Analysis	Adult Ps PK Analysis[b]	PsA PK Analysis[c]	nr-axSpA PK Analysis[d]	r-axSpA PK Analysis[e]
CL (L/hr)	0.0119 (49%)	0.0161 (37%)	0.0147 (33%)	0.0129 (36%)	0.0144 (38%)
V_{ss} (L)	4.76 (40%)	7.11 (29%)	6.02 (18%)	5.28 (46%)	6.13 (19%)
$t_{1/2}$ (days)	12 (26%)	13 (40%)	12 (32%)	12 (61%)	12 (36%)
%F (range)	72 FIXED[f]	60 to 90	61 to 84[f]	72 FIXED[f]	72 FIXED[f]
Median WT (kg)	58.6	89.9	83.1 – 87.6	76.6	77.0
WT-adjusted CL (L/hr)[g]	0.0144	0.0126	0.0123	0.0120	0.0128
WT-adjusted V_{ss} (L)[g]	5.77	5.56	5.05	4.90	5.47

Abbreviations: CL = clearance; F = bioavailability; IV = intravenous; nr-axSpA = nonradiographic-axial spondyloarthritis; %CV = percent coefficient of variation; PK = pharmacokinetics; r-axSpA = radiographic axial spondyloarthritis; Ps = plaque psoriasis; PsA = psoriatic arthritis; SC = subcutaneous; t1/2 = elimination half-life calculated as 0.693*(V2+V3)/(CL*24); Vss = total volume of distribution at steady state calculated as V2+V3; V2 = volume of distribution of the central compartment; V3 = volume of distribution of the peripheral compartment; WT = body weight.
[a] Data are summarized using the first occurrence of time-varying post hoc individual PK parameters in each analysis. Data are reported as geometric mean (geometric CV%).

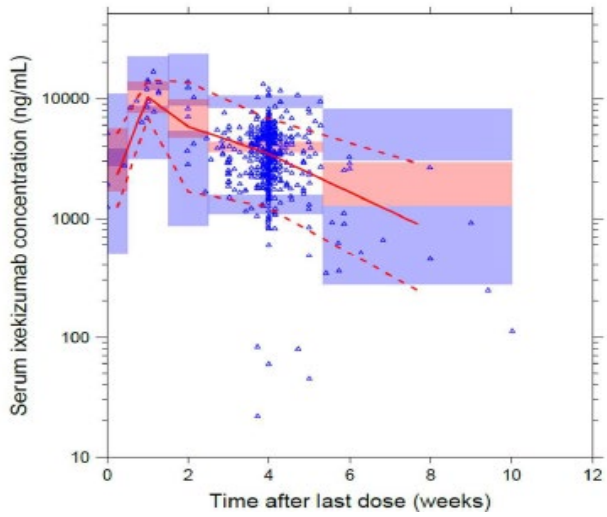
[b] Parameters estimated with data from 3 studies in adult patients with Ps (I1F-MC-RHAG [RHAG], I1F-MC- RHAJ [RHAJ], and I1F-MC-RHAZ [RHAZ]) for analysis (reported in the Ps submission).
[c] The data from the 2 PsA studies (I1F-MC-RHAP and I1F-MC-RHBE) were combined with data from 3 Ps studies (RHAG, RHAJ, and RHAZ) for analysis; parameters were calculated and summarized using post hoc values from patients in the 2 PsA studies.
[d] Parameters estimated with data from 1 study in adult patients with nr-axSpA (I1F-MC-RHBX [RHBX]) for analysis.
[e] Parameters estimated with data from 2 studies in adult patients with r-axSpA (I1F-MC-RHBV [RHBV] and (I1F- MC-RHBW [RHBW]) for analysis.
[f] Only SC administration was evaluated in Studies I1F-MC-RHBV, I1F-MC-RHBW, and I1F-MC-RHBX; therefore the typical value of bioavailability was fixed to the mean value across the Ps and PsA Phase 3 trials from the existing Ps/PsA model (F = 0.72) as the same formulation was utilized in all studies and no IV data are included in the nr-axSpA and r-axSpA analyses.
[g] Weight normalization based on the allometric relationship of the PK parameter to body weight in each population PK analysis. Data are then presented for a 70-kg individual to compare across indications having adjusted for weight.

Figure 3:Goodness-of-fit plots for the ixekizumab population pharmacokinetic model in pediatric patients with psoriasis (base and final models are the same).



Lowess fit, a smoothed value given by a weighted linear least-squares regression over the span of observations, for data is presented (red line) in addition to a line of identity (black line). The correlation of observations versus model predictions (top panel) and conditional weighted residuals versus population prediction and time (bottom panel) were presented with the red lowess fit lines. The black unity lines in the top panel show the perfect correlation between observations and predictions. The black horizontal lines in the bottom panel are reference lines that, if no bias was present in the model fitting, the residuals should randomly distribute around.

Figure 4:Pred-corrected visual predictive check based on the final Adult Ps/PsA population pharmacokinetic model plotted against the observed concentration data in pediatric patients with psoriasis in Study RHCD.



Abbreviations: Ps = Psoriasis; PsA = Psoriatic arthritis; RHCD = Study I1F-MCRHCD.

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.

Model combining paediatric data from Study RHCD and adult PK data from patients with psoriasis

Upon Request by CHMP, the paediatric PK data from Study RHCD (562 PK samples from 184 patients) were combined with the adult PK data from patients with psoriasis from the original psoriasis submission (2015). The adult dataset contained PK data from Studies I1F-MC-RHAZ (RHAZ), I1F-MC-RHAJ (RHAJ), and I1F-MC-RHAG (RHAG), and comprised 6059 samples from 1399 patients across the 3 studies.

Several steps were required to combine the adult and paediatric data, and to perform the analyses on the combined dataset. This involved rerunning the final adult-only PopPK model.

The adult data were then combined with the paediatric data and the PK analyses were rerun using the combined paediatric/adult dataset. The covariate modelling was conducted in 2 steps:

1. Evaluation of the covariates from the final adult-only PopPK model (to determine the final base combined adult/paediatric model)
2. Evaluation of additional covariates of relevance to the paediatric population using the stepwise covariate modelling (SCM) procedure to determine the final combined adult/paediatric model.

The following steps were taken to develop the final base model using the combined paediatric/adult dataset:

1. Fixed exponents of 0.75 were used to describe the allometric relationship of weight on clearance terms, and fixed exponents of 1 were used to describe the allometric relationship of weight on volume terms rather than estimating the exponents.

2. Titre and NAb were both included in the model as covariates on clearance (CL) in which all adult and paediatric NAb data were reported using the same cut point.

3. Site of injection was included on bioavailability (F).

4. F was fixed to 0.791 for paediatric patients in Study RHCD, which is the estimate of F for Study RHAZ determined in the adult PopPK model. The rationale for fixing F in Study RHCD was as follows:

- the paediatric data consisted of only subcutaneous administration and no intravenous data, and

- the formulation used in the paediatric study was the same as the formulation used in Study RHAZ in adults.

5. The development of this base model was conducted using the first-order conditional estimation with interaction (FOCEI) algorithm and excluding data below the quantitation limit of the assay (BQL) and then rerun at the end using the stochastic approximation expectation maximisation (SAEM) algorithm with importance sampling algorithm (IMP) and including BQL data in the dataset. This is similar to the approach taken in the original adult psoriasis submission where 4.9% of samples (298 of 6059) were BQL. The results of this final base model using the SAEM algorithm with IMP are summarised in **Table 12**, goodness-of-fit plots are shown in **Figure 5**. The NONMEM summary file were submitted. The parameter estimates from this model were also compared with the adult only model.

All covariate effects in the final adult model (i.e., weight on clearance and volume terms, titre, and NAb status on clearance and site of injection on bioavailability) remained significant in the final combined adult/paediatric model; all covariate effects were estimated with reasonable precision (<25% except for the NAb effect on clearance where the percent standard error of the estimate [%SEE] was 56%), and the magnitude of each effect was similar between the adult-only model and the combined adult/paediatric model.

Adding all covariate factors together in a full model using the FOCEI algorithm and removing each covariate effect individually resulted in objective function value (OFV) changes of >10.828 points (p <.001) for each covariate, as follows:

- Weight effect on clearance: OFV change of 866 points
- Weight effect on volume terms: OFV change of 113 points
- Titre effect on clearance: OFV change of 102 points
- NAb status on clearance: OFV change of 35 points, and
- Site of injection on bioavailability: OFV change of 46 points.

In addition, the effect of weight on clearance was associated with an increase in the inter-individual variability on clearance of 12.4% when it was removed from the model.

Table 12:Pharmacokinetic Parameters in the Population Pharmacokinetic Final Base Model Based on Combined Adult/Paediatric Patients with Psoriasis (Final Base Model is Same as Final Model)

Parameter Description	Population Estimate (95% CI, %SEE)[a]	Inter-individual Variability (95% CI, %SEE)[a,b]
Rate of absorption		
Parameter for Ka (hr^{-1})	0.0142 (0.0116–0.0177, 8.24)	15 (FIXED)[g]
Clearance		
Parameter for CL (L/hr)[d]	0.0128 (0.0126–0.0133, 1.26)	30.1% (28.7–32.6%, 7.95)
Titre effect on CL[d]	0.0363 (0.0269–0.0461, 11.3)	–
Neutralising antibodies on CL (fractional increase)[d]	1.42 (0.429–4.16, 55.9)	
Parameter for Q (L/hr)[e]	0.0434 (0.0400–0.0782, 11.8)	15 (FIXED)[g]
Weight effect on CL and Q[d,e]	0.75 (FIXED)	
Volume of distribution		
Parameter for V_2 (L)[f]	2.41 (1.77–3.49, 11.7)	73.2% (52.1–110%, 22.3)
Parameter for V_3 (L)[f]	3.24 (2.74–3.69, 3.77)	15 (FIXED)[g]

Weight effect on V_2 and V_3[f]	1 (FIXED)	
Bioavailability		
Bioavailability (F) for RHAG and RHAJ	0.58 (FIXED)[c]	55.7 (FIXED)[c]
Bioavailability (F) for RHAZ and RHCD	0.791 (FIXED)[c]	55.7 (FIXED)[c]
Increase in F for thigh injection site	0.598 (0.369–0.900, 24.1)	
Residual error (proportional)	32.3% (30.6–33.7%, 1.17)	

Abbreviations: ADA = antidrug antibody; BQL = below quantitation limit of assay; CI = confidence interval; CL = clearance; F = bioavailability; FOCEI = first-order conditional estimation with interaction; Ka = absorption rate constant; LOG_e = natural logarithm; NAb = neutralising anti-drug antibody; NONMEM = nonlinear mixed effects modeling program; PK = pharmacokinetic; Q = inter-compartmental clearance; SAEM = stochastic approximation expectation maximisation; 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 are not reported from the NONMEM file but were estimated using bootstrap.

b Inter-individual variability (IIV) was calculated using the following equation for log-normal distributions of the random effects for the PK parameter: $\%IIV = 100 \times \sqrt{(e^{OMEGA_N} - 1)}$, where $OMEGA_N$ is the variance of the PK parameter.

c Estimate fixed to that from FOCEI model where BQL data were not included.

d The table provides the population estimate. To obtain individual clearance estimates, use the following equation: $CL_{individual} = CL*(bodyweight/70.0)^{0.75}*(1+0.0363*LOG_e(ADA\ titre))*(1+1.42*NAb)$, where NAb is 0 or 1.

e $Q_{individual} = Q*(bodyweight/70.0)^{0.75}$

f $V_{2,individual} = V_2*(bodyweight/70.0)^{1.0}$, $V_{3,individual} = V_3*(bodyweight/70.0)^{1.0}$

g Variability fixed to 15% to optimise efficiency of SAEM algorithm (NONMEM 7.3.0 user guide).

New simulations were conducted using the updated model, and the steady-state exposures in children were compared to exposure in adults given Q2W and Q4W dosing. The observed week 12 Ctrough values were also presented (**Table 13**).

Table 13:Comparison of Observed and Model-Predicted Steady-State Pharmacokinetic Parameters for Paediatric Patients at the Proposed Posology and Adult Patients at Q2W and Q4W

Median (5th to 95th Percentile)	Predicted $C_{max,ss}$ (µg/mL)	Predicted $AUC_{0\text{-}tau,ss}$ (µg*day/mL)	Predicted $C_{trough,ss}$ (µg/mL)	Observed $C_{trough\ Week\ 12}$ (µg/mL)[a]
Peds <25 kg	7.90 (4.99, 11.8)	130 (72.0, 215)	1.84 (0.549, 4.82)	NC
Peds 25–50 kg	9.74 (5.77, 15.3)	162 (92.1, 290)	2.72 (0.818, 6.38)	3.47 (1.17, 8.45)
Peds >50 kg	12.9 (8.09, 20.6)	221 (130, 398)	3.98 (1.42, 9.49)	3.41 (1.09, 7.56)
Adults 80 mg Q2W[b]	14.7 (7.54, 27.3)	167 (81.8, 321)	8.87 (3.61, 18.6)	9.13 (3.18, 18.6)
Adults 80 mg Q4W[b]	10.1 (5.18, 18.5)	176 (83.2, 341)	3.24 (0.975, 7.99)	2.98 (0.843, 7.48)

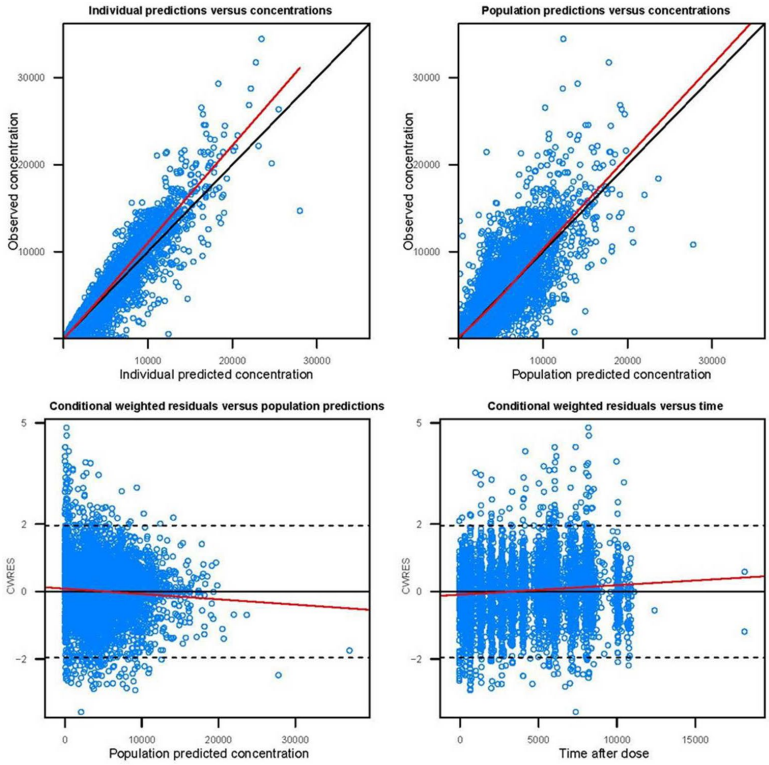
Abbreviations: AUC0-tau,ss = area under the concentration−time curve over the dosing interval (tau) at steady state; Cmax,ss = maximum observed concentration at steady state; Ctrough,ss = trough concentration at steady state; Ctrough Week 12 = trough concentration at Week 12; NC = not calculable; Peds = paediatric patients; Q2W = every 2 weeks; Q4W = every 4 weeks.

Observed trough concentrations are from ixekizumab Phase 3 psoriasis studies in adult patients (RHAZ/RHBA/RHBC) and paediatric patients (RHCD).

For the Q2W dosing regimen, data are summarised from Week 10 to Week 12, and for the Q4W dosing regimen, data are summarised from Week 8 to Week 12.

Note: Dosing regimens are as follows. For paediatric patients <25 kg: 40 mg at Week 0 then 20 mg Q4W; for paediatric patients 25−50 kg: 80 mg at Week 0 then 40 mg Q4W; for paediatric patients >50 kg: 160 mg at Week 0 then 80 mg Q4W; for adults, a 160-mg dose at Week 0 and either 80 mg Q2W or 80 mg Q4W thereafter.

Figure 5:Goodness-of-fit plots for the ixekizumab population pharmacokinetic final base model based on combined adult/paediatric patients with psoriasis (final base model isthe same as the final model).



Linear regression of the data is presented (red line) in addition to a line of identity (black line).
The correlation of observations versus model predictions (top panel) and conditional weighted residuals versus population prediction and time (bottom panel) were presented with the red linear fit lines. The black unity lines in the top panel show the perfect correlation between observations and predictions. The black horizontal lines in the bottom panel are reference lines that, if no bias was present in the model fitting, the residuals should randomly distribute around.

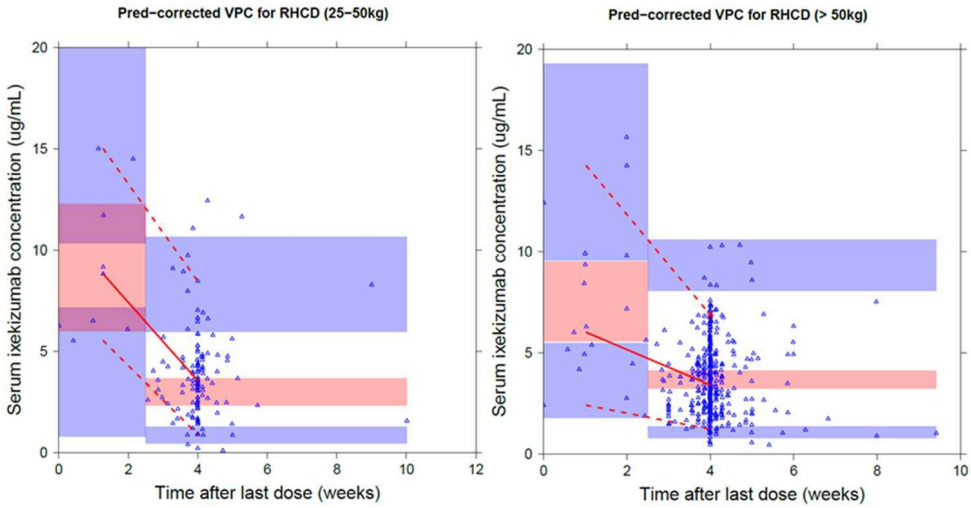
Remaining covariates of interest to paediatric patients were evaluated (body mass index [BMI], age, gender, race, and baseline disease status [static Physician's Global Assessment (sPGA) or Psoriasis Area Severity Index (PASI)]) on parameters using the stepwise covariate modelling (SCM) procedure.

The majority of effects tested on different parameters did not result in an OFV change >10.828 and were therefore not retained in the final model. A few effects did result in an OFV change >10.828 but were not retained in the final model for the following reasons:

- BMI on CL and V3 (volume of distribution of the peripheral compartment) – BMI and body weight (WT) are highly correlated. As the dosing regimen is proposed based on WT, WT was retained in the final model in preference to BMI.
- Baseline PASI score on CL – the relative decrease in the variance in CL was <10%, therefore this effect was not retained in the final model.
- Gender on CL – the relative decrease in the variance in CL was <10%, therefore this effect was not retained in the final model.
- Region of the World on Ka and F – %SEE of the estimates were poor (>40%; 42% to 196%) and the relative decrease in the variance in the relevant parameters were <10%, therefore this effect was not retained in the final model

The final combined adult/paediatric PopPK model is the same as the final base combined adult/paediatric PopPK model.

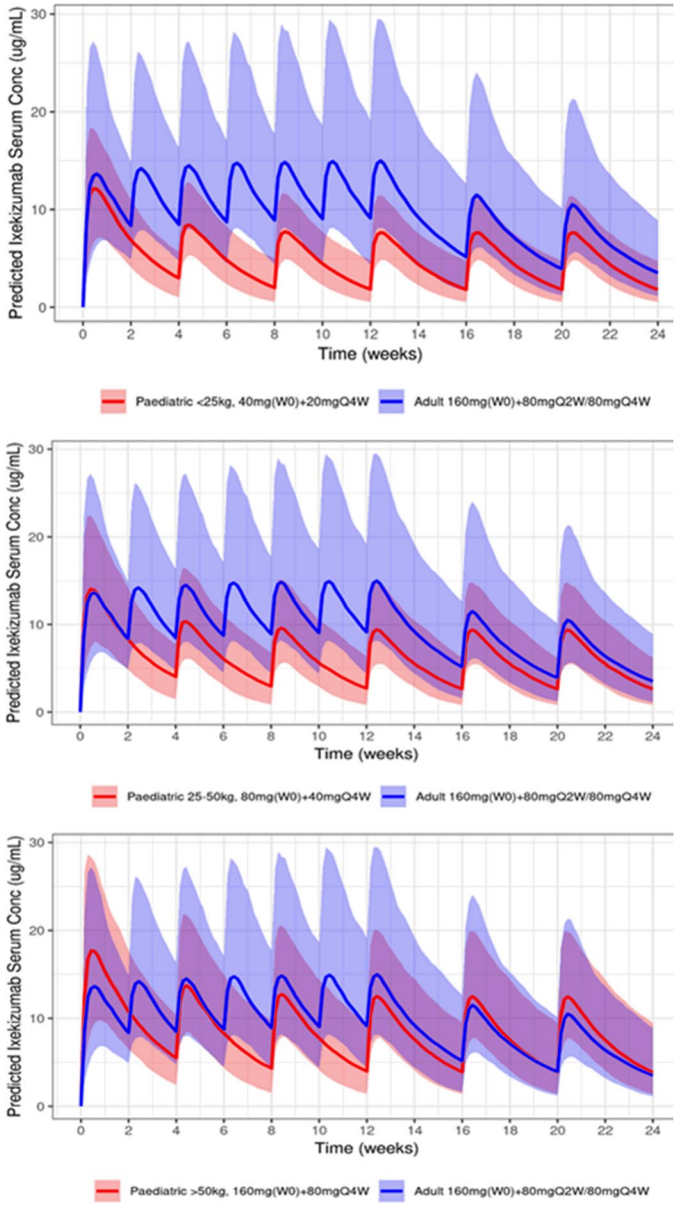
Figure 6: Pred-corrected visual predictive check of the final population pharmacokinetic model in paediatric patients with psoriasis in Study RHCD versus time after last dose (stratified by weight category).



Abbreviations: Pred = prediction; RHCD = Study I1F-MC-RHCD; VPC = visual predictive check.
Note: All paediatric data stratified by weight (25–50 kg and >50 kg). There are insufficient data to plot the <25-kg data.

Simulations were performed using the updated PopPK model to show the concentration–time curves for the proposed paediatric posology compared with the adult approved dosing regimen of a 160-mg starting dose at Week 0 followed by 80 mg Q2W at Weeks 2, 4, 6, 8, 10, and 12 and 80 mg Q4W thereafter. The 80-mg Q4W regimen in adults was simulated from Week 12 up to Week 24 to allow attainment of new steady-state.

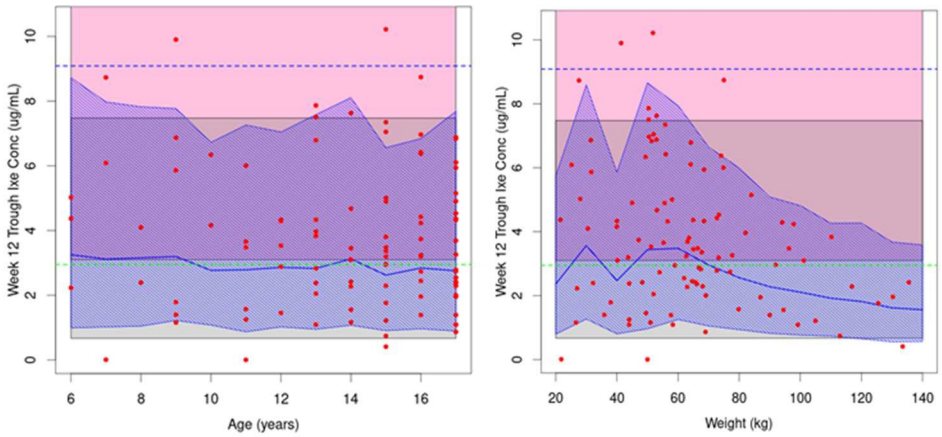
Figure 7 Comparisons of model-predicted pharmacokinetics at the proposed posology in paediatric patients weighing <25 kg, 25 to 50 kg, and >50 kg versus adult predicted pharmacokinetics with the approved adult Phase 3 dosing regimens.



Abbreviations: Conc = concentration; Q2W = every 2 weeks; Q4W = every 4 weeks; W0 = starting dose at week.
Note: Solid lines represent the median and the shaded regions correspond to the 90% prediction intervals on the plots.

The model-predicted ixekizumab trough concentration plot by weight and age of paediatric patients in Study RHCD compared with adult patients with psoriasis at Week 12 is provided in **Figure 8**.

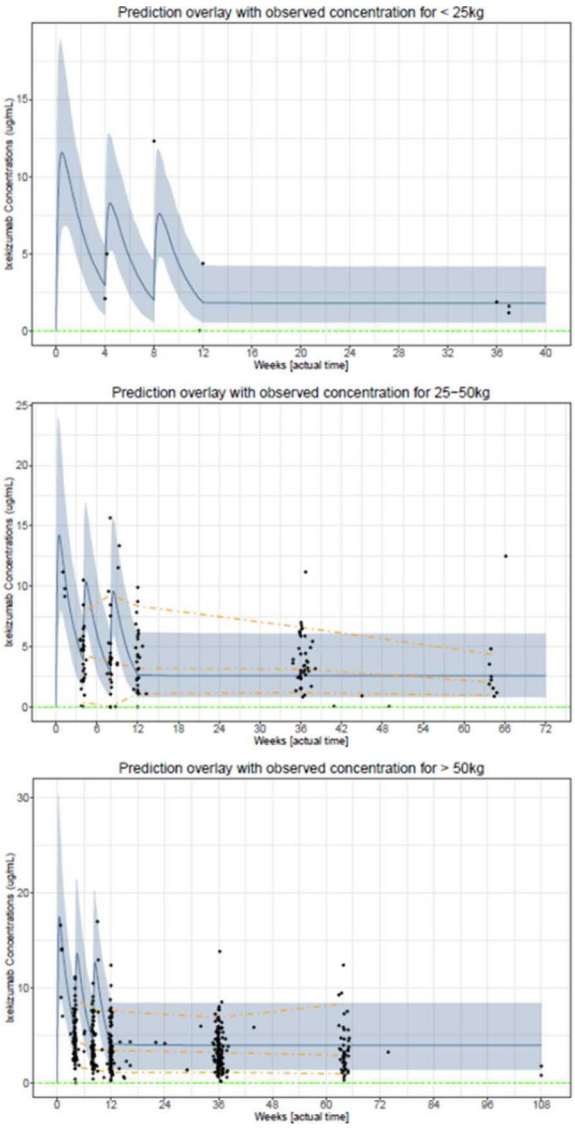
Figure 8: Model-predicted ixekizumab trough concentrations by weight and age of paediatric patients in Study RHCD compared with adult patients with psoriasis.



Abbreviations: Conc = concentration; Ctrough = trough concentration; Ixe = ixekizumab; Q2W = every 2 weeks; Q4W = every 4 weeks; RHCD = Study I1F-MC-RHCD.

The blue line is the median simulated paediatric Ctrough and the blue shaded area encompasses 90% of the simulated paediatric patients. The green dashed line represents the median adult 80-mg Q4W trough concentration and the horizontal grey band encompasses 90% of the observed adult patients receiving 80 mg Q4W from the three Phase 3 studies (RHAZ, RHBA, and RHBC). The purple dashed line represents the median adult 80-mg Q2W trough concentration and the horizontal pink band encompasses 90% of the observed adult patients receiving 80 mg Q2W from the three Phase 3 studies (RHAZ, RHBA, and RHBC).

Figure 9 Comparison of model-predicted concentrations versus observed concentrations by body weight group.



Abbreviations: PK = pharmacokinetic.

The expected PK profile of paediatric patients on each dosing regimen and weight group was simulated using the new PopPK model. Solid grey bands represent the 5th to 95th percentile and blue lines represent the median of the simulated data. Orange dashed lines represent the 5th, median, and 95th percentiles of the observed data. Full profiles were simulated and plotted for the first 12 weeks. Only trough concentrations were simulated and plotted after Week 12. The data points represent observed PK concentrations from paediatric patients in Study RHCD. Green dotted lines represent lower limit of quantification of 0.0063 μg/mL.

Anti-drug antibodies and neutralising antibodies

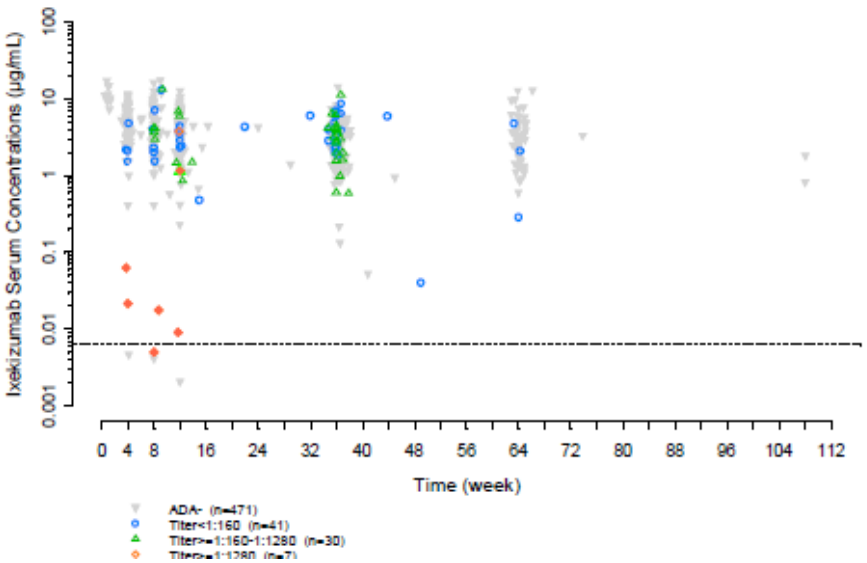
An evaluable sample is defined as either being TE-ADA positive or ADA negative; 13 samples that are ADA positive, but not TE-ADA positive are not included in the plots. Across all ixekizumab dosing regimen groups over the initial Week 0 to 12 period of the study, the majority of samples (89.3%, 291 of a total 326 immunogenicity-evaluable samples in 111 patients) are ADA negative and 10.7% (35 samples in 20 patients) are identified as TE-ADA positive. TE-ADA-positive samples are subdivided into low (<1:160), moderate (≥1:160 to <1:1280), and high (≥1:1280) titers. Maximum post-baseline titers in the TE-ADA-positive samples range from 1:10 to 1:2560. Approximately half (48.6%, n=17 of 35) of TE-ADA-positive

samples are classified as low titer, 31.4% (n=11) as moderate titer, and 20% (n= 7) as high titer. Seven samples are detected as NAb positive; of which 6 are high titer and 1 is a moderate titer.

In the current paediatric Ps population PK analysis, immunogenicity impact on CL is represented using ADA titer in the final PK model. Based on the population PK parameter estimates the model predicts that:

- an ADA in the high titer range (≥1:1280) would be associated with a predicted increase in clearance of approximately 20.9% to 22.9% compared to clearance in ADA-negative patients
- an ADA in the moderate titer range (≥1:160 to <1:1280) would be associated with a predicted increase in clearance of approximately 14.8% to 18.9% compared to clearance in ADA-negative patients
- an ADA in the low titer range (<1:160) would be associated with a predicted increase in clearance of approximately 4.70% to 12.8% compared to clearance in ADA-negative patients.

Figure 10 Observed ixekizumab concentrations versus protocol time from Week 0 to 108 of Study RHCD indicating samples that were TE-ADA positive for all patients receiving ixekizumab Q4W.



Abbreviations: ADA = antidrug antibody; BQL = below the quantifiable lower limit of the assay; n = number of samples; NAb = neutralizing antibody; PK = pharmacokinetics; Q4W = every 4 weeks; TE-ADA = treatment-emergent antidrug antibody. Notes: NAb-positive samples are represented by the solid symbols. Data that were BQL (0.0063 µg/mL) were set to a randomly assigned nominal value lower than the lower limit of the assay for the purpose of plotting the data. The dotted horizontal line represents the lower limit of the assay. The drug tolerance limit of the ADA assay was 480.5 and 1.1 µg/mL for the NAb assay. Samples collected at Weeks 1 and 9 were nontroughs. All other samples were designed to be trough samples. The plot includes patients randomized to ixekizumab at Week 0 and also patients who were randomized to placebo or etanercept at Week 0 then later received ixekizumab from Period 3 onwards.

2.3.3. Pharmacodynamics

No new pharmacodynamic data have been submitted in this application, which was considered acceptable by the CHMP.

2.3.4. PK/PD modelling

Exposure-efficacy

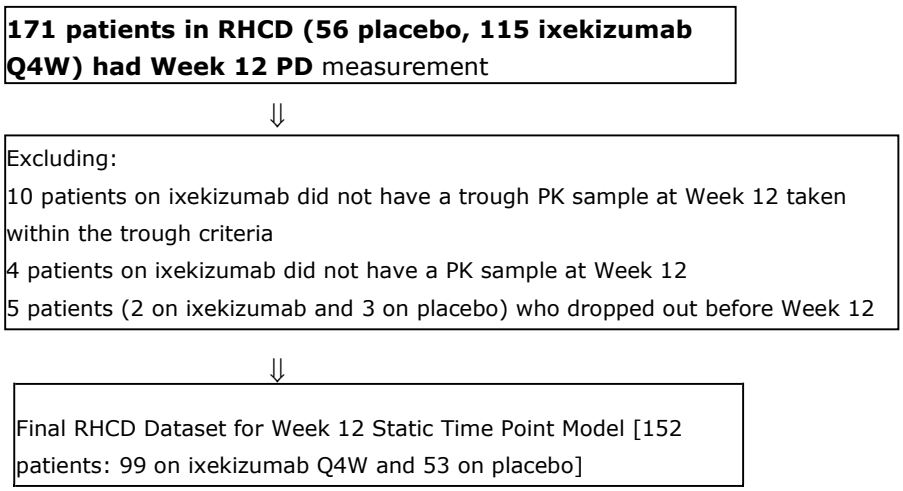
A static PASI/sPGA time point model and a PASI time course model were used to describe the exposure efficacy relationship.

The PASI and sPGA Week 12 static time point models explore the potential relationship between ixekizumab trough concentration (Ctrough) and PASI/sPGA responses at Week 12. Patients are required to have a PASI/sPGA response recorded at Week 12 and a Week 12 Ctrough as a measure of their steady-state drug exposure. If a patient has a missing efficacy response at Week 12, the patient is classified as a non-responder per non-responder imputation (NRI). However, the patient is required to have a measurable ixekizumab concentration to be included in the analysis.

The longitudinal PASI time course PK/PD model explores the potential relationship between ixekizumab concentrations in the systemic circulation and PASI responses up to and including Week 12. This model describes the temporal profile of the PASI responses and uses all data at all time points during the Week 12 double-blind period of the study; observed data are used rather than+ NRI for PASI response.

A listing of patients omitted from the Week 12 static time point PK/PD analyses is provided in **Figure 11**. The final dataset for the PASI Time course PK/PD model contains time course information from Week 0 to 12 for 115 patients randomized to ixekizumab, and 56 patients randomized to placebo.

Figure 11: Data disposition: data included in the PASI and sPGA Week 12 static time point PK/PD model analyses.



Abbreviations: PASI = Psoriasis Area Severity Index; PD = pharmacodynamics; PK = pharmacokinetic; Q4W = every 4 weeks; RHCD = Study I1F-MC-RHCD; sPGA = static Physician's Global Assessment.

For the PASI and sPGA Week 12 static time point PK/PD models, missing categorical efficacy data (e.g., PASI or sPGA response) are imputed using the NRI method, in which patients are considered non-responders for the NRI analysis if they are missing clinical response data, Ctrough measurement at Week 12 or do not meet the clinical response criteria at the primary analysis time point.

Stepwise covariate modelling is used to evaluate covariates using the same process and criterion as described for the PK model (**Table 14**). The final backward model from the SCM for each model is refined taking into account factors as described for the PK model. As no variability is estimated in the PASI and sPGA Week 12 static time point PK/PD models, the criteria related to IIV do not apply to the single time point assessments. Covariate effects may be tested on B1 and DRUG in the sPGA and PASI Week 12 static time point PK/PD models. Covariate effects may be tested on B1, RESP1, and PLA in the PASI time course PK/PD model.

Model evaluation is conducted by bootstrap and VPC.

Table 14 Patient Factors Assessed in Pharmacokinetic/Pharmacodynamic Models

Covariate	Type
Age	Continuous
Sex	Categorical
Body weight or BMI[a]	Continuous/Categorical
Race[b]	Categorical
Baseline disease severity (e.g., PASI or sPGA score)	Continuous/Categorical
Palmoplantar/Nail/Scalp Psoriasis Involvement	Categorical
Treatment-emergent ADA status (Yes/No)	Categorical
Neutralizing antibody status (Yes/No)	Categorical
ADA titer	Continuous/Categorical (high/low/medium)
Previous nonbiologic systemic therapy[c]	Categorical
Previous biologic systemic therapy[d]	Categorical
Number of previous psoriasis treatments (<3 vs ≥3)[e]	Categorical
Geographic Region (EU, US, RoW)[f]	Categorical

Abbreviations: ADA = antidrug antibody; BMI = body mass index; EU = Europe; PASI = Psoriasis Area Severity Index; RoW = Rest of the World; sPGA = static Physician's Global Assessment; TNFα = tumor necrosis factor alpha; US = United States.
aBody weight and BMI are anticipated to be highly correlated, and therefore only the most significant covariate may be required in the final model.
bRace may be evaluated as a covariate provided there is sufficient diversity of the patient population to allow an evaluation.
cPrevious nonbiologic systemic therapy may be evaluated as a covariate provided there are sufficient data to allow an evaluation. Evaluation may include an assessment of methotrexate alone.
dPrevious biologic systemic therapy may be evaluated as a covariate provided there are sufficient data to allow an evaluation. Depending on the diversity of prior biologics further subcategories by mechanism of action may be evaluated. For example TNFα inhibitors may be evaluated separately.
eNumber of previous psoriasis treatments may be evaluated as a covariate provided there are sufficient data to allow an evaluation.
fGeographic region was not tested on the drug effect parameter in the time course model.

PASI Time Course Model

The dataset used in the PASI time course PK/PD model includes all observed PASI response data up to and including Week 12. The drug effect is best described by a slope function using log-transformed drug concentrations predicted for each patient at any time by the population PK model as the exposure input. The placebo effect is best described by a time-dependent slope function.

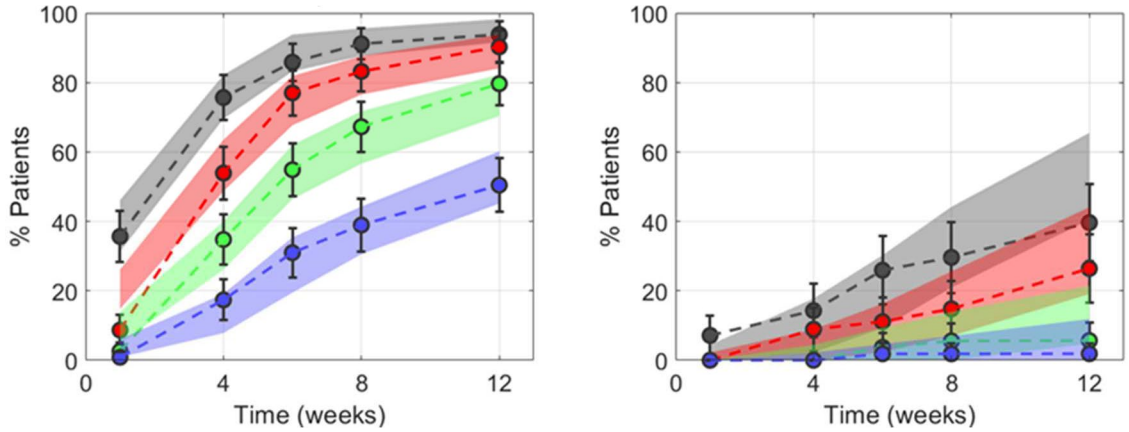
Once the base structural model was established, additional potentially significant covariates were evaluated. After forward inclusion and backward elimination from the SCM procedure in PsN, the only covariate effect that was retained in the final PASI time course PK/PD model was the involvement of palmoplantar psoriasis on B1 (decrease in OFV was 20.0 points). It was best described using a linear relationship, where patients with palmoplantar psoriasis at baseline had higher disease activity compared to patients without palmoplantar psoriasis.

Table 15 Parameter Estimates from the Final Population Ixekizumab PASI Time Course PK/PD Model

Parameter	Population Estimate (%RSE)	95% CI from Bootstrap
B1	-5.80 (9.57)	-7.01, -4.88
B2	0.935 (11.0)	0.742, 1.17
B3	0.973 (10.8)	0.794, 1.19
B4	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
Palmoplantar psoriasis effect on B1	-0.865 (38.0)	-1.67, -0.234

Abbreviations: B1 = Base value for PASI50 (DV≥1); B2 = Base value for PASI75 (DV≥2); B3 = Base value for PASI90 (DV≥3); B4 = Base value for PASI100 (DV=4); DV = dependent variable; CI = confidence interval; PASI = psoriasis area and severity index; %RSE = relative standard error; PD = pharmacodynamics; PK = pharmacokinetics; SLP = slope parameter for drug effect; SLPLA = parameter for maximum placebo effect. Palmoplantar psoriasis (PPP) effect on B1: B1PPP = –0.865 + B1.

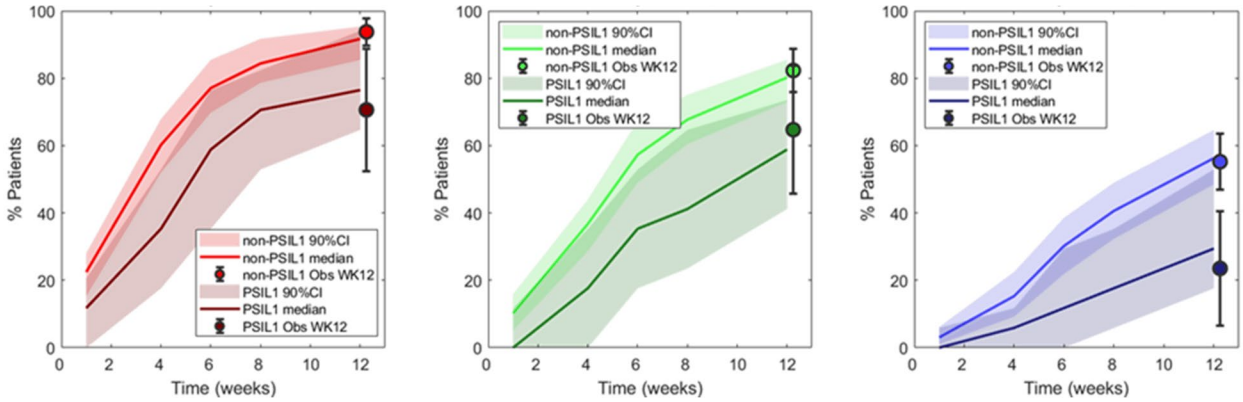
Figure 12 Visual predictive check from the final PASI time course PK/PD model - Study RHCD.



Abbreviations: CI = confidence interval; ixe = ixekizumab; PASI = psoriasis area and severity index; PD = pharmacodynamics; PK = pharmacokinetics; Q4W = every 4 weeks; RHCD = Study I1F-MC-RHCD.
Dashed lines represent the observed average percentage of patients achieving PASI50 (gray), PASI75 (red), PASI90 (green), and PASI100 (blue) by time (weeks) for ixekizumab Q4W-treated (left), and placebo-treated (right) patients. The shaded area is the predicted 90% CI from the model. The symbols represent the observed response and 90% CI.

Figure 13 displays simulations evaluating the impact of the presence/absence of palmoplantar psoriasis on PASI response rates. Note, the 90% CI for the patients with palmoplantar involvement is large due to the relatively small number of patients in this group (14%).

Figure 13: Model prediction intervals of the effect of baseline palmoplantar psoriasis status on PASI response rates over the first 12 weeks of treatment - Study RHCD.



Abbreviations: CI = confidence interval; non-PSIL1 = palmoplantar psoriasis absent; Obs = observed; PASI = psoriasis area and severity index; PSIL1 = palmoplantar psoriasis present; Q4W = every 4 weeks; RHCD = Study I1F-MC-RHCD; WK = week. Note: The shaded area is the predicted 90% CI from the model for percentage of patients on ixekizumab achieving PASI75 (red), PASI90 (green), and PASI100 (blue panels) responses over time. Solid lines correspond to the median response of the simulated Q4W dosing regimen with patients with palmoplantar psoriasis involvement in the darker color and those with no palmoplantar psoriasis involvement in the lighter color. The points are the observed percentage of patients achieving PASI75, PASI90, and PASI100 responses at Week 12. Error bars represent the observed 90% CI of the response.

Static sPGA time point model

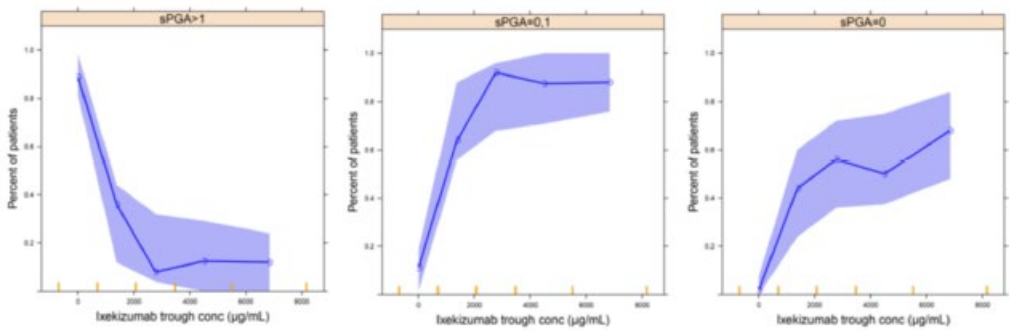
The relationship between exposures and effect (sPGA) was described using a slope model. The final parameter estimates, and visual predictive check are presented in **Table 16** and **Figure 14**, respectively.

Table 16 Pharmacodynamic Parameter Estimates from the Base Population sPGA Week 12 Static Time Point PK/PD Model

Parameter	Population Estimate (%RSE)	95% CI from Bootstrap
B_1	-2.15 (20.4)	-3.60 – -1.43
B_2	1.54 (16.0)	1.06 – 2.11
SLP	0.484 (12.9)	0.373 – 0.674

Abbreviations: %RSE = relative standard error; B_1 = Base value (for sPGA=1); B_2 = Base value (for sPGA=0); CI = confidence interval; LOG_e = natural logarithm; PD = pharmacodynamics; PK = pharmacokinetics; SLP = slope parameter for drug effect (SLP* LOG_e[CMIN+1]) where CMIN is the observed trough serum ixekizumab concentration at Week 12; sPGA = static Physician's Global Assessment.

Figure 14 Visual predictive check of final sPGA Week 12 static time point PK/PD model.



Abbreviations: conc = concentration; Ctrough = trough concentration; N = number of patients;PD = pharmacodynamics; PK = pharmacokinetics; sPGA = static Physician's Global Assessment. Circles with a solid line represent the observed proportion of patients with sPGA>1 (left), sPGA=0,1 (middle), and sPGA=0 (right) in each quartile of Week 12 Ctrough (number of patients in each bin N=24 to 25) or for placebo (number of patients N=53). The first point in the plots corresponds to a concentration of 0 µg/mL representing observed response rate in patients who received placebo. The shaded area is the predicted 90% confidence interval of response from the model. Symbols represent the observed response rates at Week 12.

Static PASI time point model

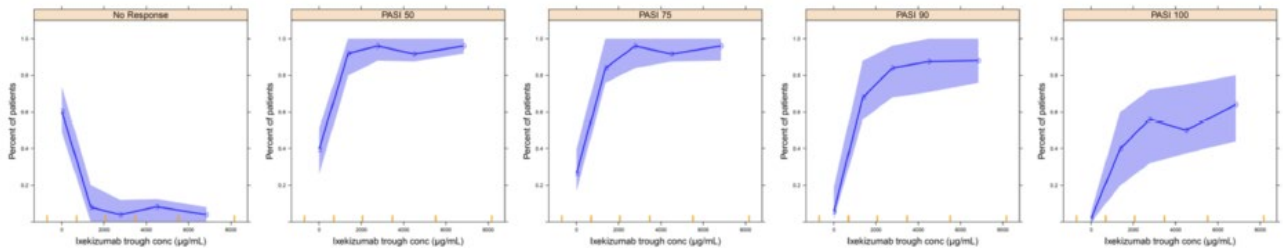
The relationship between exposures and effect (PASI) was described using a slope model. The final parameter estimates, and visual predictive check are presented in **Table 17** and **Figure 15**, respectively.

Table 17 Pharmacodynamic Parameter Estimates from the Base Population PASI Week 12 Static Time Point PK/PD Model

Parameter	Population Estimate (%RSE)	95% CI from Bootstrap
B_1	-0.456 (27.4[a])	-1.28 – 0.400
B_2	0.501 (32.7)	0.234 – 0.861
B_3	1.27 (22.1)	0.808 – 2.06
B_4	1.47 (16.9)	0.983 – 2.07
SLP	0.475 (12.3)	0.364 – 0.630

Abbreviations: B1 = Base value for PASI50 (DV≥1); B2 = Base value for PASI75 (DV≥2); B3 = Base value for PASI90 (DV≥3); B4 = Base value for PASI100 (DV=4); CI = confidence interval; LOGe = natural logarithm; PASI = Psoriasis Area Severity Index; PD = pharmacodynamics; %RSE = relative standard error; PK = pharmacokinetics; SLP = slope parameter for drug effect (SLP* LOGe[CMIN+1]) where CMIN is the observed trough serum ixekizumab concentration at Week 12.
[a] %RSE for B1 corresponds to a secondary parameter that equals B1 – B2, which was needed to improve model stability.

Figure 15 Visual predictive check of final PASI Week 12 static time point PK/PD model



Abbreviations: conc = concentration; Ctrough = trough concentration; N = number of patients; PASI = psoriasis area and severity index; PD = pharmacodynamics; PK = pharmacokinetics. Circles with a solid line represent the observed percentage of patients achieving PASI improvement <50%, 50% or greater improvement in PASI score (PASI50), 75% or greater improvement in PASI score (PASI75), 90% or greater improvement in PASI score (PASI90), and 100% improvement in PASI score (PASI100), in each quartile of Week 12 Ctrough (number of patients in each bin N=24 to 25) or for placebo (number of patients N=53). The first point in the plots corresponds to a concentration of 0 µg/mL representing observed response rate in patients who received placebo. The shaded area is the predicted 90% confidence interval of response from the model. Symbols represent the observed response rates at Week 12.

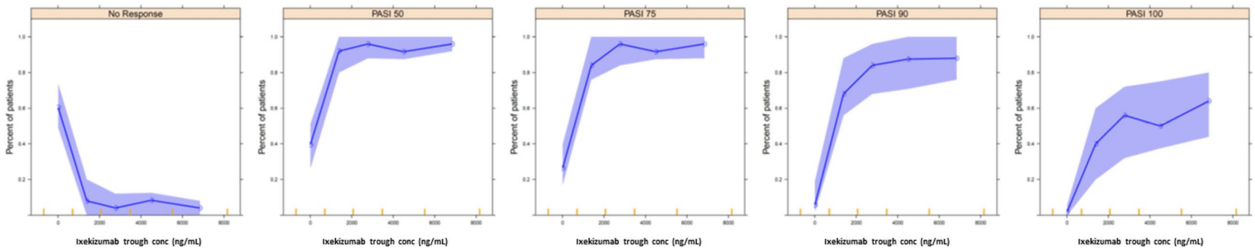
Upon request by CHMP, simulations were redone using the final PASI Week 12 static time point (**Figure 16**) and the longitudinal PK–PASI model developed in paediatric patients using the *post hoc* PK parameters from the revised PopPK model combining adult and paediatric data.

The following simulations were conducted over a 12-week period:

For patients weighing >50 kg, the proposed dosing regimen of a 160-mg starting dose at Week 0 followed by 80 mg Q4W thereafter and the adult induction dosing regimen of a 160-mg starting dose at Week 0 followed by 80 mg Q2W thereafter

- For patients weighing 25 to 50 kg, the proposed dosing regimen of an 80-mg starting dose at Week 0 followed by 40 mg Q4W thereafter and a more frequent dosing regimen of an 80-mg starting dose at Week 0 followed by 40 mg Q2W thereafter.
- For patients weighing <25 kg (16.4 to <25 kg), the proposed dosing regimen of a 40-mg starting dose at Week 0 followed by 20 mg Q4W thereafter and a more frequent dosing regimen of a 40-mg starting dose at Week 0 followed by 20 mg Q2W thereafter.

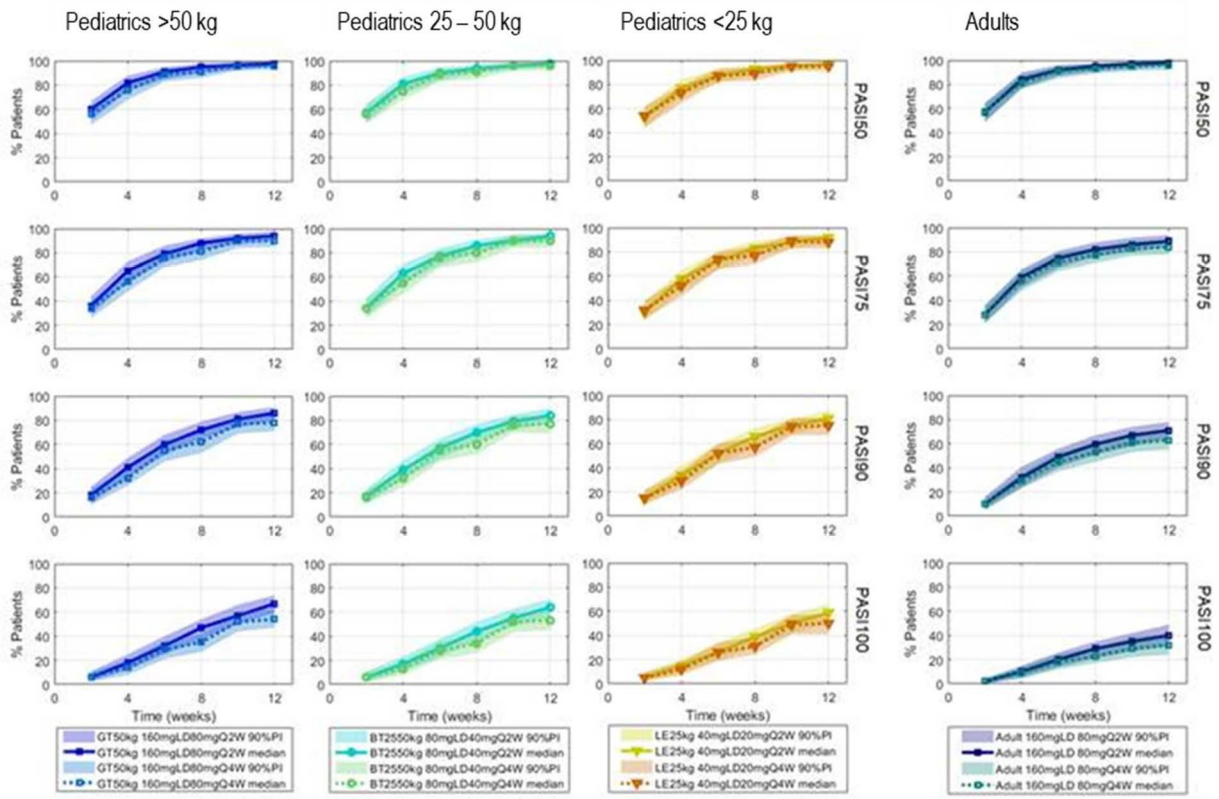
Figure 16 Visual predictive check of final PASI Week 12 static time point pharmacokinetic/pharmacodynamic model in paediatric patients (Study RHCD).



Abbreviations: conc = concentration; Ctrough = trough concentration; PASI = Psoriasis Area and Severity Index; RHCD = Study I1F-MC-RHCD.Circles with a solid line represent the observed percentage of patients achieving PASI improvement <50%, 50%, or greater improvement in PASI score (PASI 50), 75% or greater improvement in PASI score (PASI 75), 90% or greater improvement in PASI score (PASI 90), and 100% improvement in PASI score (PASI 100), in each quartile of Week 12 Ctrough (number of patients in each bin N = 24 to 25) or for placebo (number of patients N=53). The first point in the plots corresponds to a concentration of 0 µg/mL representing observed response rate in patients who received placebo. The shaded area is the predicted 90% confidence interval of response from the model. Symbols represent the observed response rates at Week 12. The median trough concentration across all paediatric patients was 3360 ng/mL.

Figure 17 shows the simulations for each of these dosing regimens in each weight category along with the adult 80-mg Q2W and 80-mg Q4W simulations over the 12-week period. **Table 18** shows the median (90% prediction interval) percent response rates and trough concentrations at Week 12 for each dosing regimen in paediatric and adult patients.

Figure 17 Model-predicted PASI response rates over the first 12 weeks of treatment in paediatric weight groups and adult patients with psoriasis across different dosing regimens.



Abbreviations: BT=between; GT=greater than; LD = loading dose; LE=less than; PI = prediction interval; PASI = Psoriasis Area and Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks.
Note: The shaded area is the predicted 90% PI from the model for percentage of patients on ixekizumab achieving PASI 50, PASI 75, PASI 90, and PASI 100 responses over time. Solid lines correspond to the median response of the simulated Q2W dosing regimen and dashed lines correspond to the median response of the simulated Q4W dosing regimen. The points are the observed percentage of patients achieving PASI 50, PASI 75, PASI 90, and PASI 100 responses at Week 12.

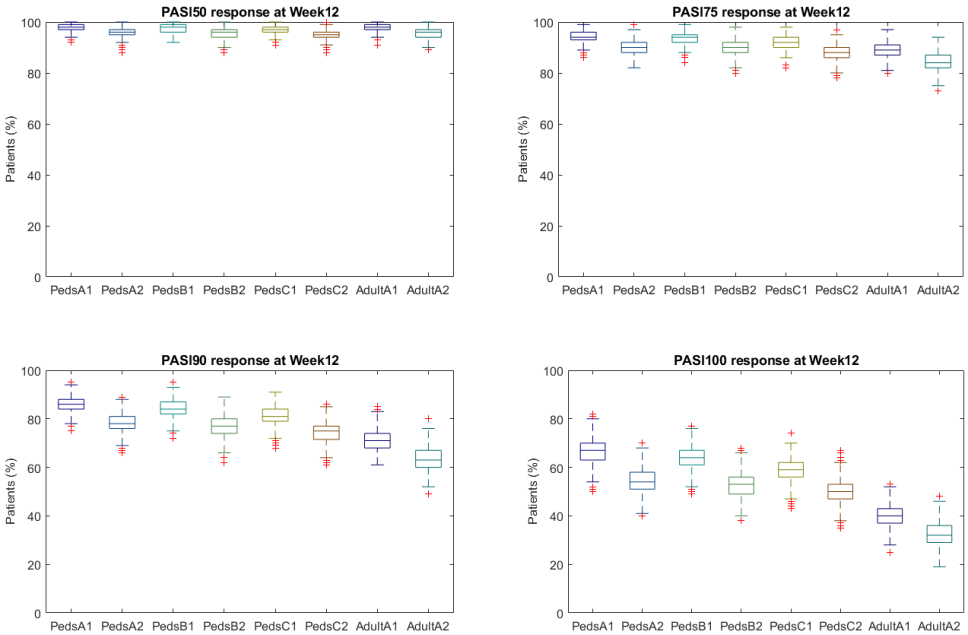
Table 18 Week 12 Predicted PASI Response Rates and Ctrough Concentrations across Paediatric Weight Category Groups and in Adult Patients

	Median [5th-95th Prediction Interval] % Responder Rates							
	Peds >50 kg 80 mgQ2W[a]	**Peds >50 kg 80 mg Q4W[a]**	**Peds 25–50 kg 40 mg Q2W[a]**	**Peds 25-50 kg 40 mg Q4W[a]**	**Peds <25 kg 20 mg Q2W[a]**	**Peds <25 kg 20 mg Q4W[a]**	**Adult 80 mg Q2W[a]**	**Adult 80 mg Q4W[a]**
PASI 50 WK12	98 [95–100]	96 [93–99]	98 [95–99]	96 [92–99]	97 [94–99]	95 [91–98]	98 [95–100]	96 [92–99]
PASI 75 WK12	94 [90–98]	90 [85–95]	94 [89–97]	90 [84–94]	92 [87–96]	88 [83–93]	89 [84–94]	84 [78–90]
PASI 90 WK12	86 [80–91]	78 [71–85]	84 [78–90]	77 [69–84]	81 [75–87.5]	75 [67–81.5]	71 [64–78]	63 [55–71]
PASI 100 WK12	67 [59–74]	54 [47–63]	64 [56–71]	53 [45–61]	59 [50.5–66]	50 [41–58]	40 [31–49]	32 [24–41]
C_{trough} WK12 [µg/mL]	12.42 [6.87–22.14]	4.53 [1.48–9.78]	9.99 [4.55–18.11]	3.11 [1.08–7.30]	6.68 [2.76–12.81]	2.24 [0.71–5.83]	8.80 [3.35–16.94]	2.97 [0.83–6.64]

Abbreviations: C_{trough} = trough concentration; PASI = Psoriasis Area and Severity Index; Peds = paediatric patients; Q2W = every 2 weeks; Q4W = every 4 weeks; WK = week.

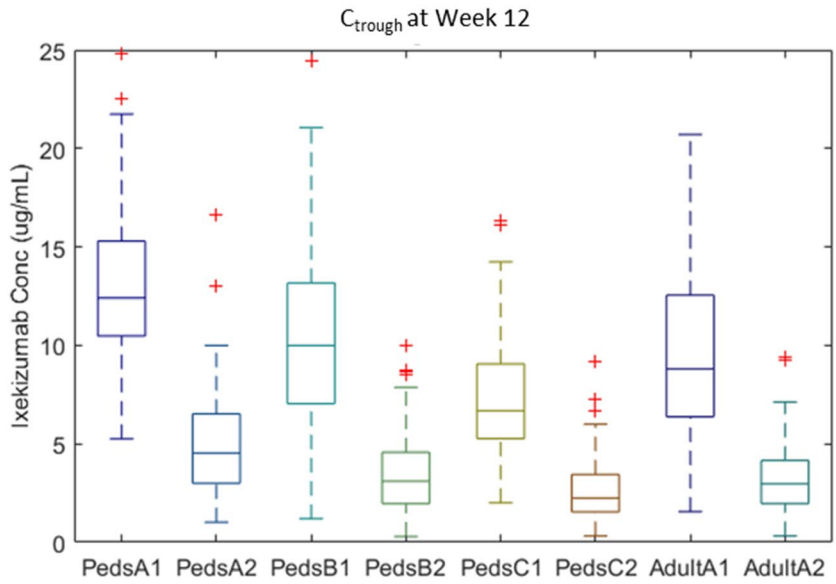
[a] All dosing regimens were simulated with a starting dose administered at Week 0 as follows: 40 mg for paediatric patients <25 kg; 80 mg for paediatric patients 25–50 kg; 160 mg for paediatric patients >50 kg and for adult dosing regimens.

Figure 18 Boxplots showing the Week 12 PASI 50/75/90/100 response rates for each simulated dosing regimen in paediatric and adult patients.



Abbreviations: AdultA1 = adult dose of 160-mg starting dose at Week 0 followed by 80 mg Q2W thereafter; AdultA2 = adult dose of 160-mg starting dose at Week 0 followed by 80 mg Q4W thereafter; PASI = Psoriasis Area and Severity Index; PedsA1= paediatric dose for >50 kg: 160-mg starting dose at Week 0 followed by 80 mg Q2W thereafter; PedsA2 = paediatric dose for >50 kg: 160-mg starting dose at Week 0 followed by 80 mg Q4W thereafter; PedsB1 = paediatric dose for 25–50 kg: 80–mg starting dose at Week 0 followed by 40 mg Q2W thereafter; PedsB2 = paediatric dose for 25–50 kg: 80-mg starting dose at Week 0 followed by 40 mg Q4W thereafter; PedsC1 = paediatric dose for <25 kg: 40-mg starting dose at Week 0 followed by 20 mg Q2W thereafter; PedsC2 = paediatric dose for <25 kg: 40-mg starting dose at Week 0 followed by 20 mg Q4W thereafter; Q2W = every 2 weeks; Q4W = every 4 weeks.
Note: The box represents the median and 25th and 75th percentiles of the data. The whiskers represent the 5th and 95th percentiles and the symbols represent the outliers.

Figure 19 Boxplots showing the Week 12 predicted trough concentrations for each simulated dosing regimen in paediatric and adult patients.



Abbreviations: AdultA1 = adult dose of 160-mg starting dose at Week 0 followed by 80 mg Q2W thereafter; AdultA2 = adult dose of 160-mg starting dose at Week 0 followed by 80 mg Q4W thereafter; Conc = concentration; C_{trough} = trough concentration; PASI = Psoriasis Area and Severity Index; PedsA1 = paediatric dose for >50 kg: 160-mg starting dose at Week 0 followed by 80 mg Q2W thereafter; PedsA2 = paediatric dose for >50 kg: 160 mg starting dose at Week 0 followed by 80 mg Q4W thereafter; PedsB1 = paediatric dose for 25–50 kg: 80-mg starting dose at Week 0 followed by 40 mg Q2W thereafter; PedsB2 = paediatric dose for 25-50 kg: 80-mg starting dose at Week 0 followed by 40 mg Q4W thereafter; PedsC1 = paediatric dose for <25 kg: 40-mg starting dose at Week 0 followed by 20 mg Q2W thereafter; PedsC2= paediatric dose for <25 kg: 40 mg starting dose at Week 0 followed by 20 mg Q4W thereafter; ; Q2W = every 2 weeks; Q4W = every 4 weeks.

Note: The box represents the median and 25th and 75th percentiles of the data. The whiskers represent the 5th and 95th percentiles and the symbols represent the outliers

Exposure-safety

The exposure-safety analysis includes data from patients treated with either ixekizumab or placebo up to and including Week 12. Week 12 observed Ctrough values are used as the exposure input and divided into quartiles.

The overall incidence of TEAEs during the first 12 weeks of treatment is plotted against the median exposure of each quartile and the incidence of each of the AESIs is summarized by exposure quartiles. The incidence of the following AESIs is considered for graphical evaluation if there are sufficient data:

- Injection site reactions (ISRs)
- infections (all, Candida, herpes, staphylococcal, and infections reported as serious adverse events [SAEs])
- hypersensitivity events (anaphylaxis and non-anaphylaxis)
- neutropenia, and
- inflammatory bowel disease ([IBD] – both Crohn's disease and ulcerative colitis).

Table 19 Summary of Ixekizumab Week 12 Exposure Data Used in Exposure-Safety Analyses

	Week 12 Exposure Summary Overall			
Quartile	N	Median Weight (kg)	Median Concentration (µg/mL)	Concentration range (µg/mL)
Q1	25	58.3	1.39	<2.25
Q2	24	66.0	2.74	2.25 - 3.36
Q3	25	63.0	4.16	3.36 - 4.96
Q4	25	52.0	6.84	≥4.96

Abbreviations: N = number of patients; Q = Quartile.

Only AESIs that occurred in sufficient numbers to permit evaluation were assessed. Note, in the statistical analyses there may be a higher incidence of AESIs reported compared to this exposure-safety analysis. All randomized patients who received at least 1 dose of study treatment are included in the statistical analyses, including patients who discontinued, whereas this exposure-safety analysis includes only patients who had completed to Week 12 and had a Ctrough value.

The incidence of ISRs appears to be similar across Quartiles 1, 3, and 4 of ixekizumab Ctrough (12% to 16%), with no ISRs reported in Quartile 2 and only 1 ISR reported in the placebo group. There is no relationship observed with ixekizumab trough concentrations and infections (all). There is no relationship observed with ixekizumab trough concentrations for the (ixekizumab, n=5 and placebo, n=1 in this dataset) reports of allergic reactions/hypersensitivity events that were non-anaphylactic in nature.

2.3.5. Discussion on clinical pharmacology

A Phase 3 pivotal study (RHCD) supporting the paediatric psoriasis indication was conducted where subjects aged 6-17 years received placebo (n=56) or ixekizumab (n=115) according to the recommended posology for 12 weeks during period 2. Study RHCD also included an active-controlled (etanercept) reference arm in period 2. Population PK and exposure–response modelling was conducted using serum drug concentration data from the pivotal Phase 3 clinical study (RHCD) in paediatric patients with Ps.

Several parts of the information necessary for assessment of the bioanalytical methods were missing in the initial submission. The MAH clarified where the within-study validation results and the study samples were reported. The pre-study result was found in report 184959, which was submitted in variation EMEA/H/C/003943/II/30. The study sample analysis of ADA and NAb were not provided, as requested. However, since it was confirmed that the methods were unchanged from previous variations and the previously validated method has been used, the issue was therefore not further pursued by CHMP. The MAH provided also Additional Matrix Effects for the Determination of LY2439821 in Human Serum by ELISA. Matrix effects were not observed in five individual lots of plaque psoriasis human serum. Overall, the bioanalytical methods were found acceptable by CHMP.

The MAH provided the demographics of the population in the different treatment arms during week 0-12. The least weighting child weighed 21.5 kg (two children, unknown age).

The model development approach was questioned by CHMP. The model is considered important to support the posology in paediatric subjects due to the sparse sampling scheme. The proposed posology was also questioned, since adults are dosed differently before (160 mg at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12) and after week 12 (80mg Q4W). Furthermore, the MAH applied initially for approval in children from the age of 6, who could weight as little as 16.5 kg. No lower weight limit had

been initially proposed by the MAH. Only two children weighed below 25 kg, however both above 21.5 kg. Therefore, extrapolation using the population pharmacokinetic model was needed, to support the dose in paediatric subjects that weigh less than 21.5 kg, as a 6-year-old child could weigh 16.5 kg. The MAH withdrew the indication in children weighing <25 kg, therefore, the issues raised for this subgroup of the patient population were not further pursued by CHMP.

- Model development

In the initially submitted model, the existing structural and stochastic PK models based on adult Ps and adult Ps/PsA data (n=1399, mainly sparse sampling) were applied, however, the parameters were re-estimated with the paediatric (study RHCD) dataset. The reason for excluding the data from adults was not understood by CHMP since it could have further informed the model (e.g. with respect to covariates) and facilitated the comparison of exposure and optimal dose in paediatric subjects versus adults. It was also unclear why covariates that had been found to be significant in adults had to be re-evaluated. The MAH tested 3 different models to explain the weight-distribution/clearance relationship. The approaches were not justified and not agreed by CHMP. The selected model was the one with estimated exponents of 0.989 for Q and CL and 0.998 for V1 and V2. The sampling scheme was sparse and there were few paediatric subjects in the lower weight cohorts, thereby very few samples informing the exponents. It was also unclear why the model with estimated exponents using the paediatric data was considered superior compared to the theoretical values. CHMP highlighted also that it is not advised to use allometric exponents estimated using adult data for paediatric PK models, as adult exponents are likely to be affected by other factors than pure body size relations (such as obesity and model misspecifications). The CHMP considers that the use of fixed allometric exponents (of 0.75 on clearance parameters and 1 on distribution parameters) is both scientifically justified and practical when developing population PK models in children. Therefore, upon request from CHMP, the MAH merged adult and paediatric data to create a population PK model in order to characterise the PK in the paediatric psoriasis population. The existing PK model based on adult Ps and adult Ps/PsA data was used to describe the ixekizumab PK from study RHCD in paediatric patients with Ps. The adult structural model was a 2-compartment linear model parameterized in terms of first-order clearance (CL), distribution volume (V2, V3), intercompartmental clearance (Q), and absolute bioavailability (F). Inter-individual variability was estimated for F, CL, and V2, and residual error was determined using a proportional error model. Fixed exponents of 0.75 were used to describe the allometric relationship of weight on clearance terms, and fixed exponents of 1 were used to describe the allometric relationship of weight on volume terms rather than estimating the exponents. Titre and NAb were both included in the model as covariates on clearance (CL) in which all adult and paediatric NAb data were reported using the same cut point. The CHMP considers that the revised model successfully describes the available ixekizumab PK data in paediatric patients with Ps.

New simulations were conducted using the updated model, and the steady-state exposures in children were compared to exposure in adults given Q2W and Q4W dosing. The observed week 12 Ctrough values were also presented. The exposure in paediatric subjects weighing <25 kg is mainly based on simulation as very few children weighing <25 kg was included. With respect to Cmaxss, AUCss and Ctroughss, the predicted exposure in children <25 kg is lower compared to adults given Q2W and Q4W treatment. In children 25-50 kg, exposure is similar to Q2W treatment in adults, and AUCss is similar to Q4W treatment, however, the Ctrough is on average lower. Subjects weighing >50 kg have Cmaxss and AUC in between adults given Q2W and Q4W treatment.

- Posology

Since studies in adult patients with plaque psoriasis that were treated with ixekizumab and had confirmed neutralizing antibodies associated with low drug concentrations had a lower clinical response, Ctrough is considered of importance for clinical effect by CHMP. The exposure with the proposed posology in paediatric patients in the different weight groups were simulated in the initial model and compared to the

exposure in adults both when given 160mg+80mg Q2W (adult posology week 0-12) and 160mg+80mg Q4W (adult posology from week 12). The Ctrough with the proposed posology in paediatric subjects weighing >50kg, was lower compared to the adult Q2W dosing i.e. lower exposure the first 12 weeks compared to adults. The AUC was similar to Q2W dosing. The AUC and Ctrough with the proposed posology in paediatric subjects weighing 25-50kg, was lower compared to the adult Q2W, i.e. subjects weighing 25-50kg would be initially underexposed for 12 weeks, compared to the adult posology. The AUC and Ctrough with the proposed posology in paediatric subjects weighing <25kg, was also lower compared to the adults when given Q2W dosing. The MAH was therefore requested to justify the dose selection with respect to the under- and overexposure with the selected posology compared to adults during the first 12 weeks of treatment and to the maintenance treatment. The MAH provided new plots using the updated popPK model and described the approach for adult exposure simulation/prediction. The MAH clarified that the proposed posology in paediatric patients does not aim to mimic exactly the trough concentrations in the induction and maintenance periods observed in adults with the approved dosing regimen. For subjects 25-50 kg, the exposure is predicted to be similar, or lower, with the proposed posology compared with adults. For subjects weighing >50 kg, the exposure is predicted to be slightly higher on average, compared with adults, after week 12. The MAH considers the slightly higher exposure in subjects in the lower weight range of the weight group to be safe as the adult 80-mg Q2W regimen has been evaluated in adult patients with psoriasis over 52 weeks of treatment in Study RHBP and had an acceptable benefit/risk profile with longer term administration.

The MAH was also requested to clarify why adolescent subjects weighing >50 kg cannot be dosed according to the approved adult dosing regimen. The MAH indicated that the intent was not to match the exposure between children and adults, but to provide the most simplified and least intrusive dosing regimen to have good compliance and achieve an acceptable benefit/risk balance. The MAH considers the use of the Q4W regimen in this group a conservative approach, taking into account the characteristics of this population in relation to the adult studies. From a clinical point of view, this approach is agreed by CHMP. In a between-study comparison, the observed response rates for PASI and sPGA endpoints in study RHCD are comparable or sometimes higher compared with the response rates in the adult, pivotal studies. A more cautious, conservative dose regimen in the paediatric population with a need for less frequent injections is thus agreed by CHMP.

The MAH presented model-predicted ixekizumab trough concentrations by weight and age of paediatric patients in study RHCD compared with adult patients with psoriasis at week 12 using the updated model and including the adult exposure when adult subjects are dosed Q2W. The provided simulations show that the paediatric subjects will have a lower Ctrough the first 12 weeks compared to adults. This lower exposure did not result in lower response rates in the paediatric subjects compared with adults as explained above.

The longitudinal PASI time course PK/PD model explores the relationship between predicted individual ixekizumab concentrations at any timepoint in the systemic circulation and PASI responses up to and including Week 12 using all data. The model parameters were estimated with adequate precision and appears to adequately predict percentage of patient that achieve PASI50/75/90 and 100 over time. As the Ctrough is lower in children during the first 12 weeks compared to adults with the approved posology, the posology in children was questioned by CHMP, as this could mean that it theoretically could take longer for children to reach maximum effect. The MAH was requested to use the longitudinal PASI-model and simulate the effect with a posology in children (for the different weight groups) that aims to match the Ctrough (and result in a similar AUC) using the updated popPK model. As the paediatric PK–PASI model is predicting outside the dose range of what was studied in Study RHCD, the MAH highlighted that the paediatric model needs to be interpreted with caution, this is agreed by CHMP. According to the simulations, both Q2W and Q4W dosing regimens are associated with high levels of response with only small increases in response rates predicted in paediatric patients for the Q2W regimens compared with

the Q4W regimens. The response rates with the Q4W regimens in paediatric patients are generally most similar to the response rates in adults receiving the Q2W regimens.

The CHMP highlighted also that adolescents in the upper age and weight range may experience a relative underdosing versus adults with the Q4W posology and a possibility to use the Q2W posology during the first 12 weeks was proposed by CHMP as an option. This proposal was not endorsed by the MAH since Q2W has not been studied in adolescents. This is acknowledged by CHMP.

The PASI and sPGA Week 12 static time point models explore the potential relationship between ixekizumab trough concentration (Ctrough) and PASI/sPGA responses at Week 12. The visual predictive check plots of the static time point PK/PD models show a clear relationship between sPGA and PASI at week 12 Ctrough and patients responding.

Since study RHCD is ongoing, the MAH was requested to discuss how immunogenicity in paediatric patients will be more fully characterised. The MAH clarified that longer-term efficacy data including data regarding the effect of treatment-emergent anti-drug antibodies (TE-ADAs) on efficacy will be provided post-approval. The MAH commits to update the wording on immunogenicity in Section 4.8 of the SmPC to include information on maintenance. This is agreed by CHMP.

2.3.6. Conclusions on clinical pharmacology

The PK in paediatric patients with plaque psoriasis above 6 years age and weighing more than 25 kg has been adequately characterized. The proposed posology is adequate to support the use of ixekizumab in this patient population.

2.4. Clinical efficacy

2.4.1. Dose response study

No dedicated dose response studies have been performed in children or adolescents.

The MAH states that efficacy, safety, and PK data from the Phase 2 and Phase 3 programmes in adults with plaque Ps have been used to guide the dose and dosing regimen for investigation in paediatric patients with plaque Ps. Weight was identified as an important covariate factor on clearance and volume terms in the adult population PK model. Therefore, the adult PK model and the adult sPGA time course exposure-response model was used to simulate the expected PK and PD responses across a range of ages and weights in paediatric patients to support selection of the weight categories, doses, and dosing frequency proposed in this study.

The recommended 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 Q4W doses, which both had a positive benefit/risk ratio.

Simulations in paediatric patients using the adult population PK model and the adult sPGA time course model were conducted and the results from the modelling and simulation exercise was used to support the doses, dosing frequencies, and weight categories applied in study RHCD.

2.4.2. Main study

The efficacy and safety of ixekizumab in paediatric psoriasis is supported by one pivotal, randomised, double-blind, placebo-controlled Phase 3 study (RHCD) which is part of the European Paediatric

Investigation Plan (PIP) ("study 6" in EMEA-001050-PIP01-10-M04 from 20 November 2018), planned to investigate the safety, efficacy, and pharmacokinetics (PK) of ixekizumab in paediatric patients (children and adolescents).

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

Methods

Study RHCD has 5 periods:

Period 1: Screening Period

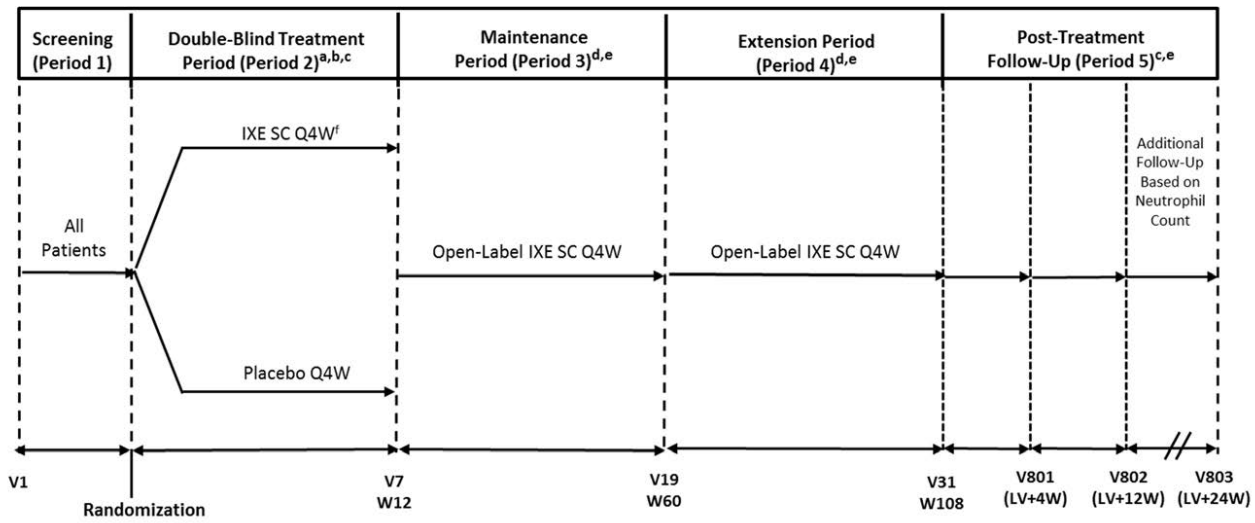
Period 2: 12-Week Double-Blind Treatment Period

Period 3: 48-Week Open-Label Maintenance Period

Period 4: 48-Week Extension Period, and

Period 5: Post-Treatment Follow-Up Period.

Figure 20 Study outline for Study I1F-MC-RHCD



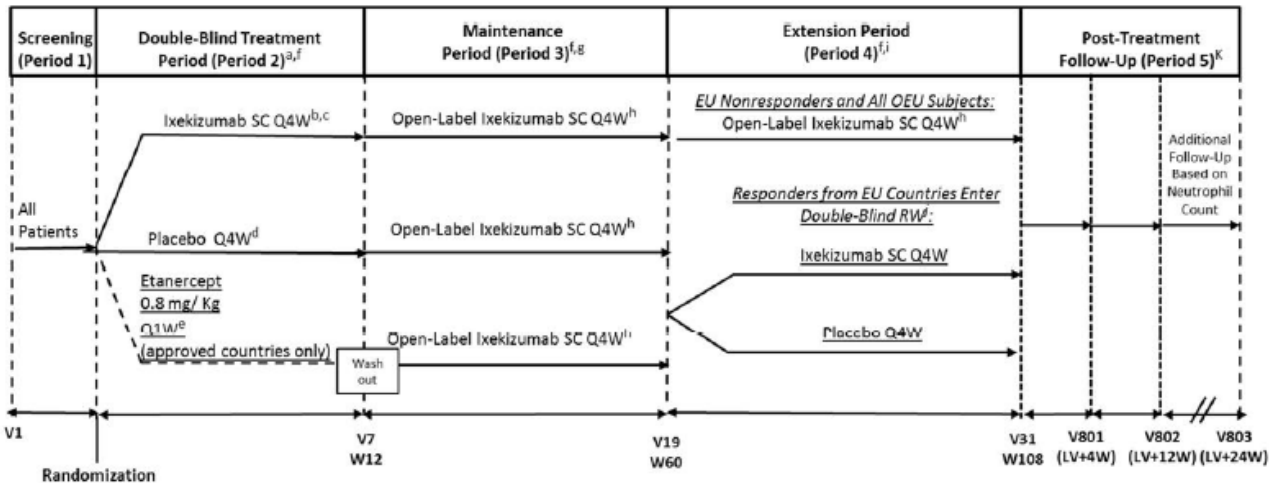
Abbreviations: EU = European Union; IXE = ixekizumab (LY2439821); LV = date of last visit; PK = pharmacokinetic(s); Q4W = every 4 weeks; SC = subcutaneous; V = visit; W = week.
Note: See corresponding figure for the RHCD EU CSR Addendum for the comparison of ixekizumab and etanercept arms in the EU-specific randomised withdrawal phase during Period 4.
a Patients were randomised to either ixekizumab or placebo in a 2:1 ratio.
b Patients receiving ixekizumab 20 mg or 40 mg received 1 SC injection of ixekizumab at Week 0 (Visit 2) and 1 SC injection of ixekizumab Q4W at Weeks 4 and 8. Patients receiving ixekizumab 80 mg received 2 SC injections of ixekizumab at Week 0 (Visit 2) and 1 SC injection of ixekizumab Q4W at Weeks 4 and 8.
Patients receiving placebo for ixekizumab 20 mg or 40 mg received 1 SC injection of placebo at Week 0 (Visit 2) and 1 SC injection of placebo Q4W at Weeks 4 and 8. Patients receiving placebo for ixekizumab 80 mg received 2 SC injections of placebo at Week 0 (Visit 2) and 1 SC injection of placebo Q4W at Weeks 4 and 8.
c Immunogenicity and time-matched PK sample collection occurred as detailed in the Schedule of Activities (RHCD Protocol Section 2).
d Patients randomised to ixekizumab during Period 2, Induction, received 1 SC injection of ixekizumab and 1 SC injection of placebo at Week 12. Patients randomised to the placebo group during Period 2, Induction, were assigned to receive ixekizumab at doses of 20, 40, or 80 mg based on weight. Patients assigned to 20 mg received a starting dose of 40 mg, patients assigned to 40 mg received a starting dose of 80 mg, and patients assigned to 80 mg received a starting dose of 160 mg. All patients received 2 SC injections of ixekizumab at Week 12 and 1 SC injection of ixekizumab Q4W at Week 16 and thereafter.
e All patients receiving study drug must enter into Period 5 and complete through Visit 802. Patients may be followed up beyond Visit 802 for continued monitoring of their neutrophil count if determined by the Sponsor/investigator that additional monitoring is needed.

f At Visit 2, randomization occurred based on the following weight groups: 1) <25 kg: randomization to ixekizumab 20 mg, receiving a starting dose of 40 mg; 2) 25 to 50 kg: randomisation to ixekizumab 40 mg, receiving a starting dose of 80 mg; and 3) >50 kg: randomisation to 80 mg, receiving a starting dose of 160 mg.

Protocol Addendum I1F-MC-RHCD(2)

The Protocol Addendum I1F-MC-RHCD(2) involved a comparison of ixekizumab administered by subcutaneous (SC) injection with placebo and with etanercept as a reference arm. This addendum was conducted in countries where etanercept is approved for severe paediatric plaque Ps treatment (European countries and other selected countries outside the US). Patients were randomised to ixekizumab every 4 weeks (Q4W), etanercept (an active-control reference group), or placebo during the Double-Blind Treatment Period.

Figure 21 Illustration of study design for Protocol Addendum I1F-MC-RHCD(2)



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

Footnotes omitted.

Study participants

The main inclusion criteria were:

- A diagnosis of moderate-to-severe plaque-type Ps for at least 6 months prior to baseline (Week 0; Visit 2), as determined by the investigator
- PASI score ≥12, sPGA ≥3, and BSA involvement ≥10% at screening (Visit 1) and baseline (Week 0; Visit 2), and
- Were candidates for phototherapy or systemic treatment or considered by the investigator as not adequately controlled by topical therapies
- Male and female subjects from 6 to <18 years of age at time of randomization;
    - Male subjects agree to use a reliable method of birth control during the study
    - Female subjects:

- Are women of childbearing potential who test negative for pregnancy and agree to use a reliable method of birth control or remain abstinent during the study and for at least 12 weeks following the last dose of study drug, whichever is longer; or:
- Are women of non–childbearing potential, defined as women who have had surgical sterilization or girls who have not had their first menstruation

- 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
- All immunizations are up-to-date in agreement with current immunization guidelines, in the opinion of the investigator.

The main exclusion criteria were:

- Had pustular, erythrodermic, and/or guttate forms of plaque Ps
- Have drug-induced plaque Ps (e.g., a new onset of plaque Ps or an exacerbation of plaque Ps from beta blockers, calcium channel blockers, or lithium)
- Had clinical and/or laboratory evidence of untreated latent or active tuberculosis (TB)
- Had evidence of or test positive for hepatitis B virus (HBV) by testing positive for (a) hepatitis B surface antigen (HBsAg+) or (b) 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.
- Had evidence of or test positive for hepatitis C virus (HCV). A positive test for HCV is defined as (a) positive for hepatitis C antibody and (b) positive via a confirmatory test for HCV (e.g., HCV polymerase chain reaction)
- 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
- Had a herpes zoster or any other clinically apparent varicella-zoster virus infection within 12 weeks of baseline
- Had any other active or recent infection, including chronic or localized infections, within 4 weeks of baseline 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
- Had sepsis or risk of sepsis
- Have an oral body temperature ≥38°C at baseline (Week 0; Visit 2); these subjects could be rescreened (1 time) ≥4 weeks after documented resolution of elevated temperature
- Subjects with a documented history of immune deficiency syndrome
- Subjects with a known history of malignancy; lymphoproliferative disease, including lymphoma; or signs and symptoms suggestive of possible lymphoproliferative disease
- 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)
- Has had any major surgical procedure within 8 weeks prior to baseline or will require such during the study that, in the opinion of the investigator, would pose an unacceptable risk to the subject

- Presence of significant uncontrolled cerebrocardiovascular disorder; respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, or neurologic disorders; or abnormal laboratory values at screening that, in the opinion of the investigator, pose an unacceptable risk to the subject if participating in the study or of interfering with the interpretation of data
- Presence of significant uncontrolled neuropsychiatric disorder that, in the opinion of the investigator, poses an unacceptable risk to the subject if participating in the study or of interfering with the interpretation of data; recent history of a suicide attempt (during the 30 days prior to screening); or marked yes to C-SSRS question 4 or 5 on ideation or yes to suicide behaviors
- Had a serious infection (eg, pneumonia, cellulitis); have been hospitalized; have received intravenous antibiotics for an infection within 12 weeks prior to baseline; 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 would pose an unacceptable risk to the subject
- For females of childbearing potential, are sexually active and not on either 1 highly effective form of contraception or 2 effective forms of contraception, or are pregnant or intending to become pregnant or are breastfeeding
- Have evidence of precocious puberty at the time of study enrolment
- At screening, have abnormal neutrophil, lymphocyte or platelet counts, ALT or AST levels, total WBC count, or hemoglobin levels (as prespecified in the protocol; not detailed here)
- Patients previously treated with etanercept
- Had used any therapeutic agent targeted at reducing interleukin-17
- Had received other therapies within the specified time frames prior to screening such as:
    - adalimumab and infliximab 60 days, abatacept 90 days, anakinra 7 days, or any other biologic disease-modifying anti-rheumatic drug 5 half-lives
    - systemic therapy for plaque Ps and PsA (other than above, e.g., methotrexate, cyclosporine) or phototherapy (e.g., photochemotherapy [psoralen plus ultraviolet A]) in the previous 4 weeks
    - any investigational drugs in the previous 4 weeks or 5 half-lives, whichever is longer
    - ultraviolet-A therapy, ultraviolet-B therapy, and topical treatments (except on face, scalp, and genital area during screening) in the previous 4 weeks
- Had a live vaccination within 12 weeks prior to baseline, 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.
- 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 or intend to have vaccination with BCG during the study or within 12 months of completing treatment in this study.

Treatments

Following a screening period (**Period 1**), a placebo-controlled, Double-Blind Treatment Period (**Period 2**) of 12 weeks followed. During Period 2, patients were randomised to receive ixekizumab Q4W or placebo. Treatment with ixekizumab is weight based. If a subject changed weight category during the study, after completing the Double-Blind Treatment Period (induction), the dose was adjusted accordingly (0).

The double-blind treatment period was followed by a 48-week open-label Maintenance Period (**Period 3**), then either:

- a 48-week Extension Period (**Period 4**), for patients from countries outside of the EU, irrespective of response, and non-responders from the EU (defined as those who did not achieve sPGA 0,1.

  OR

- a 48-week Randomised Withdrawal Period (**Period 4**), for patients from the EU who meet response criteria at Week 60 (defined as those who achieved sPGA 0,1.

After Period 4, patients enter the Post-Treatment Follow-Up Period (**Period 5**).

As part of an addendum, as described above, a group of patients were randomised to an active control group (etanercept) during the Double-Blind Treatment Period. These patients are from countries where etanercept was approved for the treatment of severe paediatric Ps at the time the study protocol was written (patients came from EU countries and other countries outside US).

Table 20 Treatment Regimens

	Period 2[a]			Period 3 and Period 4[a]
Regimen	Dose Week 0	Dose Week 4 and Week 8	Dose Week 12	Dose Week 16 through Week 104
Ixekizumab >50 kg	160 mg (administered as two 80-mg SC injections)	80-mg Q4W SC injection	80-mg SC injection + a placebo injection at Week 12	80-mg Q4W SC injection
Ixekizumab 25-50 kg	80-mg SC injection	40-mg Q4W SC injection	40-mg SC injection + a placebo injection at Week 12	40-mg Q4W SC injection
Ixekizumab <25 kg	40-mg SC injection	20-mg Q4W SC injection	20-mg SC injection + a placebo injection at Week 12	20-mg Q4W SC injection
Etanercept All weight groups	0.8 mg/kg, not exceeding 50 mg per dose		No injections because of the washout period	Ixekizumab Q4W SC per weight group[b] OR matching placebo[c]
Placebo >50 kg	Placebo for ixekizumab 160 mg (administered as 2 placebo SC injections)	Placebo for ixekizumab 80-mg Q4W SC injection	Starting ixekizumab dose: 160-mg (administered as two 80-mg SC injections)	80-mg Q4W SC injection
Placebo 25-50 kg	Placebo for ixekizumab 80-mg SC injection	Placebo for ixekizumab 40-mg Q4W SC injection	Starting ixekizumab dose: 80-mg (administered as two 40-mg SC injections)	40-mg Q4W SC injection

Placebo <25 kg	Placebo for ixekizumab 40-mg SC injection	Placebo for ixekizumab 20-mg Q4W SC injection	Starting ixekizumab dose: 40-mg (administered as two 20-mg SC injections)	20-mg Q4W SC injection

Abbreviations: EU = European Union; Q4W = every 4 weeks; SC = subcutaneous; sPGA = static Physicians Global Assessment.

a See above for a description of the study periods.

b From Week 20.

c From Week 60, for patients for patients from the EU who meet response criteria (sPGA 0,1) and are randomised to placebo.

Prior and Concomitant Therapy

Previous plaque Ps therapies and all concomitant medications taken during the study were recorded in the electronic CRF (eCRF). Plaque Ps therapy as described in the inclusion/exclusion criteria were not permitted during the study. The same applied to any biologic therapy within the washout period, concomitant medications as described in the exclusion criteria, live vaccines, and phototherapy.

The following medications were permitted during the study:

Topical Steroids: Topical steroids (that was, nonhalogenated steroids/topical calcineurin inhibitors administered no more than twice daily) were permitted for limited use.

Vaccines: Use of non-live seasonal vaccinations and/or emergency vaccinations (such as rabies or tetanus vaccinations) was allowed.

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

Additional drugs were to be avoided during the study, unless required to treat an AE or for treatment of an ongoing medical problem.

Any additional medication used at baseline and/or during the course of the study was to be documented with the start and stop dates on the eCRF. Patients were instructed to maintain their usual medication regimen for other concomitant diseases throughout the study, unless specifically excluded in the protocol.

Patients taking concomitant medications should be on stable doses at baseline and should remain at a stable dose throughout the study, unless changes needed to be made for an AE or for appropriate medical management.

Objectives

The primary objective was to assess whether ixekizumab Q4W was superior to placebo at Week 12 (Visit 7) 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).

As gated, secondary objectives, the superiority of ixekizumab Q4W to placebo was evaluated, as measured by a number of other PASI and sPGA endpoints, as well as itch (see below).

Among other secondary objectives was to compare the efficacy of ixekizumab Q4W and etanercept at Week 12 in countries where etanercept is approved.

Outcomes/endpoints

The co-primary endpoints were:

- Proportion of patients achieving PASI 75 at Week 12
- Proportion of patients achieving sPGA (0,1) at Week 12

Gated, secondary endpoints were:

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

Other secondary endpoints were assessed at Week 12 and at each postbaseline visit during the Double-Blind Treatment Period:

- Proportion of patients achieving PASI 50, PASI 75, PASI 90, and PASI 100
- Proportion of patients achieving sPGA (0,1) and sPGA (0)
- Change from baseline in itching severity (Itch NRS) score
- Proportion of patients achieving CDLQI/DLQI (0,1)
- Change from baseline in NAPSI, PSSI, and/or PPASI score in case of nail, scalp, or hand/feet involvement

For evaluation of efficacy of ixekizumab Q4W at Week 24 (Visit 10) and Week 48 (Visit 16), the proportion of patients achieving PASI 75, sPGA (0,1), sPGA (0), PASI 90 and PASI 100 at Weeks 24 and 48, respectively, were assessed

It was also assessed how PASI 75 and sPGA(0,1) at Week 12 correlated with treatment-emergent anti-drug antibody titer and by NAb status, Serum trough concentrations of ixekizumb, safety parameters, etc.

Sample size

The sample size was based on the European Medicine's Agency Paediatric Investigation Plan for ixekizumab and thereby the following regulatory requirements: (1) at least 170 randomised subjects whereof at least 90 to ixekizumab, at least 25 to etanercept, and at least 55 to placebo; and (2) at least 30% of subjects from the EU.

The initially planned total sample size was 195 subjects.

Main Protocol

In the main protocol RHCD, approximately 165 subjects were planned whereof approximately 110 subjects were to receive ixekizumab and 55 subjects were to receive placebo during the Double-Blind Treatment Period. The study was then to have >99% power to test the superiority of ixekizumab to placebo for PASI 75 and for sPGA (0,1) at Week 12, based on the 2-sided Fisher's exact test at a significance level of 0.05. The following assumptions were used for the power calculations for both sPGA (0,1) and PASI 75 responses rates; 80% response for ixekizumab and 10% response for placebo, based

on ixekizumab clinical studies in adult subjects with moderate-to severe Ps efficacy data (Griffiths et al. 2015; Gordon et al. 2016).

Protocol Addendum (2)

In the protocol addendum RHCD(2), approximately 75 subjects with severe psoriasis from etanercept-approved countries were planned whereof approximately 30 subjects in the ixekizumab arm, 30 subjects in the etanercept arm, and 15 subjects in the placebo arm.

With 30 subjects per arm the power was approximately 85% to demonstrate superiority of ixekizumab to etanercept for sPGA (0,1) and PASI 75 at Week 12, based on a Fisher's exact test with a two-sided significance level of 0.05. For the comparison of etanercept versus placebo for PASI 75 week 12, the power was approximately 45% (Fisher's exact test, two-sided significance level of 0.05).

The following assumptions were used for the power calculations for both sPGA (0,1) and PASI 75 response rates based on ixekizumab clinical studies in adult subjects with moderate-to-severe Ps efficacy data (Griffiths et al. 2015; Gordon et al. 2016): 80% responders for ixekizumab, 40% responders for etanercept, and 10% for placebo.

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

Randomisation

Assignment to treatment groups were determined by a computer-generated random sequence using an interactive web-response system (IWRS).

Since treatment with ixekizumab is weight based, randomisation occurred based on weight groups (<25 kg, 25 kg to 50 kg and >50 kg) using a staggered approach. Initially, subjects >12 years and >50 kg were enrolled. If no safety concern had been identified after an initial safety analysis of the first 12 weeks of treatment in the first 15 subjects >50 kg, subjects were to start to enrol in the 25- to 50-kg group. Once data had been obtained to Week 12 for approximately 15 subjects in the 25- to 50-kg group, an interim analysis of PK, safety, and efficacy data in all subjects in the study at that point was to be performed to confirm doses for the remaining subjects in the study. Once confirmed, all weight groups were to be open for enrolment. The interim analysis was performed under the auspices of a Data Monitoring Committee (DMC).

Main Protocol

Subjects who met all enrolment criteria at Visit 1 and Visit 2 were randomised in a 2:1 ratio to double-blind treatment with ixekizumab or placebo at Week 0 (Visit 2).

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

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

Protocol Addendum (2)

Subjects from countries where etanercept is approved and who met all criteria for enrolment at Visit 1 and Visit 2 were randomised at Week 0 (Visit 2) in a 2:2:1 ratio to ixekizumab, etanercept, or placebo.

Additionally, subjects from EU countries who met response criteria (sPGA 0,1) were to enter the Double-Blind Randomised Withdrawal Period and were to be re-randomised to double-blind treatment in a 1:1 ratio to ixekizumab or placebo at Week 60. Subjects who were re-randomised to ixekizumab were to receive ixekizumab 20, 40, or 80 mg Q4W according to their weight at the time of re-randomisation. Subjects who relapsed (sPGA ≥2) during the Double-Blind Randomised Withdrawal Period were to receive open-label treatment with ixekizumab according to their weight at the time of relapse.

Blinding (masking)

This was a double-blind study implying that subjects and study site personnel were to be blinded to treatment assignments. The syringes (and contents) containing either ixekizumab or matching placebo were to be visibly indistinguishable from each other. To preserve the blinding, a minimum number of Lilly personnel was to see the randomisation table and treatment assignments before study completion.

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

Etanercept was administered open label during the Double-Blind Treatment Period (Period 2). Placebo was not given to match etanercept. Patients received placebo to match ixekizumab. To maintain statistical validity, a blinded assessor conducted the efficacy assessments in countries where etanercept was administered. Treatment assignments of the randomised withdrawal period (Period 4) will remain blinded until the study is complete.

The first interim analysis of PK, safety, and select efficacy data was performed under the auspices of a Data Monitoring Committee (DMC). The analysis was to be conducted by statisticians and PK/PD scientists external to the study team (statistical assessment centre) who were to provide the analyses to the DMC. This committee was to consist of 2 physicians external to Lilly, a paediatrician and a dermatologist, a statistician external to Lilly, and a nonvoting PK/PD member internal to Lilly, but external to the study team. No member of the DMC was to have contact with study sites. Only the DMC was authorized to evaluate unblinded interim efficacy and safety analyses. Study sites were to receive information about interim results only if necessary, for the safety of their subjects.

Statistical methods

The statistical analysis plan (SAP), which supersedes the statistical plans described in the protocol, was approved on 18 March 2019 prior to study unblinding and was revised on 26 June 2019. The SAP Version 3 was approved after primary database lock and prior to submission database lock. The reporting database was validated and subsequently locked for analysis on 28 June 2019.

The first interim analysis was performed on 31 May 2018 under the auspices of a Data Monitoring Committee (DMC) after approximately 15 patients in the 25- to 50-kg weight group completed Study Period 2 (Week 12). Pharmacokinetic, safety, and efficacy data on all subjects were to be evaluated during this interim; the analysis was to include all data available at this time, i.e. data from subjects in both weight groups who had enrolled at the time of the interim.

The second interim database lock, unblinding, and data analysis were performed at the time (that is, a cut-off date of 22 March 2019) the last patient completed Study Period 2 (Week 12) or the Early Termination Visit (ETV). This interim analysis included the final analysis for the Double-Blind Treatment Period (Period 2) of the study.

A third interim database lock (28 June 2019) and data analysis was performed after a minimum of 100 patients were treated with ixekizumab for at least 1 year. Data and analysis from this database lock form the basis of this CSR. This interim database includes all data collected by the data cut-off date, including follow-up date from patients who have begun the Post-Treatment Follow-Up Period. The study is ongoing.

Analysis populations

Intent-to-Treat (ITT) Population (per main study): all randomised subjects. Subjects were analysed according to the treatment to which they had been assigned.

Per-Protocol Set (per main study): all randomised subjects who did not have significant protocol violations. Subjects were analysed according to the treatment to which they had been assigned.

Intent-to-Treat (ITT) – Etanercept Approved Countries: all randomised subjects in etanercept-approved countries. Subjects where analysed according to the treatment to which they had been assigned.

Safety Population (per main study): all randomised subjects who took at least 1 dose of double-blind study treatment. Subjects were analysed according to the treatment to which they had been assigned.

Analysis of the co-primary endpoints

The co-primary endpoints were proportion of patients achieving PASI 75 and proportion of patients achieving sPGA (0,1). The primary analysis was based on the ITT Population for the Double-Blind Treatment Period (Period 2) comparing ixekizumab versus placebo at Week 12. The primary analysis was performed using a Fisher's exact test. Missing data was imputed using non-responder imputation (NRI). Secondary analyses of the primary efficacy endpoints were conducted using a logistic regression model including treatment group, region, baseline sPGA score (severity of the Ps), and baseline weight category (<25kg; ≥25 to ≤50 kg; or >50 kg) as factors. Missing data was imputed using NRI.

In support, analyses were performed based also on the PPS Population using the same analysis approach as in the primary analysis.

Analyses of the gated secondary endpoints

The gated secondary endpoints were analysed using the same approach as used for the co-primary endpoints (i.e. ITT, Fisher's exact test, NRI).

Adjustment for Multiple Comparisons

A multiple testing strategy for the co-primary and major secondary endpoints was implemented to control the family-wise Type I error rate at a 2-sided α level of 0.05.

A gatekeeping approach was used; to assess whether ixekizumab Q4W was superior to placebo, the following endpoints were to be tested in the following order:

Primary 1: Proportion of subjects achieving PASI 75 at Week 12

Primary 2: Proportion of subjects achieving sPGA (0,1) at Week 12

Secondary 1: Proportion of subjects achieving PASI 90 at Week 12

Secondary 2: Proportion of subjects achieving sPGA (0) at Week 12

Secondary 3: Proportion of subjects achieving PASI 100 at Week 12

Secondary 4: Proportion of subjects achieving ≥4-point improvement for subjects who had a baseline Itch numeric rating scale (NRS) ≥4 at Week 12

Secondary 5: Proportion of subjects achieving PASI 75 at Week 4

Secondary 6: Proportion of subjects achieving sPGA (0,1) at Week 4

Testing was to continue as long as all prior tests had been successful. If not, testing was to stop.

There was no adjustment for multiple comparisons for other secondary analyses.

Protocol Addendum I1F-MC-RHCD(2)

The other secondary efficacy endpoints that were analysed to compare ixekizumab Q4W and etanercept during treatment period 2 (up to week 12) included: PASI 50, PASI 75, PASI 90 and PASI 100 and, sPGA (0,1) and sPGA (0). The analyses were based on the ITT – Etanercept Approved Countries population and was performed using the same approach as used for the main study analyses.

Other secondary analyses

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

Subgroup analyses

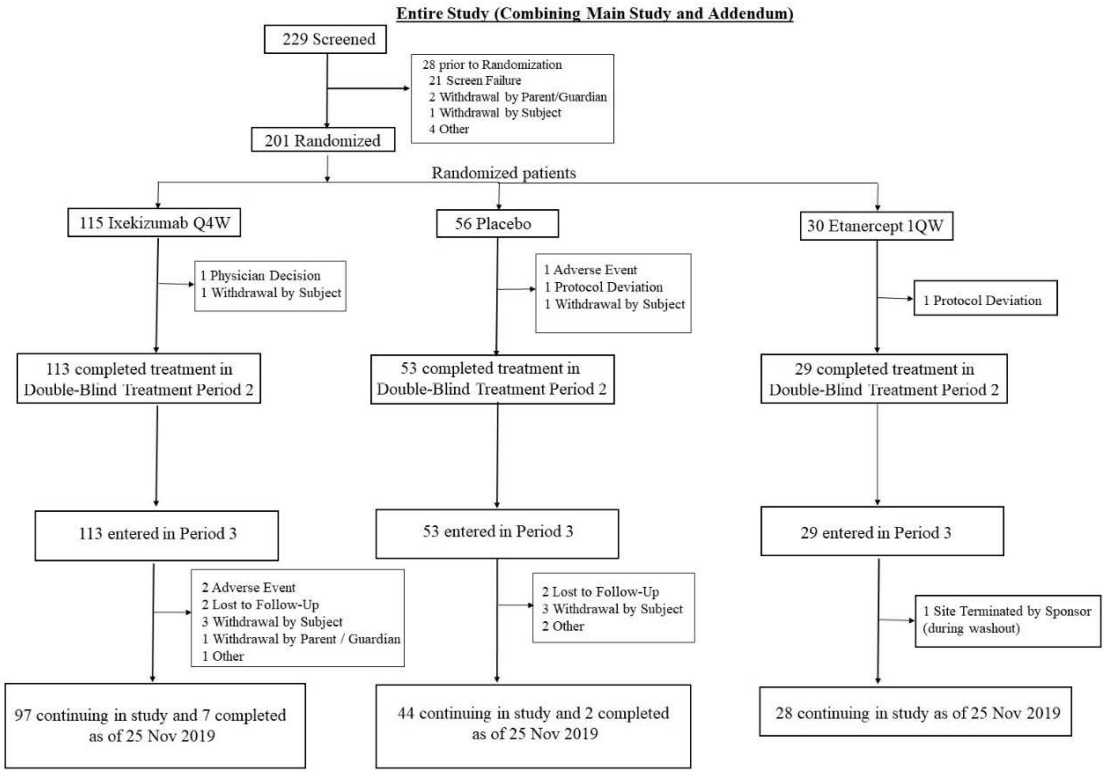
Efficacy subgroup analyses were conducted for the co-primary endpoints. A logistic regression model with treatment, subgroup, and interaction of subgroup-by-treatment included as factors was used. The subgroup-by-treatment interaction was tested at the significance level of 0.10.

Results

Participant flow

The patient disposition for the total study is provided in **Figure 22**.

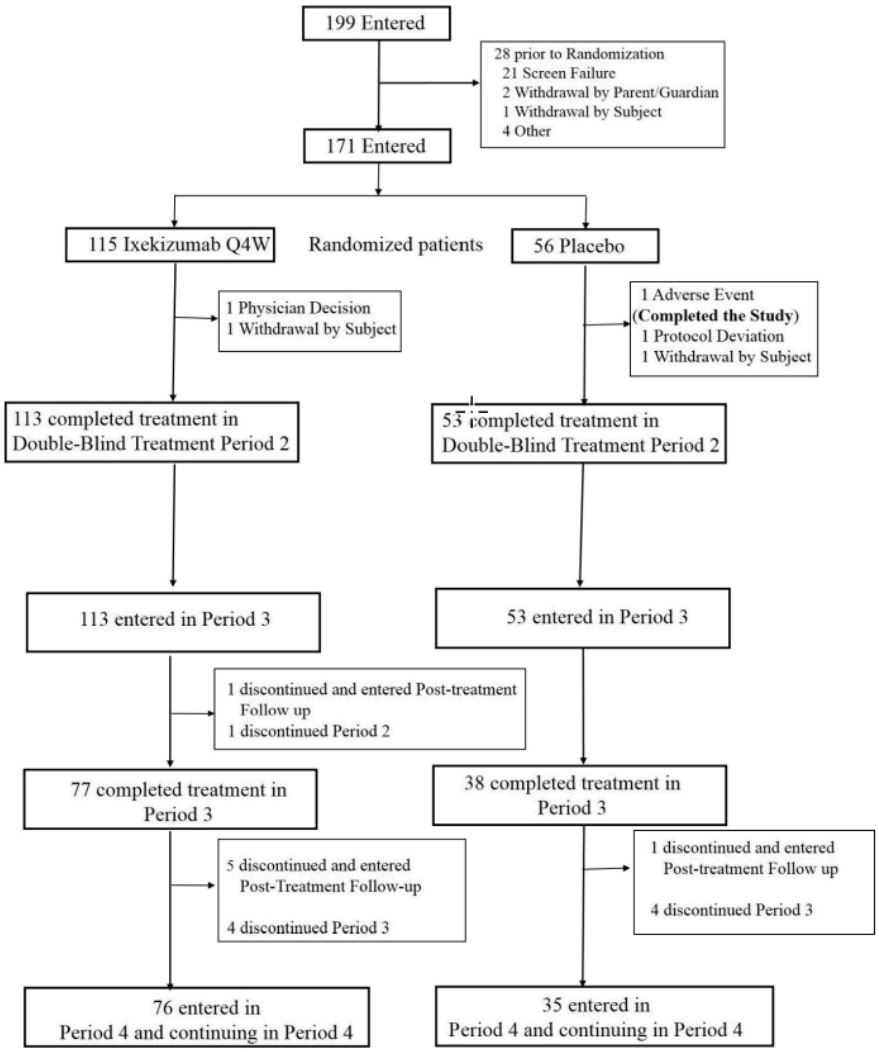
Figure 22 Patient disposition for total study.



Abbreviations: Q1W = once weekly; Q4W = every 4 weeks.

The patient disposition for the **Main Group** is shown in **Figure 23**.

Figure 23 Patient Disposition in the Double-Blind Treatment Period (Main Group)



Note: During Period 3, patients randomized to placebo during Period 2 received ixekizumab at doses of 20, 40, or 80 mg based on weight. Patients not described in the figure to be discontinued are still ongoing in the respective phase.

Prior to randomization, 28 patients (14.1% of the total screened patients) discontinued from the study; 21 of these were Screen Failures.

A total of 5 patients (2.9% of the randomized patients) discontinued study drug during the Double-Blind Treatment Period; 2 patients (1.7%), ixekizumab and 3 patients (5.4%), placebo.

Of the 171 patients randomized to either ixekizumab Q4W (N=115) or placebo (N=56), 16 patients (9.4% of the ITT population) discontinued the study, 154 patients (90.1%) are still ongoing, and 1 patient completed the study.

In the **Protocol Addendum (2) Group**, the Double-Blind Treatment Period was completed by:

- 17 of 19 (89.5%) patients in the placebo group,
- 29 of 30 (96.7%) patients in the etanercept group, and
- 37 of 38 (97.4%) patients in the ixekizumab group.

Reasons for discontinuation included AE, protocol deviation, physician decision, and withdrawal by patient.

Recruitment

The date of the first patient enrolled (assigned to therapy) was 17 April 2017. The date of Database lock was 28 June 2019.

Conduct of the study

Protocol amendments

There were 2 protocol amendments:

The first (a), approved on 20 July 2017, with the major changes being TB testing criteria for purified protein derivative (PPD) evaluation specified, changes to secondary endpoints, changed endpoint involving CDLQI/DLQI and addition of blood pressure criteria.

The second amendment (b), approved on 22 September 2018, included changes concerning an additional interim analysis, updated exclusion criteria, and other revisions to enhance clarity of the protocol.

Interim analyses

Three planned interim analyses were conducted.

A staggered approach to enrollment by weight group was used so that a minimum of 15 patients >12 years and >50 kg were enrolled and safety evaluated for the initial 12 weeks of dosing before opening enrollment in the middle weight group (25 to 50 kg). When approximately 15 patients were enrolled in the middle weight group and completed up to Week 12, an analysis of all available PK data was conducted to confirm that exposures were within the range expected. All safety data from these patients were also analysed at this time in addition to select efficacy data. This interim database lock included all available data collected at the time of database lock. The DMC recommendation was to continue as planned per protocol, all weight groups were open for enrollment of the remaining patients needed to complete the study.

The second interim database lock, unblinding, and data analysis were performed at the time (that is, a cut-off date of 22 March 2019) the last patient completed Study Period 2 (Week 12) or ETV. This interim database lock included all available data collected at the time of database lock. Because the study was still ongoing at the time of this database lock, the analysis is referred to as an interim analysis. This interim analysis included the final analysis for the Double-Blind Treatment Period (Period 2) of the study; therefore, there was no alpha adjustment due to this interim analysis. The DMC was not needed for this interim analysis.

A third interim database lock (28 June 2019) and data analysis was performed after a minimum of 100 patients were treated with ixekizumab for at least 1 year. Data and analysis from this database lock form the basis of the CSR submitted for this application. This interim database includes all data collected by the data cut-off date, including follow-up date from patients who have begun the Post-Treatment Follow-Up Period. The study is ongoing.

Additional analyses and snapshots of study data may be performed as described in the SAP.

A final database lock will occur after the Post-Treatment Follow-Up Period is completed.

Protocol deviations

Overall, 63 patients (36.8%) had at least 1 important protocol deviation. The following protocol deviations categories had more than 20% of patients with protocol deviations:

Study Procedures: 44 of the 171 ITT patients (25.7%), including 35 patients in ixekizumab Q4W group (30.4%) and 9 patients in Placebo group (16.1%) were reported with protocol deviations in the category of Study Procedures.

Other: 43 of the 171 ITT patients (25.1%), including 34 patients in the ixekizumab Q4W group (29.6%) and 9 patients in the Placebo group (16.1%), were reported with protocol deviations in the "other" category. This included 23 patients with missing CDRS-R total score and 16 patients, who were clinically assessed by unqualified site personnel.

A subset of the important protocol deviations that might have an impact on the co-primary objectives was identified. Only those patients who deviated from these criteria were excluded from the PPS analyses. In total, 21 of the 171 ITT patients (12.3%) were excluded from the PPS (14 patients in ixekizumab Q4W group [12.2%] and 7 patients in placebo group (12.5%).

Table 21 summarizes the patients with a reported misdose (18 patients), including overdose (16 patients) or underdose (2 patients), at various visits and treatment periods. There was 1 patient ([redacted]) who was misdosed at Week 0 (who received 40 mg instead of 80 mg), but who was not included in the listing of patients with important protocol deviations.

Table 21 Patients with Reported Overdose or Underdose

Treatment group	Patient number	Phase/Period	Protocol Deviation
PBO	[redacted]	Double-Blind	Overdose of IMP at Weeks 4 and 8 (received 1 mL in place of 0.5 mL)
IXEQ4W		Maintenance	Overdose of IMP at Week 12 (received 2 mL in place of 1 mL)
		Maintenance	Overdose of IMP at Weeks 16, 20, 24, 36, 40, and 44 (received 1 mL in place of 0.5 mL)
PBO/ IXEQ4W	[redacted]	Maintenance	Overdose of IMP at Weeks 16 and 24 (received 1 mL in place of 0.5 mL)
PBO	[redacted]	Double-Blind	Overdose of IMP at Week 4 (received 1 mL in place of 0.5 mL)
PBO	[redacted]	Double-Blind	Overdose of IMP at Weeks 4 and 8 (received 1 mL in place of 0.5 mL)
IXEQ4W		Maintenance	Overdose of IMP at Weeks 12, 16, 20, 24, 28, 32, 36, and 40 (received 1 mL in place of 0.5 mL)
PBO	[redacted]	Double-Blind	Overdose of IMP at Weeks 4 and 8 (received 1 mL in place of 0.5 mL)
IXEQ4W		Maintenance	Overdose of IMP at Weeks 12, 16, 20, 28,32, 36, 40, 44, and 48 (received 1 mL in place of 0.5 mL)
IXEQ4W	[redacted]	Double-Blind	Overdose of IMP at Week 4 (received 1 mL in place of 0.5 mL)
		Maintenance	Overdose of IMP at Week 12 (received 2 mL in place of 1 mL)
		Maintenance	Overdose of IMP at Weeks 16, 20, 24, 28, 32, 36, 40, and 44 (received 1 mL in place of 0.5 mL)
IXEQ4W	[redacted]	Maintenance	Underdose of IMP at Week 20; PI entered wrong dose on prescription (received 0.5 mL in place of 1 mL)
IXEQ4W	[redacted]	Maintenance	Overdose of IMP at Week 32 (received 1 mL in place of 0.5 mL)
IXEQ4W	[redacted]	Maintenance	Overdose of IMP at Week 12 (received 1 mL in place of 0.5 mL)

Treatment group	Patient number	Phase/Period	Protocol Deviation
IXEQ4W	[redacted]	Double-Blind	Overdose of IMP at Weeks 4 and 8 (received 1 mL in place of 0.5 mL)
IXEQ4W	[redacted]	Maintenance	Overdose of IMP at Week 12 (received 1 mL in place of 0.5 mL); dose was not adjusted to patient weight correctly
IXEQ4W	[redacted]	Double-Blind	Overdose of IMP at Week 4 (received 1 mL in place of 0.25 mL)
IXEQ4W	[redacted]	Maintenance	Underdose of IMP at Week 20 (received 0.5 mL in place of 1 mL
IXEQ4W	[redacted]	Double-Blind	Overdose of IMP at Weeks 4 and 8 (received 1 mL in place of 0.5 mL)
		Maintenance	Overdose of IMP at Weeks 12, 16, 20, 24, 28, 32, and 36 (received 1 mL in place of 0.5 mL)
IXEQ4W	[redacted]	Double-Blind	Overdose of IMP at Week 4 (received 1 mL in place of 0.5 mL)
IXEQ4W	[redacted]	Double-Blind	Overdose of IMP at Weeks 4 and 8 (received 1 mL in place of 0.5 mL)
		Maintenance	Overdose of IMP at Weeks 12, 16, 20, 24, 28, and 32 (received 1 mL in place of 0.5 mL)
IXEQ4W	[redacted]	Maintenance	Overdose of IMP at Weeks 12, 16, 20, 44, 48, and 52 (received 1 mL in place of 0.5 mL)
IXEQ4W	[redacted]	Maintenance	Overdose of IMP at Week 40 (received 2 mL in place of 1.6 mL)

Abbreviations: IMP = investigational medicinal product; IXE = ixekizumab; PBO = placebo; PI = principal investigator.
Notes: 1 mL = 80 mg ixekizumab ; 0.5 mL = 40 mg ixekizumab ; 0.25 mL = 25 mg ixekizumab.

Subsequent to database lock, discrepancies in the reporting database were discovered. These errors remain in the reporting database that was used for all analyses in the CSR. Specifically,

- One patient (Patient [redacted]) who was misdosed at Week 0 (who received 40 mg instead of 80 mg) was not included in the listing of patients with important protocol deviations as provided in the Important Protocol Deviations appendix listing.
- One patient (Patient [redacted]) who was misdosed with ixekizumab at multiple visits during Period 2 and Period 3 was documented as an important protocol deviation of misdoses with etanercept.
- One patient (Patient [redacted]) who was misdosed with ixekizumab at Visit 14 was documented as an important protocol deviation of misdose with etanercept.
- Two patients (Patient [redacted] and Patient [redacted]) were not included in the per-protocol set (PPS) analyses for the co-primary endpoints due to the misdose protocol deviations at Week 12 (Visit 7), which should have been mapped to the maintenance period. These 2 patients received ixekizumab during the Double-Blind Treatment Period and both achieved PASI 75 and sPGA (0,1) at Week 12. Excluding these 2 patients from the PPS was not in favor of ixekizumab and did not affect the conclusions of the PPS analyses.
- In the C-SSRS data that have been listed by patient and visit in the appendix listing, there is an apparent error in the responses from 2 patients of "Yes" for "completed suicide." There were no completed suicides during this study.
- One patient (Patient [redacted]) had Palmoplantar Psoriasis Severity Index (PPASI) scores out of range at Visit 6 and Visit 7.

Compliance

Site personnel recorded information in the Study Drug Administration Logs, including the date, time, and anatomical location of administration of study drug; syringe number; who prepared and administered the study drug; and the reason if study drug was not fully administered. Patient compliance with the study drug was assessed at each visit. Compliance was assessed by the number of injections needed versus the number of injections administered to the patients. Deviation(s) from the prescribed dosage regimen were recorded in the CRF. A patient was considered overall compliant with study treatment within each treatment period if he or she misses no more than 20% of the expected doses, does not miss 2 consecutive doses, and does not overdose (that is, take more injections at the same time point than specified in the protocol). Overall compliance in the Safety Population during the Double-Blind Treatment Period was 98.8%, with no significant differences between treatment groups.

Baseline data

Baseline demographics between treatment groups are provided in **Table 22**.

Table 22 Patient Demographics and Other Baseline Characteristics Intent to Treat Population

	Main Group		Protocol Addendum (2) Group[a]		
	Placebo (N = 56)	Ixekizumab Q4W (N = 115)	Placebo (N = 19)	Etanercept (N = 30)	Ixekizumab Q4W (N = 38)
Age (years), mean (SD)	13.1 (2.79)	13.7 (3.14)	12.6 (2.24)	13.7 (2.95)	13.2 (3.27)
Less than 12 years	16 (28.6)	27 (23.5)	5 (26.3)	6 (20.0)	10 (26.3)
12 years or over	40 (71.4)	88 (76.5)	14 (73.7)	24 (80.0)	28 (73.7)
Male, n (%)	20 (35.7)	52 (45.2)	9 (47.4)	12 (40.0)	20 (52.6)
Female, n (%)	36 (64.3)	63 (54.8)	10 (52.6)	18 (60.0)	18 (47.4)
American Indian or Alaska Native, n (%)	0	2 (1.8)	0	1 (3.4)	1 (2.7)
Asian, n (%)	2 (3.8)	4 (3.5)	1 (5.6)	0	0
Black or African American, n (%)	3 (5.7)	3 (2.6)	0	0	0
Native Hawaiian or other Pacific Islander, n (%)	0	0	0	0	0
White, n (%)	45 (84.9)	95 (83.3)	16 (88.9)	25 (86.2)	33 (89.2)
Multiple, n (%)	3 (5.7)	10 (8.8)	1 (5.6)	3 (10.3)	3 (8.1)
Weight, mean (SD)	60.3 (20.33)	63.9 (24.94)	59.4 (20.89)	58.4 (19.74)	62.0 (24.47)
Less than 25 kg, n (%)	1 (1.8)	2 (1.7)	1 (5.3)	1 (3.3)	1 (2.6)
25 to 50 kg, n (%)	14 (25.0)	29 (25.2)	4 (21.1)	7 (23.3)	10 (26.3)
More than 50 kg, n (%)	41 (73.2)	84 (73.0)	14 (73.7)	22 (73.3)	27 (71.1)
BMI, mean (SD)	23.5 (5.57)	24.1 (6.77)	23.1 (5.94)	22.5 (5.00)	23.8 (5.96)
US or Canada, n (%)	26 (46.4)	53 (46.1)	0	0	0
European Union[a], n (%)	22 (39.3)	44 (38.3)	13 (68.4)	21 (70.0)	26 (68.4)
Rest of the world, n (%)	8 (14.3)	18 (15.7)	6 (31.6)	9 (30.0)	12 (31.6)
Baseline PASI less than 20, n (%)	36 (64.3)	71 (61.7)	3 (15.8)	9 (30.0)	5 (13.2)
Baseline PASI 20 or more, n (%)	20 (35.7)	44 (38.3)	16 (84.2)	21 (70.0)	33 (86.8)
Baseline sPGA score of 3, n (%)	31 (55.4)	57 (49.6)	5 (26.3)		6 (15.8)

Baseline sPGA score of 4 or 5, n (%)	25 (44.6)	58 (50.4)	14 (73.7)	30 (100.0)	32 (84.2)

Abbreviations: BMI = body-mass index; N = number of patients in the analysis population; n = number of patients in the specified category; PASI = Psoriasis Area and Severity Index; Q4W = every 4 weeks; sPGA = static Physician's Global Assessment.

a Includes placebo, etanercept, and ixekizumab patients with severe disease in countries where etanercept is used as a reference arm. Countries included in this group are: Czech Republic, France, Germany, Hungary, Netherlands, Poland, and Spain from the European Union; and Argentina, Mexico, and Russia.

Numbers analysed

Main study group

A total of 171 randomised patients were included in the primary efficacy analysis based on the ITT Population.

Table 23 Study Analysis Population All Entered Patients (per Main Study) I1F-MC-RHCD1

Period Population and Status	PBO n (%)	IXEQ4W n (%)	Total n (%)
Period 1 - Screening			
All entered patients			199
Discontinued prior to randomization			28
Screen Failure			21
Withdrawal by Parent/Guardian			2
Withdrawal by Subject			1
Other			4
Period 2 - Double-Blind Treatment Period			
Randomized patients	56	115	171
Intent to Treat (ITT)	56	115	171
Completed Period 2 treatment (% relative to ITT)	53 (94.6%)	113 (98.3%)	166 (97.1%)
Completed Period 2 treatment and entered Post-Treatment Follow-Up Period directly (% relative to ITT)	0	0	0
Completed Period 2 treatment and entered Period 3 (% relative to ITT)	53 (94.6%)	113 (98.3%)	166 (97.1%)
Discontinued from Period 2 treatment and entered Post-Treatment Follow-Up Period (% relative to ITT)	1 (1.8%)	1 (0.9%)	2 (1.2%)
Discontinued from Period 2 treatment but did not enter Post-Treatment Follow-Up Period (% relative to ITT)	2 (3.6%)	1 (0.9%)	3 (1.8%)
Per Protocol Set (PPS) (% relative to ITT)	49 (87.5%)	101 (87.8%)	150 (87.7%)
Completed Period 2 treatment (% relative to PPS)	47 (95.9%)	100 (99.0%)	147 (98.0%)
Safety (% relative to ITT)	56 (100.0%)	115 (100.0%)	171 (100.0%)
Completed Period 2 treatment (% relative to Safety)	53 (94.6%)	113 (98.3%)	166 (97.1%)

Notes: IXEQ4W = Ixekizumab Q4W; n = number of patients in the specified category; PBO = Placebo.

Protocol Addendum I1F-MC-RHCD(2)

A total of 87 patients were randomised at Week 0; 38 patients to ixekizumab Q4W, 30 patients to etanercept Q1W, and 19 patients to placebo.

Table 24 Study Analysis Population All Entered Patients – Etanercept Approved Countries (per Protocol Addendum 2) I1F-MC-RHCD- Addendum (2)

Period Population and Status	PBO n (%)	ETN n (%)	IXEQ4W n (%)	Total n (%)
Period 1 - Screening				
All entered patients				87
Discontinued prior to randomization				0
Period 2 - Double-Blind Treatment Period				
Randomized patients	19	30	38	87
Intent to Treat (ITT)	19	30	38	87
Completed Period 2 treatment (% relative to ITT)	17 (89.5%)	29 (96.7%)	37 (97.4%)	83 (95.4%)
Completed Period 2 treatment and entered Post-Treatment Follow-Up Period directly (% relative to ITT)	0	0	0	0
Completed Period 2 treatment and entered Period 3 (% relative to ITT)	17 (89.5%)	29 (96.7%)	37 (97.4%)	83 (95.4%)
Discontinued from Period 2 treatment and entered Post-Treatment Follow-Up Period (% relative to ITT)	1 (5.3%)	1 (3.3%)	1 (2.6%)	3 (3.4%)
Discontinued from Period 2 treatment but did not enter Post-Treatment Follow-Up Period (% relative to ITT)	1 (5.3%)	0	0	1 (1.1%)
Per Protocol Set (PPS) (% relative to ITT)	15 (78.9%)	25 (83.3%)	34 (89.5%)	74 (85.1%)
Completed Period 2 treatment (% relative to PPS)	13 (86.7%)	25 (100.0%)	34 (100.0%)	72 (97.3%)
Safety (% relative to ITT)	19 (100.0%)	30 (100.0%)	38 (100.0%)	87 (100.0%)
Completed Period 2 treatment (% relative to Safety)	17 (89.5%)	29 (96.7%)	37 (97.4%)	83 (95.4%)

Notes: ETN = Etanercept; IXEQ4W = Ixekizumab Q4W; n = number of patients in the specified category; PBO = Placebo.

Outcomes and estimation

Efficacy and health outcome analyses for the Double-Blind Treatment Period (Week 0 to Week 12) were based on data from all patients who completed the Week 12 Visit or discontinued study drug early, either on or prior to Week 12. The primary and gated secondary efficacy analyses were performed and are presented separately for all placebo and ixekizumab patients (i.e. the main study group) and placebo, etanercept, and ixekizumab patients with severe disease in countries where etanercept was used as a reference arm (i.e. the protocol addendum [2] group).

Co-primary outcomes

Based on the *main study group* the study achieved both co-primary objectives.

The ixekizumab treatment group showed a statistically significant higher PASI 75 response compared to placebo at Week 12 (NRI):

- 88.7%, ixekizumab Q4W (p<.001 vs placebo) and
- 25.0%, placebo.

The ixekizumab treatment group also had a statistically significant higher sPGA (0,1) response compared to placebo at Week 12 (NRI):

- 80.9%, ixekizumab Q4W (p<.001 vs placebo) and
- 10.7%, placebo.

For the *protocol addendum [2] group*, a greater percentage of patients achieved PASI 75 at Week 12 (NRI) in the ixekizumab Q4W group compared to the etanercept Q1W group; however, it was not statistically significant.

The PASI 75 response rates at Week 12 (NRI) were:

- 84.2%, ixekizumab Q4W (p=0.089 vs. etanercept; p<0.001 vs. placebo)

- 63.3%, etanercept Q1W (p <0.019 vs. placebo)
- 26.3%, placebo

A greater percentage of patients achieved sPGA (0,1) at Week 12 (NRI) in the ixekizumab Q4W group compared to the etanercept Q1W group; however, it was not statistically significant.

The sPGA (0,1) response rates at Week 12 (NRI) were:

- 76.3%, ixekizumab Q4W (p=0.070 vs. etanercept; p<0.001 vs. placebo);
- 53.3%, etanercept Q1W (p<0.001 vs. placebo)
- 5.3%, placebo

Table 25 PASI 75 and sPGA (0,1) Response Rates at Week 12 (NRI) Intent-to-Treat Population of Main Group and Protocol Addendum (2) Group

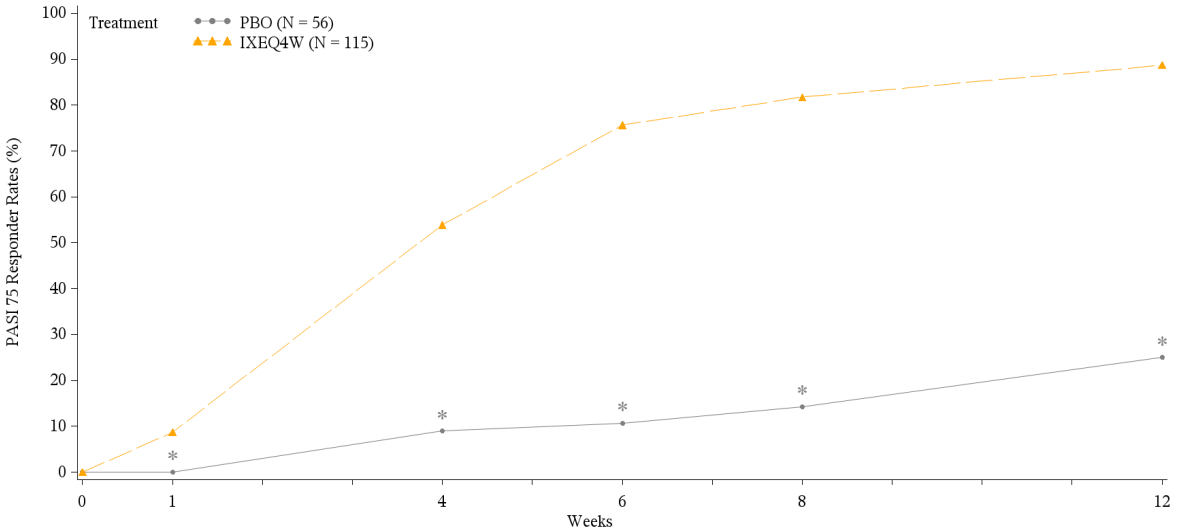
	Main Group		Protocol Addendum (2) Group		
	Placebo (N = 56)	Ixekizumab Q4W (N = 115)	Placebo (N = 19)	Etanercept (N = 30)	Ixekizumab Q4W (N = 38)
PASI 75					
PASI 75 response at Week 12, n (%)	14 (25.0)	102 (88.7)	5 (26.3)	19 (63.3)	32 (84.2)
Difference vs. placebo (95% CI)		63.7 (51.0, 76.4)		37.0 (10.8, 63.3)	57.9 (35.0, 80.8)
p-value		<.001		.019	<.001
Difference vs. etanercept (95% CI)					20.9 (0.1, 41.7)
p-value					.089
sPGA (0,1)					
sPGA (0,1) response at Week 12, n (%)	6 (10.7)	93 (80.9)	1 (5.3)	16 (53.3)	29 (76.3)
Difference vs. placebo (95% CI)		70.2 (59.3, 81.0)		48.1 (27.6, 68.6)	71.1 (54.2, 87.9)
p-value		<.001		<.001	<.001
Difference vs. etanercept (95% CI)					23.0 (0.6, 45.4)
p-value					.070

Abbreviations: CI = confidence interval; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = non-responder imputation; PASI 75 = 75% improvement from baseline in Psoriasis Area and Severity Index; Q4W = every 4 weeks; sPGA (0,1) = a score of 0 or 1 on the static Physician's Global Assessment; vs. = versus.

For both PASI 75 and sPGA (0,1), the results for the PPS were consistent with the results of the primary analysis with the ITT Population.

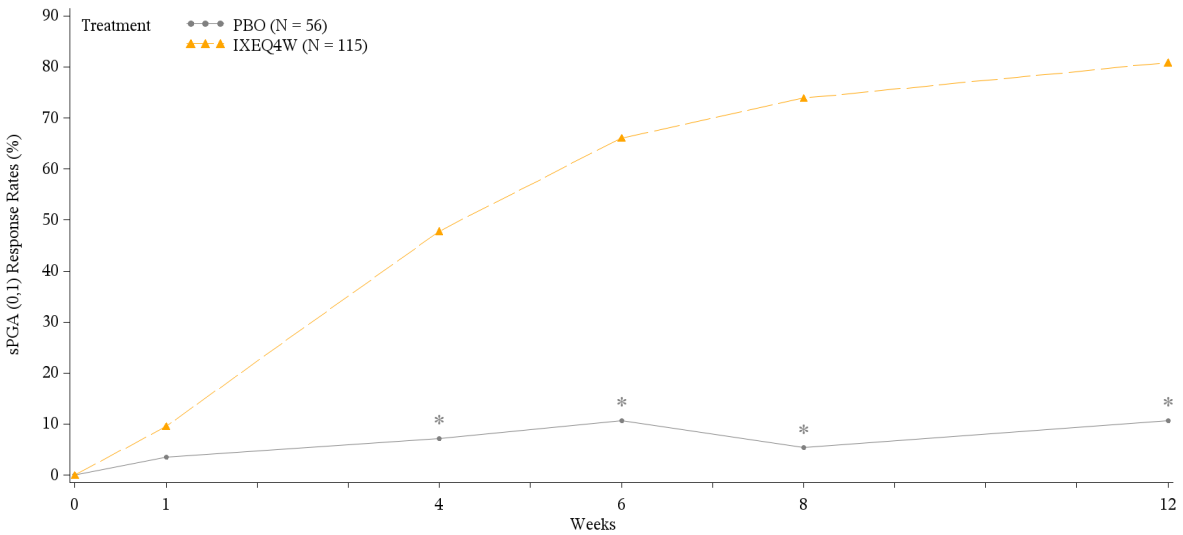
The PASI 75 and sPGA (0,1) results over time are depicted below.

Figure 24 PASI 75 response rates at each postbaseline visit (NRI), ITT Population of Main Group



Abbreviations: IXEQ4W = ixekizumab every 4 weeks; N = number of patients in the analysis population; NRI = nonresponder imputation; PASI 75 = 75% improvement from baseline in Psoriasis Area and Severity Index;PBO = placebo.
* = p<.05 versus IXEQ4W.

Figure 25 sPGA (0,1) response rates at each postbaseline visit (NRI), ITT Population, Main Group



Abbreviations: IXEQ4W = ixekizumab every 4 weeks; N = number of patients in the analysis population; NRI = nonresponder imputation; sPGA (0,1) = a score of 0 or 1 on the static Physician's Global Assessment; PBO = placebo.
* = p<.05 versus IXEQ4W.

Gated secondary outcomes

Study RHCD achieved all its of gated secondary objectives (**Table 26**).

Table 26 PASI 90, sPGA (0), PASI 100, Itch NRS ≥4-Point Improvement Response Rates at Week 12 (NRI) PASI 75 and sPGA (0,1) Response Rates at Week 4 (NRI) Intent-to-Treat Population of Main Group and Protocol Addendum (2) Group

	Main Group		Protocol Addendum (2) Group		
	Placebo (N = 56)	Ixekizumab Q4W (N = 115)	Placebo (N = 19)	Etanercept (N = 30)	Ixekizumab Q4W (N = 38)
PASI 90					
PASI 90 response at Week 12, n (%)	3 (5.4)	90 (78.3)	0	12 (40.0)	29 (76.3)
Difference vs. placebo (95% CI)		72.9 (63.3, 82.5)		40.0 (22.5, 57.5)	76.3 (62.8, 89.8)
p-value		<.001		.001	<.001
Difference vs. etanercept (95% CI)					36.3 (14.2, 58.5)
p-value					.003
sPGA (0)					
sPGA (0) response at Week 12, n (%)	1 (1.8)	60 (52.2)	0	5 (16.7)	24 (63.2)
Difference vs. placebo (95% CI)		50.4 (40.6, 60.2)		16.7 (3.3, 30.0)	63.2 (47.8, 78.5)
p-value		<.001		.142	<.001
Difference vs. etanercept (95% CI)					46.5 (26.2, 66.8)
p-value					<.001
PASI 100					
PASI 100 response at Week 12, n (%)	1 (1.8)	57 (49.6)	0	5 (16.7)	23 (60.5)
Difference vs. placebo (95% CI)		47.8 (38.0, 57.6)		16.7 (3.3, 30.0)	60.5 (45.0, 76.1)
p-value		<.001		.142	<.001
Difference vs. etanercept (95% CI)					43.9 (23.4, 64.3)
p-value					<.001
Itch NRS ≥4-point improvement[a]	N = 40	N = 83			
Itch NRS >4 response at Week 12, n (%)	8 (20.0)	59 (71.1)	Not evaluated		
Difference vs. placebo (95% CI)		51.1 (35.3, 66.9)			
p-value		<.001			
Difference vs. etanercept (95% CI)					
p-value					
PASI 75					
PASI 75 response at Week 4, n (%)	5 (8.9)	62 (53.9)	0	3 (10.0)	17 (44.7)
Difference vs. placebo (95% CI)		45.0 (33.2, 56.8)		10.0 (-0.7, 20.7)	44.7 (28.9, 60.5)
p-value		<.001		.273	<.001
Difference vs. etanercept (95% CI)					34.7 (15.6, 53.8)
p-value					.003
sPGA (0,1)					
sPGA (0,1) response at Week 4, n (%)	4 (7.1)	55 (47.8)	0	0	14 (36.8)
Difference vs. placebo (95% CI)		40.7 (29.3, 52.0)			36.8 (21.5, 52.2)
p-value		<.001			.002
Difference vs. etanercept (95% CI)					36.8 (21.5, 52.2)

	Main Group		Protocol Addendum (2) Group		
	Placebo (N = 56)	Ixekizumab Q4W (N = 115)	Placebo (N = 19)	Etanercept (N = 30)	Ixekizumab Q4W (N = 38)
p-value					<.001

Abbreviations: CI = confidence interval; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = nonresponder imputation; NRS = numeric rating scale; PASI 75 = 75% improvement from baseline in psoriasis area and severity index; PASI 90 = 90% improvement from baseline in Psoriasis Area and Severity Index; PASI 100 = 100% improvement from baseline in Psoriasis Area and Severity Index; Q4W = every 4 weeks; sPGA (0,1) = a score of 0 or 1 on the static Physician's Global Assessment; sPGA (0) = a score of 0 on the static Physician's Global Assessment; vs. = versus.

[a] Evaluated in patients with baseline Itch NRS score of at least 4 (40 patients in the placebo group; 83 patients in the ixekizumab Q4W group).

Additional efficacy outcomes

Nail and scalp change from baseline results

In patients with baseline nail or scalp Ps, respectively, there were significantly greater improvements from baseline to Week 12 for ixekizumab Q4W compared with placebo in Nail Psoriasis Severity Index (NAPSI) and Psoriasis Scalp Severity Index (PSSI). The NAPSI and PSSI mean change from baseline (least squares mean [LSM] and standard error [SE]) at Week 12 for placebo and ixekizumab were:

- **NAPSI:** 0.17 (5.331) versus -16.87 (3.110), p=.005
- **PSSI:** -12.28 (2.572) versus -27.64 (2.320), p<.001

Nail, scalp, and palmoplantar responses

In patients with baseline nail psoriasis, patients in the ixekizumab group had numerically but not statistically significant greater NAPSI = 0 responses versus placebo at Week 12 (NRI).

In patients with baseline scalp psoriasis, patients in the ixekizumab treatment group had statistically significant higher PSSI = 0 responses versus placebo at Week 12 (NRI). Among patients in the Protocol Addendum (2) Group, patients in both the etanercept treatment group and the ixekizumab treatment group had statistically significant higher PSSI = 0 responses versus placebo at Week 12 (NRI).

In patients with baseline palmoplantar psoriasis, patients in the ixekizumab treatment group had statistically significant higher by at least 50% from baseline improvement rate in Palmoplantar Psoriasis Severity Index (PPASI 50) responses versus placebo at Week 12 (NRI).

Itch NRS results

Patients in the ixekizumab treatment group had statistically significant higher Itch NRS score ≥4-point improvement from baseline responses from Week 1. Similarly, there were significantly greater improvements from baseline to Week 12 for ixekizumab Q4W compared with placebo in Itch NRS score.

Dermatology Quality of Life Index results

Patients in the ixekizumab treatment group had statistically significant CDLQI/DLQI (0,1) responses at Week 12 (NRI). The difference between treatment groups was apparent from Week 4.

Patient Global Assessment of disease severity

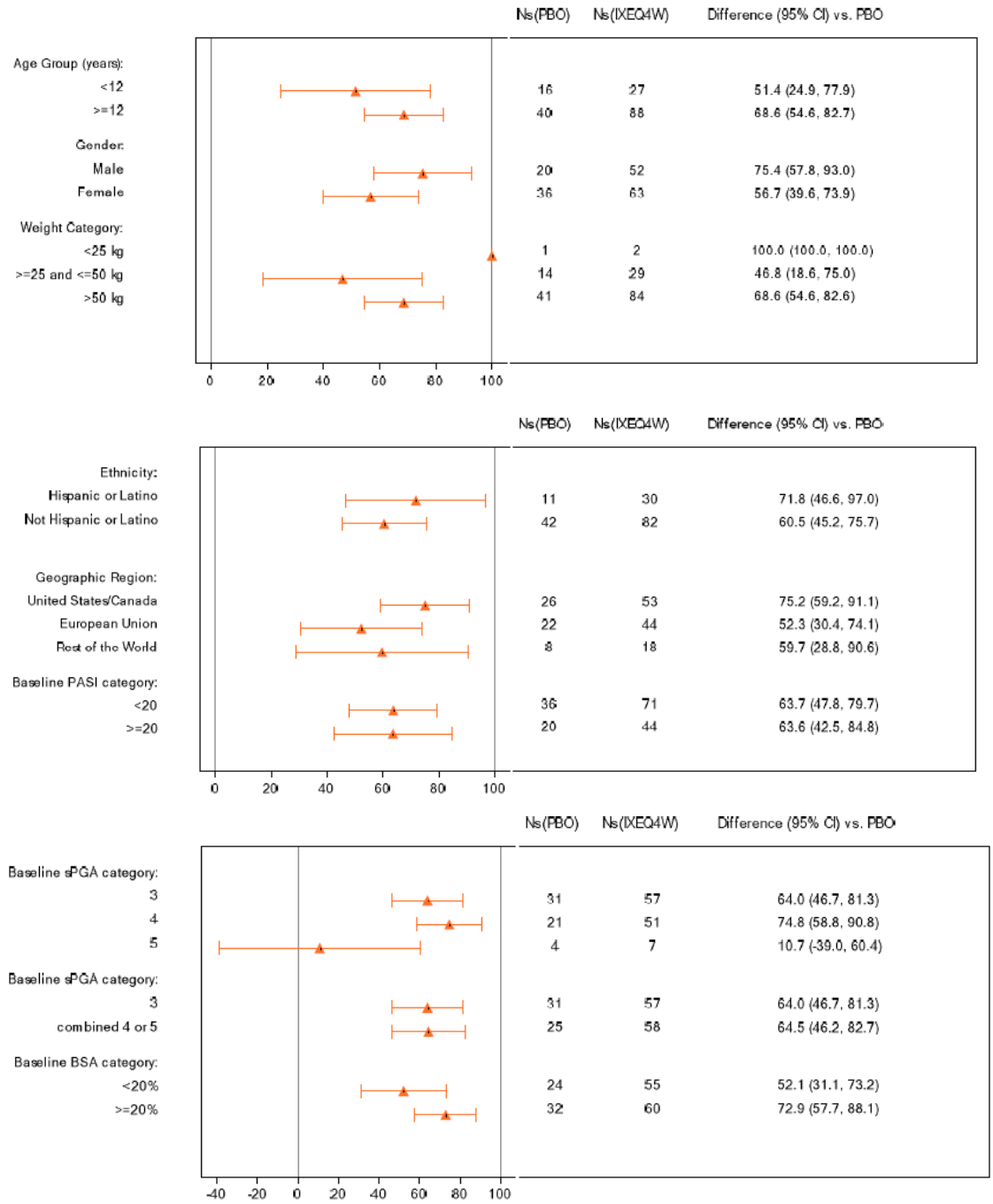
Patients in the ixekizumab treatment group had statistically significant higher Patient's Global Assessment of disease severity 0 or 1 (PatGA 0,1) responses at Week 12 (NRI). The difference between treatment groups was apparent from Week 1.

Ancillary analyses

Subgroup analyses

Sub-group analyses for age, weight, gender, ethnicity, region, baseline disease severity and previous treatments were performed within the pivotal study.

Figure 26 Forest plot of PASI 75 response rates at Week 12 (NRI) by subgroups ITT population (per main study) I1F-MC-RHCD - Double-Blind Treatment Period.



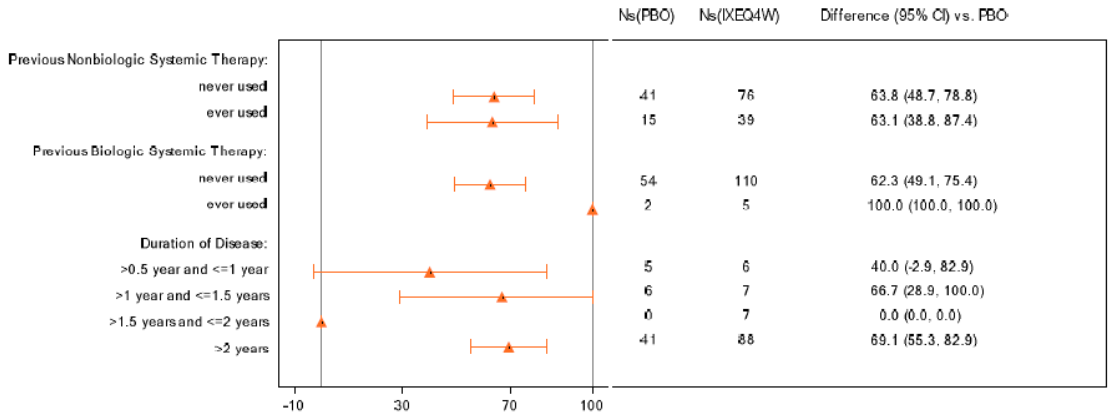
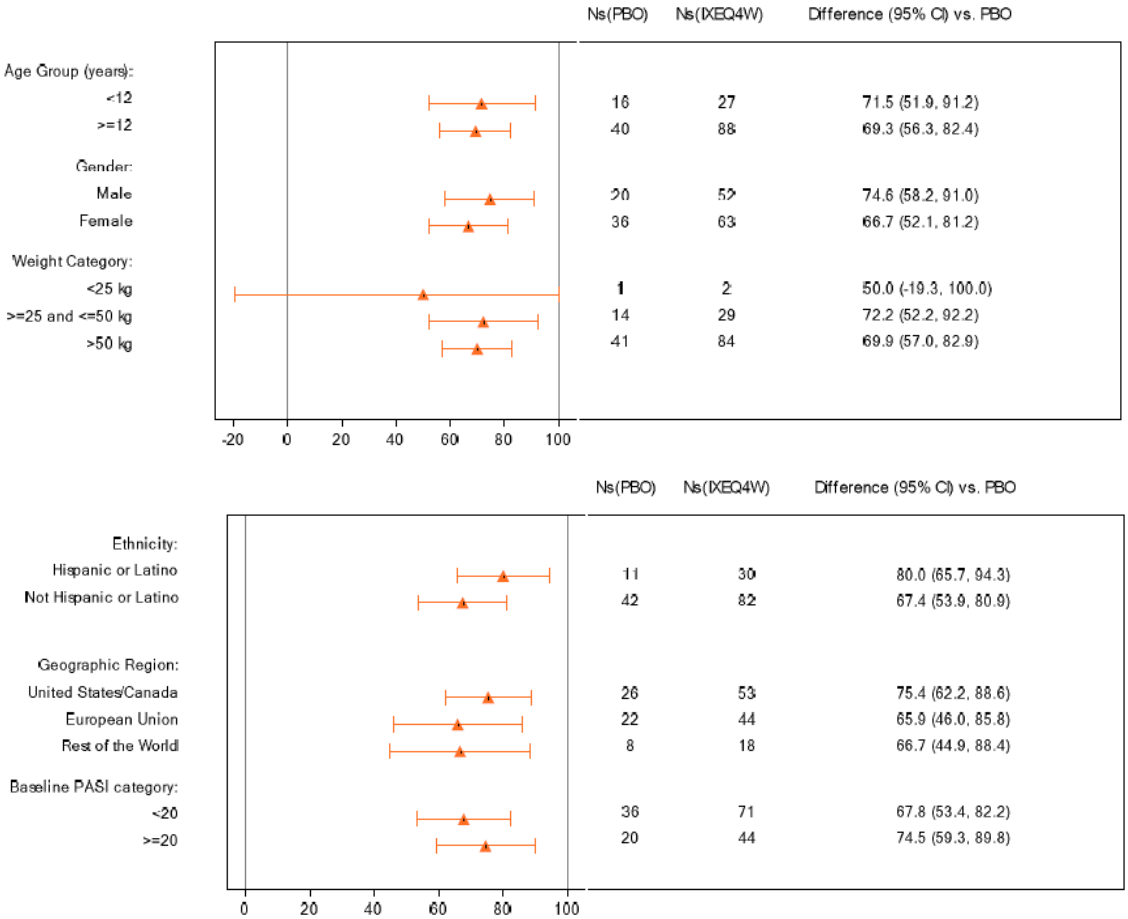
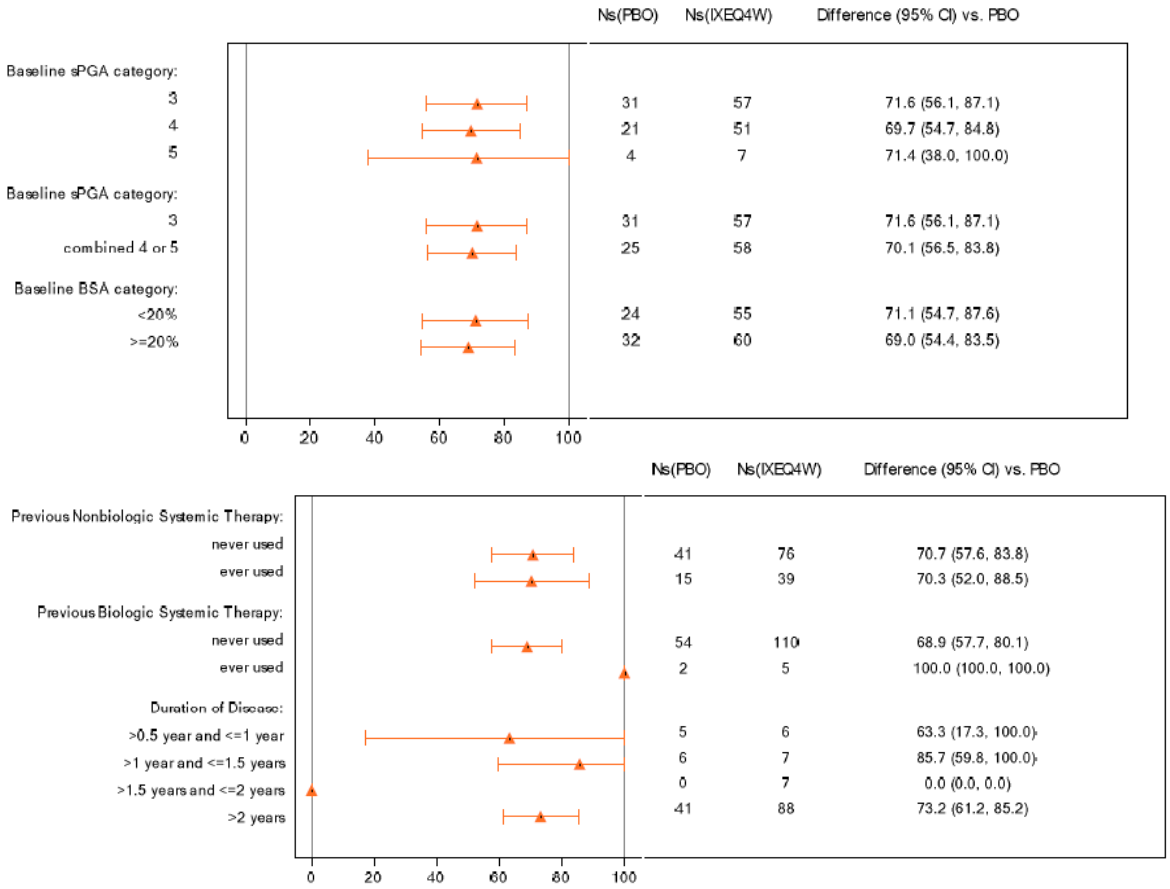


Figure 27 Forest plot of sPGA (0,1) response rates at Week 12 (NRI) by subgroups ITT population (per main study). I1F-MC-RHCD- Double-Blind Treatment Period.





Long-term efficacy

No efficacy data beyond 12 weeks have been presented in this application.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 27 Summary of Efficacy for trial I1F-MC-RHCD

Study Details		
Title: Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Efficacy of Ixekizumab in Patients from 6 to Less than 18 Years of Age with Moderate-to-Severe Plaque Psoriasis		
Study identifier	I1F-MC-RHCD	
Design	Phase 3, multicentre, randomized, double-blind, randomized, placebo-controlled study	
	Duration of Main phase: Duration of Maintenance phase:	12 weeks (Double-Blind Treatment Period) 48 weeks (Maintenance Period)
	Duration of Extension phase	48 weeks (either an Extension Period or a Randomised Withdrawal Period)
Hypothesis	Superiority)	
Treatment groups	Ixekizumab Q4W	Ixekizumab Q4W. Weight-based dosing. Duration: 12 weeks (Double-Blind Treatment Period), 48 weeks (Maintenance Period), 48 weeks (Extension or Randomised Withdrawal Period) Number randomized at Week 0 = 115
	Placebo	Placebo Duration: 12 weeks (Double-Blind Treatment Period), 48 weeks (Randomised Withdrawal Period) Number randomized at Week 0 = 56
	Etanercept (patients with severe psoriasis only, in countries where etanercept was approved)	Etanercept 0.8 mg/kg Q1W. Duration: 12 weeks (Double-Blind Treatment Period). Number randomized at Week 0 = 30.

Endpoints and definitions	Co-primary endpoints		PASI 75 response at Week 12 sPGA (0,1) response at Week 12.
	Gated secondary endpoint	PASI 90 at Week 12	To assess whether ixekizumab is superior to placebo in the treatment of paediatric patients (children and adolescents) with moderate-to-severe plaque psoriasis as measured by the proportion of patients achieving PASI 90 at Week 12.
	Gated secondary endpoint	sPGA (0) at Week 12	To assess whether ixekizumab is superior to placebo in the treatment of paediatric patients (children and adolescents) with moderate-to-severe plaque psoriasis as measured by the proportion of patients achieving sPGA (0) at Week 12.
	Gated secondary endpoint	PASI 100 at Week 12	To assess whether ixekizumab is superior to placebo in the treatment of paediatric patients (children and adolescents) with moderate-to-severe plaque psoriasis as measured by the proportion of patients achieving PASI 100 at Week 12.
	Gated secondary endpoint	≥4-point improve in Itch NRS at Week 12	To assess whether ixekizumab is superior to placebo in the treatment of paediatric patients (children and adolescents) with moderate-to-severe plaque psoriasis as measured by the proportion of patients achieving a ≥4-point improvement in Itch NRS score at Week 12 (among patients with baseline Itch NRS score ≥4).
	Gated secondary endpoint	PASI 75 at Week 4	To assess whether ixekizumab is superior to placebo in the treatment of paediatric patients (children and adolescents) with moderate-to-severe plaque psoriasis as measured by the proportion of patients achieving PASI 75 at Week 4.
	Gated secondary endpoint	sPGA (0,1) at Week 4	To assess whether ixekizumab is superior to placebo in the treatment of paediatric patients (children and adolescents) with moderate-to-severe plaque psoriasis as measured by the proportion of patients achieving sPGA (0,1) at Week 4.
Database lock	12-week database lock (Double-Blind Treatment Period: 22 March 2019 Database lock after 100 patients completed 1 year of ixekizumab treatment: 28 June 2019. This submission includes data from this lock.		

Results and Analysis				
Analysis Description	**Co-Primary Analysis:** PASI 75 response at Week 12			
Analysis population, time point description, and statistical model	ITT Population 12 weeks Fisher's Exact Test (NRI)			
Descriptive statistics and estimate variability (moderate-to-severe patients)	Treatment group	Ixekizumab Q4W	Placebo	
	Number of patients	115	56	
	PASI 75	102/115 (88.7%)	14/56 (25.0%)	
Descriptive statistics and estimate variability (severe patients in countries where etanercept was approved)[a]	Treatment group	Ixekizumab Q4W	Placebo	Etanercept
	Number of patients	38	19	30
	PASI 75	32/38 (84.2%)	5/19 (26.3%)	19/30 (63.3%)
Effect estimate per comparison (moderate-to-severe patients)	Co-Primary endpoint: PASI 75 at Week 12	Comparison groups	Ixekizumab Q4W vs. Placebo	
		% Difference vs. Placebo	63.7	
		95% CI	51.0, 76.4	
		p-value	<.001	
Effect estimate per comparison (severe patients in countries where etanercept was approved)[a]	Other Secondary endpoint: PASI 75 at Week 12	Comparison groups	Ixekizumab Q4W vs. Placebo	
		% Difference vs. Placebo	57.9	
		95% CI	35.0, 80.8	
		p-value	<.001	
	Other Secondary endpoint: PASI 75 at Week 12	Comparison groups	Etanercept vs. Placebo	
		% Difference vs. Placebo	37.0	
		95% CI	10.8, 63.3	
		p-value	.019	
	Other Secondary endpoint: PASI 75 at Week 12	Comparison groups	Ixekizumab Q4W vs. Etanercept	
		% Difference vs. Placebo	20.9	
		95% CI	0.1, 41.7	
		p-value	.089	

Analysis Description	**Co-Primary Analysis:** sPGA (0,1) response at Week 12			
Analysis population, time point description, and statistical model	ITT Population 12 weeks Fisher's Exact Test (NRI)			
Descriptive statistics and estimate variability (moderate-to-severe patients)	Treatment group	Ixekizumab Q4W	Placebo	
	Number of patients	115	56	
	sPGA (0,1)	93/115 (80.9%)	6/56 (10.7%)	
Descriptive statistics and estimate variability (severe patients in countries where etanercept was approved)[a]	Treatment group	Ixekizumab Q4W	Placebo	Etanercept
	Number of patients	38	19	30
	sPGA (0,1)	29/38 (76.3%)	1/19 (5.3%)	16/30 (53.3%)
Effect estimate per comparison (moderate-to-severe patients)	Co-Primary endpoint: sPGA (0,1) at Week 12	Comparison groups	Ixekizumab Q4W vs. Placebo	
		% Difference vs. Placebo	70.2	
		95% CI	59.3, 81.0	
		p-value	<.001	
Effect estimate per comparison (severe patients in countries where etanercept was approved)[a]	Other Secondary endpoint: sPGA (0,1) at Week 12	Comparison groups	Ixekizumab Q4W vs. Placebo	
		% Difference vs. Placebo	71.1	
		95% CI	54.2, 87.9	
		p-value	<.001	
	Other Secondary endpoint: sPGA (0,1) at Week 12	Comparison groups	Etanercept vs. Placebo	
		% Difference vs. Placebo	48.1	
		95% CI	27.6, 68.6	
		p-value	<.001	
	Other Secondary endpoint: sPGA (0,1) at Week 12	Comparison groups	Ixekizumab Q4W vs. Etanercept	
		% Difference vs. Placebo	23.0	
		95% CI	0.6, 45.4	
		p-value	.070	

Analysis Description	**Key Secondary Analysis:** PASI 90 response at Week 12			
Analysis population, time point description, and statistical model	ITT Population 12 weeks Fisher's Exact Test (NRI)			
Descriptive statistics and estimate variability (moderate-to-severe patients)	Treatment group	Ixekizumab Q4W	Placebo	
	Number of patients	115	56	
	PASI 90	90/115 (78.3%)	3/56 (5.4%)	
Descriptive statistics and estimate variability (severe patients in countries where etanercept was approved)[a]	Treatment group	Ixekizumab Q4W	Placebo	Etanercept
	Number of patients	38	19	30
	PASI 90	29/38 (76.3%)	0	12/30 (40.0%)
Effect estimate per comparison (moderate-to-severe patients)	Gated Secondary endpoint: PASI 90 at Week 12	Comparison groups	Ixekizumab Q4W vs. Placebo	
		% Difference vs. Placebo	72.9	
		95% CI	63.3, 82.5	
		p-value	<.001	
Effect estimate per comparison (severe patients in countries where etanercept was approved)[a]	Other Secondary endpoint: PASI 90 at Week 12	Comparison groups	Ixekizumab Q4W vs. Placebo	
		% Difference vs. Placebo	76.3	
		95% CI	62.8, 89.8	
		p-value	<.001	
	Other Secondary endpoint: PASI 90 at Week 12	Comparison groups	Etanercept vs. Placebo	
		% Difference vs. Placebo	40.0	
		95% CI	22.5, 57.5	
		p-value	<.001	
	Other Secondary endpoint: PASI 90 at Week 12	Comparison groups	Ixekizumab Q4W vs. Etanercept	
		% Difference vs. Placebo	36.3	
		95% CI	14.2, 58.5	
		p-value	.003	

Analysis Description	**Key Secondary Analysis:** sPGA (0) response at Week 12			
Analysis population, time point description, and statistical model	ITT Population 12 weeks Fisher's Exact Test (NRI)			
Descriptive statistics and estimate variability (moderate-to-severe patients)	Treatment group	Ixekizumab Q4W	Placebo	
	Number of patients	115	56	
	sPGA (0)	60/115 (52.2%)	1/56 (1.8%)	
Descriptive statistics and estimate variability (severe patients in countries where etanercept was approved)[a]	Treatment group	Ixekizumab Q4W	Placebo	Etanercept
	Number of patients	38	19	30
	sPGA (0)	24/38 (63.2%)	0	5/30 (16.7%)
Effect estimate per comparison (moderate-to-severe patients)	Gated Secondary endpoint: sPGA (0) at Week 12	Comparison groups	Ixekizumab Q4W vs. Placebo	
		% Difference vs. Placebo	50.4	
		95% CI	40.6, 60.2	
		p-value	<.001	
Effect estimate per comparison (severe patients in countries where etanercept was approved)[a]	Other Secondary endpoint: sPGA (0) at Week 12	Comparison groups	Ixekizumab Q4W vs. Placebo	
		% Difference vs. Placebo	63.2	
		95% CI	47.8, 78.5	
		p-value	<.001	
	Other Secondary endpoint: sPGA (0) at Week 12	Comparison groups	Etanercept vs. Placebo	
		% Difference vs. Placebo	16.7	
		95% CI	3.3, 30.0	
		p-value	.142	
	Other Secondary endpoint: sPGA (0) at Week 12	Comparison groups	Ixekizumab Q4W vs. Etanercept	
		% Difference vs. Placebo	46.5	
		95% CI	26.2, 66.8	
		p-value	<.001	

Analysis Description	**Key Secondary Analysis:** PASI 100 response at Week 12			
Analysis population, time point description, and statistical model	ITT Population 12 weeks Fisher's Exact Test (NRI)			
Descriptive statistics and estimate variability (moderate-to-severe patients)	Treatment group	Ixekizumab Q4W	Placebo	
	Number of patients	115	56	
	PASI 100	57/115 (49.6%)	1/56 (1.8%)	
Descriptive statistics and estimate variability (severe patients in countries where etanercept was approved)[a]	Treatment group	Ixekizumab Q4W	Placebo	Etanercept
	Number of patients	38	19	30
	PASI 100	23/38 (60.5%)	0	5/30 (16.7%)
Effect estimate per comparison (moderate-to-severe patients)	Gated Secondary endpoint: PASI 100 at Week 12	Comparison groups	Ixekizumab Q4W vs. Placebo	
		% Difference vs. Placebo	47.8	
		95% CI	38.0, 57.6	
		p-value	<.001	
Effect estimate per comparison (severe patients in countries where etanercept was approved)[a]	Other Secondary endpoint: PASI 100 at Week 12	Comparison groups	Ixekizumab Q4W vs. Placebo	
		% Difference vs. Placebo	60.5	
		95% CI	45.0, 76.0	
		p-value	<.001	
	Other Secondary endpoint: PASI 100 at Week 12	Comparison groups	Etanercept vs. Placebo	
		% Difference vs. Placebo	16.7	
		95% CI	3.3, 30.0	
		p-value	.142	
	Other Secondary endpoint: PASI 100 at Week 12	Comparison groups	Ixekizumab Q4W vs. Etanercept	
		% Difference vs. Placebo	43.9	
		95% CI	23.4, 64.3	
		p-value	<.001	
Analysis Description	**Key Secondary Analysis:** Itch NRS ≥4-point improvement response at Week 12			
Analysis population, time point description, and statistical model	ITT Population 12 weeks Fisher's Exact Test (NRI)			
Descriptive statistics and estimate variability (moderate-to-severe patients)	Treatment group	Ixekizumab Q4W	Placebo	
	Number of patients	115	56	
	Itch NRS ≥4-point improvement	59/83[b] (71.1%)	8/40[b] (20.0%)	
Effect estimate per comparison (moderate-to-severe patients)	Gated Secondary endpoint: Itch NRS ≥4-point improvement at Week 12	Comparison groups	Ixekizumab Q4W vs. Placebo	
		% Difference vs. Placebo	51.1	
		95% CI	35.3, 66.9	
		p-value	<.001	

Analysis Description	**Key Secondary Analysis:** PASI 75 response at Week 4			
Analysis population, time point description, and statistical model	ITT Population 4 weeks Fisher's Exact Test (NRI)			
Descriptive statistics and estimate variability (moderate-to-severe patients)	Treatment group	Ixekizumab Q4W	Placebo	
	Number of patients	115	56	
	PASI 75	62/115 (53.9%)	5/56 (8.9%)	
Descriptive statistics and estimate variability (severe patients in countries where etanercept was approved)[a]	Treatment group	Ixekizumab Q4W	Placebo	Etanercept
	Number of patients	38	19	30
	PASI 75	17/38 (44.7%)	0	3/30 (10.0%)
Effect estimate per comparison (moderate-to-severe patients)	Gated Secondary endpoint: PASI 75 at Week 4	Comparison groups	Ixekizumab Q4W vs. Placebo	
		% Difference vs. Placebo	45.0	
		95% CI	33.2, 56.8	
		p-value	<.001	
Effect estimate per comparison (severe patients in countries where etanercept was approved)[a]	Other Secondary endpoint: PASI 75 at Week 4	Comparison groups	Ixekizumab Q4W vs. Placebo	
		% Difference vs. Placebo	44.7	
		95% CI	28.9, 60.5	
		p-value	<.001	
	Other Secondary endpoint: PASI 75 at Week 4	Comparison groups	Etanercept vs. Placebo	
		% Difference vs. Placebo	10.0	
		95% CI	-0.7, 20.7	
		p-value	.273	
	Other Secondary endpoint: PASI 75 at Week 4	Comparison groups	Ixekizumab Q4W vs. Etanercept	
		% Difference vs. Placebo	34.7	
		95% CI	15.6, 53.8	
		p-value	.003	

Analysis Description	**Key Secondary Analysis:** sPGA (0,1) response at Week 4			
Analysis population, time point description, and statistical model	ITT Population 4 weeks Fisher's Exact Test (NRI)			
Descriptive statistics and estimate variability (moderate-to-severe patients)	Treatment group	Ixekizumab Q4W	Placebo	
	Number of patients	115	56	
	sPGA (0,1)	55/115 (47.8%)	4/56 (7.1%)	
Descriptive statistics and estimate variability (severe patients in countries where etanercept was approved)[a]	Treatment group	Ixekizumab Q4W	Placebo	Etanercept
	Number of patients	38	19	30
	sPGA (0,1)	14/38 (36.8%)	0	0
Effect estimate per comparison (moderate-to-severe patients)	Gated Secondary endpoint: sPGA (0,1) at Week 4	Comparison groups	Ixekizumab Q4W vs. Placebo	
		% Difference vs. Placebo	40.7	
		95% CI	29.3, 52.0	
		p-value	<.001	
Effect estimate per comparison (severe patients in countries where etanercept was approved)[a]	Other Secondary endpoint: sPGA (0,1) at Week 4	Comparison groups	Ixekizumab Q4W vs. Placebo	
		% Difference vs. Placebo	36.8	
		95% CI	21.5, 52.2	
		p-value	.002	
	Other Secondary endpoint: sPGA (0,1) at Week 4	Comparison groups	Etanercept vs. Placebo	
		% Difference vs. Placebo	0	
		95% CI		
		p-value		
	Other Secondary endpoint: sPGA (0,1) at Week 4	Comparison groups	Ixekizumab Q4W vs. Etanercept	
		% Difference vs. Placebo	36.8	
		95% CI	21.5, 52.2	
		p-value	<.001	

Abbreviations: CI = confidence interval; ITT = intent-to-treat; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = nonresponder imputation; NRS = numeric rating scale; PASI 75 = 75% improvement from baseline in psoriasis area and severity index; PASI 90 = 90% improvement from baseline in psoriasis area and severity index; PASI 100 = 100% improvement from baseline in psoriasis area and severity index; Q1W = every week; Q4W = every 4 weeks; sPGA (0,1) = a score of 0 or 1 on the static physician's global assessment; sPGA (0) = a score of 0 on the static physician's global assessment; vs = versus.

a Evaluations in the etanercept group, and comparisons to the etanercept group, were other secondary objectives.

b Evaluated in patients with baseline Itch NRS score of at least 4 (40 patients in the placebo group; 83 patients in the ixekizumab Q4W group)

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of ixekizumab in paediatric psoriasis (Ps) is supported by one pivotal, randomised, double-blind, placebo-controlled Phase 3 study (RHCD).

Following a screening period (Period 1), a placebo-controlled, Double-Blind Treatment Period (Period 2) of 12 weeks followed. During Period 2, patients were randomized to ixekizumab (dosed based on the subjects body weight) or placebo in a 2:1 ratio. The double-blind treatment period was followed by a 48-week open-label Maintenance Period (Period 3), then either a 48-week Extension Period (Period 4), a 48-week Randomised Withdrawal Period (Period 4), for patients from the EU who meet response criteria at Week 60 (defined as those who achieved sPGA 0,1). After Period 4, patients entered a Post-Treatment Follow-Up Period (Period 5).

The treatments and study design are considered adequate by CHMP. The inclusion of a placebo control, which is a standard requirement for chronic plaque psoriasis trials to ascertain assay sensitivity and the inclusion of an active comparator in a sub-part of the study is endorsed by CHMP. The ixekizumab dosing regimens were selected based on PK/PD modelling.

As part of an addendum, a group of patients from countries where etanercept was approved for the treatment of severe paediatric Ps were randomised to an active control group (etanercept) during the Double-Blind Treatment Period. Etanercept (Enbrel) is approved for the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. The posology of etanercept was in accordance with the labelling for Enbrel in paediatric plaque psoriasis.

The patients included in the study were males and females from 6 to <18 years of age at time of randomization who had a diagnosis of moderate-to-severe plaque-type Ps for at least 6 months prior to baseline, a PASI score ≥12, sPGA ≥3, and BSA involvement ≥10% at screening and baseline and were candidates for phototherapy or systemic treatment or considered by the investigator as not adequately controlled by topical therapies. The inclusion and exclusion criteria are agreed by CHMP and in line with the CHMP psoriasis guideline (CHMP/EWP/2454/02 corr.). The inclusion criteria were essentially the same as those used in the pivotal ixekizumab adult studies.

The primary objective was to assess whether ixekizumab Q4W was 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). The co-primary endpoints are considered adequate by CHMP and the same as used in the pivotal ixekizumab Ps studies supporting the MAA in adults. However, these endpoints did not seem to be in accordance with the endpoint stated in the PIP, being difference in PASI at week 12. The MAH clarified that a PIP modification was concluded in parallel of this extension of indication to change the endpoint to co-primary end-points difference in PASI at week 12 and sPGA at week 12. Even though it remained not fully clear to CHMP that this refers to responder-based endpoints, e.g. PASI75, the co-primary endpoints used are relevant and accepted by CHMP.

As gated, secondary objectives, the superiority of ixekizumab Q4W to placebo was evaluated by a number of other PASI and sPGA endpoints, as well as itch. The gated secondary endpoints are also endorsed by CHMP, addressing complete or near complete clearance of psoriasis plaques (PASI 90, PASI 100 and sPGA(0)), itch (via Itch NRS) and onset of effect (PASI 75 and sPGA (0,1) at Week 4).

The main comparison was versus placebo. The comparison versus etanercept was described in an addendum to the study protocol (Protocol Addendum I1F-MC-RHCD (2). Upon request by CHMP, the MAH submitted protocol Addendum I1F-MC-RHCD (2.1) and clarified that this addendum was to be performed in addition to all procedures required by Protocol RHCD or any subsequent amendments to that protocol.

Treatment with etanercept was administered open label. Since this is not the primary comparison, this is accepted by CHMP. The use of a blinded assessor is endorsed by CHMP.

The sample size was planned to meet EMA requirements stating that the total number of subjects randomised was to be at least 170. In total, 195 subjects were planned; a total of 201 subjects were randomised: 171 patients within the main protocol (115 patients to ixekizumab Q4W and 56 patients to

placebo) and 87 patients within the protocol addendum (38 patients to ixekizumab Q4W, 30 patients to etanercept Q1W, and 19 patients to placebo).

The majority of subjects were >12 years and weighed >50 kg. Very few subjects were randomised that belonged to the lower end of the age/weight scale. A cap or criteria to ensure a minimum number of subjects randomised to different weight/age groups would have been preferred.

The Statistical Analysis Plan (SAP) was submitted upon request by CHMP. The SAP version 1 (dated 06 June 2017) was approved prior to unblinding of treatment assignments for Study Period 2. The SAP version 2 (approved on 18 March 2019) was stated to have been approved prior to primary database lock (for the week 12 analysis). According to the CSR for the main study, the second interim database lock, unblinding, and data analysis were performed at the time (cut-off date of 22 March 2019) the last patient completed Study Period 2 (Week 12) or ETV. A third version of the SAP (version 3) was approved after primary database lock (DBL on 22 March 2019) and prior to submission database lock (DBL on 28 June 2019). From the initial submission, it was unclear when the second interim analysis, i.e. the primary analysis, was performed. The MAH clarified that all efficacy and safety analyses as described in the SAP were conducted based on the second interim lock with the date of treatment unblinding being 22 March 2019 after which all efficacy data up to week 12 were locked. All efficacy and safety analyses were re-run at the third interim lock (28 June 2019). The MAH confirmed that the primary and major secondary analysis results were compared between the two locked databases and that they were the same. The approach was agreed by CHMP.

According to the revision history there was one change in SAP (version 3) made that implied an update to important protocol violations concerning patients with moderate-to-severe plaque psoriasis from etanercept approved countries randomised as severe plaque psoriasis at baseline. The MAH clarified that the revision concerned a potential protocol deviation and that there was only one patient with moderate-to-severe psoriasis in an etanercept-approved country who was randomised as a patient with severe psoriasis. This patient was randomised to the ixekizumab group. This is not considered by CHMP to have any impact on the interpretability of the efficacy data.

Within study protocol amendment (b) (approved 22 September 2018); wording was added that allowed for additional interim analyses. This was a general text that did not *per se* described the third interim analysis performed. The chosen time-point for the third interim analysis is however endorsed by CHMP, i.e. when a minimum of 100 patients had been treated with ixekizumab for at least one year.

The MAH was requested to fully describe the Data Monitoring Committee (DMC) and to clarify if the composition was external to Lilly staff, as requested by the PDCO since it is a PIP requirement. The MAH provided details of DMC showing that some members are independent of the MAH. This is agreed by CHMP.

With regards to changes made to the planned analyses for the main study group, no concerns were raised by CHMP; according to the CSRs a few *post-hoc* analyses were performed that concerned safety and added tabulations of data.

The efficacy analyses were performed separately for all placebo and ixekizumab patients (the main study group) and placebo, etanercept, and ixekizumab patients with severe disease randomised and treated in countries where etanercept was used as a reference arm (i.e. the protocol addendum [2] group). For the main comparison versus placebo, a multiple testing strategy had been implemented for the co-primary and key secondary endpoints to control the family-wise error rate at a 2-sided α. The use of a gatekeeping approach is agreed by CHMP. The comparison of ixekizumab Q4W and etanercept was not part of the multiplicity-controlled endpoint analyses.

The primary analysis population was ITT based on all randomised patients; this is endorsed by CHMP. Patients randomised to ixekizumab Q4W or placebo in etanercept-approved countries were a subset of

the ITT population used for the main comparison in the study. The primary approach regarding the method for handling missing data was non-responder imputation which concerned the co-primary as well as all gated secondary endpoints. Albeit depending on the amount of and missing data pattern, this is considered by CHMP as a non-controversial approach. Discontinuations prior to the assessment of the primary endpoint were low overall and no apparent difference was noted between patients receiving placebo and those receiving ixekizumab. The main test used for the primary comparison of ixekizumab Q4W versus placebo was the Fisher's exact test; the difference of the proportions and the 95% CI of the difference were presented. Secondary analyses were defined for the co-primary endpoints, that were performed using a logistic regression model; odds ratios and corresponding 95% CIs were presented. The logistic regression model included treatment group, region, baseline sPGA score (severity of the Ps), and baseline weight category (<25kg; ≥25 to ≤50 kg; or >50 kg) as factors. The chosen analysis model is agreed by CHMP.

Efficacy data and additional analyses

A total of 171 patients were randomized to either ixekizumab Q4W (N=115) or placebo (N=56) (**Main** study group), and 16 patients (9.4% of the ITT population) discontinued the study, 154 patients (90%) are still ongoing, and 1 patient completed the study. In the Protocol **Addendum (2)** Group, the Double-Blind Treatment Period was completed by 17 of 19 (89.5%) patients in the placebo group, 29 of 30 (96.7%) patients in the etanercept group, and 37 of 38 (97.4%) patients in the ixekizumab group. Therefore, the rate of completion in the double-blind phase was overall high (less than 3% of the randomized patients discontinued) and the rate of completion was high also in the Protocol Addendum Group.

The baseline demographics and baseline disease characteristics were overall well balanced between the treatment groups.

For the **Main** study group, the mean age was 13.5 years and the majority (about 75%) were ≥12 years of age, white (>80%), and female. The mean weight was 63 kg and the mean BMI 23.9 kg/m^2. The majority of patients were in the >50-kg weight group (73%), 25% were in the ≥25- to ≤50-kg weight group, and only 1.8% in the <25-kg weight group. Patients were enrolled in 12 countries; 46% in the US or Canada, 39% of patients in the European Union, and 15% of patients from the rest of the world.

Patients had a median baseline PASI of 17. Baseline sPGA score was severe or very severe in 49% of patients and moderate in 52% of patients. The majority of patients (54%) had ≥20 percent body surface area (%BSA) of Ps at baseline. Of all patients, 22% had received prior phototherapy and 32% had received prior conventional systemic therapy for the treatment of Ps. Only a few patients had used previous biologic systemic therapy.

In the **Addendum (2)** study group, the age, race, gender and weight distributions were rather similar as for the Main study group. Patients were enrolled in 9 countries, with 69% of patients enrolled in the EU and 31% of patients enrolled in the rest of the world.

Patients had a median baseline PASI score of 23. The majority of patients (80.5%) had baseline PASI score ≥20. Baseline sPGA score was severe or very severe in 87% of patients and moderate in 13% of patients. The majority of patients (84%) had ≥20 percent body surface area (%BSA) of psoriasis at baseline. Of all patients, 33% had received prior phototherapy and 29% had received prior conventional systemic therapy for the treatment of psoriasis. The more severe psoriasis in the **Addendum (2)** group reflects the target population for etanercept, being indicated in *severe* psoriasis in children.

There were a large number of protocol deviations relating to mis-dosing, primarily over-dosing (16 patients). Upon request by CHMP, the MAH made an overview of the cases of mis-dosing in study RHCD.

Common reasons for mis-dosing were that patients in the 25- to 50-kg group were close to weighing 50 kg (and hence, included in the > 50 kg category) or that the subjects weight was fluctuating between visits or compared to the baseline weight. There were also some errors from site staff when entering the weight for randomisation in the system. It is acknowledged by CHMP that if a subject weighs 45-50 kg, it can be easy to round up the weight to 50 kg, even if this is formally incorrect in a clinical trial situation. The issue of fluctuating weight is also understood, i.e. if a subject weighs >50 kg at baseline, there may be reluctance to reduce the dose on subsequent dosing occasions even if the weight drops slightly below 50 kg. Ixekizumab is not to be regarded as a product with narrow therapeutic range and a strict weight-based (i.e. mg/kg BW) posology is not proposed. The cases of mis-dosing did not seem to be associated with any obvious impact on efficacy or safety for the concerned patients, although a possible relation can be difficult to establish from the available data. Some AEs were reported close and some more distant in time from the reported overdoses in different individuals. There were some cases of injection site reactions which could be related to a larger injection volume of the IMP. The majority of patients experiencing overdoses continued in the study. Overall, the numerous instances of over- or underdosing are remarkable in a clinical trial setting. However, the MAH considers that these overdoses may not be more likely to occur in routine clinical practice, since the process is not as complex as in the clinical study setting (no interactive web response system involved and not so many blinded/unblinded staff members involved). It is also stressed out by the MAH that in real life, care and communication with patients is more straightforward and instructions will be provided in all EU languages, which will actually be the case since the product information will be available in all local languages. Reference is also made to other products (e.g. Enbrel, Humira), for which a dedicated paediatric formulation or strength is not always available. It is acknowledged by CHMP that a dedicated paediatric dosage form (strength) for Taltz would have been appreciated and that the need for a health care professional to administer the smallest dose is not ideal. However, since the posology does no longer include children with a weight below 25 kg, there is only one weight group that will need a specifically prepared dose from the prefilled syring, the 25-50 kg group that should receive 40 mg Q4W, i.e. 0.5 ml. The instructions for use in the SmPC section 6.6 of the prefilled syringe are adequate to ensure a safe administration of Taltz by a qualified healthcare professional in the maintenance phase for patients weighing 25-50kg.

Regarding the significant number of medication errors and other important protocol violations relating to conduct of the pivotal study, upon request by CHMP, the MAH outlined that corrective actions taken by the sponsor and requiring actions at study sites took months to be put in place after the issue was identified towards the end of 2018. The DMC was not made aware of the >12% medication error rate on this study since the DMC was in place until 2018 when the first interim analysis occurred at week 12. The reported corrective actions appear to have been slowly implemented but are nonetheless considered appropriate by CHMP.

For the co-primary endpoints, patients in the ixekizumab treatment group had statistically significant higher PASI 75 and sPGA (0,1) responses versus placebo at Week 12 (NRI). For PASI 75, ixekizumab had a response rate of 88.7% vs. 25.0% for placebo (ITT, NRI). For sPGA (0,1), the corresponding responder rates were 80.9% vs. 10.7%. Hence, Study RHCD achieved both its co-primary objectives.

In the Protocol **Addendum (2)** Group, patients in both the etanercept treatment group and the ixekizumab treatment group had statistically significant higher PASI 75 and sPGA (0,1) responses versus placebo at Week 12 (NRI). The ixekizumab treatment group had numerically higher PASI 75 and sPGA (0,1) responses versus etanercept at Week 12 (63.3% and 53.3%, respectively; NRI), although not statistically significant.

The gated secondary endpoints were all met, e.g. superiority for ixekizumab vs. placebo was demonstrated for the endpoints showing complete or almost complete clearance of psoriasis (PASI 90, sPGA (0) and PASI 100 responses at Week 12). Among patients in the Protocol Addendum (2) Group, patients in the etanercept treatment group had statistically significant higher PASI 90 responses versus

placebo at Week 12 (NRI), while statistical significance was not reached for sPGA (0) or PASI 100 responses versus placebo. Among patients in the Protocol Addendum (2) Group, patients in ixekizumab treatment group had statistically significant higher PASI 90, sPGA (0), and PASI 100 responses versus both placebo and etanercept at Week 12 (NRI).

For the gated secondary endpoint Itch NRS score improvement of at least 4 points, patients in the ixekizumab treatment group had statistically significant higher Itch NRS ≥4-point improvement responses versus placebo at Week 12 (NRI).

For the gated secondary endpoints PASI 75 and sPGA (0,1) responses at Week 4, patients in the ixekizumab treatment group had statistically significant higher PASI 75 and sPGA (0,1) responses versus placebo at this time point (NRI). Among patients in the Protocol Addendum (2) Group, patients in the etanercept treatment group did not have significant different PASI 75 or sPGA (0,1) responses at Week 4 versus placebo.

The MAH was requested to present the data for the primary and key secondary endpoints adjusting for the imbalance in baseline PASI and sPGA and imbalance in prior topical corticosteroid and systemic therapy (biological and non-biological) use. No statistically significant differences in main efficacy parameters were noted when these baseline imbalances were adjusted for.

When administered at the proposed doses, Taltz is efficacious in paediatric subjects who have plaque psoriasis and weigh greater than 25 kg. However, only 2 subjects received the 20 mg Q4W ixekizumab dose (those weighing <25 kg) in the pivotal study, thereforeno conclusion on clinical efficacy in subjects weighing less than 25 kg could be made. Of the two subjects in the <25 kg group, one inadvertently received 80 mg at Week 4 instead of 20 mg resulting in a high Week 8 concentration (12.3 µg/mL), and the other subject's Week 12 trough was associated with a TE-ADA-positive of high titer that was also NAb positive. The CHMP requested further justification to support efficacy in patients below 25kg. However, the issue was not pursued since the MAH withdrew the application in patients weighing below 25kg.

The high overdose rate of ixekizumab in the pivotal clinical trial was considered by CHMP to undermine the reliability of the efficacy data, as does the medication errors in the placebo and etanercept arms also. Upon request by CHMP, additional efficacy analyses were provided where patients with any dosing error prior to Week 12 assessment, were imputed as non-responders. These analyses showed generally somewhat lower response rates and slightly smaller differences versus placebo. However, the response for ixekizumab remained superior over placebo and all results were consistent with the original ITT population analysis results. Therefore, CHMP considered that the cases of mis-dosing did not have a major impact on the efficacy conclusions.

The issue of required rescue treatment prior to Week 12 was not discussed by the MAH in the initial submission. Upon request by CHMP, the MAH clarified that no subjects assessed for the primary endpoints required rescue treatment.

The results on etanercept arm were initially not considered robust enough to be included in the SmPC section 5.1, since the results were not multiplicity adjusted and also came from a small subgroup (n=30). However, the MAH clarified that the etanercept arm is a key binding element of the agreed PIP foreseeing that at least 30 patients treated with etanercept should be enrolled to comply with the PIP requirements. It is agreed by CHMP that the information on etanercept may be of value for the prescriber and it is also noted that no claims about statistical significance are made. Hence, the CHMP agrees to include information on etanercept arm in Section 5.1 of the SmPC.

There were relatively few patients with nail psoriasis and palmoplantar psoriasis while more subjects had scalp involvement. Positive effects were seen for ixekizumab vs. placebo for endpoints assessing effects on these locations (NAPSI, PSSI, PPASI), in some cases also reaching p-values <0.05. Similarly, for the Itch NRS over time, (C)DLQI and PatGA results, positive results were observed for ixekizumab. None of

these endpoints were included in the multiplicity-controlled testing, and upon request by CHMP, the MAH revised the description of these results in section 5.1 of the SmPC.

Subgroup analyses were performed for relevant demographic and disease-related characteristics for the two co-primary endpoints. For some subgroups, the size of the groups was very small (e.g. those <25 kg and those with previous biologic treatment). Further justification was requested for the dosing and B/R balance in patients with low body weight (<25kg). The MAH agreed that the number of patients in the body weight group <25 kg is small, as only 4 patients were enrolled in the main study and the addendum (2 in the ixekizumab group; 1 in the placebo group; and 1 in the etanercept group in the Double-Blind Treatment Period [Induction Period]). The MAH restricted the indication to patients weighing at least 25kg. This is agreed by CHMP.

The vast majority of subjects recruited in the pivotal study were white (~85- 90%). The MAH was requested to justify the generalisability of the paediatric efficacy data generated to people of other backgrounds (e.g. Asian or black African). Large-scale studies of heterogeneity in biologic treatment response are not available. A literature review conducted to identify patient characteristics associated with psoriasis treatment responses did not find evidence of differential efficacy by racial/ethnic group in clinical studies of biologics (Edson-Heredia et al. 2014). No differences in treatment effect by race/ethnicity were observed among adults in the ixekizumab clinical development programme. While there is no definitive evidence of no effect of non-caucasian ethnicity on response to treatment in the paediatric population and given the consistent treatment effect observed in the adult studies, the paediatric efficacy results are considered applicable to non-Caucasian populations.

With respect to long-term efficacy, no efficacy data beyond 12 weeks have been presented in this application. The MAH commits to provide longer-term efficacy results of the ongoing Study RHCD *post-approval*. This is agreed by CHMP.

2.4.4. Conclusions on the clinical efficacy

Study RHCD met its co-primary endpoints higher PASI 75 and sPGA (0,1) responses versus placebo at Week 12 (NRI). Key secondary endpoints were also met (superiority for ixekizumab vs. placebo demonstrated for the endpoints showing complete or almost complete clearance of psoriasis (PASI 90, sPGA (0) and PASI 100 responses at Week 12)).

The initially proposed indication targeted patients above 6 years, with no body weight restrictions. However, in view of the limited data available for ixekizumab in children weighing less than 25kg, the MAH restricted the use to patients weighing more than 25kg.

The wording of the final indication is as follows:

Paediatric plaque psoriasis

Taltz is indicated for the treatment of moderate to severe plaque psoriasis in children from the age of 6 years and with a body weight of at least 25 kg and adolescents who are candidates for systemic therapy.

2.5. Clinical safety

Introduction

In support of this application, results from one pivotal study (Study I1F-MC-RHCD) are submitted.

Study RHCD included patients from 6 to <18 years of age with moderate-to-severe Ps (PASI score ≥12, sPGA ≥3, and BSA ≥10% at screening and baseline). The eligibility criteria of Study RHCD permitted enrolment of a patient population with active disease and a significant disease burden.

Data from Study RHCD, the pivotal Phase 3 paediatric Ps study, are summarised from:

- the **Double-Blind Treatment Period** (Weeks 0 to 12), and
- the **Combined Treatment Periods** (that is, the Double-Blind Treatment Period, Maintenance Period, and the Extension Period [Periods 2, 3 and 4].

At the time of data lock for this submission, Periods 3 and 4 are ongoing.

Safety was assessed by summarising and analysing study drug exposure, AEs, SAEs, laboratory analytes, including neutrophil counts and immunogenicity, vital signs, Children's Depression Rating Scale (CDRS), Columbia-Suicide Severity Rating Scale (C-SSRS), standardised growth, and Tanner stage.

Safety analyses for the Double-Blind Treatment Period were conducted on the Safety Population. The Safety Population is defined as all randomised patients who take at least 1 dose of double-blind study treatment.

Safety analyses for the Combined Treatment Periods were conducted on the All Ixekizumab Safety Population. The All Ixekizumab Safety Population is defined as all patients who have at least 1 dose of ixekizumab, including patients in the Main Study Group and the Protocol Addendum (2) Group.

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

Safety subgroup analyses for common TEAEs and AESIs of infections and ISRs were summarised for the Safety Population. A logistic regression model with treatment, subgroup, and the interaction of subgroup-by-treatment included as factors will be used. The subgroup-by-treatment interaction will be tested at the significance level of 0.10.

Patient subsets for safety results

Because etanercept was only approved in certain countries and for patients with severe disease, selected safety analyses in the Double-Blind Treatment Period are presented separately for:

- all placebo and ixekizumab patients (the **Main Study Group**)
- placebo, etanercept, and ixekizumab patients with severe disease in countries where etanercept is used as a reference arm (the **Protocol Addendum [2] Group**).

In addition, safety analyses during the Combined Treatment Periods were conducted on the All Ixekizumab Safety Population. This population included all patients who received at least 1 dose of ixekizumab, including patients in the Main Study Group and Protocol Addendum (2) Group.

Patient exposure

Study drug exposure in the Combined Treatment Periods includes 196 patients. Of these, 114 have been exposed to ixekizumab for at least 1 year.

Table 28 Study Drug Exposure Double-Blind Treatment Period (Weeks 0 to12) and Combined Treatment Periods - Study RHCD

	Main Group – Double Blind Treatment Period		Protocol Addendum (2) Group – Placebo-Controlled Treatment Period			Combined Treatment Periods
	Placebo (N = 56)	Ixekizumab Q4W (N = 115)	Placebo (N = 19)	Etanercept (N = 30)	Ixekizumab Q4W (N = 38)	Ixekizumab Q4W (N = 196)a
Mean duration, days	84.1	85.5	82.5	85.4	85.5	385.3
Total patient-years	12.9	26.9	4.3	7.0	8.9	206.8

Abbreviations: N = number of patients in the analysis population; Q4W = every 4 weeks.
[a] Note that 201 patients were randomised, but 3 patients in the placebo group and 2 patients in the etanercept group discontinued the study before receiving ixekizumab.

Study drug exposure

Study drug exposure is provided in **Table 29**.

Table 29 All ixekizumab safety population - Combined treatment periods (periods 2, 3 and 4)

	Total IXE (N=196)
Days of exposure, n (%)	
> 0 day	**196 (100.0)**
>= 7 days	**196 (100.0)**
>= 14 days	**196 (100.0)**
>= 30 days	**196 (100.0)**
>= 60 days	**194 (99.0)**
>= 84 days	**192 (98.0)**
>= 90 days	**188 (95.9)**
>= 120 days	**185 (94.4)**
>= 183 days	**175 (89.3)**
>= 365 days	**114 (58.2)**
>= 548 days	**28 (14.3)**
>= 730 days	**3 (1.5)**
Days of exposure, n (%)	
> 0 to < 7 days	**0**
>= 7 to < 14 days	**0**
>= 14 to < 30 days	**0**
>= 30 to < 60 days	**2 (1.0)**
>= 60 to < 84 days	**2 (1.0)**
>= 84 to < 90 days	**4 (2.0)**
>= 90 to < 120 days	**3 (1.5)**
>= 120 to < 183 days	**10 (5.1)**
>= 183 to < 365 days	**61 (31.1)**
>= 365 to < 548 days	**86 (43.9)**
>= 548 to < 730 days	**25 (12.8)**
>= 730 days	**3 (1.5)**

Abbreviations: IXE = Ixekizumab; N = number of patients in the analysis population; n = number of patients in the specified category; SD = standard deviation.

Table 30 and **Table 31** summarise the Prespecified Medical history for the ITT population for the Main study and for the protocol addendum (2).

Table 30 Prespecified Medical history for the ITT population for the Main study report.

	PBO (N=56) n (%)	IXEQ4W (N=115) n (%)	Total (N=171) n (%)	Overall p-value [1]
Hypertension, n(%)				>0.999
Number of patients, Nx	56	115	171	
Yes	0	1 (0.9%)	1 (0.6%)	
No	56 (100.0%)	114 (99.1%)	170 (99.4%)	
Diabetes mellitus, Type I, n(%)				NA
Number of patients, Nx	56	115	171	
Yes	0	0	0	
No	56 (100.0%)	115 (100.0%)	171 (100.0%)	
Diabetes mellitus, Type II, n(%)				NA
Number of patients, Nx	56	115	171	
Yes	0	0	0	
No	56 (100.0%)	115 (100.0%)	171 (100.0%)	
Dyslipidemia, n(%)				0.327
Number of patients, Nx	56	115	171	
Yes	1 (1.8%)	0	1 (0.6%)	
No	55 (98.2%)	115 (100.0%)	170 (99.4%)	
Psoriatic arthritis, n(%)				0.549
Number of patients, Nx	56	115	171	
Yes	1 (1.8%)	1 (0.9%)	2 (1.2%)	
No	55 (98.2%)	114 (99.1%)	169 (98.8%)	
Inflammatory bowel disease, n(%)				>0.999
Number of patients, Nx	56	115	171	
Yes	0	1 (0.9%)	1 (0.6%)	
No	56 (100.0%)	114 (99.1%)	170 (99.4%)	
Crohn's disease, n(%)				NA
Number of patients, Nx	56	115	171	
Yes	0	0	0	
No	56 (100.0%)	115 (100.0%)	171 (100.0%)	
Ulcerative colitis, n(%)				NA
Number of patients, Nx	56	115	171	
Yes	0	0	0	
No	56 (100.0%)	115 (100.0%)	171 (100.0%)	

Table 31 Prespecified Medical History, Intent to Treat Population - Etanercept Approved Countries (per Protocol Addendum (2))

					p-value [1]			
	PBO (N=19) n (%)	ETN (N=30) n (%)	IXEQ4W (N=38) n (%)	Total (N=87) n (%)	Overall	IXEQ4W vs. ETN	IXEQ4W vs. PBO	ETN vs. PBO
Hypertension, n(%)					>0.999	>0.999	>0.999	NA
Number of patients, Nx	19	30	38	87				
Yes	0	0	1 (2.6%)	1 (1.1%)				
No	19 (100.0%)	30 (100.0%)	37 (97.4%)	86 (98.9%)				
Diabetes mellitus, Type I, n(%)					NA	NA	NA	NA
Number of patients, Nx	19	30	38	87				
Yes	0	0	0	0				
No	19 (100.0%)	30 (100.0%)	38 (100.0%)	87 (100.0%)				
Diabetes mellitus, Type II, n(%)					NA	NA	NA	NA
Number of patients, Nx	19	30	38	87				
Yes	0	0	0	0				
No	19 (100.0%)	30 (100.0%)	38 (100.0%)	87 (100.0%)				
Dyslipidemia, n(%)					0.314	0.441	0.333	>0.999
Number of patients, Nx	19	30	38	87				
Yes	1 (5.3%)	1 (3.3%)	0	2 (2.3%)				
No	18 (94.7%)	29 (96.7%)	38 (100.0%)	85 (97.7%)				
Psoriatic arthritis, n(%)					>0.999	>0.999	>0.999	>0.999
Number of patients, Nx	19	30	38	87				
Yes	0	1 (3.3%)	1 (2.6%)	2 (2.3%)				
No	19 (100.0%)	29 (96.7%)	37 (97.4%)	85 (97.7%)				

Inflammatory bowel disease, n(%)					>0.999	>0.999	>0.999	NA
Number of patients, Nx	19	30	38	87				
Yes	0	0	1 (2.6%)	1 (1.1%)				
No	19 (100.0%)	30 (100.0%)	37 (97.4%)	86 (98.9%)				
Crohn's disease, n(%)					NA	NA	NA	NA
Number of patients, Nx	19	30	38	87				
Yes	0	0	0	0				
No	19 (100.0%)	30 (100.0%)	38 (100.0%)	87 (100.0%)				
Ulcerative colitis, n(%)					NA	NA	NA	NA
Number of patients, Nx	19	30	38	87				
Yes	0	0	0	0				
No	19 (100.0%)	30 (100.0%)	38 (100.0%)	87 (100.0%)				

Adverse events

Table 32 provides an overview of AEs reported during the double-blind treatment period (weeks 0 to 12) and combined treatment periods.

Table 32 Double-Blind Treatment Period (Weeks 0 to 12) and Combined Treatment Periods Study RHCD

	Main Group – Double Blind Treatment Period		Protocol Addendum (2) Group – Placebo-Controlled Treatment Period			Combined Treatment Periods
Treatment Group	Placebo (N = 56)	Ixekizumab Q4W (N = 115)	Placebo (N = 19)	Etanercept (N = 30)	Ixekizumab Q4W (N = 38)	Ixekizumab Q4W (N = 196)
Category, n (%)						
Patients with ≥1 TEAE	25 (44.6)	64 (55.7)	5 (26.3)	13 (43.3)	18 (47.4)	158 (80.6)
Mild[a]	16 (28.6)	47 (40.9)	2 (10.5)	7 (23.3)	11 (28.9)	81 (41.3)
Moderate[a]	9 (16.1)	17 (14.8)	3 (15.8)	4 (13.3)	7 (18.4)	69 (35.2)
Severe[a]	0	0	0	2 (6.7)	0	8 (4.1)
Death	0	0	0	0	0	0
Patient with ≥1 SAE	0	1 (0.9)	0	1 (3.3)	1 (2.6)	13 (6.6)
Discontinuation due to AE	1 (1.8)	0	1 (5.3)	0	0	3 (1.5)

Abbreviations: AE = adverse event; N = number of patients in the analysis population; n = number of patients in the specified category; Q4W = every 4 weeks; SAE = serious adverse events; TEAE = treatment-emergent adverse event
Note: Patients with multiple occurrences are counted once for each category. Patients may be counted in more than one category.
a Patients with multiple occurrences of the same event are counted under the highest severity.

Overview of adverse events in the All Ixekizumab Safety Population by double-blind treatment assignments (provided upon request by CHMP during the procedure)

Frequency of adverse events

The IXE/IXE group had the highest proportion of patients who reported at least 1 TEAE (87%), followed by the PBO/IXE group (77%), and the ETN/IXE group (61%). Similarly, the IXE/IXE group had the highest proportion of patients who reported at least 1 SAE (8%), followed by the PBO/IXE group (6%), and the ETN/IXE group (4%).

The most common adverse events of special interest (AESIs) in the All Ixekizumab Safety Population were infections, injection site reactions, and allergic reactions/hypersensitivities. For each of these AESIs, the IXE/IXE group had the highest proportion of patients who reported at least 1 event.

The IXE/IXE group also had the highest proportion of patients who reported at least 1 adjudicated inflammatory bowel disease (IBD) event (2.6%), followed by the PBO/IXE group (1.9%) and the ETN/IXE group (0).

The proportions of patients who reported at least 1 depression event were similar between the ETN/IXE (3.6%) and IXE/IXE (3.5%) groups, followed by the PBO/IXE group (1.9%).

Incidence rates of adverse events

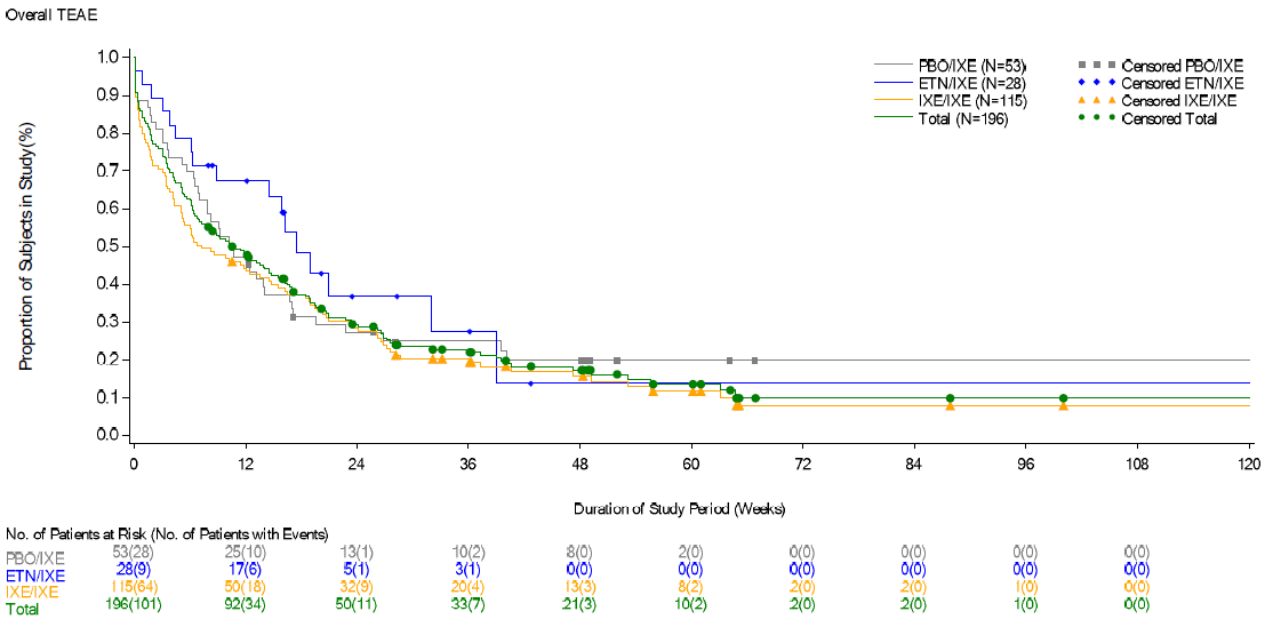
The ETN/IXE group had the highest IR of TEAEs (107.1 per 100 patient-years [PY]), followed by the PBO/IXE group (77.9), and the IXE/IXE group (72.3). The IXE/IXE group had the highest IR of SAEs (6.5), followed by the ETN/IXE group (6.3) and the PBO/IXE group (5.7).

The most common AESIs in the All Ixekizumab Safety Population were infections, injection site reactions, and allergic reactions/hypersensitivities. For infections, the ETN/IXE group had the highest IR. For injection site reactions and allergic reactions/hypersensitivities, the IXE/IXE group had the highest IR.

The IXE/IXE group also had the highest IR of adjudicated IBD (2.2), followed by the PBO/IXE group (1.9) and the ETN/IXE group (0).

The IR of depression was highest in the ETN/IXE group (6.3), followed by the IXE/IXE group (2.9) and the PBO/IXE group (1.9).

Table 33 Kaplan-Meier Plot of Time from First Dosing to First Occurrence of Treatment-Emergent Adverse Events – All ixekizumab safety population – Study I1F-MC-RHCD - Combined treatment periods (Periods 2, 3 and 4)



Notes: ETN = Etanercept; IXE = Ixekizumab; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = Placebo.
TEAE is defined as an event that first occurred or worsened in severity after baseline and on or prior to the date of the last visit within current ixekizumab treatment period.

Table 34 Treatment-Emergent Adverse-Events – Overall TEAE and SOC, Events occurred over 12-week time intervals– All ixekizumab safety population – Study I1F-MC-RHCD - Combined treatment periods (Periods 2, 3 and 4)

System Organ Class	Total (N=196) n (%) (95% CI)	Week [0-12) n (%) (95% CI)	Week [12-24) n (%) (95% CI)	Week [24-36) n (%) (95% CI)	Week [36-48) n (%) (95% CI)
Number of Patients (Ns)	196	196	192	179	165
Patients with >=1 TEAE	158 (80.6%) (75.1, 86.1)	101 (51.5%) (44.5, 58.5)	100 (52.1%) (45.0, 59.1)	87 (48.6%) (41.3, 55.9)	79 (47.9%) (40.3, 55.5)
Mild	81 (41.3%) (34.4, 48.2)	72 (36.7%) (30.0, 43.5)	65 (33.9%) (27.2, 40.5)	60 (33.5%) (26.6, 40.4)	53 (32.1%) (25.0, 39.2)
Moderate	69 (35.2%) (28.5, 41.9)	28 (14.3%) (9.4, 19.2)	35 (18.2%) (12.8, 23.7)	24 (13.4%) (8.4, 18.4)	23 (13.9%) (8.7, 19.2)
Severe	8 (4.1%) (1.3, 6.9)	1 (0.5%) (0.0, 1.5)	0 (0.0%) (0.0, 1.6)	3 (1.7%) (0.0, 3.6)	3 (1.8%) (0.0, 3.9)

System Organ Class	Week [48-60) n (%) (95% CI)	Week [60-72) n (%) (95% CI)	Week [72-84) n (%) (95% CI)	Week [84-96) n (%) (95% CI)	Week [96-108) n (%) (95% CI)	Week [108-) n (%) (95% CI)
Number of Patients (Ns)	132	88	42	19	7	3
Patients with >=1 TEAE	51 (38.6%) (30.3, 46.9)	27 (30.7%) (21.0, 40.3)	12 (28.6%) (14.9, 42.2)	4 (21.1%) (2.7, 39.4)	3 (42.9%) (6.2, 79.5)	0 (0.0%) (0.0, 100.0)
Mild	36 (27.3%) (19.7, 34.9)	16 (18.2%) (10.1, 26.2)	7 (16.7%) (5.4, 27.9)	3 (15.8%) (0.0, 32.2)	1 (14.3%) (0.0, 40.2)	0 (0.0%) (0.0, 100.0)
Moderate	14 (10.6%) (5.4, 15.9)	10 (11.4%) (4.7, 18.0)	5 (11.9%) (2.1, 21.7)	1 (5.3%) (0.0, 15.3)	2 (28.6%) (0.0, 62.0)	0 (0.0%) (0.0, 100.0)
Severe	1 (0.8%) (0.0, 2.2)	1 (1.1%) (0.0, 3.4)	0 (0.0%) (0.0, 7.1)	0 (0.0%) (0.0, 15.8)	0 (0.0%) (0.0, 42.9)	0 (0.0%) (0.0, 100.0)

Table 35 Treatment-Emergent Adverse-Events – Overall TEAE and SOC, Patient-Time-Ajusted Incidence Rate, Events occurred over 12-week time intervals– All ixekizumab safety population – Study I1F-MC-RHCD - Combined treatment periods (Periods 2, 3 and 4)

System Organ Class	Total (N=196) n (IR) (95% CI)	Week [0-12) n (IR) (95% CI)	Week [12-24) n (IR) (95% CI)	Week [24-36) n (IR) (95% CI)	Week [36-48) n (IR) (95% CI)
Patients with >=1 TEAE	158 (76.4) (65.4, 89.3)	101 (227.9) (187.5, 276.9)	100 (235.8) (193.8, 286.9)	87 (221.2) (179.3, 273.0)	79 (233.7) (187.4, 291.3)
Mild	81 (39.2) (31.5, 48.7)	72 (162.4) (128.9, 204.7)	65 (153.3) (120.2, 195.5)	60 (152.6) (118.5, 196.5)	53 (156.8) (119.8, 205.2)
Moderate	69 (33.4) (26.4, 42.3)	28 (63.2) (43.6, 91.5)	35 (82.5) (59.3, 115.0)	24 (61.0) (40.9, 91.0)	23 (68.0) (45.2, 102.4)
Severe	8 (3.9) (1.9, 7.7)	1 (2.3) (0.3, 16.0)	0 (0.0) (0.0, 18.9)	3 (7.6) (2.5, 23.7)	3 (8.9) (2.9, 27.5)
Total Patient-Years	206.8	44.3	42.4	39.3	33.8

System Organ Class	Week [48-60) n (IR) (95% CI)	Week [60-72) n (IR) (95% CI)	Week [72-84) n (IR) (95% CI)	Week [84-96) n (IR) (95% CI)	Week [96-108) n (IR) (95% CI)	Week [108-) n (IR) (95% CI)
Patients with >=1 TEAE	51 (204.7) (155.6, 269.3)	27 (219.9) (150.8, 320.7)	12 (190.2) (108.0, 334.8)	4 (172.1) (64.6, 458.5)	3 (289.1) (93.2, 896.4)	0 (0.0) (0.0, 36496.5)
Mild	36 (144.5) (104.2, 200.3)	16 (130.3) (79.8, 212.7)	7 (110.9) (52.9, 232.7)	3 (129.1) (41.6, 400.2)	1 (96.4) (13.6, 684.2)	0 (0.0) (0.0, 36496.5)
Moderate	14 (56.2) (33.3, 94.9)	10 (81.5) (43.8, 151.4)	5 (79.2) (33.0, 190.4)	1 (43.0) (6.1, 305.4)	2 (192.7) (48.2, 770.7)	0 (0.0) (0.0, 36496.5)
Severe	1 (4.0) (0.6, 28.5)	1 (8.1) (1.1, 57.8)	0 (0.0) (0.0, 126.7)	0 (0.0) (0.0, 343.9)	0 (0.0) (0.0, 770.4)	0 (0.0) (0.0, 36496.5)
Total Patient-Years	24.9	12.3	6.3	2.3	1.0	0.0

Adverse events of special interest

An overview of adverse events of special interest double-blind treatment period (weeks 0 to 12) and combined treatment periods study RHCD is provided in **Table 36**.

Table 36 Overview of Adverse Events of Special Interest Double-Blind Treatment Period (Weeks 0 to 12) and Combined Treatment Periods Study RHCD

	Main Group – Double Blind Treatment Period		Protocol Addendum (2) Group – Placebo-Controlled Treatment Period			Combined Treatment Periods
Treatment Group	Placebo (N = 56)	Ixekizumab Q4W (N = 115)	Placebo (N = 19)	Etanercept (N = 30)	Ixekizumab Q4W (N = 38)	Ixekizumab Q4W (N = 196)
Category, n (%)						
Hepatic	0	0	0	0	0	3 (1.5)
Cytopenias	0	1 (0.9)	0	0	0	3 (1.5)
Infections	14 (25.0)	37 (32.2)	3 (15.8)	6 (20.0)	13 (34.2)	123 (62.8)
Allergic reactions / HS	1 (1.8)	6 (5.2)	0	0	3 (7.9)	15 (7.7)
Potential Anaphylaxis	0	0	0	0	0	0
Non-anaphylaxis	1 (1.8)	6 (5.2)	0	0	3 (7.9)	15 (7.7)
Injection-site reactions	1 (1.8)	14 (12.2)*	0	0	0	39 (19.9)
Malignancies	0	0	0	0	0	0
Depressions	0	1 (0.9)	0	0	0	6 (3.1)
Interstitial lung disease	0	0	0	0	0	0
IBD - adjudicated	0	1 (0.9)	0	0	1 (2.6)	4 (2.0)

Abbreviations: HS = hypersensitivity; IBD = inflammatory bowel disease; N = number of patients in the analysis population; n = number of patients in the specified category; Q4W = every 4 weeks.
* p<.05 versus placebo.
Note: Patients with multiple occurrences are counted once for each category. Patients may be counted in more than 1 category.

Infections

Key infection-related TEAE findings include:

Incidence of infection-related TEAEs

During the Double-Blind Treatment Period, the percentage of patients with at least 1 infection-related TEAE was numerically higher in the ixekizumab Q4W group compared to either the placebo or etanercept groups.

Severity of infection-related TEAEs

The majority of infections were mild to moderate in severity. In the Main Group, no patients reported severe or serious infection-related TEAEs. In the Protocol Addendum (2) Group, 1 patient in the etanercept Q1W group reported severe Pharyngitis. In the Combined Treatment Periods, 1 ixekizumab-treated patient reported severe Pharyngitis. Two ixekizumab-treated patients reported SAEs (1 patient reported Otitis media acute and 1 patient reported Tonsillitis).

No patient discontinued study drug due to an infection-related TEAE.

Opportunistic infections

One patient, in the Combined Treatment Periods, reported a TEAE of Varicella zoster virus infection (moderate severity). No opportunistic infections were reported in the Protocol Addendum (2) Group.

Most frequently reported infections

In the Main Group, the most frequently reported infections (at least 2% of patients in either group) were Nasopharyngitis and Upper respiratory tract infection (both groups), Tonsillitis and Vaginitis gardnerella (placebo group), and conjunctivitis (ixekizumab Q4W group).

In the Protocol Addendum (2) Group, the most frequently reported infections (at least 5% of patients in any group), were Nasopharyngitis, Tonsillitis, and Vaginitis gardnerella (placebo), Pharyngitis and Influenza (etanercept group), and Nasopharyngitis, Upper respiratory tract infection, and Viral infection (ixekizumab Q4W group).

In the Combined Treatment Periods, the most frequently reported infections (at least 5% of patients) were Nasopharyngitis, Upper respiratory tract infection, Pharyngitis, Conjunctivitis, Impetigo, and Tonsillitis.

Infection subgroup analyses
In the Main Group, the frequency of infections was higher in the > 25 kg and < 50 kg subgroup compared to the > 50 kg subgroup, and in the EU than in North America or the Rest of the World.

Infection subgroups were not assessed in the Protocol Addendum (2) Group.

In the Combined Treatment Periods, the frequency of infections was higher in the > 25 kg to < 50 kg subgroup compared to the < 25 kg and > 50 kg subgroups, and in North America than in the European Union and the Rest of the World.

No discontinuations due to an AE were noted in either subgroup.

Injection Site Reactions

Key ISR-related TEAE findings include:

Incidence of ISR-related TEAEs

During the Double-Blind Treatment Period, the percentage of patients with at least 1 ISR-related TEAE was significantly higher in the ixekizumab Q4W group compared to the placebo group, in the Main Group. There were no ISR-related TEAEs reported in the Protocol Addendum (2) Group.

Severity of ISR-related TEAEs

All ISRs were mild to moderate in severity. There were no ISR-related SAEs, no patient discontinued due to an ISR-related TEAE.

The exposure-adjusted incidence rate was 1.9 per 100 PY.

Inflammatory bowel disease - adjudicated

Severity of IBD-related TEAEs

The patient RHCD-401-1180 with adjudicated CD in the Double-Blind Treatment Period reported AEs of moderate Gastrointestinal inflammation and mild Abdominal pain, the same day as starting the Double-Blind Treatment Period. On Study Day 43, the patient reported the TEAE of Diarrhoea. None of the events were reported as an SAE. The remaining 3 patients with adjudicated CD events in the Combined Treatment Periods reported SAEs (2 with the preferred term Crohn's disease, 1 with Inflammatory bowel disease).

A positive dechallenge/rechallenge was reported in 1 patient.

Case summaries are presented for the 4 patients who reported adjudicated IBD-related TEAEs.

- One patient, in the ixekizumab Q4W group, 25 to 50 kg weight group, reported AEs of Gastrointestinal inflammation (moderate) and Abdominal Pain (mild) on Study Day 1, the same day as starting the double-blind treatment period.
  On Study Day 43, the patient reported an AE of Diarrhoea (moderate). Study drug was temporarily interrupted due to the AEs of Diarrhoea and Gastrointestinal inflammation. The patient was seen by a gastroenterologist. Study drug was permanently discontinued on Study Day 64 due to physician decision (suspected inflammatory bowel disease). No treatment details were reported for the AEs.
  The AEs of Abdominal pain and Diarrhoea were reported as resolved on Study Day 138. The patient permanently discontinued from the Post-Treatment Follow-up Period of the study on Study Day 356 due to the AE of Gastrointestinal inflammation, which was not resolved.
  The investigator considered the AEs of Gastrointestinal Inflammation, Abdominal pain, and Diarrhoea as related to study drug. The case was adjudicated as probable Crohn's disease.
- One patient, in the ixekizumab Q4W group, 25 to 50 kg weight group, reported 4 events of CD, on Study Day 151 (severe; study drug interrupted, patient recovered), Study Day 172 (SAE, study drug interrupted, severe; patient recovered), Study Day 177 of the maintenance period (moderate; study drug withdrawn, patient recovered), and Study Day 404 (Study Day 118 of post-treatment period; [SAE, severe; patient recovered]). The events were related by the investigator to the study treatment. The case was adjudicated as probable Crohn's disease.
- One patient, in the ixekizumab Q4W group, 25 to 50 kg weight group, reported 2 events of CD, 1 of which was an SAE which was moderate in severity, reported on Study Day 248 (Maintenance Period). The patient was hospitalised for abdominal pain, diagnosed with Crohn's disease, received corrective treatment, and was discharged (not recovered) 7 days later on Study Day 255. The second event was reported on Study Day 255 and was moderate in severity. At the time of database lock for this submission, the AE of Crohn's disease is ongoing and the patient has not recovered. Both events were related by the investigator to study treatment. The patient permanently discontinued from study treatment on Study Day 344 (from date of randomisation) due to the AE of Crohn's disease. The case was adjudicated as probable Crohn's disease.
- One patient, in the ixekizumab Q4W group, over 50 kg weight group, reported an SAE of Inflammatory bowel disease (severe) on Study Day 281 of the maintenance period.
  This SAE was not related to study drug per the investigator and no change was made in the dose of study drug. The patient was hospitalised, received corrective treatment, and recovered on Study Day 288. Subsequently, the patient withdrew from study drug and the study per request of his primary care physician. The case was adjudicated as probable Crohn's disease.

Inflammatory bowel disease in Study RHCD and other populations

Over longer-term exposure (206.8 PY of exposure), a total of 4 positively adjudicated CD cases were reported in Study RHCD, with an exposure-adjusted incidence rate of 1.9 per 100 PY. This is substantially higher than the incidence rates reported among all 8421 patients with Ps, PsA, and axSpA (including adults and paediatric patients; 21064.1 PY of exposure) in the ixekizumab clinical programme (0.1 per 100 PY), and paediatric patients in the literature (0.097 per 100 patient-years; Paller et al. 2019).

There was also a consistent numeric imbalance of IBD in the ixekizumab arm (<1%) compared to the placebo arm reported in adult Ps, PsA, and axSpA studies.

Upon request by the CHMP, the MAH provided incidence rates (IR) of CD in the paediatric psoriasis and paediatric general US populations:

- US paediatric psoriasis population is 0.097 per 100 PY (Paller et al. 2019)
- US paediatric general population is 0.0027 per 100 PY (Abramson et al. 2010)
- All-ixekizumab exposure group in the paediatric psoriasis study is 1.9 per 100 PY, and
- All-ixekizumab exposure group in adult psoriasis is 0.1 per 100 PY.

The IR of CD is 19 times higher in the ixekizumab paediatric psoriasis study than in both the paediatric psoriasis population and the ixekizumab adult psoriasis studies.

Allergic Reactions/Hypersensitivity

Key allergic reaction/hypersensitivity-related TEAE findings include:

Nature of allergic reaction/hypersensitivity-related TEAEs

All allergic reaction/hypersensitivity-related TEAEs in the study were non-anaphylactic.

Incidence of allergic reaction/hypersensitivity-related TEAEs

During the Double-Blind Treatment Period, the percentage of patients with at least 1 allergic reaction/hypersensitivity-related TEAE was numerically higher in the ixekizumab Q4W group compared to either the placebo or etanercept groups (there were no allergic reaction/hypersensitivity TEAEs reported in the etanercept or placebo groups).

Severity of allergic reaction/hypersensitivity-related TEAEs

The majority of allergic reaction/hypersensitivity-related TEAEs were mild to moderate in severity, in the Main Group and the Combined Treatment Periods. There was 1 severe allergic reaction/hypersensitivity-related TEAE (Urticaria), in an ixekizumab-treated patient. No patient discontinued due to an allergic reaction/hypersensitivity-related TEAE.

Reported allergic reaction/hypersensitivity-related TEAEs

In the Main Group, the reported allergic reaction/hypersensitivity-related events wereRash pustular (placebo group), and Urticaria, Bronchospasm, Dermatitis atopic, Eczema, and Rash maculo-papular (ixekizumab Q4W group).

In the Protocol Addendum (2) Group, the reported allergic reaction/hypersensitivity-related events were Urticaria, Bronchospasm, and Rash maculo-papular (ixekizumab Q4W group).

In the Combined Treatment Periods, the reported allergic reaction/hypersensitivity-related events were reported by more than 1 patient were Dermatitis atopic, and Urticaria.

Allergic reaction/hypersensitivity subgroup analyses

Allergic reaction/hypersensitivity-related TEAEs occurred more frequently in patients with at least one positive TE-ADA titre than in patients who were TE-ADA titre-negative.

Depression and Suicidal Ideation and Behaviour

Key depression-related TEAE findings include:

Incidence of depression-related TEAEs

During the Double-Blind Treatment Period, 1 patient (0.9%) reported a depression-related TEAE. This patient was in the ixekizumab Q4W group of the Main Group only. In the Protocol Addendum (2) Group, no depression-related TEAEs were reported in any of the treatment groups.

During the Combined Treatment Periods, 6 patients (3.1%) reported a depression-related TEAE.

Severity of depression-related TEAEs

There were no severe or serious depression-related TEAEs, and no patient discontinued study drug due to a depression-related TEAE.

Reported depression-related TEAEs

In the Double-Blind Treatment Period, the reported depression-related TEAE was Depression.

In the Combined Treatment Periods, the reported depression-related TEAEs were 3 patients reported Depression, 2 patients reported Depressed mood, and 1 patient reported Adjustment disorder with depressed mood.

CDRS-R findings

In the Double-Blind Treatment Period, there was no statistically significant difference in the change in the CDRS-R total score from baseline at Week 12 between treatment groups, in the Main Group.

In the etanercept Q1W group, the majority of patients (80%) had no categorical shift in the maximum postbaseline CDRS-R total score compared with their maximum baseline score. Four patients (13%) had improvement from baseline and 2 patients (7%) had worsening from baseline. The majority of patients (95%) in the ixekizumab Q4W and placebo groups had no categorical shift in the maximum postbaseline CDRS-R total score compared with their maximum baseline score. In the ixekizumab Q4W group, 1 patient (2.6%) had improvement from baseline and no patients had worsening from baseline. In the placebo group, 1 patient (5.3%) had improvement from baseline and 1 patient (5.3%) had worsening from baseline.

In the Combined Treatment Periods, the majority of patients (90.1%) had no change in the maximum postbaseline CDRS-R total score.

Upon request by CHMP, a review of the cases of depression was provided.

During the Combined Treatment Periods, 6 (3.1%) ixekizumab-treated patients reported at least 1 depression-related TEAE. Of those 6 patients, 3 patients (1.5%) reported depression, 2 patients (1.0%) reported depressed mood, and 1 patient (0.5%) reported adjustment disorder with depressed mood.

Across the 6 cases, 2 patients had baseline Children's Depression Rating Scale-Revised (CDRS-R) scores indicative of mild depression (>28). Both these patients' events were considered by the investigator not to be related to study drug and both remained on study treatment after the event. Further, 1 of these 2 patients had a history of anxiety and nonsuicidal self-injurious behaviour. Four patients' events were considered by the investigator not to be related to study drug. All patients remained on study drug after the event. No events were serious or severe.

Suicidal ideation and behaviour findings

Overall, two patients in the etanercept Q1W group, 4 patients in the ixekizumab Q4W group, and one patient in the placebo group reported Suicidal ideation and related behavioural findings during the Double-Blind Treatment Period.

In the Combined Treatment Periods, 4 patients treated with ixekizumab Q4W reported suicidal ideation and behaviour findings. Three of the patients answered 'yes' to only suicidal ideation questions, 1 patient answered 'yes' to both suicidal ideation questions and suicidal behaviour questions (actual attempt, interrupted attempt, aborted attempt, preparatory acts or behaviour, and suicidal behaviour).

None of these patients reported TEAEs of depression, depressed mood, or suicidal ideation or behaviours.

Serious adverse event/deaths/other significant events

Summaries of SAEs reported during the Double-Blind Treatment Period (Weeks 0 to 12) and the Combined Treatment Periods are displayed in **Table 37**.

Table 37 Serious Adverse Events Double-Blind Treatment Period (Weeks 0 to 12) and Combined Treatment Periods Study RHCD

	Main Group – Double Blind Treatment Period		Protocol Addendum (2) Group – Placebo-Controlled Treatment Period			Combined Treatment Periods
Treatment Group	Placebo (N = 56)	Ixekizumab Q4W (N = 115)	Placebo (N = 19)	Etanercept (N = 30)	Ixekizumab Q4W (N = 38)	Ixekizumab Q4W (N = 196)
Category, n (%)						
Patients with ≥1 SAE	0	1 (0.9)	0	1 (3.3)	1 (2.6)	13 (6.6)
Injury, poisoning, and procedural complications						
Total	0	1 (0.9)	0	1 (3.3)	1 (2.6)	3 (1.5)
Accidental overdose	0	1 (0.9)	0	0	1 (2.6)	1 (0.5)
Overdose	0	0	0	1 (3.3)	0	0
Ankle fracture	0	0	0	0	0	1 (0.5)
Postoperative ileus	0	0	0	0	0	1 (0.5)
Rib fracture	0	0	0	0	0	1 (0.5)
Splenic rupture	0	0	0	0	0	1 (0.5)
Gastrointestinal disorders						
Total	0	0	0	0	0	3 (1.5)
Crohn's disease	0	0	0	0	0	2 (1.0)
Diarrhoea	0	0	0	0	0	1 (0.5)
Inflammatory bowel disease	0	0	0	0	0	1 (0.5)
Vomiting	0	0	0	0	0	1 (0.5)
Infections and infestations						
Total	0	0	0	0	0	2 (1.0)
Otitis media acute	0	0	0	0	0	1 (0.5)
Tonsillitis	0	0	0	0	0	1 (0.5)
Metabolism and nutrition disorders						
Dehydration	0	0	0	0	0	2 (1.0)
General disorders and administrations site conditions						
Pyrexia	0	0	0	0	0	1 (0.5)
Investigations						
Glucose tolerance decreased	0	0	0	0	0	1 (0.5)
Renal and urinary disorders						
Renal haematoma	0	0	0	0	0	1 (0.5)
Reproductive system and breast disorders						
Ovarian cyst ruptured [a]	0	0	0	0	0	1 (0.9)
Respiratory, thoracic and mediastinal disorders						
Pneumothorax	0	0	0	0	0	1 (0.5)

Treatment Group	Main Group – Double Blind Treatment Period		Protocol Addendum (2) Group – Placebo-Controlled Treatment Period			Combined Treatment Periods
	Placebo (N = 56)	Ixekizumab Q4W (N = 115)	Placebo (N = 19)	Etanercept (N = 30)	Ixekizumab Q4W (N = 38)	Ixekizumab Q4W (N = 196)
Surgical and medical procedures						
Open reduction of fracture	0	0	0	0	0	1 (0.5)

There were no deaths in Study RHCD.

Laboratory findings

During the Double-Blind Treatment Period, 1 patient in the Main Group reported an AE of Neutropenia, in the ixekizumab Q4W group. No patient reported cytopenia in the Protocol Addendum (2) Group.

During the Combined Treatment Periods, 3 patients reported cytopenia, maximum Grade 2: 2 patients reported Neutropenia (1 mild and 1 moderate), and 1 patient reported both Neutropenia (mild) and Leukopenia (mild).

All events of cytopenia were transient. Patients continued on ixekizumab and recovered. In 2 patients, concurrent infection-related nonserious TEAEs were reported. No patient discontinued from study due to cytopenia.

During the Combined Treatment Periods, 3 patients reported at least 1 hepatic TEAE: 1 patient reported both Alanine aminotransferase increased (mild) and Transaminase increased (moderate), and 1 patient reported Hepatic enzyme increased only (mild), and 1 patient reported Hepatic enzyme increased (mild) and Hepatic steatosis (mild).

Three of the events had not resolved at the time of data base lock for the study. No patients developed progressive liver disease and all patients continued ixekizumab therapy. No patient discontinued from study due to hepatic TEAE.

Safety in special populations

Pregnancy

There are limited available data on ixekizumab use in pregnant women or male partners exposed to ixekizumab to inform any drug associated risks during pregnancy or potential effects on fetus and/or neonates. Animal studies do not indicate direct or indirect harmful effects of ixekizumab with respect to pregnancy, embryonic/foetal development, parturition, lactation, or postnatal development in animals exposed to ixekizumab.

The effects of ixekizumab on pregnancy and lactation will continue to be monitored throughout the duration of the ixekizumab clinical development programme and via routine pharmacovigilance.

Safety related to drug-drug interactions and other interactions

There are no known interactions of ixekizumab with other medicinal products.

Discontinuation due to adverse events

Discontinuations due to an adverse event (AE) were reported during the Double-Blind Treatment Period by 0 patients in ixekizumab Q4W; 0 patients in etanercept Q1W group and 1 patient placebo. In the Combined Treatment Periods, discontinuations due to an AE occurred in 3 ixekizumab-treated patients.

Post marketing experience

There is limited post marketing data available for paediatric patients with psoriasis.

As noted in PSUR 1, a signal for serious immediate hypersensitivity reactions consistent with anaphylaxis was identified from post marketing spontaneous AE reports of ixekizumab, leading to a review of data for serious immediate hypersensitivity reactions. Based on findings from post marketing spontaneous reports and mechanistic plausibility, the MedDRA Preferred Term of Anaphylaxis was added to section 4.4 "Special warnings and precautions for use" of the SmPC. Following PSUR 2, sections 4.4 "Special warnings and precautions for use" and 4.8 "Undesirable effects" of the SmPC were updated to reflect this information.

2.5.1. Discussion on clinical safety

The total safety population from study RHCD, a pivotal phase 3 study with the goal to show superiority when treating paediatric psoriasis patients with Taltz, includes 196 patients.

This application was initially to seek approval for treating children from the age of 6 and adolescents with moderate to severe plaque psoriasis who are candidates for systemic therapy. During the procedure, the indication was revised to restrict the use to paediatric patients weighing at least 25kg.

The study was divided into two timetables the first covering 12 weeks and consisting of two groups: the **main** group (double blind treatment period) and the protocol **addendum** group (placebo-controlled treatment period) and the second timetable covering week 16 through 104: the combined treatment periods, which includes the patients in the other two groups. In study RHCD, 196 patients have been exposed to ixekizumab of which 114 have been exposed to ixekizumab for at least 1 year.

For analyses based on the safety population, patients were to be randomised according to the treatment to which they had been assigned while the general and more appropriate approach is to analyse subjects according to treatment actually received. The MAH clarified that there were no patients where actual treatment received deviated from assigned treatment.

55.7% in the experiment arm (N=115) experienced 1-or more adverse events in the **main** group as compared to 44.6% in the placebo arm (N=56). In the **addendum** group (the treatment arm were divided into two arms: one with etanercept treatment and the other with ixekizumab treatment and one placebo arm): 47.45% in the ixekizumab arm experience some kind of AE (N= 38) as compared to 43.3% in the etanercept arm (N=30) and 26.3% in the placebo arm (N=19). After one year of treatment (combined treatment periods) 80.6 % of the patients experienced 1 or more adverse events.

Due to the mixed treatment background in the combined treatment periods, it was difficult to initially assess whether the increasing number of adverse events and increasing severity of the events with time was due to a cumulative effect of the dosage or other reason. The MAH provided an overview of adverse events (frequency and incidence rates) in the All Ixekizumab Safety Population by double-blind treatment assignments. Although the proportion of patients who reported at least 1 TEAE and severe TEAEs were highest in the IXE/IXE group, the analysis using exposure-adjusted IRs shows a different pattern with highest IR of TEAEs reported for the ETN/IXE group, followed by the PBO/IXE group and the IXE/IXE

group and the highest IR of severe TEAEs reported for the ETN/IXE group, followed by the IXE/IXE group and the PBO/IXE group. Furthermore, for TEAEs related to study treatment, the PBO/IXE group showed the highest IR and IR for serious adverse events showed only minor differences between treatment groups. Analyses with time-to-event plots for all TEAEs and AESIs were provided. It is agreed by CHMP that patients in the IXE/IXE and PBO/IXE groups were similarly likely to have reported first occurrence of a TEAE at time points after Week 12. In addition, the presented data are in support of an overall trend that the severity of TEAEs does not increase over time with cumulative dosage of ixekizumab.

The most common adverse event was infections (62.8%), and thereafter injection- site reactions (39%), allergic reactions (7.7%), depression and IBD, (3.2 and 2% respectively) during the combined treatment periods.

Most of the AEs were of mild or modest intensity and there were no deaths reported.

Three patients had to discontinue their medication due to adverse events.

The observed safety profile for paediatric patients from 6 to <18 years of age with moderate-to-severe plaque Ps in this multicenter study was fairly consistent with that reported for ixekizumab in adult patients with moderate-to-severe plaque Ps, PsA, and r-axSpA, except for Crohn's disease, infections, and allergic reaction, which were reported at a higher frequency in paediatric patients with Psoriasis. This is appropriately reflected in Section 4.8 of the SmPC.

Crohn's disease (CD) is a potential severe condition and, in the cases, presented there is a temporal relationship, in some of the cases there are dechallenge. In the adult study, the incidence of IBD is much lower (0.1 per 100 PY) than in the Taltz paediatric study (1.9 per 100 PY) as well as in the paediatric population in general in which the incidence is 0.097 per 100 PY according to MAH. While there is a known relationship with IBD and psoriasis, the MAH was requested to make a search for incidence data of IBD among paediatric psoriasis patients, if available, to assess whether the higher incidence among paediatric patients is due to treatment or not and further discuss the outcome of the IBD study events in relation to epidemiology. The MAH has provided information about the incidence of CD both in the US general paediatric population and the US paediatric psoriasis population and the incidence of CD is 35 times higher in the paediatric psoriasis population than in the general population. The IR of CD is 19 times higher in the All-ixekizumab exposure group in the paediatric psoriasis study than in the US paediatric psoriasis population. However, given the disproportion observed in frequency and incidence of IBD in paediatric patients treated with ixekizumab versus adult patients treated with ixekizumab (and versus the incidence of IBD in paediatric) and the additional clinical sequelae which children may experience as a result of this adverse reaction, the MAH was further requested to discuss the impacts this ADR has on the benefit risk for paediatric patients in particular. LEG-004 procedure on IBD was finalised during this type II variation and led to the update of Sections 4.4 (update of warning on IBD) and 4.8 (addition of IBD as uncommon adverse reaction) of the SmPC. A type IB variation is ongoing to implement the changes. The MAH indicates that the product information will alert HCPs to the potential for new onset IBD which may facilitate careful selection and monitoring of paediatric patients. Section 4.8 of the SmPC is updated to inform on the higher frequency of IBD in paediatric patients. However, IBD is an important identified risk, longer term safety of ixekizumab in paediatric patients with psoriasis will be collected to characterise this risk in the planned post authorisation study. This is agreed by CHMP.

The MAH was further requested to provide details on the patients assigned to treatment with ixekizumab with a prespecified medical history of inflammatory bowel disease. However, since there was only one patient with a history of IBD, CHMP considers that no conclusions can be drawn on the use of ixekizumab in paediatric patients with a history of IBD.

A total of 3.1% patients in the combined treatment periods experienced depression. In order to understand if this adverse event could be related to the treatment or not, the MAH explained that the

incidence of depression among paediatric patients with psoriasis in general (Kimball et al. 2012; Paller et al. 2019) is the same as the incidence of depression observed during the combined treatment period of paediatric psoriasis patients in the study. Furthermore, a review of the reported cases indicated that none had a certain relation to the study drug. The CHMP agrees that there does not appear to be an increased incidence of depression in paediatric patients treated with Taltz.

One patient presented a positive response on the Columbia-Suicide Severity Rating Scale (C-SSRS) at Week 6, however, the investigator did not report an AE. The MAH explained that adverse events in Study RHCD are unsolicited and, since the C-SSRS consists of solicited responses, these responses would not be considered as AEs and should not be reported as such. However, since Study RHCD was a pivotal study to extend the therapeutic indication, the disregarding of AEs which are notified from solicited responses is considered by CHMP to be inappropriate. The MAH provided an analysis of the frequency of suicidal ideation and suicidal behaviour in the double-blind period with the events experienced by this patient (0.9% and 0.5%, respectively). These frequencies are consistent with the incidence of suicidal ideation among paediatric patients with psoriasis reported in 2 US administrative insurance claims databases (0.5% [Kimball et al. 2012] and 1.0% [Paller et al. 2019]). It is agreed by CHMP that there does not appear to be an increased incidence of suicidal ideation in treated paediatric patients, though the low numbers preclude firm conclusions.

Three patients from the combined treatment periods experienced cytopenia and for 2 of the patients it was only neutropenia and another patient experienced both neutropenia and leukopenia. The MAH clarified that cytopenias was a designated category of adverse events of special interest in the study protocol. Cytopenias included leukopenia, neutropenia, and/or thrombocytopenia. No SmPC update was needed since neutropenia and thrombocytopenia are already included in the approved SmPC (Section 4.8).

A disproportionality of occurrence of abdominal pain was noted during the placebo controlled period of the study: 6 patients (over 5%) of ixekizumab patients versus 0 patients treated with placebo in the **Main** study group reported abdominal pain and 2 patients (over 5%) treated with ixekizumab in the Protocol Addendum (2) Group experienced abdominal pain/abdominal pain upper versus no patients treated with placebo and 1 patient treated with etanercept (3.3%). The MAH clarified that all of the ixekizumab-treated patients in the Protocol **Addendum** (2) Group are a subset of those in the **Main** Study. Therefore, across the Main Study and the Protocol Addendum, 6 ixekizumab-treated patients reported Abdominal pain and 1 ixekizumab-treated patient reported Abdominal pain upper during the Double-Blind Treatment Period. Of the 6 ixekizumab-treated patients who reported Abdominal pain as an AE, 1 patient (17%) reported Abdominal pain in the context of other AEs associated with inflammatory bowel disease (Gastrointestinal inflammation and Diarrhoea). This patient's case was adjudicated as probable CD. The other 5 patients (83%) reported Abdominal pain in the context of AEs associated with other GI disorders or non-GI disease states (Nausea, Vomiting, Diarrhoea, Influenza like illness, Pyrexia, Headache, Oropharyngeal pain, and Dizziness). In these 5 patients, abdominal pain did not persist or progress. The rational for not including abdominal pain in section 4.8 of the SmPC is agreed by CHMP.

Three patients experienced mild to moderate hepatic AE. Three of the events reported in 2 patients had not resolved at the time of database lock for the study. Follow-up data on these patients were provided during the procedure. One patient reported an AE of Weight increased and the other patient was obese. The hepatic AEs are thought to be linked with obesity and weight gain even though no firm conclusion can be drawn. No SmPC update is therefore needed.

There was an imbalance in the frequency of impetigo reported in study RHCD. In the Double-Blind Treatment Period, 1 ixekizumab-treated patient (0.9%) reported Impetigo compared with 0 patients in the placebo group. In the All Ixekizumab Safety Population, 13 patients (6.6%) reported the AE of Impetigo. The reported frequencies are consistent with the background prevalence of impetigo in children

and adolescents, which ranges from 5% in urban environments to 16% in rural environments (Bowen et al. 2015). No SmPC update is therefore needed. This is agreed by CHMP.

The frequency of discontinuation due to an AE was uncommon throughout the study, with a slight increase during prolonged treatment.

No conclusion can be drawn with respect to withdrawal and rebound in the paediatric population with psoriasis. Information on withdrawal and rebound is available in the SmPC based on data in adult patients with plaque psoriasis. The MAH commits to submit the results of the randomised withdrawal period (Period 4) in paediatric patients *post-approval* and to update accordingly the SmPC. This is agreed by CHMP.

Long term safety data in children and adolescents is limited. In light of the fact that there are currently no other IL-17A inhibitors licensed in children, the MAH was requested to comment on how the long-term safety and the long-term impact on growth and development would be characterised in paediatric psoriasis patients. In particular, the increased frequency of IBD observed in study RHCD is considered concerning by the CHMP. The MAH commits to conduct an observational post-authorisation safety study (PASS) to further characterise the long-term safety of ixekizumab in paediatric patients with psoriasis as an additional pharmacovigilance activity in the Risk Management Plan (RMP) with a focus on the important identified risks of IBD and serious infections.

2.5.2. Conclusions on clinical safety

The safety profile in patients 6-17 year of age with moderate-to-severe plaque Psoriasis appears to be consistent with the known safety profile for ixekizumab described in the currently approved EU product information although there is an elevated risk of allergic reactions (non-anaphylactic), infections, IBD and depression in paediatric patients as compared to adults. This is appropriately reflected in Section 4.8 of the SmPC.

Long term safety data in children is limited, as long-term use of ixekizumab has not been evaluated in this population. Longer-term safety data will be available from the ongoing study RHCD. In addition, the MAH commits to perform a post-authorisation study in paediatric patients with plaque psoriasis to characterise the long-term safety profile of ixekizumab with a focus on the important identified risks of IBD and serious infections.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The PRAC considered that the risk management plan version 7.2 is acceptable. The CHMP endorsed the Risk Management Plan with the following content:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Inflammatory bowel disease (Crohn's disease	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
and ulcerative colitis)	SmPC Section 4.4 SmPC Section 4.8 Additional risk minimisation measures: None proposed	signal detection: Spontaneous Follow-up Form-General Additional pharmacovigilance activities: Study I1F-MC-RHBT (final study report due 31 May 2030) [Trial alias pending] An Observational Study to Assess the Utilization and Safety of Ixekizumab Among Pediatric Patients Treated in the Course of Routine Clinical Care
Serious infections	Routine risk minimisation measures: SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.8 Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Spontaneous Follow-up Form-Candida Infection Spontaneous Follow-up Form-Extrapulmonary Tuberculosis Spontaneous Follow-up Form-Herpes Zoster Spontaneous Follow-up Form-Pneumonia Spontaneous Follow-up Form-Pulmonary Tuberculosis Spontaneous Follow-up Form-Tinea Infection Spontaneous Follow-up Form-Unspecified Infection Spontaneous Follow-up Form-Viral Reactivation Additional pharmacovigilance activities: Study I1F-MC-RHBT (final study report due 31 May 2030) [Trial alias pending] An Observational Study to Assess the Utilization and Safety of Ixekizumab Among Pediatric Patients Treated in the Course of Routine Clinical Care
MACE a	Routine risk minimisation measures: None proposed Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Spontaneous Follow-up Form-Cardiac Disorders Spontaneous Follow-up Form-Cerebrovascular Accident Additional pharmacovigilance activities: Study I1F-MC-RHBT (final study report due 31 May 2030

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Malignancy a	Routine risk minimisation measures: None proposed Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Spontaneous Follow-up Form-Cancer/Neoplasm Additional pharmacovigilance activities: Study I1F-MC-RHBT (final study report due 31 May 2030
Long-term safety in adults (such as events with a low frequency and/or long latency)	Routine risk minimisation measures: None proposed Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Spontaneous Follow-up Form-Cancer/Neoplasm Spontaneous Follow-up Form-Cardiac Disorders Spontaneous Follow-up Form-Cerebrovascular Accident Additional pharmacovigilance activities: Study I1F-MC-RHBT (final study report due 31 May 2030
Use in pregnancy and lactation	Routine risk minimisation measures: SmPC Section 4.6 Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Spontaneous Follow-up Form-Pregnancy Data Collection – Maternal Spontaneous Follow-up Form-Pregnancy Data Collection – Paternal Spontaneous Follow-up Form-Pregnancy Outcome – Maternal Spontaneous Follow-up Form-Pregnancy Outcome – Paternal Spontaneous Follow-up Form-Breast Feeding Additional pharmacovigilance activities: Study I1F-MC-B005 (final report due 30 June 2022)
Use in very elderly (≥75 years)	Routine risk minimisation measures: SmPC Section 5.2 Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study I1F-MC-RHBT (final study report due 31 May 2030
Use in paediatrics	Routine risk minimisation measures: SmPC Section 4.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None proposed	None Additional pharmacovigilance activities: None
Long-term safety in paediatrics	Routine risk minimisation measures: SmPC Section 4.2 Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: [Trial alias pending] An Observational Study to Assess the Utilization and Safety of Ixekizumab Among Pediatric Patients Treated in the Course of Routine Clinical Care
Use in patients with active infections	Routine risk minimisation measures: SmPC Section 4.3 SmPC Section 4.4 Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Immune response to live vaccinations	Routine risk minimisation measures: SmPC Section 4.4 SmPC Section 5.1 Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Abbreviations: MACE = major adverse cerebro-cardiovascular events; SmPC = summary of product characteristics.

a For adult population.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.4 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current QRD template (v10.1), which were accepted by the CHMP.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: there have not been revisions that significantly affect the overall readability and design of the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Paediatric plaque Psoriasis (Ps) affects approximately 1% of children and adolescents globally (Gelfand et al. 2005; Napolitano et al. 2016). It is estimated that 35% to 50% of adults with psoriasis developed their disease before 20 years of age (De Jager et al. 2009).

In literature reports, the prevalence of plaque Ps in children across three EU countries (UK, Germany and NL) was in the range 0.37% to 0.55% for those aged 0-10 years and 1.01% to 1.37% in those aged 10-19 years (Gelfand et al. 2005; Augustin et al. 2010; De Jager et al. 2009).

Paediatric patients with plaque Ps experience a particularly high disease burden and impact to quality of life during the formative years of life. Paediatric Ps is especially burdensome because it often presents on the face and scalp, as well as other highly visible areas. Accordingly, paediatric psoriasis can have a profound long-term impact on the psychological health of affected children by interfering with self-esteem, family and social relationships, and school activities. Additionally, paediatric psoriasis has been associated with certain comorbidities, such as obesity, hypertension, hyperlipidaemia, diabetes mellitus, inflammatory bowel disease (IBD), anxiety, depression, and rheumatoid arthritis, making early diagnosis and management essential (Bronckers et al. 2015; Paller et al. 2019).

3.1.2. Available therapies and unmet medical need

The indication initially applied for in the current submission for Taltz was treatment of moderate to severe plaque psoriasis in children from the age of 6 years and adolescents who are candidates for systemic therapy.

In paediatric patients, topical therapies and phototherapy have been the mainstay of treatment due to the limited number of approved systemic therapies for plaque Ps in children. There are few systemic therapies available for paediatric plaque Ps, and most have significant side effects or are not as effective as desired (e.g., methotrexate and cyclosporine) (Bronckers et al. 2015).

Three biological products (monoclonal antibodies) are approved for the treatment of paediatric plaque Ps; etanercept (Enbrel; approved for treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies), adalimumab (Humira, approved for treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies) and Stelara (ustekinumab, approved for treatment of moderate to severe plaque psoriasis in adolescent patients from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or

phototherapies). During the course of the procedure, the authorised indication for Stelara was extended to the treatment of paediatric patients as of 6 years of age with moderate to severe plaque psoriasis who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

Although several products are approved in paediatric Ps, an unmet medical need still exists for therapies for children and adolescents with moderate-to-severe plaque Ps. There are limited highly effective and safe treatment options, as well as options approved across a broad age-range of paediatric patients.

3.1.3. Main clinical studies

The efficacy and safety of ixekizumab in paediatric Ps is supported by one pivotal, randomised, double-blind, placebo-controlled Phase 3 study (RHCD) performed in children and adolescents from 6 years of age with moderate to severe plaque psoriasis. Patients were randomized to ixekizumab (dosed based on the subjects' body weight) or placebo in a 2:1 ratio. The ixekizumab dosing regimens were selected based on PK/PD modelling with an aim to achieve exposures similar to those in the pivotal studies supporting the adult psoriasis indication approval. As part of an addendum, a group of patients were also randomised to an active control group (etanercept) during the Double-Blind Treatment Period. The primary objective was to assess whether ixekizumab Q4W was 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 total of 171 patients were randomized to either ixekizumab Q4W (N=115) or placebo (N=56), and 16 patients (9.4% of the ITT population) discontinued the study. The majority of subjects (about 75%) were ≥12 years of age and had a body weight >50 kg (73%).

3.2. Favourable effects

For the co-primary endpoints, patients in the ixekizumab treatment group had statistically significant higher PASI 75 and sPGA (0,1) responses versus placebo at Week 12 (NRI). For PASI 75, ixekizumab had a response rate of 88.7% vs. 25.0% for placebo (ITT, NRI). For sPGA (0,1), the corresponding responder rates were 80.9% vs. 10.7%. Hence, Study RHCD achieved both its co-primary objectives.

In the Protocol Addendum (2) Group, patients in both the etanercept and the ixekizumab treatment groups had statistically significant higher PASI 75 and sPGA (0,1) responses versus placebo at Week 12 (NRI). The ixekizumab treatment group had numerically higher PASI 75 and sPGA (0,1) responses versus etanercept at Week 12 (63.3% and 53.3%, respectively; NRI), although not statistically significant.

The gated secondary endpoints were all met, e.g. superiority for ixekizumab vs. placebo was demonstrated for the endpoints showing complete or almost complete clearance of psoriasis (PASI 90, sPGA (0) and PASI 100 responses at Week 12).

Among patients in the Protocol Addendum (2) Group, patients in ixekizumab treatment group had statistically significant higher PASI 90, sPGA (0), and PASI 100 responses versus both placebo and etanercept at Week 12 (NRI).

For the gated secondary endpoint Itch NRS score improvement of at least 4 points, patients in the ixekizumab treatment group had statistically significant higher Itch NRS ≥4-point improvement responses versus placebo at Week 12 (NRI), 71.1% vs. 20.0%.

For the gated secondary endpoints PASI 75 and sPGA (0,1) responses at Week 4, patients in the ixekizumab treatment group had statistically significant higher PASI 75 and sPGA (0,1) responses versus placebo at this time point (NRI).

3.3. Uncertainties and limitations about favourable effects

No dedicated dose response studies have been performed in children or adolescents and the recommended doses were selected to target exposures in paediatric patients to be within the range of exposures observed in the Phase 3 Ps adult studies. The proposed posology in paediatrics is Q4W dosing while the adult posology is Q2W up to 12 weeks and Q4W thereafter. For subjects 25-50 kg, the exposure is predicted to be similar, or lower, with the proposed posology compared with adults. For subjects weighing >50 kg, the exposure is predicted to be slightly higher on average, compared with adults, after week 12. The observed response rates for PASI and sPGA endpoints in study RHCD were comparable or sometimes higher compared with the response rates in the adult, pivotal studies, based on a between-study comparison. A more cautious, conservative dose regimen in the paediatric population with a need for less frequent injections is agreed by CHMP.

The study population mainly (>70%) included patients aged >12 years and with a body weight >50 kg. A total of 27 individuals <12 years received ixekizumab and 31 subjects with a body weight <50 kg. There were only two subjects with a body weight <25 kg who received ixekizumab. The MAH has introduced a weight cut-off of 25 kg in the therapeutic indication and posology, in addition to the age cut-off 6 years.

More than 12% of subjects experienced medication errors in the pivotal study. In the majority of these cases, double the allocated dose of the active investigational medicinal product was administered to subjects, it was unclear how this affected the efficacy data. Further clarifications about the mis-dosing and its causes have been provided. The cases of mis-dosing did not seem to be associated with any obvious impact on efficacy or safety for the concerned patients, although a possible relation can be difficult to establish. For instance, there were some cases of injection site reactions (which could be related to a larger injection volume of the IMP). The majority of patients experiencing overdoses continued in the study, though. Additional efficacy analyses were also provided where patients with any dosing error prior to Week 12 assessment were imputed as Non-responders. These analyses showed lower response rates and slightly smaller differences vs. placebo, but still a clear superior response for ixekizumab over placebo.

No efficacy data beyond 12 weeks have been presented in this application. Longer-term efficacy results of the ongoing Study RHCD (48-week open-label maintenance period, Period 3) will be provided *post-approval*. The impact of withdrawal of Taltz in paediatric plaque psoriasis is assessed in period 4 (randomised withdrawal period) of Study RHCD; results will also be provided *post-approval*.

Subject numbers in the etanercept arm of the pivotal study were low (n=30).

Subject numbers for sub-group analyses were also low which makes interpretation difficult.

3.4. Unfavourable effects

80.6 % of the patients experienced one or more adverse events.

The most common adverse event was infections (62.8%), and injection- site reactions (39%), allergic reactions (7.7%), depression and IBD, 3.2 and 2% respectively during the combined treatment periods.

Most of the adverse events were of mild or modest intensity and there were no deaths reported.

Three patients had to discontinue their medication due to adverse events.

The paediatric population experience more infections, allergic reactions and IBD as well as depression when treated with Taltz than the adult population. The infections were non-serious and mild or moderate

in severity and none led to treatment discontinuation. The safety profile of ixekizumab in the paediatric population is appropriately reflected in Section 4.8 of the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

The safety analysis appears to demonstrate that the safety profile is consistent with the known safety profile of Taltz in the adult population except for a higher frequency of infections, IBD, allergic reactions and depressions.

In the initially proposed indication, no restriction on body weight was proposed. However, only very few children weighing 25 kg and below were included in the pivotal study, which means that there is an uncertainty with regard to the youngest children and their safety profile. The young child has a much more unmatured nervous system and could develop cognitive disorders but that will take some time to discover. The MAH has restricted the use of ixekizumab to patients weighing more than 25 kg.

Long term safety in children is an uncertainty. Longer-term safety data will be available from the ongoing study RHCD. In addition, the MAH commits to perform a post-authorisation study in paediatric patients with plaque psoriasis to characterise the long-term safety profile of ixekizumab with a focus on the important identified risks of IBD and serious infections.

3.6. Effects Table

Table 38 Effects Table for Taltz (ixekizumab), paediatric plaque psoriasis, Study RHCD

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PASI 75 response	Week 12	%	88.7	25.0	p<0.001	Main group
sPGA (0,1) response	Week 12	%	80.9	10.7	p<0.001	Main group
PASI 90 response	Week 12	%	78.3	5.4	p<0.001	Main group
Itch NRS ≥ 4-point improve-ment	Week 12	%	71.1	20.0	p<0.001	Main group. Among those with NRS ≥4 at baseline
Unfavourable Effects						
Adverse Events		%	Ixekizumab Q4w N=115 Main Group-Double Blind	Placebo N=56	Treated 12 weeks	Combined treatment periods Week 104 N=196
	Patients with 1 or more AEs		55.7	44.6		80.6
	Patients with 1 or more serious AE		0.9	0		6.6
	Discontinuation due to AE		0	1.8		1.5

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
infections			32.2	25.0		62.8
Injection site reaction			12.2	1.8		19.9
Allergic reactions	Non-anaphylaxis		5.2	1.8		7.7
Depressions			0.9	0		3.1
IBD			0.9			2.0

Abbreviations: IBD=inflammatory bowel disease

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The response rates for PASI 75 and sPGA (0,1) in paediatric patients with Ps are comparable to response rates in adult patients with psoriasis at Week 12 for adult Q4W patients in the adult psoriasis studies (UNCOVER 1, 2, and 3). The approved adult dose is 80 mg Q2W (after the initial loading dose), hence, a comparison with that dose level would have been more appropriate. The adult Ps PASI 75 and sPGA (0,1) response rates at week 12 were somewhat higher than those for the Q4W posology. The placebo responder rates in paediatrics were generally higher (e.g. 25% for PASI 75, 11% for sPGA (0,1) at week 12) compared with those in adults (2-7% for both endpoints across the three pivotal studies). Whithin their responses to the request for supplementary information, the MAH made further between-study comparisons, and it seems like the observed response rates for PASI and sPGA endpoints in study RHCD were comparable or sometimes higher compared with the response rates in the adult, pivotal studies. A more cautious, conservative dose regimen in the paediatric population with a need for less frequent injections is agreed by CHMP.

The gated secondary endpoints showed also high PASI 90, PASI 100 and sPGA (0) response rates in children, as well as a rather rapid onset of effect, based on PASI 75 and sPGA (0,1) response rates at week 4 (54% and 48%, respectively). These response rates were comparable to those in the adult studies (both for Q2W and Q4W dosing). Thus, although the approved adult posology is Q2W after the initial loading dose, Q4W seemed to provide a comparable onset of action in children and adolescents, at least when the total paediatric group is considered. The PK simulations and exposure results raised some concerns related to the proposed posology in paediatric patients vs. adults and relative under- vs. overexposure over time. It is thought that further patients may reach the high hurdle responder endpoints like PASI90, PASI100 or sPGA0 with a dosing frequency similar to that in adults (Q2W). However, this would require more frequent injections. Therefore, the proposed posology in paediatric patients was agreed by CHMP.

The comparison with etanercept was not included among the multiplicity-controlled endpoints and come from a small subgroup. However, based on the data presented, ixekizumab showed numerically higher response rates for PASI 75 and sPGA (0,1), as well as for the gated secondary endpoints. Initially, the CHMP did not consider these results robust enough to be included in the SmPC section 5.1. However, the etanercept arm is a key binding element of the agreed PIP foreseeing that at least 30 patients treated with etanercept should be enrolled. The CHMP agrees that this information may be of value for the prescriber and it is also noted that no claims about statistical significance are made. Hence, the CHMP agrees to include information on etanercept arm in Section 5.1 of the SmPC.

Maintenance of effect and impact of withdrawal of Taltz in paediatric patients with plaque psoriasis is investigated in the ongoing study RHCD. The MAH commits to submit the results *post-approval*.

The safety profile is partly consistent with the known safety profile for ixekizumab although the paediatric patients has an elevated risk for infections, IBD, allergic reactions and depressions as compared to the adult population. Long term safety data in the paediatric population are limited. Longer-term safety data will be available from the ongoing study RHCD. In addition, the MAH commits to perform a post-authorisation study in paediatric patients with plaque psoriasis to characterise the long-term safety profile of ixekizumab with a focus on the important identified risks of IBD and serious infections.

3.7.2. Balance of benefits and risks

Study RHCD has demonstrated a high and clearly clinically relevant treatment effect of ixekizumab vs. placebo in children and adolescents with moderate to severe chronic plaque Ps.

Some issues were raised related to the chosen posology. Sufficient justification has been provided to show that slightly higher or lower exposure in paediatric subgroups compared to adults is not be associated with lower efficacy or safety issues in paediatric subjects. Also, a lower induction dosing in adolescent subjects weighing >50 kg (dosing at Week 0 and then Q4W) than adults (dosing at Week 0, Q2W up to Week 12, then Q4W after Week 12) is recommended by the MAH. This is agreed by CHMP since it allows a more cautious, conservative dose regimen in the paediatric population with a need for less frequent injections. The numbers of patients with a body weight < 25 kg were small and an appropriate dosing could not be established. The MAH has introduced a weight limit of 25 kg in the posology as well as in the indication.

The impact of the lack of a paediatric-suitable presentation on the high medication error rate and sterility risks have been addressed by the MAH. The proposal is to withdraw the correct dose from the adult syringe. The MAH believes that these overdoses may not be more likely to occur in routine clinical practice, as the process is not as complex as in the clinical study setting (no interactive web response system involved and not so many blinded/unblinded staff members involved). The level of medication errors in the pivotal study is of concern but did not appear to adversely affect the overall benefit-risk profile of Taltz. It is also claimed that in real life, care and communication with patients is more straightforward and instructions will be provided in all EU languages. Reference is also made to other products with paediatric Pso indications, for which no dedicated paediatric formulation or strength is always available and for which there is a need to administer the dose by withdrawing the correct volume.

A dedicated paediatric dosage form (strength) for Taltz would have been preferred by CHMP. Since the posology does no longer include children with a weight below 25 kg, there is only one weight group that will need a specifically prepared dose by a healthcare professional, the 25-50 kg group that should receive 40 mg Q4W, i.e. 0.5 ml. To reduce real-world risk of medication errors, a paediatric-specific formulation that can safely deliver a 40 mg dose is required, which is also a MAH commitment from the agreed PIP planned to be completed in June 2023. The Product Information wording for Taltz administration was required to be very clear, in particular for administration of the 40 mg dose until a suitable paediatric formulation is developed. The SmPC and PL have been updated, e.g. to state that doses below 80 mg have to be prepared by a healthcare professional and that paediatric weights must be recorded and regularly re-checked prior to dosing, to reduce the risk of medication error rates seen in the pivotal study for this product. It is concluded that the lack of a dedicated paediatric dosage form for Taltz is a deficiency but does not *per se* constitute an obstacle for approval in the concerned weight group.

Concerning other safety aspects, while there is a risk for infection, IBD, allergic reaction and depression, the risk profile for paediatric patients is for most parts consistent with the known safety profile for ixekizumab described in the currently approved SmPC. Nevertheless, concerning IBD, it cannot be said that the safety profile in children is consistent with the safety profile of adults at this time. Given the disproportion observed in frequency and incidence of IBD in paediatric patients treated with ixekizumab

versus adult patients treated with ixekizumab (and the additional clinical sequelae which children may experience as a result of this adverse reaction), the impact of this ADR on the benefit risk for paediatric patients has been further discussed by the MAH. It is acknowledged by CHMP that, taking into consideration the product information updates in conclusion of LEG-004 for which a Type IB variation is ongoing to implement the changes, the product information will alert HCPs to the potential for new onset IBD which may facilitate careful selection and monitoring of paediatric patients. The MAH commits to conduct an observational post-authorisation safety study (PASS) to further characterise the long-term safety of ixekizumab in paediatric patients with psoriasis with a focus on the important identified risks of IBD and serious infections. This is acceptable by CHMP.

3.8. Conclusions

The overall B/R of Taltz for the treatment of moderate to severe plaque psoriasis in children from the age of 6 years and with a body weight of at least 25 kg and adolescents who are candidates for systemic therapy is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change to therapeutic indications - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include the treatment of moderate to severe plaque psoriasis in children from the age of 6 years and with a body weight of at least 25 kg and adolescents who are candidates for systemic therapy; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.4 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. The PI was also brought in line with the latest QRD template version 10.1. The RMP version 7.2 has also been agreed.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Taltz-H-C-003943-II-31'