24 July 2025
EMA/265031/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Taltz

International non-proprietary name: Ixekizumab

Procedure No. EMEA/H/C/003943/II/0053

Note

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

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List of abbreviations

ACR	American College of Rheumatology
ACR30/50/70/90/100	30%/50%/70%/90%/100% improvement in American College of Rheumatology criteria
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
axSpA	axial spondyloarthritis
bDMARD	biologic DMARD
BSA	body surface area
CHAQ	childhood health assessment questionnaire
COVID-19	coronavirus disease 2019
csDMARD	conventional synthetic DMARD
CSR	clinical study report
DMARD	disease-modifying antirheumatic drug
EMEA	European Agency for the Evaluation of Medicinal Products
EQ-5D-Y	EuroQol-five-dimensions-youth
ERA	enthesitis-related arthritis
ESR	erythrocyte sedimentation rate
ETV	early termination visit
hsCRP	high sensitivity C-reactive protein
IBD	inflammatory bowel disease
IL-1/6/17	interleukin-1/6/17
ILAR	International League of Associations for Rheumatology
ITT	intent-to-treat
JADAS-27	juvenile arthritis disease activity score-27
JIA	juvenile idiopathic arthritis
JoAS	juvenile onset ankylosing spondylitis
JPsA	juvenile psoriatic arthritis
LEI	Leeds enthesitis index

LTE	long-term extension
NK	natural killer
NSAID	nonsteroidal anti-inflammatory drug
OLE	open-label extension
OLT	open-label treatment
PASI	psoriasis area and severity index
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
PsA	psoriatic arthritis
PY	patient-years
SAE	serious adverse event
SAP	statistical analysis plan
SCS	Summary of Clinical Safety
SD	standard deviation
SmPC	summary of product characteristics
TEAE	treatment-emergent adverse event
TE-ADA	treatment-emergent anti-drug antibody
Th17	T helper 17
WBC	white blood cell

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly and Co (Ireland) Limited submitted to the European Medicines Agency on 22 July 2024 an application for a variation.

The following changes were proposed:

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 and IIIB

Extension of indication to include treatment of juvenile idiopathic arthritis for TALTZ, based on week 16 results from study I1F-MC-RHCG; this is a multicenter, open-label, efficacy, safety, tolerability, and pharmacokinetic study (COSPIRIT-JIA) of subcutaneous ixekizumab with adalimumab reference arm, in children from 2 to less than 18 years of age with juvenile idiopathic arthritis subtypes of enthesitis-related arthritis (including juvenile-onset ankylosing spondylitis) and juvenile psoriatic arthritis was performed to evaluate the efficacy and safety of ixekizumab for 16 weeks after treatment initiation. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.1 of the RMP has also been submitted. Furthermore, the PI is in line with the latest QRD template version 10.4.

The requested variation proposed amendments to the Summary of Product Characteristics 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(s) P/0049/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0049/2023 was completed.

The PDCO issued an opinion on compliance for the PIP P/0049/2023.

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: N/A

Timetable	Actual dates
Submission date	22 July 2024
Start of procedure:	17 August 2024
CHMP Rapporteur Assessment Report	11 October 2024
PRAC Rapporteur Assessment Report	18 October 2024
Updated PRAC Rapporteur Assessment Report	24 October 2024
PRAC Outcome	31 October 2024
CHMP members comments	4 November 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	7 November 2024
Request for supplementary information (RSI)	14 November 2024
CHMP Rapporteur Assessment Report	25 February 2025
PRAC Rapporteur Assessment Report	24 February 2025
PRAC Outcome	13 March 2025
CHMP members comments	17 March 2025
Updated CHMP Rapporteur Assessment Report	20 March 2025
Request for supplementary information (RSI)	27 March 2025
CHMP Rapporteur Assessment Report	24 June 2025
PRAC Rapporteur Assessment Report	26 June 2025
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	10 July 2025
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	17 July 2025
Opinion	24 July 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Within the current variation application, the MAH is seeking an extension of indication for ixekizumab. The MAH's initially claimed therapeutic indications were:

Juvenile idiopathic arthritis (JIA)

Juvenile psoriatic arthritis (JPsA)

Taltz is indicated for the treatment of active juvenile psoriatic arthritis in patients 6 to less than 18 years of age.

Enthesitis-related arthritis (ERA)

Taltz is indicated for the treatment of active enthesitis-related arthritis in patients 6 to less than 18 years of age.

Disease or condition

Clinical presentation, diagnosis

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of diseases characterised by idiopathic arthritis that starts before the age of 16 years and persists for at least 6 weeks. JIA is the most common chronic rheumatic disease in children and a leading cause of short- and long-term disability (Ravelli and Martini 2007). The incidence and prevalence estimate for JIA vary greatly from 1.6 to 23 and from 3.8 to 400 per 100,000 respectively, depending on the classification, methodology, timing, and geography (Thierry et al. 2014). ERA and JPsA are 2 of the 7 subtypes of the JIA defined by ILAR.

Enthesitis-related arthritis (including juvenile onset ankylosing spondylitis)

Enthesitis-related arthritis (ERA) (including juvenile onset ankylosing spondylitis (JoAS)) is characterised by the association of arthritis and enthesitis and is considered as the paediatric counterpart of ankylosing spondylitis or axial spondyloarthritis (axSpA). Main features of JoAS are familial aggregation, strong association with human leukocyte antigen-B27, as well as peripheral arthritis and enthesitis at onset and sacroiliitis and spondylitis throughout the course of the disease (Burgos-Vargas and Gutiérrez-Suárez 2012). ERA accounts for approximately 10% of JIA cases in Europe and North America compared to certain countries in Asia where it represents the most common JIA subtype (35% to 40% of JIA patients) (Kunjir et al. 2010; Shen et al. 2013; Guzman et al. 2015; Davies et al. 2016; Arkachaisri et al. 2017; Tanya et al. 2020; Pagnini et al. 2021). ERA mainly affects male patients and typically starts in late childhood or adolescence (Burgos-Vargas et al. 1997; Ravelli and Martini 2007; Consolaro et al. 2019).

Juvenile psoriatic arthritis

The juvenile psoriatic arthritis (JPsA) category by International League of Associations for Rheumatology (ILAR) criteria requires the simultaneous presence of arthritis and psoriasis or, if psoriasis is absent, the presence of arthritis and at least 2 of the following:

- family history of psoriasis in a first-degree relative
- nail psoriasis (nail pitting or onycholysis), and
- dactylitis (Petty et al. 1998, 2004).

JPsA represents about 1% to 7% of JIA cases and occurs with a biphasic distribution. Early peak is at 2 to 4 years and later peak is at 9 to 11 years of age (Ravelli and Martini 2007; Naddei et al. 2023).

Management

Treatment of juvenile idiopathic arthritis

The goals of JIA treatment are

1. rapid suppression of inflammation to reduce pain
2. prevent joint damage maintain
3. physical function and quality of life, and
4. promote normal growth and development.

Primary treatment

Pharmacologic first-line treatment available for patients with non-systemic JIA consists of

- nonsteroidal anti-inflammatory drugs
- intra-articular and systemic corticosteroids, and
- disease-modifying antirheumatic drug (DMARD) therapy: methotrexate (MTX).

Short-term systemic use of corticosteroids may be considered in more severe cases of JIA. Persistent arthritis requires DMARD therapy. MTX is the most used conventional synthetic DMARD (csDMARD). However, a substantial proportion of patients do not achieve adequate response, may lose disease control over time, or experience tolerability problems with these treatment options (Ringold et al. 2013; Hinze et al. 2015).

Biological agents

Biological agents

The approved biologic treatment of patients with ERA, JPsA, or both in the EU are shown in the table below.

Table 1 Biological agents approved for ERA and JPsA treatment in the EU.

Biologic agent	Target	Role in pathogenesis	Indication
Adalimumab	TNF alpha	Adalimumab binds specifically to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.	Approved by EMA for the treatment of ERA in patients aged 6 years and older and for polyarticular juvenile arthritis in patients aged 2 years and older
Etanercept	TNF alpha	Proinflammatory cytokine, found elevated in skin and synovial fluid in psoriasis and PsA	Approved by EMA for the treatment of JPsA in patients aged 12 years and older
Secukinumab	IL-17A	Main proinflammatory cytokine produced by Th17 lymphocytes, which plays a crucial role in skin and synovium inflammation in PsA	Approved by EMA for the treatment of JPsA and ERA and by FDA for the treatment of ERA in patients older than 6 years

Abbreviations: ERA = enthesitis-related arthritis; IL = interleukin; JPsA = juvenile psoriatic arthritis; PsA = psoriatic arthritis; Th17 = T helper 17; TNF = tumour necrosis factor.

The table below shows the approved Janus kinas inhibitors for treatment of patients with ERA, JPsA, or both in the EU.

Table 2 JAK inhibitors approved for ERA and JPsA treatment in the EU.

JAK Inhibitor	Target	Role in pathogenesis	Indication
Tofacitinib	JAK-1, JAK-2, and JAK-3 Enzyme	Tofacitinib works therapeutically by inhibiting the JAK-STAT pathway to decrease the inflammatory response.	Approved by EMA for the treatment of JPsA in patients aged 2 years and older, who have responded inadequately to previous therapy with DMARDs.
Baricitinib	JAK-1 and JAK-2 Enzyme	Baricitinib works therapeutically by inhibiting the JAK-STAT pathway to decrease the inflammatory response.	Approved by EMA for the treatment of active juvenile idiopathic arthritis in patients aged 2 years and older who have had an inadequate response or intolerance to one or more prior conventional synthetic or biologic DMARDs: polyarticular juvenile idiopathic arthritis (polyarticular rheumatoid factor positive [RF+] or negative [RF-], extended oligoarticular), ERA, and JPsA.

Abbreviations: DMARDs = disease-modifying antirheumatic drugs; ERA = enthesitis-related arthritis; JAK = Janus kinase; JPsA = juvenile psoriatic arthritis; STAT = signal transducer and activator of transcription.

2.1.2. About the product

Ixekizumab is an immunoglobulin G4 monoclonal antibody that binds with a high affinity and specificity to IL-17A, a key proinflammatory cytokine in the pathophysiology of plaque psoriasis, PsA, and axSpA (Leonardi et al. 2012; Taams et al. 2018; Robinson et al. 2019). IL-17A, a member of the IL-17 family, is mainly produced by inflammatory Th17 cells, a subset of T helper cells, but also by other T cells, neutrophils, and mast cells. Animal studies established the role of IL-17 signalling in ankylosing enthesitis and bone remodelling (Abe et al. 2009; Glatigny et al. 2012), and prophylactic administration of anti-IL-17 antibodies blocked the development of ankylosis in a spontaneous ankylosis mouse model (Ebihara et al. 2015).

Previously approved indications for ixekizumab include:

- treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.
- 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.
- treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drug (DMARD) therapies.
- active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.
- treatment of adult patients with active non-radiographic axSpA with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs).

The MAH states that inhibition of IL-17A by ixekizumab may provide novel therapeutic approach to disease management of JIA. Ixekizumab has demonstrated clinical safety and efficacy in adult patients with PsA, radiographic-axSpA, non-radiographic-axSpA, and moderate-to-severe plaque psoriasis in paediatric patients.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Study RHCG was initially part of the European PIP (EMEA-001050-PIP01-18), approved on 29 May 2012. The PIP was subsequently split into dermatology and rheumatology PIPs and approved on 20 November 2018, resulting in a new, rheumatology PIP, EMEA-001050-PIP02-18. The first PIP modification of this rheumatology PIP (EMEA-001050-PIP02-18-M01), which primarily updated the study from placebo-controlled to open-label and added an adalimumab reference arm, was approved on 16 August 2019. A second PIP modification (EMEA-001050-PIP02-18-M02), which extended the target date of completion due to slow study enrolment, was approved on 14 July 2023. The current study design was aligned with the modifications of this PIP.

A full compliance check to PIP EMEA-001050-PIP02-18-M02 was submitted on 31 May 2024.

2.1.4. General comments on compliance with GCP

The MAH states that study RHCG was conducted in accordance with Good Clinical Practices (ICH 2016) and applicable local laws and regulations (see also below).

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

Ixekizumab is a non-GMO (non-genetically modified organism) containing medicinal product. The EMA guideline for environmental risk assessment of medicinal products for human use (CHMP 2006) was consulted to conduct the Phase I environmental risk assessment for ixekizumab. Ixekizumab will be eliminated by degradation to smaller peptides and amino acids by a variety of proteolytic processes in the cells following receptor-mediated endocytosis or undergo biodegradation outside of the human body; therefore, there should be no environmental exposure to ixekizumab.

Because there is no expected environmental exposure and because there is no expectation that ixekizumab would be classified as persistent, bioaccumulative, and toxic, a Phase II assessment is not necessary and environmental studies with ixekizumab were not conducted.

The use of ixekizumab in humans is not expected to result in a significant risk to environmental organisms.

2.2.2. Discussion on non-clinical aspects

The MAH has submitted justification for not performing the ERA studies as the active substance is a monoclonal antibody, and as such is broken down by naturally occurring proteolytic enzymes into smaller (inactive) polypeptides or amino acids which are either further degraded by similar pathways or reabsorbed. Therefore, the use of ixekizumab in humans is not expected to result in a significant risk to environmental organisms.

2.2.3. Conclusion on the non-clinical aspects

The justification submitted for the absence of ERA studies is acceptable. This extension of indication is approvable from a non-clinical perspective.

2.3. Clinical aspects

2.3.1. Introduction

This variation comprises the clinical study report from an ongoing multicentre, open-label, randomised, Phase 3 study (protocol I1F-MC-RHCG, hereafter referred to as RHCG) of subcutaneous ixekizumab, with adalimumab as reference arm, to evaluate efficacy, safety, tolerability, and pharmacokinetics in children from 2 to less than 18 years of age diagnosed with JIA subtypes of ERA (including JoAS) and JPsA, who are bDMARD-naive or bDMARD-inadequate responder as per investigator's judgement.

GCP

The Clinical trial RHCG 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 the clinical study

Table 3. Overview of clinical study RHCG

Type of Study	Study Identifier	Location of Study Report	Objective of the Study	Study Design	Test Products; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	I1F-MC-RHCG	5.3.5.2	**Primary endpoint:** Percentage of participants meeting the JIA ACR 30 response criteria at Week 16	Multicentre, open-label, randomised, Phase 3 study of ixekizumab with adalimumab as a reference arm	**Test products:** Ixekizumab: SC injection Adalimumab: SC injection **Dosage regimen:** Ixekizumab arm: • Weight >50.0 kg: 80 mg Q4W (starting dose of 160 mg) • Weight 25.0 to 50.0 kg: 40 mg Q4W (starting dose of 80 mg) • Weight 10.0 to <25.0 kg: 20 mg Q4W (starting dose of 40 mg) Adalimumab arm: • Weight ≥30 kg: 40 mg Q2W • Weight 10 to <30 kg: 20 mg Q2W	Total enrolled: 101 Ixekizumab: 81 Adalimumab: 20	Children with JIA subtypes of ERA (including JoAS) aged 6 to <18 years and JPsA aged 2 to <18 years	The study has • OLT period: 16 weeks • OLE period: 88 weeks • LTE period: 160 weeks, and • PTFU period (Visits 801, 802, and 803): 4 to 12 weeks after the last visit.	Ongoing; Interim

Abbreviations: ACR 30 = 30% improvement in American College of Rheumatology criteria; ERA = enthesitis-related arthritis; JIA = juvenile idiopathic arthritis; JoAS = juvenile onset ankylosing spondylitis; JPsA = juvenile psoriatic arthritis; LTE = long-term extension; OLE = open-label extension; OLT = open-label treatment; PTFU = posttreatment follow-up; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous.

2.3.2. Pharmacokinetics

The general pharmacokinetic (PK) properties of ixekizumab are described in procedure number EMEA/H/C/003943/0000. In this application, new PK data are provided for paediatric juvenile idiopathic arthritis (JIA) patients (enthesitis-related arthritis [ERA] and juvenile psoriatic arthritis [JPsA]) participating in study I1F-MC-RHCG.

Bioanalytical methods

Determination of ixekizumab in human serum

Human serum samples were analysed for ixekizumab concentrations using a validated ELISA method at ICON Laboratory Services, Inc. located in Whitesboro, NY, USA (Table 4).

Table 4. Assay methodology for measuring ixekizumab (LY2439821) in study I1F-MC-RHCG.

Analyte	LY2439821
Sample Matrix	Human serum
Validated Method	M08.LY2439821.huse.1
Laboratory Name	ICON Laboratory Services, Inc.
Laboratory Location	8282 Halsey Road, Whitesboro, NY 13492
Lower Limit Quantification	6.30 ng/mL
Upper Limit of Quantification	400 ng/mL
Inter-assay Accuracy (% relative error)	4.0% to 10.0% (iBio) 2.0% to 8.0% (Watson)
Inter-assay Precision (% coefficient of variation)	≤ 6.5% (iBio) ≤ 5.7% (Watson)
Analyte Stability When Stored at -20° C	365 days
Analyte Stability When Stored at -70° C	1095 days

Immunogenicity assay

Human serum samples were analysed for anti-drug antibodies using a validated affinity capture and elution ELISA method (Table 5).

Table 5. Parameters for the ixekizumab screening anti-drug antibody assay

Assay Parameter	Result	Conclusion
Minimum Required Dilution (MRD)	1:5	This MRD maintained optimal balance between matrix effect and sensitivity. All subsequent analyses are performed at the MRD of 1:5.
Cut Point	≥0.169 OD (Tier 1) ≥65.9% (Tier 2)	Disease-state-specific cut points were calculated using the method described by Shankar et al. (2008), including the removal of outliers. The Tier 1 cut point was verified against the Phase 3 disease state population.
Sensitivity	4.6 ng/mL	The assay exceeds the sensitivity of 100 ng/mL proposed by FDA guidance (FDA 2016).
Drug Tolerance	480.5 mg/mL for radiographic axial spondyloarthritis	Using affinity-purified polyclonal anti-ixekizumab antibody from hyperimmune monkey serum (500 ng/mL), the assay demonstrated drug tolerance above the expected maximum ixekizumab concentration (95th percentile of Cmax, 24 mg/mL) in the dosing regimen tested for Phase 3 studies.
Precision	Intra-assay: 7.4% to 14.6% CV Inter-assay: 13.6% to 18.4% CV	The CV of ≤20% is acceptable.
Specificity	No signal above cut point obtained with a matched irrelevant antibody.	Specificity of the assay for anti-ixekizumab ADA was confirmed by use of an irrelevant species-matched control antibody.
	Positive controls inhibited >80% with excess ixekizumab, but not by an irrelevant IgG4.	Specificity of the assay for anti-ixekizumab ADA was confirmed by inhibition of positive controls >80% with excess ixekizumab, but not by an irrelevant IgG4.
Robustness	Deliberate changes in test method evaluated included incubation time, buffer pH, and hold time of plate prior to reading final results.	Assay is demonstrated to be robust, with all samples falling within a range of ±30% from baseline values.
Stability	6 freeze/thaw cycles: -17.9% to 6.2% difference; 4 and 24 hours at ambient temperature (20°C to 25°C) and 2°C to 8°C: -5.5% to 12.6% difference	Assay is stable across 6 freeze/thaw cycles. Assay is stable at ambient temperature (20°C to 25°C) and 2°C to 8°C up to 24 hours, with all samples falling within a range of ±25% from reference values.
Serum Factor Interference	Haemolysis: -7.1% (2 mg/mL) to 12.6% (1 mg/mL) Lipaemia: -11.0% (1 mg/mL) to 17.4% (2 mg/mL) Bilirubin: -6.3% (0.02 mg/mL) to 18.2% (0.02 mg/mL)	Multiple serum factors evaluated do not significantly affect the ability of the assay to detect ADA.

Assay Parameter	Result	Conclusion
Titration	Signal titrates below cut point	Demonstrates the ability of the assay to titrate the high control below the cut point(s).

Abbreviations: ADA = anti-drug antibody; Cmax = maximum plasma concentration; CV = coefficient of variation; FDA = Food and Drug Administration; IgG4 = immunoglobulin G subclass 4; MRD = minimum required dilution; OD = optical density.

Study I1F-MC-RHCG

The study consisted of an open-label treatment (OLT) period (Week 0 to Week 16), followed by an open-label extension (OLE) period (Week 16 to Week 104) and a long-term extension (LTE) period (Week 104 to Week 264) (Figure 9). The same weight-based dosing categories were used as in the paediatric plaque psoriasis (PsO) study (I1F-MC-RHCD) and the same dosing frequency as the adult psoriasis arthritis (PsA) and axial spondyloarthritis (axSpA) approved doses (Table 6).

Table 6. Weight-based dosing categories and corresponding posology used in study I1F-MC-RHCG.

Study	Patient Population	Body Weight	Starting Dose (Week 0)	Dose Thereafter (Q4W)
I1F-MC-RHCG	JIA (enthesitis-related arthritis and juvenile psoriatic arthritis)	>50.0 kg	160 mg (two 80-mg injections)	80 mg
		25.0 to 50.0 kg	80 mg	40 mg
		10.0 to <25.0 kg	40 mg	20 mg

All the enrolled patients were 5 to less than 18 years of age at baseline. In the ixekizumab group (during OLT), the enrolled patients by age group were: 1 patient <6 years of age, 20 patients 6 to <12 years of age, and 60 patients 12 to <18 years of age. In the ixekizumab group (during OLT), the enrolled patients by weight group were: 6 patients in the weight range 10.0 to <25.0 kg, 20 patients in the weight range 25.0 to ≤50.0 kg, and 55 patients in the weight range >50.0 kg. The body weight was reassessed at each visit and the administered doses were hence adjusted over time.

Descriptive pharmacokinetics

Only sparse PK sampling was conducted, and all samples were designed to be trough samples (Table 7).

Table 7. Pharmacokinetic and immunogenicity sampling schedule in study I1F-MC-RHCG.

Sample Number	Visit	Weeks (+/-7days)	Timepoints	Dosing Period
1	2	W0	Predose	Open-Label Treatment Period (OLT)
2	4	W4	Predose	
3	6	W12	Predose	
4	7	W16	Predose	
5	8	W20	Predose	Open-Label Extension Period (OLE)
6	11	W32	Predose	
7	17	W56	Predose	
8	23	W80	Predose	
9	29	W104	Predose	

Abbreviation: W = Week.

A total of 239 quantifiable ixekizumab concentrations from 81 patients up to Week 16 were available at the time of database lock (02 April 2024), which contains all PK data collected up to Week 16. Mean ixekizumab trough concentrations at predicted steady state (at Weeks 12 and 16) were consistent over time and overlap substantially between the 3 weight dosing groups, with mean concentrations in the range of 2.80 to 3.47 µg/mL (Table 8).

Table 8. Summary (geometric mean [%CV]) of ixekizumab serum trough concentrations (µg/mL) versus protocol time by body weight category and overall, during Weeks 0 to 16.

Treatment Group	OLT Period		
	W4	W12	W16
<25-kg Group (N = 6)	3.28 (56)	2.95 (41)	2.80 (46)
25- to 50-kg Group (N = 20)	5.09 (38)	3.39 (57)	3.32 (37)
>50-kg Group (N = 55)	4.43 (71)	3.25 (68)	3.47 (55)
Overall – All patients (N = 81)	4.48 (63)	3.26 (63)	3.36 (49)

Abbreviations: %CV = percent coefficient of variation; N = number of patients; OLT= open-label treatment; W = week.

Note: Data are presented as geometric mean and %CV. Only the 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.

A total of 248 quantifiable ixekizumab concentrations from 79 patients after Week 16 were available at the time of database lock (02 April 2024). Concentration data after Week 16 include data from patients assigned to ixekizumab at Week 0 and patients who were assigned to adalimumab at Week 0 and decided to switch to ixekizumab after the OLT Period (n = 3 in PK dataset). This study is ongoing [at submission of the application] so not all the PK data have been collected post Week 16 (see discussion for more information). Mean ixekizumab trough concentrations at predicted steady state were consistent over time and across the 3 weight dosing groups, with mean concentrations in the range of 2.65 to 4.18 µg/mL (Table 9).

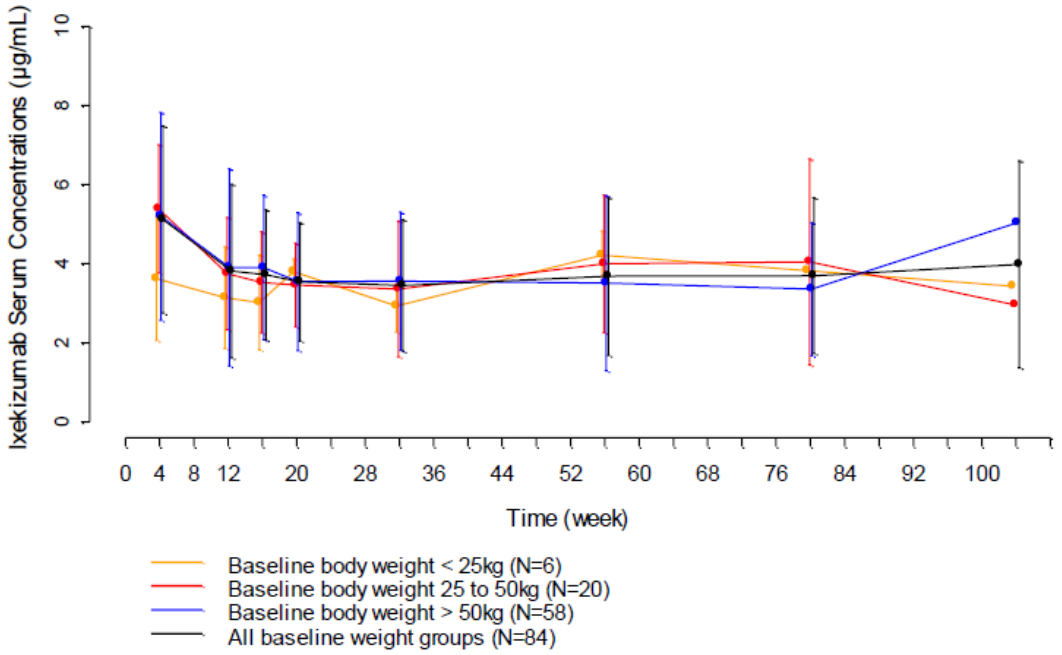
Table 9. Summary (geometric mean [%CV]) of ixekizumab serum trough concentrations (µg/mL) versus protocol time by body weight category and overall, during Weeks 20 to 104.

Treatment Group	OLE Period				
	W20	W32	W56	W80	W104
<25-kg Group (N = 6)	3.78 (9)	2.87 (23)	4.18 (14)	3.7 (37)	3.30 (42)
25- to 50-kg Group (N = 20)	3.28 (36)	2.80 (85)	3.66 (49)	3.36 (76)	2.65 (76)
>50-kg Group (N = 58)	3.13 (56)	3.04 (70)	2.97 (64)	2.83 (84)	4.16 (86)
Overall – All patients (N = 84)	3.22 (48)	2.96 (70)	3.22 (58)	3.14 (72)	3.42 (62)

Abbreviations: %CV = percent coefficient of variation; N = number of patients; OLE = open-label extension; W = Week.

Note: Data are presented as geometric mean and %CV. Only the 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.

Mean serum trough concentration profile versus protocol sampling time up to Week 104, stratified on baseline body weight, is shown in Figure 1.



Abbreviations: N = number of patients; SD = standard deviation.

Notes: All samples were designed to be trough samples. Only the samples that met the predefined trough criteria were included in the summary statistical calculation.

Figure 1. Mean (SD) ixekizumab serum trough concentrations versus protocol times from Week 0 to Week 104 by baseline body weight category and overall.

Two subtypes of JIA patients were enrolled in the study, ERA patients and JPsA patients. The overlap between the ERA and JPsA patients in terms of exposure, both during the OLT and the OLE periods, are shown in Table 10 and Figure 2. No PK difference was identified.

Table 10. Summary (geometric mean [%CV]) of ixekizumab serum trough concentrations (µg/mL) versus protocol time by juvenile idiopathic arthritis subtypes, and body weight category and overall, during weeks 0 to 104.

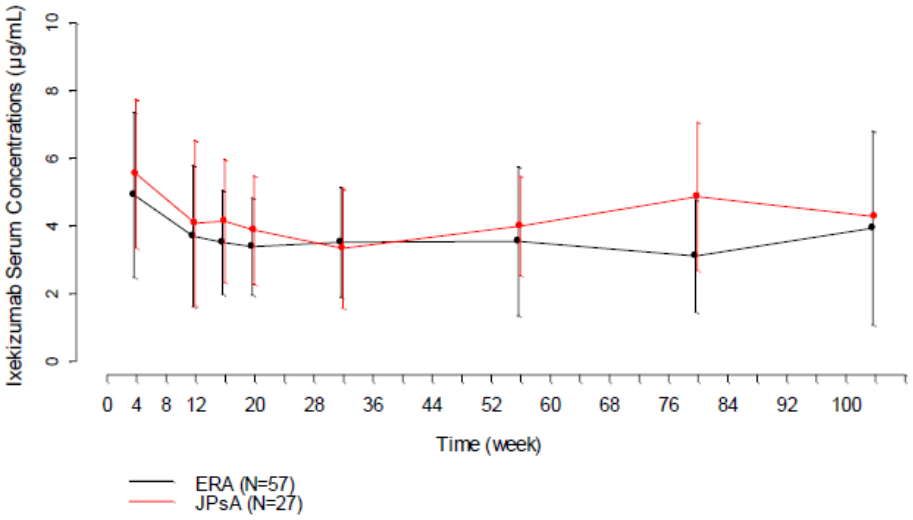
ERA Indication					
Period	**Week**	**<25-kg Group (N = 3)**	**25- to 50-kg Group (N = 8)**	**>50-kg Group (N = 46)**	**Overall – All patients (N = 57)**
OLT	W4	2.59 (72)	4.94 (44)	4.26 (69)	4.24 (66)
	W12	2.67 (36)	3.67 (36)	3.17 (64)	3.21 (58)
	W16	2.44 (63)	3.12 (36)	3.25 (53)	3.16 (51)
OLE	W20	3.89 (8)	3.17 (40)	2.96 (56)	3.06 (51)
	W32	2.13-3.02[a]	3.39 (50)	3.06 (67)	3.08 (62)
	W56	4.32-5.04[a]	2.49 (40)	2.99 (66)	3.03 (61)
	W80	4.77[b]	1.90 (25)	2.81 (95)	2.63 (75)
	W104	2.49-4.37[a]	1.64[b]	4.16 (86)	3.3 (68)
JPsA Indication					
Period	**Week**	**<25-kg Group (N = 3)**	**25- to 50-kg Group (N = 12)**	**>50-kg Group (N = 12)**	**Overall – All patients (N = 27)**
OLT	W4	4.15 (32)	5.2 (35)	5.08 (80)	5.01 (55)
	W12	3.43 (59)	3.18 (74)	3.58 (84)	3.39 (74)
	W16	3.20 (32)	3.45 (40)	4.60 (52)	3.79 (45)
OLE	W20	3.63 (12)	3.37 (35)	3.93 (53)	3.60 (40)
	W32	3.11 (23)	2.47 (108)	2.97 (86)	2.75 (85)
	W56	3.70-3.80[a]	4.87 (29)	2.92 (62)	3.68 (49)
	W80	2.88[b]	5.96 (33)	2.98[b]	4.48 (48)
	W104	Not collected	4.27[b]	Not collected	4.27[b]

Abbreviations: %CV = percent coefficient of variation; ERA = enthesitis-related arthritis; JPsA = juvenile psoriatic arthritis; N = number of patients; OLE = open-label extension; OLT = open label treatment; W = week.

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.

[a] Only 2 samples collected at the time of this database lock.

[b] Only 1 sample collected at the time of this database lock.



Abbreviations: ERA = enthesitis-related arthritis; JPsA = juvenile psoriatic arthritis; N = number of patients; SD = standard deviation.
Notes: All samples were designed to be trough samples. Only the samples that met the predefined trough criteria were included in the summary statistical calculation.

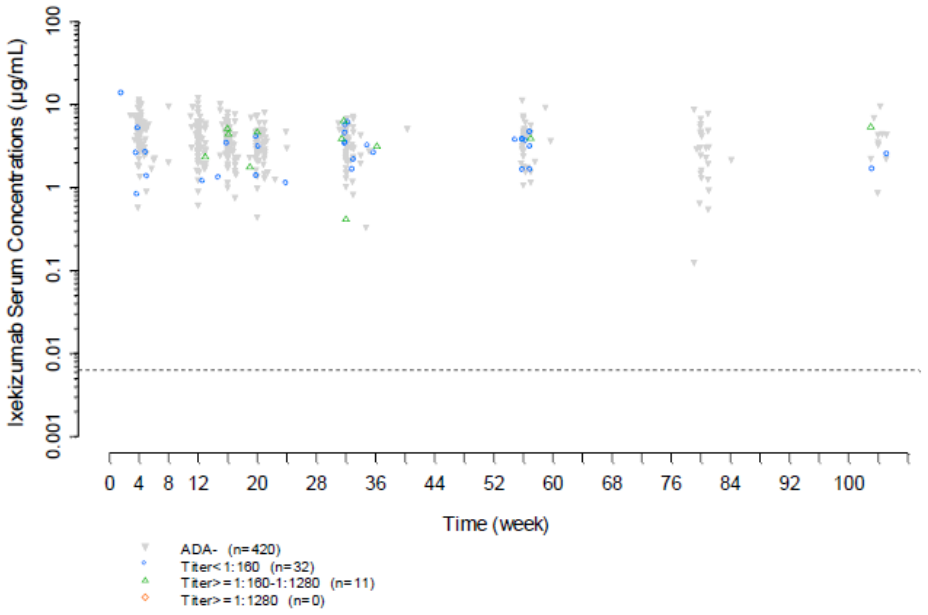
Figure 2. Mean (SD) ixekizumab serum trough concentrations versus protocol times from Week 0 to Week 104 by enthesitis-related arthritis or juvenile psoriatic arthritis subtypes.

Analysis of immunogenicity and pharmacokinetics

Pharmacokinetic data were summarised for evaluable samples (defined as being either treatment-emergent ADA [TE-ADA] positive or ADA negative). Samples that were ADA positive, but TE-ADA negative were not included in the figures. TE-ADA-positive samples are subdivided into low (<1:160), moderate (≥1:160 to <1:1280), and high (≥1:1280) titres. A patient is defined as overall TE-ADA positive if, at minimum, he experienced one TE-ADA positive sample during the OLT and OLE Periods.

Across all ixekizumab dosing regimen groups over the Week 0 to Week 104 period of the study for samples collected to date, the majority of samples (90.7% [420 of a total of 463 immunogenicity evaluable samples]) were ADA negative and 9.3% (43 samples) were identified as TE-ADA positive (Figure 3). This includes samples taken from patients randomised to ixekizumab at Week 0 and also patients who were randomised to adalimumab at Week 0, then switched to ixekizumab in OLE period onwards.

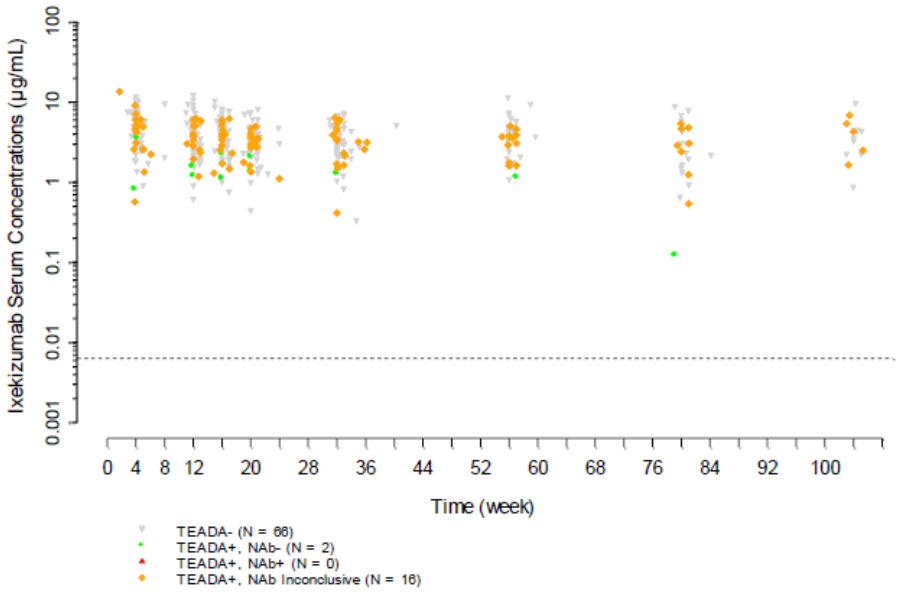
Maximum postbaseline titre in the TE-ADA-positive samples ranged from 1:10 to 1:640. Approximately three quarters (74.4% [n = 32 of 43]) of TE-ADA-positive samples were classified as low titre, 25.6% (n = 11) as moderate titre, and none as high titre. All TE-ADA positive samples were associated with drug concentrations that overlapped with drug concentrations associated with samples that were ADA negative.



Abbreviations: ADA = anti-drug antibody; n = number of samples; TE-ADA = treatment-emergent anti-drug antibody.
Notes: The dotted horizontal line represents the lower limit of the assay (0.0063 µg/mL). The drug tolerance limit of the ADA assay was 480.5 µg/mL.

Figure 3. Observed ixekizumab concentrations versus time from Weeks 0 to 104 indicating samples that were treatment-emergent anti-drug antibody positive.

From the 18 overall TE-ADA positive patients, 2 patients were neutralising antibody (Nab) negative (11.1%, n = 2 of 18), 16 were NAb inconclusive (88.9%, n = 16 of 18), and none were NAb positive. For the 16 NAb-inconclusive patients, their ixekizumab concentrations were in the same range as concentrations in the TE-ADA negative patients, which was also the case for the 2 NAb negative patients up to Week 56 (Figure 4). Only 1 PK sample after Week 56 appears lower than the rest of the population and is associated with a TE-ADA positive and NAb negative status at the patient level.



Abbreviations: ADA = anti-drug antibody; N = number of patients; NAb = neutralizing antibodies; TE-ADA = treatment-emergent anti-drug antibody.
Legend: grey triangles represent patients who were TE-ADA negative at all time points; green circles represent patients with TE-ADA-positive status who had only NAb-negative samples; orange diamonds represent patients with TE-ADA-positive status who had at least 1 NAb-inconclusive sample; and red triangles represent patients with TE-ADA-positive status who had at least 1 NAb-positive sample.
Notes: The dotted horizontal line represents the lower limit of the assay (0.0063 µg/mL). The drug tolerance limits were 480.5 µg/mL and 1.55 µg/mL for the ADA and NAb assays, respectively.

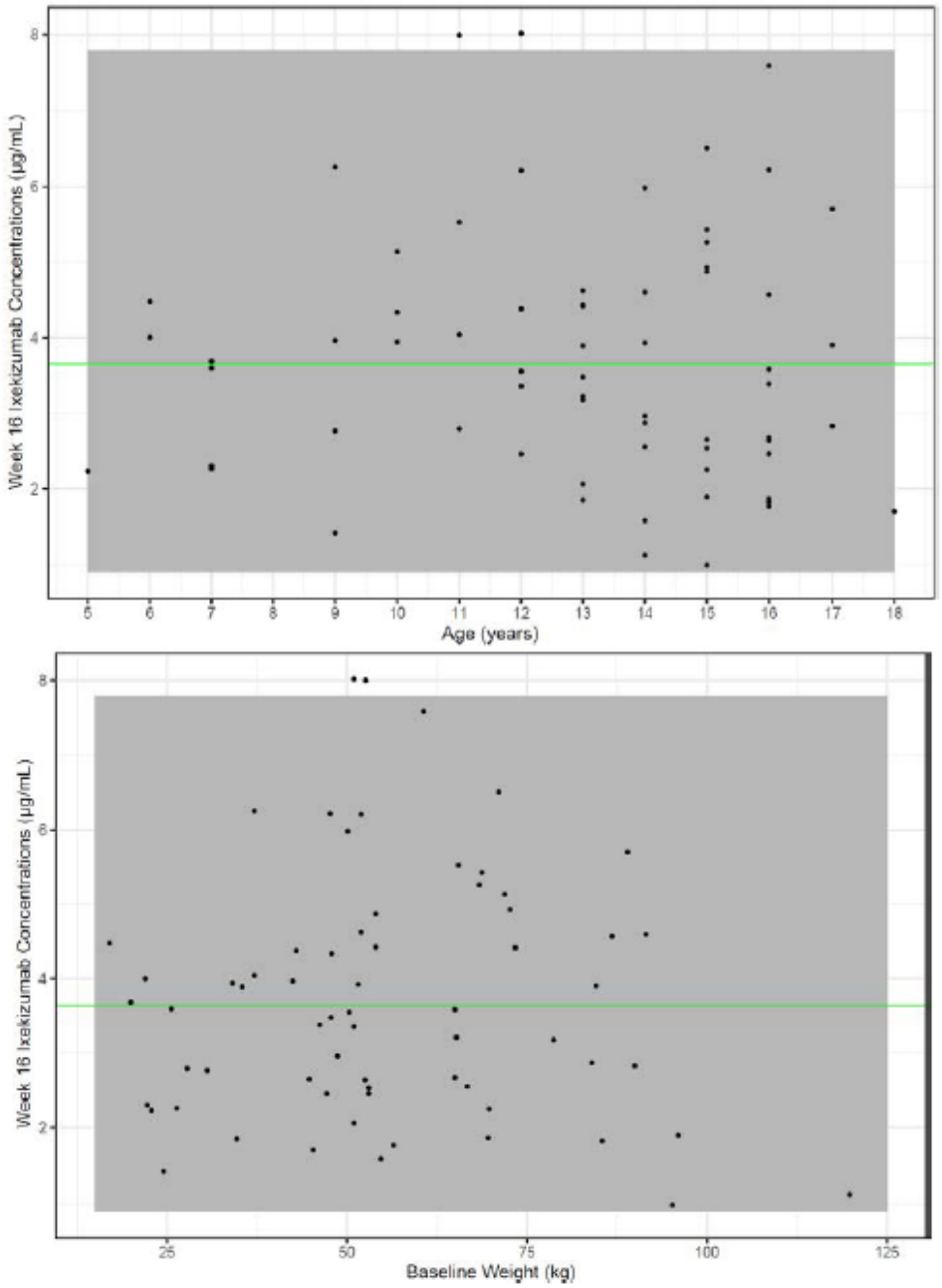
Figure 4. Observed ixekizumab concentrations versus time from Weeks 0 to 104 indicating patient level data with treatment-emergent anti-drug antibody and neutralising antibody status.

Comparison of pharmacokinetic results across studies

Comparison between JIA patients and adult patients with PsA and axSpA

Study I1F-MC-RHAP and Study I1F-MC-RHBE were Phase 3 studies examining the effect of ixekizumab compared with placebo during the double-blind, 24-week treatment period in patients with active PsA. Study I1F-MC-RHBV and Study I1F-MCRHBW were Phase 3 studies evaluating the efficacy and safety of ixekizumab in biological disease-modifying antirheumatic drug–naive patients and in tumour necrosis factor inhibitor–experienced patients with radiographic-axSpA, respectively. Study I1F-MC-RHBX evaluated the efficacy and safety of patients with nonradiographic-axSpA treated with ixekizumab who have never received biological disease-modifying antirheumatic drugs. In all these studies, the approved dosing regimen per indication was tested and PK data were collected at Week 16.

The observed ixekizumab trough concentrations at Week 16 across the full range of age and weight of the patients enrolled in the JIA study (Study I1F-MC-RHCG) are shown in Figure 5. The observed PsA and axSpA adult trough concentration data at the approved dosing regimen are included as a reference (grey-shaded area). These figures show that the range of observed trough concentrations achieved with the dosing regimens evaluated in this study is similar across ages and body weights, and within the range of the adult observed data with the approved dosing regimen.



Abbreviations: axSpA = axial spondyloarthritis; C_{trough} = trough concentration; PsA = psoriatic arthritis; Q4W = once every 4 weeks; RHAP = Study I1F-MC-RHAP; RHBE = Study I1F-MC-RHBE; RHBV = Study I1F-MC-RHBV; RHBW = Study I1F-MC-RHBW; RHBX = Study I1F-MC-RHBX; RHCG = Study I1F-MC-RHCG.
Note: The black dots are the observed C_{trough} in the paediatric patients. The solid grey band represents the 5th to 95th percentiles of the observed Week 16 adult concentration following a dose regimen of 160 mg then 80 mg Q4W from the 5 studies (RHAP, RHBE, RHBV, RHBW, and RHBX), and the green solid line represents the median adult concentration.

Figure 5. Observed ixekizumab trough concentrations by baseline body weight and age of paediatric patients in study I1F-MC-RHCG compared with adult patients with psoriasis arthritis or axial spondyloarthritis.

The observed ixekizumab trough concentrations at Week 16, following the proposed and approved dosing regimens, are also tabulated in Table 11, comparing data from paediatric subjects with the JIA subtype ERA to data from adult subjects with axSpA, and data from paediatric subjects with the JIA subtype JPsA to data from adult subjects with PsA. The observed trough concentrations from paediatric patients with ERA and JPsA, respectively, are within the range of observed trough concentrations from adult patients with axSpA and PsA, respectively.

Table 11. Summary of ixekizumab serum trough concentrations (µg/mL) at Week 16 by adult and paediatric indication.

Population	Study	Indication	No of Patients	Ixekizumab Observed Trough Concentrations (µg/mL) at Week 16 Geometric Mean (%CV)	Ixekizumab Observed Trough Concentrations (µg/mL) at Week 16 Median (min-max)
Paediatric	RHCG	ERA <25 kg	3	2.44 (63)	2.30 (1.42-4.47)
		ERA 25-50 kg	7	3.12 (36)	3.59 (1.70-4.38)
		ERA >50kg	34	3.25 (53)	3.51 (0.987-8.00)
		ERA overall	44	3.16 (51)	3.51 (0.987-8.00)
Adult	RHBV, RHBW, and RHBX	axSpA overall	122	3.14 (100)	3.42 (0.0204-11.6)
Paediatric	RHCG	JPsA <25 kg	3	3.20 (32)	3.68 (2.23-4.00)
		JPsA 25-50kg	11	3.45 (40)	3.38 (1.85-6.25)
		JPsA >50kg	8	4.60 (52)	5.22 (2.25-8.02)
		JPsA overall	22	3.79 (45)	3.79 (1.85-8.02)
Adult	RHAP and RHBE	PsA overall	57	3.01 (74)	3.38 (0.55-11.6)

Abbreviations: %CV = percent coefficient of variation; axSpA = axial spondyloarthritis; ERA = enthesitis-related arthritis; JPsA = juvenile psoriatic arthritis; N = number of patients; PsA= psoriatic arthritis.

Note: Data are presented as geometric mean and %CV or range. 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.

Comparison between JIA patients and paediatric patients with PsO

Study I1F-MC-RHCD was a Phase 3, multicentre, double-blind, randomised, placebo-controlled study examining the effects of ixekizumab versus placebo in patients from 6 to <18 years of age with moderate-to-

severe plaque psoriasis (PsO). The JIA study (Study I1F-MC-RHCG) used the same dosing regimen as the study in paediatric plaque psoriasis patients.

In Table 12, ixekizumab trough concentrations by weight category and overall, per week, are compared between JIA patients and paediatric patients with PsO. Weeks 12 and 16 are in a similar range and both are considered at steady state.

Table 12. Summary of ixekizumab serum trough concentrations (µg/mL) versus protocol time at steady state, by body weight category and overall.

Study Code	RHCG	RHCD	RHCG
Week	W12	W12	W16
<25-kg group (N of patients)	6	2	6
<25-kg group C_{trough} values	2.95 (41)	0.009 – 4.37[a]	2.80 (46)
25- to 50-kg group (N of patients)	20	29	20
25- to 50-kg group C_{trough} values	3.39 (57)	3.23 (73)	3.32 (37)
>50-kg group (N of patients)	55	80	55
>50-kg group C_{trough} values	3.25 (68)	3.20 (71)	3.47 (55)
Overall (N of patients)	81	111	81
Overall – C_{trough} values	3.26 (63)	3.03 (106)	3.36 (49)

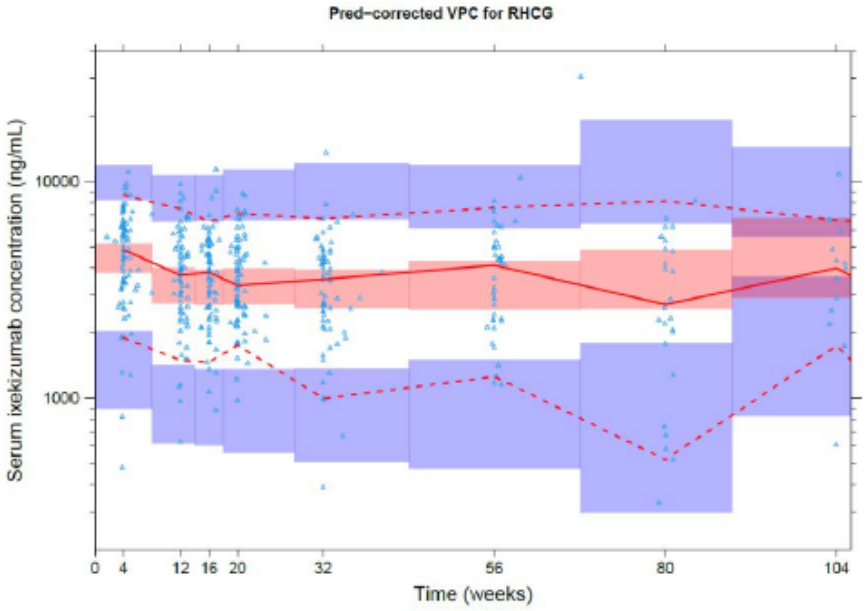
Abbreviations: %CV = percent coefficient of variation; C_{trough} = trough concentration; N = number of patients; RHCD = Study I1F-MC-RHCD; RHCG = Study I1F-MC-RHCG; W = week.

[a] Due to small N, individual data for patients in Study RHCD are shown for the <25-kg weight group since there were insufficient samples to calculate summary statistics.

Note: Data are presented as geometric mean and %CV. Only samples that were taken within ±7 days of the scheduled time from the 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 combined adult and paediatric population PK (popPK) model for ixekizumab was previously developed following Committee for Medicinal Products for Human Use feedback on the paediatric PsO EU submission. Simulations of PK using this popPK model were used to compare against the observed PK data from JIA patients. The model was not refitted to the JIA data and no new model analysis report was submitted. The model used was submitted and assessed in procedure EMEA/H/C/003943/II/0031 (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).

Prediction-corrected visual predictive check based on the final combined adult and paediatric popPK model plotted against the observed concentration data from JIA patients are represented in Figure 6.



Abbreviations: RHCG = Study I1F-MC-RHCG; VPC = visual predictive check.
Note: Blue triangles are observations, solid red lines depict the median of the observed data, and red-dashed lines represent the 5th and 95th percentiles of the observed data. Pink-shaded areas define the 95% confidence interval around the median of the simulated data, and blue-shaded areas are the model-predicted 95% confidence intervals of 5th and 95th percentiles of the simulated data.

Figure 6. Prediction-corrected visual predictive check, based on the previously accepted adult and paediatric final population pharmacokinetic model, plotted against the observed concentration data from the juvenile idiopathic arthritis patients in Study I1F-MC-RHCG.

2.3.3. Pharmacodynamics

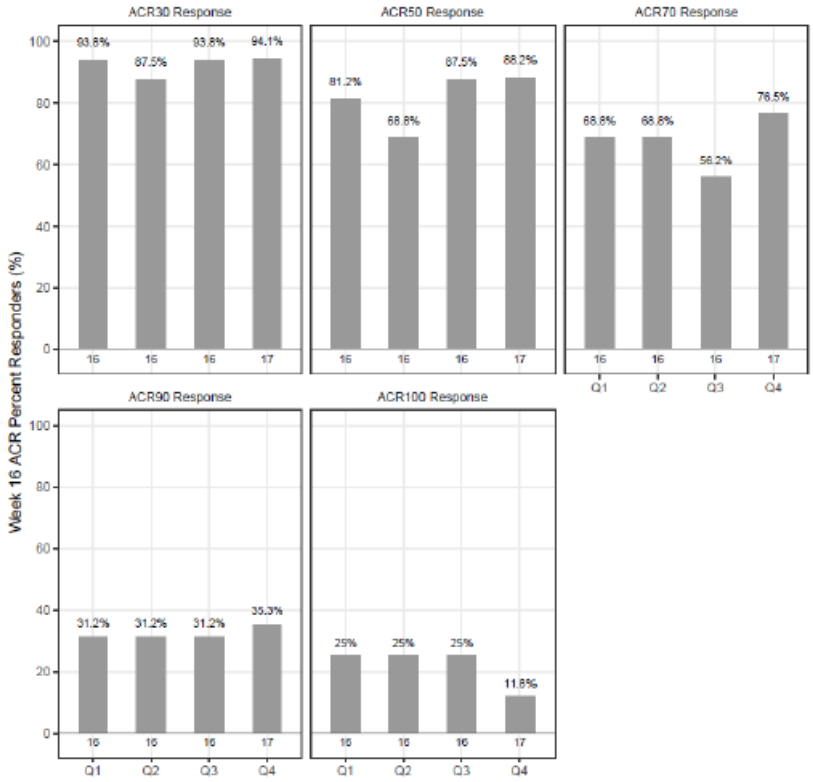
Please refer to previous procedures for details on the pharmacodynamics (PD) of ixekizumab. No new PD data reported.

2.3.4. Exposure-response relationships

Study I1F-MC-RHCG

Efficacy

The relationship between exposure and ACR30/50/70/90/100 response was explored with the exposure quartile analysis based on observed trough concentration quartiles. Using this assessment, no relationship could be established between exposure and ACR responses at Week 16 (Figure 7).



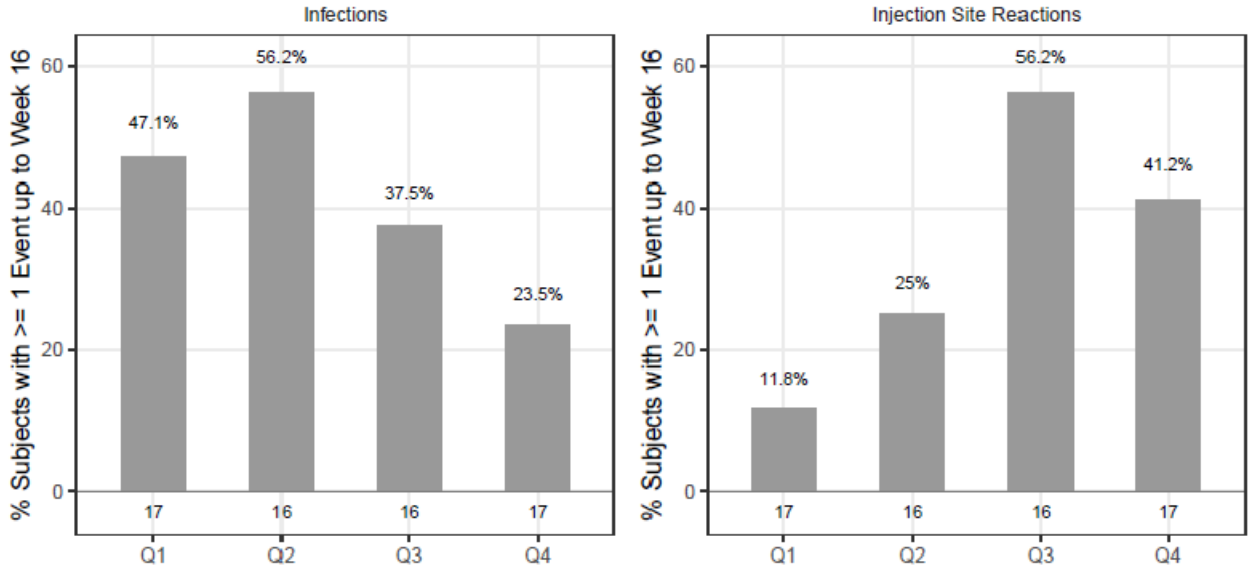
Abbreviations: ACR = American College of Rheumatology; ACR30/50/70/90/100 = 30%/50%/70%/90%/100% improvement in ACR criteria; Ctrough = trough concentration; Q = quartile.

Notes: All samples were designed to be trough samples. Only the samples that met the predefined trough criteria were included in this exploratory analysis. Values below each bar represent the number of patients at each C_{trough} quartile.

Figure 7. Observed ACR30/50/70/90/100 response by observed trough concentration quartiles at Week 16.

Safety

The two major adverse events of special interest (AESI) in this study, incidence of 'injection site reactions' and 'infections', are known and consistent with the safety profile for ixekizumab across indications. The exposure-response relationship for these two AESIs was explored with the exposure quartile analysis based on observed trough concentration quartiles. No relationship could be established between exposure and cumulative incidence of infections at Week 16 (Figure 8). There appears to be a concentration relationship with injection site reactions, with higher incidences at higher ixekizumab concentrations for the two higher quartiles (Figure 8). However, this is based on a small number of patients per quartile with the Q3 incidence higher than the Q4 incidence.



Abbreviations: C_{trough} = trough concentration; ISR = injection site reaction; Q = quartile.

Notes: All samples were designed to be trough samples. Only the samples that met the predefined trough criteria were included in this exploratory analysis. Values below each bar represent the number of patients at each C_{trough} quartile.

Figure 8. Observed cumulative incidence of infections (left panel) and injection site reactions (right panel) by observed trough concentration quartiles at Week 16.

2.3.5. Discussion on clinical pharmacology

The general pharmacokinetic (PK) properties of ixekizumab are described in procedure EMEA/H/C/003943/0000. In this application, new PK data are provided for paediatric juvenile idiopathic arthritis (JIA) patients (enthesitis-related arthritis [ERA] and juvenile psoriatic arthritis [JPsA]) participating in study I1F-MC-RHCG.

Bioanalytical methods

The assays for determination of ixekizumab and anti-drug antibodies in human serum has previously been assessed and found acceptable.

Study I1F-MC-RHCG

Only trough PK samples were collected in paediatric patients with JIA. The first dose administered was a loading dose (2x maintenance dose), followed by maintenance dosing Q4W from Week 4 an onwards. Steady state is expected from Week 12. The exposure was similar across the evaluated JIA subtypes (ERA and JPsA) and no differences in exposure were observed across baseline body weight categories ≥25 kg (SmPC section 5.2). Due to limited data in subjects <6 years old and subjects weighing <25 kg, the MAH suggests limiting the indication to paediatric JIA subjects with ERA or JPsA ≥6 years of age, and is not proposing a dosing regimen for subjects weighing <25 kg. This is supported, and the age and body weight limits are stated in the indication.

Of the collected immunogenicity samples, 9.3% (43 samples) were identified as TE-ADA positive. None of these were classified as high titre. The corresponding exposures are overlapping between TE-ADA positive and ADA negative samples. None of the TE-ADA positive patients had a sample that was NAb positive; however, 16 patients had at least one sample that was NAb inconclusive. The corresponding exposures are overlapping

between TE-ADA positive NAb negative patients, TE-ADA positive NAb inconclusive patients, and ADA negative patients. Since most TE-ADA positive patients were NAb inconclusive, the MAH agreed to delete their statement that "No patients had neutralizing antibodies" from the SmPC.

Comparison of pharmacokinetic results across studies

The study in JIA patients were only partially randomised and without placebo, and it is therefore not considered robust enough to solely conclude upon a beneficial effect for the paediatric JIA patients (for further information, see Discussion on clinical efficacy). The JIA subtype ERA is considered similar to the axSpA disease in adults, and the JIA subtype JPsA is considered similar to the PsA disease in adults. The MAH has shown that the observed trough concentrations for JIA patients in Study I1F-MC-RHCG are within the range of the adult (axSpA and PsA patients) observed data with the approved dosing regimen, both across age and across body weight. Furthermore, the MAH has shown that the observed trough concentrations from paediatric patients with ERA and JPsA, respectively, are within the range of observed trough concentrations from adult patients with axSpA and PsA, respectively. There is no analysis report presenting the comparisons of data across studies; however, the clinical study reports, for all adult studies included in the comparisons, have been submitted in previous applications for respective indications.

The study in JIA patients used the same body weight-based dosing regimen as was used in the paediatric PsO study (EMEA/H/C/003943/II/0031 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). The MAH has shown that observed trough concentrations by weight category and overall were similar in the two paediatric populations. Furthermore, the previously developed popPK model can describe the data from JIA patients which also supports that the PK of ixekizumab is similar in these populations.

Exposure-response relationships

Within the exposure range evaluated in the JIA study, the exposure-response relationship for ACR response at Week 16 is overall flat. However, for the JPsA subpopulation, there is a trend towards lower ACR90 and ACR100 response with higher exposure (not shown). The JPsA subpopulation analysis is based on a small number of patients per exposure quartile (5-6 subjects). Furthermore, the body weight-based dosing limits the exposure range and there is no obvious explanation for the observed trend (the higher incidence of injection site reactions [see below] is driven by the ERA subpopulation). It is therefore likely that this 'trend' is a random chance finding which does not represent a true relationship.

Within the exposure range evaluated in the JIA study, there is overall no trend in infections across exposure, whereas there is a trend towards an increase of injection site reactions with increasing exposure. No such trend was observed in the paediatric PsO study (procedure number EMEA/H/C/003943/II/0031), applying the same body weight-based dosing as in the JIA study. It is uncertain whether this trend in the JIA study represents a true exposure-response relationship in this population or not. See 'Discussion on clinical safety' for further discussion on safety-related findings.

2.3.6. Conclusions on clinical pharmacology

The MAH has shown that the observed exposure in JIA patients, following the proposed body weight-based dosing regimen, are within the range of the adult (axSpA and PsA patients) observed data with the approved dosing regimen, both across age and across body weight, and for each JIA subtype separately. This extension of indication is approvable from a PK perspective.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response study was performed in the paediatric population.

2.4.2. Main study

The title of the main study I1F-MC-RHCG is "*Multicenter, Open-Label, Efficacy, Safety, Tolerability, and Pharmacokinetic Study of Subcutaneous Ixekizumab with Adalimumab Reference Arm, in Children with Juvenile Idiopathic Arthritis Subtypes of Enthesitis-Related Arthritis (Including Juvenile Onset Ankylosing Spondylitis) and Juvenile Psoriatic Arthritis*".

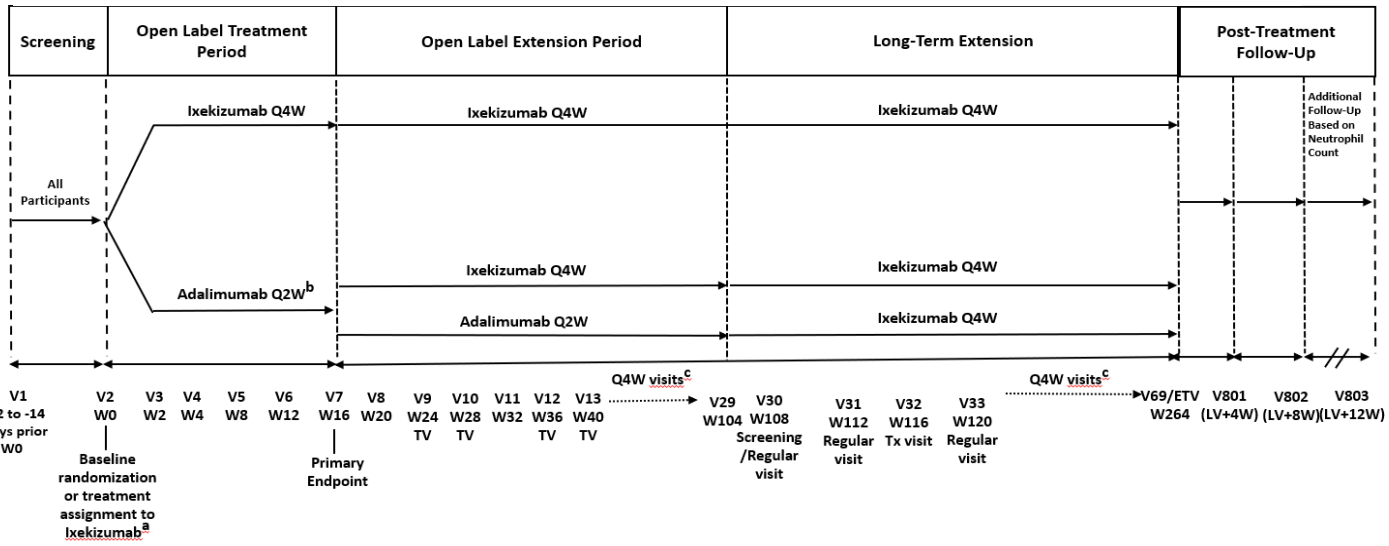
Methods

The ixekizumab clinical development programme for JIA, as agreed in PIP (EMEA-001050-PIP02-18-M02), includes 1 pivotal Phase 3 study (Study I1F-MC-RHCG [RHCG]) with primary endpoint database lock date of 02 April 2024. The primary endpoint of the study was to determine percentage of patients meeting the JIA ACR30 response criteria at Week 16 in patients with JIA. As of database lock date, all patients who continued the study had completed the OLT Period, through Week 16. The study remains ongoing for patients in the OLE and LTE Periods [at the time of submission].

Study RHCG is an ongoing, multicentre, open-label, randomised, Phase 3 study of ixekizumab administered subcutaneously, with adalimumab as a reference arm in children from 2 to younger than 18 years of age with JIA subtypes of ERA (including JoAS) and JPsA. The study was conducted in 3 treatment periods: a 16-week OLT Period followed by an OLE Period proceeding to Week 104, followed by an open-label LTE Period out to a total of 264 weeks.

Adalimumab (TNFα inhibitor) was included as an active reference arm during the OLT and OLE Periods to provide within-trial control and contextualisation of study results. Adalimumab was selected, as it was 1 of the 2 bDMARDs that was approved for the treatment of ERA in patients aged 6 years or older at the time of protocol development. Selection of adalimumab was further supported by positive clinical experience with adalimumab in the treatment of JPsA (Klein et al. 2019) and well-established efficacy and safety profiles in adult axSpA and PsA. Another approved bDMARD was etanercept (TNF inhibitor), which is indicated for the treatment of PsA and ERA in patients aged 12 years or older, hence it was not an appropriate reference treatment to be considered for the planned study in patients aged at least 2 years.

Figure 9. Study design for RHCG.



Abbreviations: ACR30 = 30% improvement in American College of Rheumatology criteria; bDMARD = biologic disease-modifying antirheumatic drug; ERA = enthesitis-related arthritis; ETV = early termination visit; IR = inadequate response; JIA = juvenile idiopathic arthritis; JPsA = juvenile psoriatic arthritis; LV = last visit; OLE = open-label extension; OLT = open-label treatment; PTFU = post-treatment follow-up; Q2W = every 2 weeks; Q4W = every 4 weeks; Tx = treatment; TV = treatment visit; V = visit; W = week.
[a] Patients who were bDMARD-naive were randomly assigned to ixekizumab or adalimumab in a ratio of 1:1. Twenty patients were randomly assigned to ixekizumab and 20 patients to adalimumab. Randomisation was stratified based on the category of JIA (ERA or JPsA). The remaining patients (61 patients) who were bDMARD-naive or bDMARD-IR were assigned to ixekizumab.
[b] Patients receiving adalimumab during the OLT Period who did NOT attain a JIA ACR30 response at Week 16 were switched to ixekizumab in the OLE Period. Patients receiving adalimumab during the OLT Period who did attain a JIA ACR30 response at Week 16 were given the option to switch or not to switch to ixekizumab in the OLE Period.
[c] Regular visits occurred every 3 months, but patients had monthly treatment visits to the site primarily for injection purposes. Patients who were treated with adalimumab through Week 104 may decide not to switch to ixekizumab at Week 104 and entered the PTFU period.

Study participants

Number of Participants (planned and analysed):

- Planned: 100
- Intent-to-treat (ITT) population: 101
- Open-label treatment (OLT) safety population: 101
- Open-label extension (OLE) period population: 99
- Open-label extension (OLE) period adalimumab switchers (switchers): 9
- Week 104 ixekizumab population: 16
- Long-term extension (LTE) safety population: 16
- Pharmacokinetic (PK) analysis population (ITT population): OLT Period = 81, OLE Period = 84.

Inclusion criteria:

Patients were eligible to be included in the study only if they met all of the following criteria at enrolment:

- had a diagnosis of JIA (ERA or JPsA) as defined by the ILAR criteria (Petty et al. 2004).
- had at least 3 active peripheral joints at screening and baseline.
    - Active peripheral joint is defined as the presence of joint swelling or, in the absence of swelling, joint with limitation of motion plus pain on motion and/or tenderness on palpation.

- age of patient with ERA was 6 to less than 18 years at screening and baseline.
- age of patient with JPsA was 2 to less than 18 years at screening and baseline.
- had weighed at least 10.0 kg.

Key exclusion criteria:

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

Medical conditions

- fulfilled the ILAR classification criteria for any other JIA category than ERA or JPsA.
- had active or a history of IBD or history of IBD in a first-degree relative: Crohn's disease, ulcerative colitis, or undifferentiated IBD.
- had evidence of active uveitis within 4 weeks prior to baseline.
- had active fibromyalgia or other chronic pain condition or musculoskeletal disease that, in the investigator's opinion, would make it difficult to appropriately assess disease activity for the purposes of this study.
- had a serious infection (for example, pneumonia and cellulitis), had been hospitalised, had received intravenous antibiotics for an infection (within 12 weeks prior to baseline [Week 0; Visit 2]), had a serious bone or joint infection (within 24 weeks prior to baseline), have ever had an infection of an artificial joint, or were immunocompromised to an extent that participation in the study would pose an unacceptable risk to the patient.
- had herpes zoster or other clinically apparent varicella-zoster virus infection within 12 weeks prior to baseline.
- had a positive test for hepatitis B virus at screening.
- had hepatitis C virus infection (hepatitis C antibody-positive and confirmed presence of hepatitis C virus RNA).
- had an infection typical of an immunocompromised host and/or that occurred with increased incidence in an immunocompromised host (including, but not limited to, Pneumocystis jiroveci pneumonia, histoplasmosis, or coccidioidomycosis) or had a known immunodeficiency.
- had household contact with a person with active TB and did not receive appropriate and documented prophylaxis for TB.
- had evidence of active TB or latent TB.

Prior/concomitant therapy

- had used or was using any therapeutic agent targeted at reducing IL-17.
- had initiated concomitant csDMARDs (such as, but not limited to, MTX, sulfasalazine, and leflunomide) within 12 weeks prior to baseline or changed the dose within 8 weeks prior to baseline.
- concurrently used any biologic agent (bDMARD) including adalimumab within 28 days; anakinra and etanercept within 14 days; abatacept within 90 days; infliximab, certolizumab pegol, or alefacept within 60 days; golimumab within 90 days; rituximab within 12 months; or any other biologic agent or small molecule (targeted synthetic DMARD) within 5 half-lives prior to baseline (Week 0; Visit 2).

- used MTX at doses of more than 0.65 mg/kg per week or sulfasalazine at doses more than 30 mg/kg per day.
- was currently receiving concomitant treatment with a combination of at least 2 csDMARDs (including MTX).

Treatments

Study interventions were administered subcutaneously based on the patient's body weight as detailed in Table 13. The interventions were administered as shown in Table 14.

Table 13. Interventions based on body weight.

Study treatment	Body weight (kg)	Dose regimen
Ixekizumab	>50.0	80 mg every 4 weeks (Q4W) (with a starting dose of 160 mg)
	25.0 to 50.0	40 mg Q4W (with a starting dose of 80 mg)
	10.0 to <25.0	20 mg Q4W (with a starting dose of 40 mg)
Adalimumab	≥30.0	40 mg every 2 weeks (Q2W)
	10.0 to <30.0	20 mg Q2W

Table 14. Study interventions administered.

Regimen (Body Weight)	Induction Dose Week 0	Dose OLT Period (Week 2 to Week 14)	Dose OLE Treatment Period (Week 16 to Week 104)	Dose LTE Treatment Period (Week 104 to Week 264)
Ixekizumab (>50.0 kg)	160 mg (administered as two 80-mg SC injections)	80-mg Q4W SC injection	80-mg Q4W SC injection	80-mg Q4W SC injection
Ixekizumab (25.0 to 50.0 kg)	80-mg SC injection	40-mg Q4W SC injection	40-mg Q4W SC injection	40-mg Q4W SC injection
Ixekizumab (10.0 to <25.0 kg)	40-mg SC injection	20-mg Q4W SC injection	20-mg Q4W SC injection	20-mg Q4W SC injection
Adalimumab (≥30.0 kg)	40-mg SC injection	40-mg Q2W SC injection	**Responder[a]:** Adalimumab 40-mg Q2W SC injection **Non-responders or patients opting to switch to ixekizumab[a]:** Appropriate dose according to weight Q4W (without an induction dose)	All adalimumab patients were switched to ixekizumab. Ixekizumab was administered according to weight Q4W (without a starting dose). Patients who were not switched to ixekizumab underwent ETV at Visit 29 (Week 104)
Adalimumab (10.0 to <30.0 kg)	20-mg SC injection	20-mg Q2W SC injection	**Responders[a]:** Adalimumab 20-mg Q2W SC injection **Non-responders or patients opting to switch to ixekizumab[a]:** Appropriate dose according to weight Q4W (without an induction dose)	

Abbreviations: ACR30 = 30% improvement in American College of Rheumatology criteria; ETV = early termination visit; JIA = juvenile idiopathic arthritis; LTE = long-term extension; OLE = open-label extension; OLT = open-label treatment; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous.

[a] Patients receiving adalimumab during the OLT Period who did NOT attain a JIA ACR30 response at Week 16 were switched to ixekizumab in the OLE Period. Patients receiving adalimumab during the OLT Period who did attain a JIA ACR30 response at Week 16 were given the option to switch or not to switch to ixekizumab in the OLE Period. The decision to switch for patients who achieved a JIA ACR30 response was left to the patient/patient's caregiver and investigator. A switch from adalimumab to ixekizumab during the OLE Period may also occur at any other visit after Week 16 based on the patient/patent's caregiver and investigator's decision.

Notes: When switching from adalimumab to ixekizumab, the patient did not receive the ixekizumab induction dose but received the appropriate ixekizumab dose per the patient's weight. The minimum required period between the last dose of adalimumab and first dose of ixekizumab was 2 weeks.

Objectives, outcomes and endpoints

The aim of the study is to evaluate the efficacy, safety, tolerability, and PK of ixekizumab when administered to paediatric patients with JIA categories of ERA (including JoAS) and JPsA. The objectives and endpoints are listed in the table below.

Table 15. Objectives and endpoints.

Objectives	Endpoints
Primary Objective • To evaluate the efficacy of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JPsA based on the JIA ACR30 response	Percentage of patients meeting the JIA ACR30 response criteria at Week 16
Secondary Objectives for OLT and OLE Periods • To evaluate the efficacy of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JPsA based on the other clinical responses, disease activity, and physical function measures • To evaluate the efficacy of adalimumab (reference arm) in children with JIA subtypes of ERA (including JoAS) and JPsA based on JIA ACR30 and the other clinical responses, disease activity, and physical function measures	The following outcomes were assessed at each regular study visit[a]: • Percentage of patients meeting the JIA ACR30/50/70/90/100 response criteria • Changes from baseline in each of the 6 individual components of the JIA ACR core set variables as follows: o Number of active joints o Number of joints with limited range of motion o Physician's Global Assessment of Disease Activity o Parent's Global Assessment of Well-Being o Physical function as measured by the CHAQ o Acute-phase reactant hsCRP and ESR • Change from baseline in PASI for JPsA patients with at least 3% BSA at baseline • Change from baseline in LEI for patients with enthesitis at baseline • Proportion of patients with disease flare[b]
• To characterise ixekizumab PK in children with JIA subtypes of ERA (including JoAS) and JPsA	• Trough concentrations of ixekizumab in patients with JIA subtypes of ERA (including JoAS) and JPsA
• To evaluate the potential development of anti-ixekizumab antibodies and their impact on the efficacy and safety of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JPsA	• Percentage of patients with anti-ixekizumab antibodies
• Describe the safety of ixekizumab in patients with JIA subtypes of ERA (including JoAS) and JPsA	• AEs including SAEs • Safety parameters including, but not limited to, infections, injection site reactions, and laboratory data including B-cell level, T-cell level, NK-cell level, WBC count, RBC count, ALT level, and AST level

Secondary Objectives for LTE Period • To evaluate the long-term safety, tolerability, and efficacy of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JPsA	The following outcomes were assessed at each regular study visit[c]: • AEs including SAEs and AESIs • Safety parameters including, but not limited to, infections, injection site reactions, and laboratory evaluations (including chemistry and haematology) • Permanent and temporary discontinuations of the study intervention • Vital signs, growth, and development
Exploratory for the OLT and OLE Periods • To evaluate the efficacy of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JPsA based on additional disease activity and quality of life measures • To evaluate the efficacy of adalimumab (reference arm) in children with JIA subtypes of ERA (including JoAS) and JPsA based on additional disease activity and quality of life measures	The following outcomes were assessed at each applicable regular study visit[a]: • Change from baseline in total and tender dactylitic digit count • Change from baseline in JSpADA • Change from baseline in JADAS-27 score • Proportion of patients achieving low disease activity and inactive disease by JADAS-27 score • Change from baseline in EQ-5D-Y score • Incidence of new onset uveitis or uveitis flares
• To explore the relationship between ixekizumab exposure and efficacy, and exposure and immunogenicity	• Trough concentrations of ixekizumab by ACR30 response • Trough concentrations of ixekizumab by TE-ADA status
Exploratory Objectives for the LTE Period • To evaluate the efficacy of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JPsA	The following outcomes were assessed at each applicable regular study visit[c]: • Change from baseline (from the originating study) in EQ-5D-Y score • Incidence of new onset uveitis or uveitis flares
• To explore the relationship between ixekizumab exposure and immunogenicity	• Trough concentrations of ixekizumab by TE-ADA status

• To evaluate the long-term efficacy of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JPsA	Through Week 264:
	• Percentage of patients meeting the JIA ACR30/50/70/90/100 response criteria using baseline of the originating study
	• Changes from baseline in each of the 6 individual components of the JIA ACR core set variables as follows (using baseline of the originating study):
	  • Number of active joints
	  • Number of joints with limited range of motion
	  • Physician's Global Assessment of Disease Activity
	  • Parent's Global Assessment of Well-Being
	  • Physical function as measured by the CHAQ
	  • Acute-phase reactant hsCRP and ESR
	• Change from baseline (of the originating study) in PASI for JPsA patients with at least 3% BSA.

	• Change from baseline (of the originating study) in LEI for patients with enthesitis.

Abbreviations: ACR = American College of Rheumatology criteria; ACR30/50/70/90/100 = 30%/50%/70%/90%/100% improvement in American College of Rheumatology criteria; AE = adverse event; AESI = adverse events of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSA = body surface area; CHAQ = Childhood Health Assessment Questionnaire; EQ-5D-Y = EuroQol-Five Dimensions-Youth; ERA = enthesitis-related arthritis; ESR = erythrocyte sedimentation rate; ETV = early termination visit; hsCRP = high-sensitivity C-reactive protein; JADAS-27 = Juvenile Arthritis Disease Activity Score-27; JIA = juvenile idiopathic arthritis; JoAS = juvenile onset ankylosing spondylitis; JPsA = juvenile psoriatic arthritis; JSpADA = Juvenile Spondyloarthritis Disease Activity Index; LEI = Leeds Enthesitis Index; LTE = long-term extension; NK = natural killer; OLE = open-label extension; OLT = open-label treatment; PASI = Psoriasis Area and Severity Index; PK = pharmacokinetic; RBC = red blood cell; SAE = serious adverse event; TE-ADA = treatment-emergent anti-drug antibody; WBC = white blood cell.

[a] During the OLE Period, regular visits and assessments occurred every 3 months (Visits 8, 11, 14, 17, 20, 23, 26, and 29/ETV). Patients will also have monthly treatment visits to the site primarily for dispensation and/or administration of study drug.

[b] Disease flare is defined as worsening of ≥30% from baseline in at least 3 of the 6 JIA ACR core set criteria and an improvement of ≥30% in no more than one of the criteria.

[c] During the LTE Period, regular visits and assessments occurred every 12 weeks, with the exception of Visits 30 and 31.

The primary efficacy endpoint was the percentage of ixekizumab treated patients meeting JIA ACR30 response criteria at Week 16 using NRI imputation method. A JIA ACR30 responder is defined as a patient who demonstrated disease response improvement of at least 30% from baseline in 3 of any 6 variables in the core set, with no more than 1 of the remaining variables worsening by more than 30% (Giannini et al. 1997).

The JIA ACR core set variables are:

- number of active joints in 73 joints (active joint defined as a joint that is swollen, or in the absence of swelling, has loss of passive motion accompanied by either pain on motion or joint tenderness)
- number of joints with limited range of motion in 69 joints
- Physician's Global Assessment of Disease Activity (21-Circle VAS)
- Parent's Global Assessment of Patient's Overall Well-being
- physical function as assessed by the CHAQ
- acute-phase reactant hsCRP, and
- ESR.

An interim analysis was conducted previously, and at the time of interim data evaluation, when 40 evaluable patients treated with ixekizumab had completed the OLT Period, the stopping criteria was not met because posterior probability was more than 80% satisfying the critical success factor (posterior probability more than 99%).

Sample size

The primary objective of this study was to detect a JIA ACR 30 response rate of at least 50% for ixekizumab-treated patients at Week 16.

A sample size of at least 80 patients assigned to ixekizumab was shown via simulation to have reasonable operating characteristics as follows:

• a study success rate greater than 80% if the true JIA ACR 30 response is at 60%

• a false-positive rate of less than 1% if the true JIA ACR 30 response is placebo-like at 35%.

These rates were derived from the Bayesian decision criterion (see statistical methods below) to be similar to a traditional power calculation.

Overall, approximately 100 patients were to be assigned to therapy in this study.

Of the 80 ixekizumab-treated patients in this study, 20 bDMARD naive patients were to be randomised to ixekizumab. An additional 20 patients were to be randomised to adalimumab (1:1 randomisation to ixekizumab or adalimumab). The remaining 60 patients who were either bDMARD-naive or bDMARD-IR were to be assigned to ixekizumab in the OLT period.

Randomisation

Patients who were bDMARD-naive were randomised to ixekizumab or adalimumab in a 1:1 ratio. At least 20 patients were randomised to ixekizumab and 20 patients to adalimumab. Randomisation was stratified based on the category of JIA (ERA or JPsA). The remaining patients (approximately 60 patients) who were bDMARD-naive or bDMARD-IR were assigned to ixekizumab. In practice, this was accomplished by randomising the first 40 bDMARD-naive patients entering the study according to the ratio and stratification described above, with all the subsequent bDMARD-naive patients being assigned to ixekizumab.

Assignment to treatment groups was determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign cartons containing investigational product to each patient. Site personnel confirmed that they have located the correct cartons by entering a confirmation number found on the cartons into the IWRS before dispensing to patients.

In the OLE period, all patients who were receiving ixekizumab in the OLT period continued to receive ixekizumab for approximately 88 weeks.

Patients receiving adalimumab during the OLT period who did NOT attain a JIA ACR 30 response at Week 16 were switched to ixekizumab in the OLE period.

Patients receiving adalimumab during the OLT period who attained a JIA ACR 30 response at Week 16 were given the option to switch or not to switch to ixekizumab in the OLE period.

A switch from adalimumab to ixekizumab during the OLE period could also occur at any other visit after Week 16 based on the patient/patent’s caregiver and investigator’s judgment.

Blinding (masking)

This was an open-label study.

Statistical methods

Interim analysis

A futility analysis was to be conducted using the JIA ACR 30 response rate observed in the first 40 ixekizumab participants who had the opportunity to complete OLT period (Week 16). The study was to stop for futility if the observed JIA ACR 30 response rate was less than 40%.

Due to the open-label feature, and because there is no stopping rule for early efficacy, there was no adjustment for multiple testing in the interim analysis or final Bayesian primary analysis.

Analysis sets

Unless otherwise specified, efficacy and health outcomes analyses were conducted on the intent-to-treat (ITT) Population during the OLT period. All patients were included, even if the participant did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Patients were analysed according to the treatment to which they were assigned.

Efficacy analysis

All efficacy data collected were summarised using descriptive statistics without any inferential statistics.

Bayesian analysis was used as the primary analysis method for the primary endpoint, JIA ACR30 at Week 16. If the study was not stopped for futility, the posterior probability of the Week 16 JIA ACR30 response rate exceeding 50% was to be calculated, and the study objective was successfully met (i.e., a positive study) if this posterior probability was at least 80%. The posterior distribution was computed using the relatively noninformative Jeffreys' prior, Beta (0.5, 0.5). The posterior mean and 95% credible interval were summarised from the posterior distribution.

Missing data

Non-response imputation may be used to address missingness when the estimand of interest uses the composite strategy for handling intercurrent events. Non-response imputation was used for categorical efficacy and health outcome variables. Patients were considered non-responders if they had missing clinical response data at the analysis time point of interest.

Last observation carried forward (LOCF) was used to handle missing data for individual components of a composite endpoint, such as JIA ACR or Disease Flare. Patients without at least 1 postbaseline observation were not included for evaluation.

Modified baseline-observation-carried-forward was performed on continuous secondary efficacy, exploratory, and health outcomes variables to handle the intercurrent event of discontinuing study drug due to an AE. That is the participant is defined as reverting back to baseline regardless of any continuing efficacy benefits they may still have received after the event. The while-on-study-intervention strategy was applied for other intercurrent events. That is, the endpoint is defined as the last observed value at or before the visit of interest before the participant discontinued study intervention.

If any patients missed a visit or discontinued study treatment due to the restriction of coronavirus disease 2019 (COVID-19) in the OLT period for the OLT period population, a multiple imputation (MI) method was

used to impute missing data for each component of JIA ACR30, and JIA ACR30 up to Week 16 was derived using the MI-imputed components. In the MI analyses, missing data were imputed to estimate what the observations would have been if the patient had not missed a visit or discontinued due to COVID-19. Specifically, MI was the partial imputation of nonmonotone missing data using Markov chain Monte Carlo method with the simple imputation model, followed by a sequential regression. All other missing JIA ACR30 up to Week 16 due to other reasons were imputed with non-response imputation.

Subgroup analyses

The protocol stated that summary statistical analyses will be conducted for JIA ACR 30 at each regular visit for the following subset of participants: ERA and JPsA. The statistical analysis plan further stated that subgroup analyses would be performed by Prior biologic JIA therapy (ever user, never user), Prior csDMARDsj therapy for JIA (ever user, never user), prior nonbiologic (Non-DMARD) therapy for JIA (ever user, never user), methotrexate use at baseline, and Sulfasalazine use at baseline.

Multiplicity

No multiplicity control measures were used.

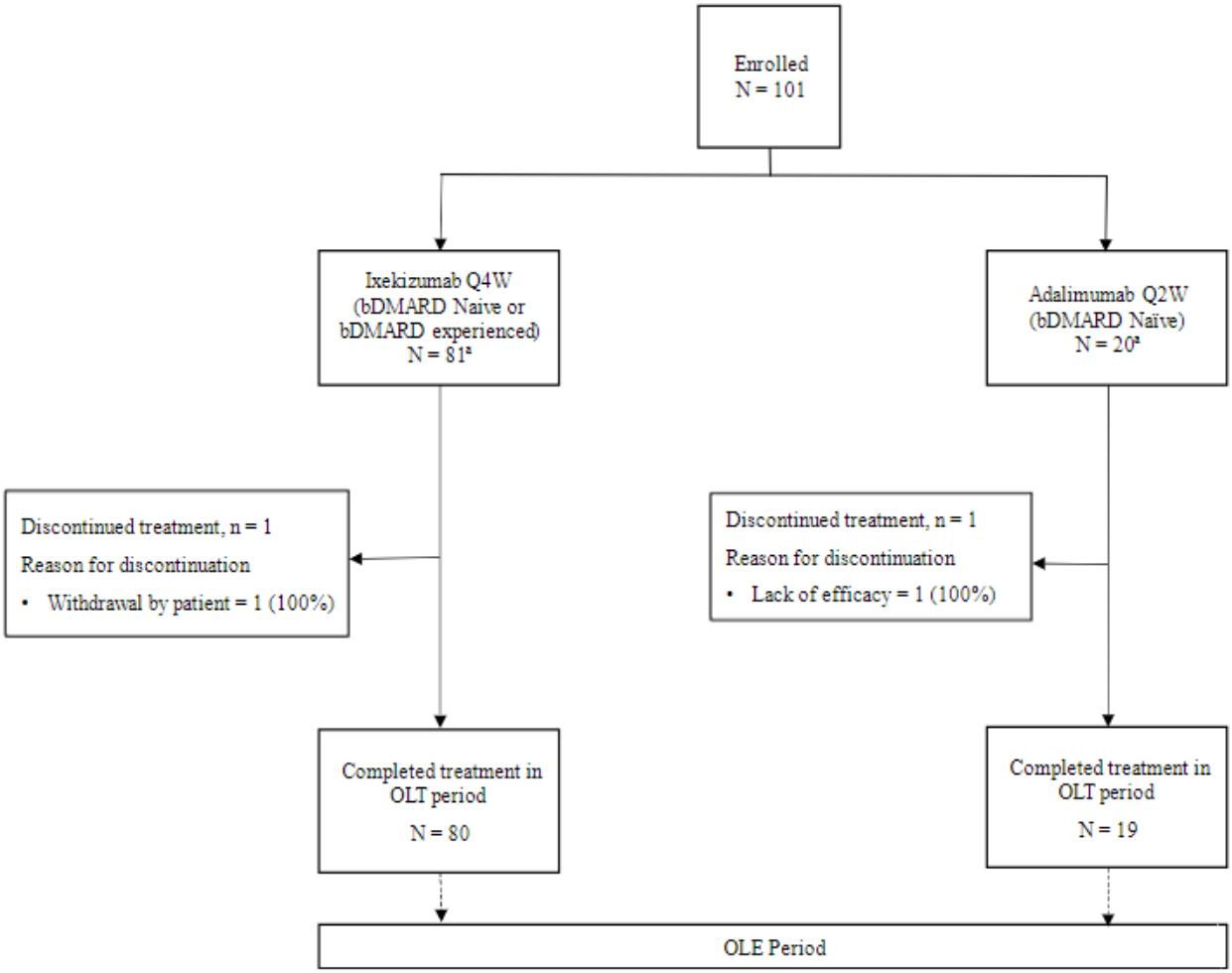
Results

Participant flow

A total of 101 patients were enrolled in the study. Of which, 81 patients received ixekizumab and 20 patients received adalimumab at any period.

Subject disposition in study RHCG is outlined in Figure 10 and 11, and reasons for discontinuation are displayed in Table 16.

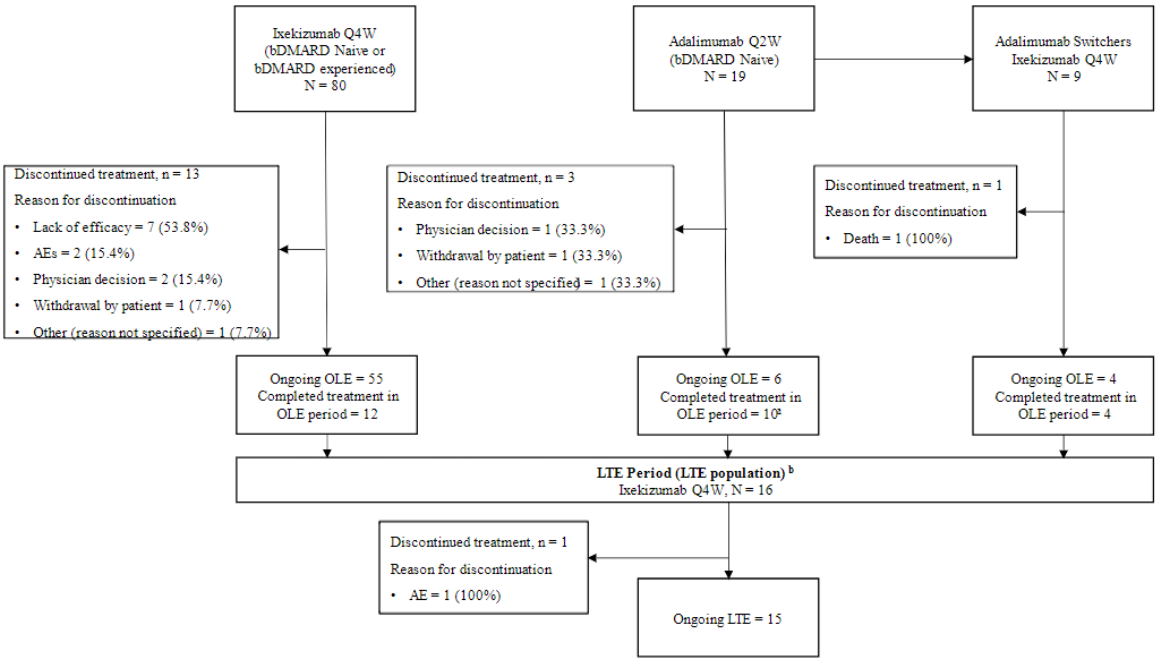
Figure 10. Subject disposition in study RHCG, OLT period



Abbreviations: bDMARD = biologic disease-modifying antirheumatic drug; IR = inadequate responder; n = number of patients in the specified category; N = number of patients in the analysis population; OLT = open-label treatment; OLE = open-label extension; Q2W = every 2 weeks; Q4W = every 4 weeks.

[a] The first 40 patients who were bDMARD-naive enrolled in the study were randomised in a 1:1 ratio to either ixekizumab or adalimumab. The remaining 61 patients (bDMARD naive or bDMARD experienced) were assigned to ixekizumab.

Figure 11. Subject disposition in study RHCG, OLE and LTE Periods



Abbreviations: AE = adverse event; bDMARD = biologic disease-modifying antirheumatic drug; LTE = long-term extension; n = number of patients in the specified category; N = number of patients in the analysis population; OLE = open-label extension; Q2W = every 2 weeks; Q4W = every 4 weeks.

[a] Patients who remained on their original treatment of adalimumab during OLE Period and opted not to switch to ixekizumab did not participate in the subsequent period, that is, LTE Period.

[b] Patients who completed OLE Period entered the LTE Period.

Table 16. Summary of patient disposition, all enrolled patients.

	ADAQ2W n (%)	IXEQ4W n (%)
N*a	20 (100)	81 (100)
Study Disposition *b		
Completed	0	2 (2.5)
Ongoing	15 (75.0)	69 (85.2)
Permanently Discontinued Study	5 (25.0)	10 (12.3)
Reasons for Study Discontinuation *c		
Adverse Event	0	1 (10.0)
Death	1 (20.0)	0
Failure to Meet Randomization Criteria	0	0
Lack of Efficacy	1 (20.0)	4 (40.0)
Lost to Follow-up	0	0
Physician Decision	1 (20.0)	1 (10.0)
Pregnancy	0	0
Site Terminated by Sponsor	0	0
Study Terminated by IRB / ERB	0	0
Study Terminated by Sponsor	0	0
Withdrawal by Subject	2 (40.0)	2 (20.0)
Other	0	2 (20.0)

Abbreviations: ADAQ2W = Adalimumab; IXEQ4W = Ixekizumab; N = number of subjects in population;
n = number of subjects within category.
*a - denominator is the number of patients who enrolled into the study.
*b - denominator is the number of patients in the intent-to-treat population.
*c - denominator is the number of patients who discontinued the study.
*d - denominator is the number of patients who discontinued the study treatment.

Recruitment

Study Initiation Date: 13 April 2021 (first patient first visit).

Primary Completion Date: 19 February 2024 (last patient visit for open-label treatment period). The analyses presented in this report are based on a database lock date of 02 April 2024.

This study was conducted at 33 centres that enrolled patients in 11 countries (Argentina, Belgium, Czech Republic, France, Germany, Italy, Mexico, Netherlands, Spain, Switzerland, and United Kingdom).

Conduct of the study

The protocol was amended 3 times (twice after the study initiation date):

- Original (approved on 06-Feb-2020)

- Amendment a: substantial (approved on 06-Nov-2020)

Since this amendment was made before the study initiation date (first patient's first visit on 13 April 2021), the amendments will not be described in this report.

- Amendment b: substantial (approved on 21-Sep-2022)

Rationale: to include a Long-Term Extension Study.

- Amendment c: not substantial (approval date not provided)

Rationale: align with EU Clinical Trial Regulation 536/2014 (EUCTR) requirements.

Table 17. Summary of important protocol deviations.

Protocol Deviation Category	OLT Period		OLE Period			LTE Period
			OLE Period (Including Adalimumab Data Prior to Switch to Ixekizumab)		Adalimumab Switchers to Ixekizumab	
	Ixekizumab (N = 81) n (%)	Adalimumab (N = 20) n (%)	Ixekizumab (N = 80) n (%)	Adalimumab (N = 19) n (%)	Ixekizumab (N = 9) n (%)	Ixekizumab (N = 16) n (%)
At least 1 important protocol deviation	15 (18.5)	3 (15.0)	24 (30.0)	8 (42.1)	2 (22.2)	1 (6.2)
Study procedure compliance	8 (9.9)	2 (10.0)	6 (7.5)	1 (5.3)	0	0
Informed consent	6 (7.4)	0	18 (22.5)	6 (31.6)	2 (22.2)	1 (6.2)
Investigational medicinal product and/or investigational device	3 (3.7)	1 (5.0)	4 (5.0)	1 (5.3)	0	0
Concomitant medication	3 (3.7)	0	0	0	0	0
Safety reporting	2 (2.5)	0	0	0	0	0
Visit schedule criteria	0	1 (5.0)	0	1 (5.3)	0	0

Abbreviations: LTE = long-term extension; n = number of patients in the specified category; N = number of patients in the analysis population; OLE = open-label extension; OLT = open-label treatment.

Baseline data

All the enrolled patients were 5 to less than 18 years of age at baseline and diagnosed with JIA before the age of 16 years.

Majority of the patients treated with ixekizumab were white (85.2%) and more than half of the patients were males (55.6%).

In the ixekizumab group, the enrolled patient by age group were:

- 1 patient less than 6 years of age
- 20 patients 6 to less than 12 years of age, and
- 60 patients 12 to less than 18 years of age.

In the ixekizumab group, the enrolled patients by weight group were:

- 6 patients in the weight range 10.0 to 25.0 kg
- 20 patients in the weight range 25.0 to 50.0 kg, and
- 55 patients in the weight range more than 50.0 kg.

Table 18. Baseline characteristics.

Demographic Parameter	Adalimumab bDMARD-Naive (N = 20)	Ixekizumab		Total Ixekizumab (N = 81)
		bDMARD-Naive (N = 60)	bDMARD-Experienced (N = 21)	
Age (years)[a]				
Mean (SD)	13.3 (3.2)	12.8 (2.9)	14.0 (3.4)	13.1 (3.1)
Median (range)	14.0 (6-17)	13.0 (6-17)	15.0 (5-18)	14.0 (5-18)
Sex, n (%)				
Female	8 (40.0)	23 (38.3)	13 (61.9)	36 (44.4)
Male	12 (60.0)	37 (61.7)	8 (38.1)	45 (55.6)
Race, n (%)				
White	15 (75.0)	51 (85.0)	18 (85.7)	69 (85.2)
American Indian or Alaska Native	4 (20.0)	8 (13.3)	3 (14.3)	11 (13.6)
Asian	0	1 (1.7)	0	1 (1.2)
Black or African American	1 (5.0)	0	0	0
Weight (kg)				
Mean (SD)	54.76 (20.03)	56.25 (21.56)	59.54 (22.17)	57.10 (21.62)
Height (cm)				
Mean (SD)	159.77 (18.64)	157.00 (15.04)	158.90 (16.12)	157.49 (15.24)
BMI category, n (%)				
Underweight (<18.5 kg/m^2)	5 (25.0)	17 (28.3)	6 (28.6)	23 (28.4)
Normal (≥18.5 and <25 kg/m^2)	13 (65.0)	26 (43.3)	9 (42.9)	35 (43.2)
Overweight (≥25 and <30 kg/m^2)	2 (10.0)	10 (16.7)	2 (9.5)	12 (14.8)
Obese (≥30 and <40 kg/m^2)	0	7 (11.7)	4 (19.0)	11 (13.6)
Country / Region, n (%)				
Germany	10 (50.0)	16 (26.7)	5 (23.8)	21 (25.9)
United Kingdom	3 (15.0)	9 (15.0)	4 (19.0)	13 (16.0)
Italy	0	3 (5.0)	4 (19.0)	7 (8.6)
Spain	0	3 (5.0)	2 (9.5)	5 (6.2)
France	0	2 (3.3)	1 (4.8)	3 (3.7)
Czech Republic	0	2 (3.3)	1 (4.8)	3 (3.7)
Belgium	1 (5.0)	2 (3.3)	0	2 (2.5)
Switzerland	1 (5.0)	0	1 (4.8)	1 (1.2)
Netherlands	0	1 (1.7)	0	1 (1.2)
Mexico	4 (20.0)	14 (23.3)	3 (14.3)	17 (21.0)
Argentina	1 (5.0)	8 (13.3)	0	8 (9.9)

Abbreviations: bDMARD = biologic disease-modifying antirheumatic drug; BMI = body mass index; eCRF = electronic case report form; ITT = intent-to-treat; n = number of patients in the specified category; N = number of patients in the analysis population; OLT = open-label treatment; SD = standard deviation.

[a] Age in years was calculated as length of the time interval from the imputed date of birth (July 1st in the year of birth collected in the eCRF) to the informed consent date.

Table 19. Baseline disease characteristics.

Baseline Parameter	Adalimumab bDMARD-Naive (N = 20)	Ixekizumab		Total Ixekizumab (N = 81)
		bDMARD-Naive (N = 60)	bDMARD-Experienced (N = 21)	
JIA subtype, n (%)				
ERA	16 (80.0)	40 (66.7)	14 (66.7)	54 (66.7)
JPsA	4 (20.0)	20 (33.3)	7 (33.3)	27 (33.3)
Age at JIA onset (years)				
Mean (SD)	12.35 (2.89)	11.32 (3.33)	9.29 (4.69)	10.79 (3.80)
Duration of JIA diagnosis, n (%)				
0 to <2 years	18 (90.0)	47 (78.3)	5 (23.8)	52 (64.2)
≥2 to <5 years	2 (10.0)	8 (13.3)	6 (28.6)	14 (17.3)
≥5 to <10 years	0	5 (8.3)	8 (38.1)	13 (16.0)
≥10 years	0	0	2 (9.5)	2 (2.5)
Time since JIA diagnosis (years)				
Mean (SD)	0.74 (0.72)	1.49 (1.99)	4.70 (3.72)	2.32 (2.89)
Number of active joints				
Mean (SD)	7.45 (4.48)	7.87 (5.57)	6.76 (4.00)	7.58 (5.21)
Physicians global assessment of disease activity (cm)				
Mean (SD)	5.15 (2.00)	5.18 (1.97)	4.92 (1.92)	5.12 (1.95)
Parent's global assessment of well-being (mm)				
Mean (SD)	53.95 (28.58)	39.52 (24.43)	52.00 (25.00)	42.75 (25.04)
Percentage of BSA for patients who had baseline plaque psoriasis				
Mean (SD)	0.45 (1.79)	1.80 (4.88)	2.81 (5.55)	2.06 (5.05)
Worst joint pain (NRS)				
Mean (SD)	5.70 (2.64)	5.12 (2.29)	6.57 (2.09)	5.49 (2.32)
Pain VAS (mm)				
Mean (SD)	53.75 (26.08)	44.47 (23.66)	59.71 (22.99)	48.42 (24.29)
CDI-2 SR (S)				
Mean (SD)	4.68 (3.76)	4.26 (2.86)	5.10 (4.53)	4.47 (3.35)
C-SSRS				
Suicidal ideation[a], n (%)	0	2 (100.0)	2 (100.0)	4 (100%)

Abbreviations: bDMARD = biologic disease-modifying antirheumatic drug; BSA = body surface area; CDI-2 = children's depression inventory - 2; C-SSRS = Columbia-suicide severity rating scale; ERA = enthesitis-related arthritis; ITT = intent-to-treat; JIA = juvenile idiopathic arthritis; JoAS = juvenile onset ankylosing spondylitis; JPsA = juvenile psoriatic arthritis; N = number of patients in the analysis population; n = number of patients in the specified category; SD = standard deviation; VAS = visual analogue score.

Prior therapy

According to the MAH, 76 (93.8%) patients received at least 1 prior therapy (including JIA therapy) in the ixekizumab group. The table below summarises the previous JIA therapies used by the ITT population.

Table 20. Previous therapies used for JIA treatment in the ITT population.

Prior JIA Therapy	Adalimumab Bio-Naïve (N = 20) n (%)	Ixekizumab		Total Ixekizumab (N = 81) n (%)
		Bio-Naïve (N = 60) n (%)	Bio-Experienced (N = 21) n (%)	
Patients with any prior JIA therapy	15 (75.0)	34 (56.7)	21 (100.0)	55 (67.9)
csDMARD	5 (25.0)	14 (23.3)	12 (57.1)	26 (32.1)
Azathioprine	0	0	0	0
Ciclosporin	0	0	1 (4.8)	1 (1.2)
Leflunomide	0	1 (1.7)	0	1 (1.2)
Methotrexate	4 (20.0)	11 (18.3)	11 (52.4)	22 (27.2)
Mycophenolate	0	0	0	0
Sulfasalazine	1 (5.0)	3 (5.0)	4 (19.0)	7 (8.6)
Tacrolimus	0	0	0	0
NSAIDs	12 (60.0)	21 (35.0)	4 (19.0)	25 (30.9)
bDMARD	0	0	21 (100.0)	21 (25.9)
Abatacept	NA	NA	1 (4.8)	1 (1.2)
Adalimumab	NA	NA	11 (52.4)	11 (13.6)
Canakinumab	NA	NA	0	0
Etanercept	NA	NA	12 (57.1)	12 (14.8)
Golimumab	NA	NA	2 (9.5)	2 (2.5)
Infliximab	NA	NA	1 (4.8)	1 (1.2)
Rituximab	NA	NA	0	0
Tocilizumab	NA	NA	2 (9.5)	2 (2.5)
tsDMARD	0	1 (1.7)	1 (4.8)	2 (2.5)
Baricitinib	0	1 (1.7)	0	1 (1.2)
Tofacitinib	0	0	1 (4.8)	1 (1.2)
Glucocorticoid	3 (15.0)	6 (10.0)	1 (4.8)	7 (8.6)
Number of prior bDMARDs				
0	20 (100.0)	60 (100.0)	0	60 (74.1)
1	NA	NA	14 (66.7)	14 (17.3)
≥2	NA	NA	7 (33.3)	7 (8.6)

Concomitant JIA Therapies

Table 21 presents summary of concomitant JIA therapies used at baseline in ITT population. In the patients treated with ixekizumab, proportion of patients using concomitant csDMARD was similar between the bDMARD-naive and bDMARD-experienced patients.

Table 21. Summary of concomitant JIA therapies used at baseline – ITT population.

JIA Therapies	Adalimumab Bio-Naïve (N = 20) n (%)	Ixekizumab		Total Ixekizumab (N = 81) n (%)
		Bio-Naïve (N = 60) n (%)	Bio-Experienced (N = 21) n (%)	
Patients with any concomitant JIA therapy at baseline	18 (90.0)	43 (71.7)	16 (76.2)	59 (72.8)
Concomitant medication use at baseline				
csDMARD	7 (35.0)	27 (45.0)	10 (47.6)	37 (45.7)
Azathioprine	0	0	0	0
Ciclosporin	0	0	0	0
Leflunomide	0	0	0	0
Methotrexate	5 (25.0)	24 (40.0)	9 (42.9)	33 (40.7)
Mycophenolate	0	0	0	0
Sulfasalazine	2 (10.0)	3 (5.0)	1 (4.8)	4 (4.9)
Tacrolimus	0	0	0	0
NSAIDs	13 (65.0)	29 (48.3)	11 (52.4)	40 (49.4)
Glucocorticoid	2 (10.0)	8 (13.3)	1 (4.8)	9 (11.1)

Table 22. Summary of DMARD Use as Prior and/or Concomitant Treatment – ITT Population

	Adalimumab Bio-Naïve (N = 20) n (%)	Ixekizumab		Total Ixekizumab (N = 81) n (%)
		Bio-Naïve (N = 60) n (%)	Bio-Experienced (N = 21) n (%)	
Patients with DMARD use (prior and/or concomitant at baseline)	10 (50.0)	35 (58.3)	21 (100.0)	56 (69.1)
Prior bDMARD use	0	0	21 (100.0)	21 (25.9)
Patients with csDMARD use (prior and/or concomitant at baseline)	10 (50.0)	35 (58.3)	19 (90.5)	54 (66.7)
Prior csDMARD use	5 (25.0)	14 (23.3)	12 (57.1)	26 (32.1)
Azathioprine	0	0	0	0
Ciclosporin	0	0	1 (4.8)	1 (1.2)
Leflunomide	0	1 (1.7)	0	1 (1.2)
Methotrexate	4 (20.0)	11 (18.3)	11 (52.4)	22 (27.2)
Mycophenolate	0	0	0	0
Sulfasalazine	1 (5.0)	3 (5.0)	4 (19.0)	7 (8.6)
Tacrolimus	0	0	0	0
Concomitant csDMARD use at baseline	7 (35.0)	27 (45.0)	10 (47.6)	37 (45.7)
Azathioprine	0	0	0	0
Ciclosporin	0	0	0	0
Leflunomide	0	0	0	0
Methotrexate	5 (25.0)	24 (40.0)	9 (42.9)	33 (40.7)
Mycophenolate	0	0	0	0
Sulfasalazine	2 (10.0)	3 (5.0)	1 (4.8)	4 (4.9)
Tacrolimus	0	0	0	0

Numbers analysed

Table 23 lists the populations that were defined based on different treatment periods with the number of patients included in each analysis population.

Table 23. Populations defined based on different treatment periods with the number of patients included in each analysis population.

Population	Period	Description	Number of Patients
Enrolled	Screening	All patients who signed informed consent	101
ITT population	OLT Period	All patients, even if the patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Unless otherwise specified, efficacy and health outcomes analyses were conducted on the ITT population during the OLT Period. Patients were analysed according to the treatment to which they were assigned.	101
OLT safety population	OLT Period	All patients who received at least 1 dose of either treatment product in OLT.	101
OLE Period population	OLE Period	All patients who received at least 1 dose of either treatment in OLE	99
OLE Period adalimumab switchers (switchers)	OLE Period	Patients initially randomly assigned to adalimumab who switch to ixekizumab in the OLE Period.	9
Week 104 ixekizumab population[a]	OLE Period	All ixekizumab treated patients who got a chance to complete Week 104 of OLE Period by primary outcome cutoff date 19 Feb 2024	16
PK Analysis Population (ITT population)[b]	OLT and OLE	All patients randomly assigned to ixekizumab who received at least 1 dose of ixekizumab drug and have evaluable PK samples and sufficient dosing information	OLT: 81 OLE: 84
LTE safety population	LTE	All patients who received at least 1 dose of ixekizumab in the LTE Period	16

Abbreviations: ITT = intent-to-treat; OLE = open-label extension; OLT = open-label treatment; LTE = long-term extension; N = number of patients in the analysis set; NA = not applicable; PK = pharmacokinetic(s).

[a] This analysis population was defined at the time of database lock based on the availability of data and will be included in statistical analysis plan for future analysis.

[b] Only ixekizumab treated patients in the OLT and OLE Periods constituted the PK population.

Outcomes and estimation

Study RHCG met its primary endpoint of JIA ACR30 response at Week 16. The posterior probability of JIA ACR30 response at Week 16 for ixekizumab treated JIA patients was more than 99%, which is greater than protocol specified 50% posterior probability. The results of the primary endpoint are presented in Table 24 and Table 25.

Table 24. Results of the primary endpoint.

JIA Category	N	Response n (%)	Posterior 95% Credible Interval	Posterior Probability
All JIA	81	72 (88.9)	80.71%, 94.36%	>99%

Abbreviations: ACR30 = 30% improvement in American College of Rheumatology; ITT = intent-to-treat; JIA = juvenile idiopathic arthritis; n = number of patients in the specified category; N = number of patients in the analysis population; NRI = non-responder imputation; OLT = open-label treatment.

Table 25. JIA ACR30/50/70/90/100 Response Rates at Week 16 (NRI) by JIA Category at Baseline Intent-to-Treat Population – Patients Initially Randomized to Ixekizumab Open-label treatment Period.

Parameter:JIA ACR30 Response

	All (N=81) n (%)	ERA (N=54) n (%)	JPsA (N=27) n (%)
Week 16 (Visit 7) (Observed)			
Nx	79	53	26
Response*a, n(%)	71 (89.9%)	48 (90.6%)	23 (88.5%)
Week 16 (Visit 7) (Observed, LOCF*b)			
Nx	80	53	27
Response*a, n(%)	72 (90.0%)	48 (90.6%)	24 (88.9%)
Week 16 (Visit 7) (LOCF, NRI)			
Response, n(%)	72 (88.9%)	48 (88.9%)	24 (88.9%)
Posterior Mean (Variance)	0.88 (0.00)	0.88 (0.00)	0.88 (0.00)
Posterior 95% Credible Interval	(80.71%, 94.36%)	(78.53%, 95.23%)	(73.23%, 96.77%)
Posterior Probability	100.00%	100.00%	100.00%

Abbreviations: ERA = Enthesitis-Related Arthritis; JPsA = Juvenile Psoriatic Arthritis; N = number of patients in the analysis population; n = number of patients in the specified category; Nx = number of patients with non-missing values; NRI = nonresponder imputation; LOCF = Last Observation Carried Forward.

*a - Percentage is calculated by n/Nx*100%.
*b - Includes subjects for who LOCF was performed for missing data imputation at the component level.

Subgroup analysis of primary endpoint JIA ACR30

The JIA ACR30 response rate at Week 16 was consistent across subgroups of patients who were bDMARD-naive and those who were bDMARD-experienced. The below table presents the results of this subgroup analysis.

Table 26. Results of the subgroup analysis.

Response	Adalimumab bDMARD-Naive (N = 20) n (%)	Ixekizumab bDMARD-Naive (N = 60) n (%)	Ixekizumab bDMARD-Experienced (N = 21) n (%)
JIA ACR30 response rate at Week 16	19 (95.0)	54 (90.0)	18 (85.7)

Abbreviations: ACR30 = 30% improvement in American College of Rheumatology; bDMARD = biologic disease-modifying antirheumatic drug; ITT = intent-to-treat; JIA = juvenile idiopathic arthritis; n = number of patients in the specified category; N = number of patients in the analysis population; NRI = non-responder imputation; OLT = open-label treatment.

Sensitivity analysis of primary endpoint JIA ACR30

Sensitivity analysis was planned to estimate the observation if patients had not missed a visit or discontinued due to COVID-19, using the modified NRI method; however, it was not performed since there were no patient discontinuations due to the COVID-19.

Secondary Efficacy Endpoints

Percentage of Patients Meeting the JIA ACR30/50/70/90/100 Response Criteria

Percentage of patients meeting JIA ACR30/50/70/90/100 in the OLT Period was analysed at each postbaseline visit using the ITT population. For patients who received ixekizumab during the OLE Period, JIA ACR30 response was analysed using the Week 104 analysis population.

OLT Period

Ixekizumab

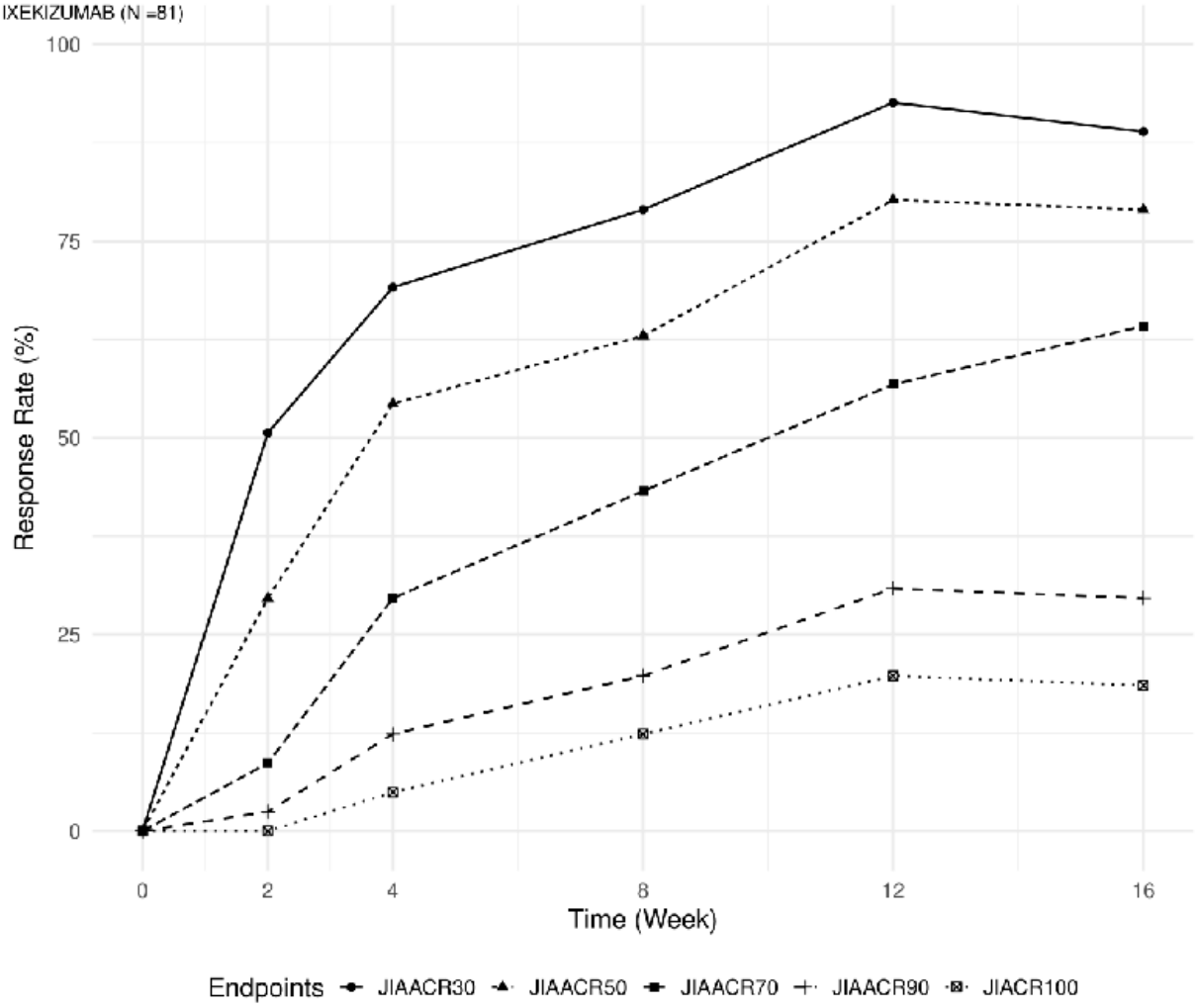
An improvement in JIA ACR30/50/70/90/100 response rates was observed through Week 16, using the NRI method. Table 27 summarises the JIA ACR30/50/70/90/100 response rates in the ixekizumab group up to Week 16. Figure 12 presents the JIA ACR30/50/70/90/100 response rates over time in the ixekizumab group.

Table 27. JIA ACR Responses at each postbaseline visit. NRI method ixekizumab treatment group, OLT period – ITT population.

JIA ACR	Week 2 (N = 81) n (%)	Week 4 (N = 81) n (%)	Week 8 (N = 81) n (%)	Week 12 (N = 81) n (%)	Week 16 (N = 81) n (%)
JIA ACR30	41 (50.6)	56 (69.1)	64 (79.0)	75 (92.6)	72 (88.9)
JIA ACR50	24 (29.6)	44 (54.3)	51 (63.0)	65 (80.2)	64 (79.0)
JIA ACR70	7 (8.6)	24 (29.6)	35 (43.2)	46 (56.8)	52 (64.2)
JIA ACR90	2 (2.5)	10 (12.3)	16 (19.8)	25 (30.9)	24 (29.6)
JIA ACR100	0	4 (4.9)	10 (12.3)	16 (19.8)	15 (18.5)

Abbreviations: ACR = American College of Rheumatology; ACR30/50/70/90/100 = 30%/50%/70%/90%/100% improvement in ACR; ERA = enthesitis-related juvenile idiopathic arthritis; ITT = intent-to-treat; JIA = juvenile idiopathic arthritis; n = number of patients in the specified category; N = number of patients in the analysis population; NRI = non-responder imputation; OLT = open-label treatment.

Figure 12. JIA ACR30/50/70/90/100 response rates over time in the ixekizumab group.



Abbreviations: ACR30/50/70/90/100 = 30%/50%/70%/90%/100% improvement in American College of Rheumatology; ITT = intent-to-treat; JIA = juvenile idiopathic arthritis; N = number of patients in the analysis population; NRI = non responder imputation.

Adalimumab

An improvement in JIA ACR30 response was observed at Week 16 in 19 patients (95.0%) who received adalimumab.

Ixekizumab and Adalimumab

There was also an improvement in JIA ACR50 response (table below).

Table 28 *JIA ACR50 response observed at Week 16.*

Parameter: JIA ACR50 Response	ADAQ2W (N=20)	IXEQ4W (N=81)	Total (N=101)
WEEK16 (VISIT7) (NRI)			
Response, n (%)	18 (90.0)	64 (79.0)	82 (81.2)
95% CI *b	(76.9, 100.0)	(70.1, 87.9)	(73.6, 88.8)
Difference (95% CI) vs. ADALIMUMAB *b		-11.0 (-26.8, 4.9)	

In addition, an improvement in JIA ACR70 was seen.

Table 29 *JIA ACR70 response observed at Week 16.*

Parameter: JIA ACR70 Response	ADAQ2W (N=20)	IXEQ4W (N=81)	Total (N=101)
WEEK16 (VISIT7) (NRI)			
Response, n (%)	13 (65.0)	52 (64.2)	65 (64.4)
95% CI *b	(44.1, 85.9)	(53.8, 74.6)	(55.0, 73.7)
Difference (95% CI) vs. ADALIMUMAB *b		-0.8 (-24.2, 22.6)	

Ixekizumab

Change from baseline in the JIA ACR core set variables.

Overall, compared with the baseline, ixekizumab treatment demonstrated improvement in all 6 individual components of the JIA ACR core set variables by Week 16, using modified baseline observation carried forward method for the ITT population (Table 30).

Table 30. Change from baseline in JIA ACR core set variables scores at each postbaseline visit.

Response	Baseline		Week 2		Week 4		Week 8		Week 12		Week 16	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Number of active joints	81	7.58 (5.208)	77	-3.30 (4.202)	81	-4.31 (4.197)	81	-5.07 (5.417)	81	-6.21 (4.590)	81	-6.36 (4.630)
Number of joints with limited range of motion	81	5.30 (5.038)	77	-2.16 (3.815)	81	-2.75 (4.051)	81	-3.14 (4.987)	81	-4.12 (4.971)	81	-4.12 (4.943)
Physician's global assessment of disease activity	79	5.12 (1.952)	75	-2.09 (1.937)	78	-2.66 (1.761)	79	-3.18 (2.035)	79	-3.70 (1.877)	79	-3.85 (2.114)
Parent's global assessment of well-being (CHAQ)	81	42.75 (25.037)	79	-10.65 (22.751)	81	-12.54 (22.632)	81	-13.84 (26.210)	81	-18.06 (26.051)	81	-19.63 (29.030)
Physical function (CHAQ)	81	0.89 (0.675)	79	-0.16 (0.392)	81	-0.29 (0.458)	81	-0.27 (0.508)	81	-0.40 (0.521)	81	-0.41 (0.557)
Acute-phase reactant (ERA) - ESR (mm/hr)	79	23.13 (24.106)	73	-8.92 (17.899)	79	-6.89 (20.521)	79	-6.99 (23.395)	79	-7.46 (21.687)	79	-7.96 (22.887)

Abbreviations: ACR = American College of Rheumatology; CHAQ = Childhood Health Assessment Questionnaire; ERA = enthesitis-related juvenile idiopathic arthritis; ESR = erythrocyte sedimentation rate; ITT = intent-to-treat; JIA = juvenile idiopathic arthritis; mBOCF = modified baseline observation carried forward; n = number of patients with non-missing data; OLT = open-label treatment; SD = standard deviation.
The mean (SD) presented for postbaseline visits are change from baseline.

The descriptive statistical analysis was conducted for JIA ACR30 response rates at each postbaseline visit for the OLT Period (ITT population) for the subsets of patients listed in Table 31.

Table 31. Subgroup analysis of JIA ACR30 response rates at Week 16.

Subgroups	JIA ACR30 n (%)
JIA subtypes	
ERA (N = 54)	48 (88.9)
JPsA (N = 27)	24 (88.9)
Prior biologics for JIA	
Never used (bDMARD-naive) (N = 60)	54 (90.0)
Ever used (bDMARD-experienced) (N = 21)	18 (85.7)
Prior biologics for ERA	
Never used (bDMARD-naive) (N = 40)	37 (92.5)
Ever used (bDMARD-experienced) (N = 14)	11 (78.6)
Prior biologics for JPsA	
Never used (bDMARD-naive) (N = 20)	17 (85.0)
Ever used (bDMARD-experienced) (N = 7)	7 (100.0)
Prior csDMARDs for JIA	
Never used (N = 67)	60 (89.6)
Ever used (N = 14)	12 (85.7)
Prior NSAIDs for JIA	
Never used (N = 65)	57 (87.7)
Ever used (N = 16)	15 (93.8)
Methotrexate at baseline (JIA)	
Yes (N = 22)	19 (86.4)
No (N = 59)	53 (89.8)
Methotrexate at baseline (ERA)	
Yes (N = 12)	10 (83.3)
No (N = 42)	38 (90.5)
Methotrexate at baseline (JPsA)	
Yes (N = 10)	9 (90.0)
No (N = 17)	15 (88.2)
Body weight	
>50 kg (N = 55)	47 (85.5)
25 to 50 kg (N = 20)	20 (100.0)
10 to <25 kg (N = 6)	5 (83.3)

Abbreviations: ACR30= 30% improvement in American College of Rheumatology criteria; bDMARD = biologic DMARD; csDMARD = conventional synthetic DMARD; ERA = enthesitis-related arthritis; ITT = intent-to-treat; JIA = juvenile idiopathic arthritis; JPsA = juvenile psoriatic arthritis; n = number of patients in the specified category; N = number of patients in the analysis population; NRI = non-responder imputation; NSAID = nonsteroidal anti-inflammatory drug; OLT = open-label treatment.

Ixekizumab and Adalimumab

Change from baseline in LEI in ERA patients in the OLT Period

LEI measures enthesitis at 3 bilateral sites (lateral epicondyle, left and right; medial femoral condyle, left and right; and Achilles tendon insertion, left and right). Each of the 6 sites is assigned a score of 0 (absent) or 1 (present); the results from each site are then added to produce a total score (range 0 to 6) (Healy and

Helliwell 2008; Mease 2011). Change from baseline in LEI was assessed in patients with enthesitis at baseline in the ITT population (n=40) for the OLT Period. The table below presents the change from baseline in LEI total score in patients with ERA who received ixekizumab during the OLT Period. Compared with the baseline, an improvement of 83.13% in LEI total score in ERA patients was observed at Week 16. For adalimumab, mean (SD) change from baseline in LEI total score in ERA patients at Week 16 was -1.50 (0.577), which is 83% improvement from baseline.

Table 32. Change from baseline and percent improvement in LEI total score in ERA patients at each postbaseline visit, ixekizumab treatment group.

Response	Baseline		Week 2		Week 4		Week 8		Week 12		Week 16	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
LEI total score, Change from baseline[a]	40	2.10 (1.150)	39	-1.03 (1.614)	40	-1.33 (1.474)	40	-1.55 (1.319)	40	-1.65 (1.210)	40	-1.63 (1.005)
Percent improvement in LEI	NA		39	52.14 (72.364)	40	70.21 (66.154)	40	74.79 (51.595)	40	78.54 (44.812)	40	83.13 (32.713)

Abbreviations: ERA = enthesitis-related arthritis; ITT = intent-to-treat; LEI = Leeds enthesitis index; mBOCF = modified baseline observation carried forward; n = number of patients with non-missing data; NA = not applicable; OLT = open-label treatment; SD = standard deviation.

[a] The mean (SD) presented for postbaseline visits are change from baseline.

Analysis included ITT population with baseline enthesitis (LEI >0).

Ixekizumab

Proportion of patients with disease flare

Disease flare is defined as worsening of ≥30% from baseline in at least 3 of the 6 JIA ACR core set criteria and an improvement of ≥30% in no more than one of the criteria. One (1.2%) patient in the ixekizumab group met the protocol defined disease flare criteria at Week 8 during the OLT Period. The clinical interpretation of the data is limited and further evaluation of disease flare through OLE and LTE Periods will be provided in the final study report upon study completion.

Ancillary analyses

Not applicable.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 33. Summary of Efficacy for trial RHCG.

Title: Multicentre, Open-Label, Efficacy, Safety, Tolerability, and Pharmacokinetic Study of Subcutaneous Ixekizumab with Adalimumab Reference Arm, in Children with Juvenile Idiopathic Arthritis Subtypes of Enthesitis-Related Arthritis (Including Juvenile-Onset Ankylosing Spondylitis) and Juvenile Psoriatic Arthritis			
Study Identifier	I1F-MC-RHCG		
Design	Multicentre, open-label, randomised, Phase 3 study of ixekizumab with adalimumab as a reference arm		
	Duration of main phase:		16 Weeks (Open-Label Treatment Period)
	Duration of extension phase:		88 Weeks (Open-Label Extension Period)
	Duration of long-term extension phase:		160 Weeks (Long-Term Extension Period)
	Duration of follow-up phase:		12 Weeks minimum (Post-Treatment Follow-Up Period)
Hypothesis	Not applicable		
Treatment Groups	Ixekizumab weight-based dosing ixekizumab (>50.0 kg) • 160 mg, one-time starting dose • 80 mg Q4W SC injection for all treatment periods Ixekizumab (25.0 to 50.0 kg) • 80 mg, one-time starting dose • 40 mg Q4W SC injection for all treatment periods Ixekizumab (10.0 to <25.0 kg) • 40 mg, one-time starting dose • 20 mg Q4W SC injection for all treatment periods		Open-Label Treatment Period • Number of patients in ixekizumab group = 81 Open-Label Extension Period (prior to switch) • Number of patients in ixekizumab group = 80 Open-Label Extension Period (adalimumab switchers) • Number of patients in ixekizumab group = 9 Long-term extension period • Number of patients in ixekizumab group = 16
	Adalimumab weight-based dosing adalimumab (≥30.0 kg) • 40 mg Q2W SC injection for all treatment periods Adalimumab (10.0 to <30.0 kg) • 20 mg Q2W SC injection for all treatment periods		Open-Label Treatment Period • Number of patients in adalimumab group = 20 Open-Label Extension Period (prior to switch) • Number of patients in adalimumab group = 19
Endpoints and Definitions	Primary endpoint	Percentage of patients meeting the JIA ACR30 response criteria at Week 16	To evaluate the efficacy of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JPsA based on the JIA ACR30 response

	Secondary endpoint	Percentage of patients meeting the JIA ACR30/50/70/90/100 response criteria in OLT and OLE Periods	To evaluate the efficacy of ixekizumab and adalimumab (reference arm) in children with JIA subtypes of ERA (including JoAS) and JPsA based on clinical responses, disease activity, and physical function measures
	Secondary endpoint	Changes from baseline in each of the 6 individual components of the JIA ACR core set variables as follows in OLT and OLE Periods: • number of active joints • number of joints with limited range of motion • Physician's Global Assessment of Disease Activity • Parent's Global Assessment of Well-Being • physical function as measured by the CHAQ, and • acute-phase reactant hsCRP and ESR.	To evaluate the efficacy of ixekizumab and adalimumab (reference arm) in children with JIA subtypes of ERA (including JoAS) and JPsA based on clinical responses, disease activity, and physical function measures
	Secondary endpoint	Change from baseline in PASI for patients with JPsA with at least 3% BSA at baseline in OLT and OLE Periods	To evaluate the efficacy of ixekizumab and adalimumab (reference arm) in children with JIA subtypes of ERA (including JoAS) and JPsA based on clinical responses, disease activity, and physical function measures
	Secondary endpoint	Change from baseline in LEI for patients with enthesitis at baseline in OLT and OLE Periods	To evaluate the efficacy of ixekizumab and adalimumab (reference arm) in children with JIA subtypes of ERA (including JoAS) and JPsA based on clinical responses, disease activity, and physical function measures
	Secondary endpoint	Proportion of patients with disease flare (flare defined as worsening of ≥30% from baseline in at least 3 of the 6 JIA ACR core set criteria and an improvement of ≥30% in no more than 1 of the criteria) in OLT and OLE Periods	To evaluate the efficacy of ixekizumab and adalimumab (reference arm) in children with JIA subtypes of ERA (including JoAS) and JPsA based on clinical responses, disease activity, and physical function measures
Database Lock	02 April 2024		

Results and Analysis		
Analysis Description	**Primary analysis: JIA ACR30 response at Week 16**	
Analysis Population, Time Point Description, and Statistical Model	ITT Population – patients initially randomised to ixekizumab. 16 Weeks (OLT Period) Bayesian analysis (NRI)	
Descriptive Statistics and Estimate Variability	Treatment group	Ixekizumab Q4W
	Number of patients in the analysis population	81
	Primary endpoint: JIA ACR30 response at Week 16 (NRI) n (%)	72 (88.9)
	Primary endpoint: Posterior 95% credible interval	80.71, 94.36
	Primary endpoint: Posterior probability of patient treated with ixekizumab meeting JIA ACR30 at Week 16 >50%	>99%

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study design

To support this extension of indication application, the MAH has submitted an ongoing, multicentre, open-label, partially randomised, Phase 3 study (study RHCG) of subcutaneous ixekizumab, with adalimumab as reference arm, to evaluate efficacy, safety, tolerability, and pharmacokinetics in children from 2 to less than

18 years of age diagnosed with JIA subtypes of ERA (including JoAS) and JPsA, who are bDMARD-naive or bDMARD-inadequate responder as per investigator's judgement.

The study was conducted as agreed in the PIP for ixekizumab. One substantial modification to the protocol was made after the start of the trial, and this was the addition of the long-term-extension study, which is acceptable.

Although the MAH describes study RHCG as a randomised study, this description is only partially correct. Randomisation was indeed used to assign the first 40 bDMARD-naïve patients to ixekizumab or adalimumab (in a 1:1 ratio, stratified by ERA/JPsA), but the remaining 61 patients, who could be either bDMARD-naïve or bDMARD-IR, were all assigned to ixekizumab. The MAH argues that this design allowed for a descriptive comparison of ixekizumab with adalimumab, thus providing assay sensitivity, study method validation, and context for efficacy data. Although the descriptive comparison indeed provides context, it does not guarantee assay sensitivity or ensure study validity. Therefore, the between-group comparison is of limited value in the efficacy evaluation.

The duration of the OLT period (16 weeks) is sufficient according to the CHMP Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (EMA/CHMP/239770/2014 Rev. 2) for evaluating short-term efficacy.

In principle, the eligibility criteria are consistent with the proposed indication. The inclusion criteria also correspond to those proposed by the CHMP Guideline. The exclusion criteria are also relevant. It is noted that the study inclusion criteria did not mention that the patients should have failed conventional treatment (i.e. NSAID, DMARD), thus implying that ixekizumab was given as first line treatment. However, the current treatment practice is to begin with conventional treatment before proceeding to or adding biological treatment and the study was not designed to compare ixekizumab with conventional treatment. Upon request, the MAH has changed the wording of the indication to clarify that ixekizumab is not a first-line treatment in JIA subtypes of ERA and JPsA. The MAH has also clarified that ixekizumab may be used with or without MTX.

Endpoints

According to the CHMP Guideline, the ACR paediatric improvement criteria are an established assessment tool of clinically relevant improvement in disease activity. The level of improvement to be met should be pre-defined, be clinically meaningful and the results should be statistically significant. The guideline states that demonstration of clinically highly relevant decrease in disease activity, such as ACR Pedi 70 response is expected. The RHCG study used JIA ACR30 as the primary efficacy endpoint, which corresponds to less improvement compared with JIA ACR70. According to the CHMP Guideline, JIA ACR30 or 50 could be acceptable primary endpoints in hard-to-treat patients with adequate justification. It could be questioned whether this patient population, consisting of mostly bio-naïve patients, are considered hard-to-treat patients. Stricter JIA ACR response criteria (50/70/90/100) were however evaluated as secondary endpoints, including separate evaluation of each component in the JIA ACR criteria. JIA ACR30 has also been used previously as primary endpoint (Humira, Enbrel) and was agreed as primary endpoint in the PIP.

Of note, the JIA ACR response criteria include subjective variables, making the scale less appropriate as endpoint in an open-label study in which both patient and physician are aware of what treatment the patient receives. Nonetheless, the MAH has provided data on the changes from baseline in each of the 6 individual components of the JIA ACR core set variables at each postbaseline visit. The MAH has also evaluated other secondary endpoints including change from baseline in LEI for patients with enthesitis at baseline, and proportion of patients with disease flare.

Conduct of the study and demographics

Study discontinuation during the 16-week OLT period was low; only one study subject in each treatment arm discontinued the study during this period. All other patients completed the study and completed treatment during the OLT period.

During the OLT period, the proportion of important protocol deviations was similar in the ixekizumab group (18.5%) and the adalimumab group (15.0%). In both groups, study procedure compliance was the most common protocol deviation. Protocol deviations regarding informed consent were more common in the ixekizumab group. Overall, the protocol deviations are not considered to impact the reliability of the study results.

Demographic parameters were generally comparable between treatment groups. The study subjects in the adalimumab group had a shorter history of JIA diagnosis and to a larger extent ERA subtype of the disease. Of note, all patients in the adalimumab group were bDMARD-naïve, compared with 25% in the ixekizumab group. As this study is considered as primarily single-armed (only randomised in a subgroup) and only descriptive comparisons are made, this difference in baseline characteristics is acceptable. Demographic dissimilarities are not considered to impact the study result reliability.

Of the 81 patients in the ixekizumab group, 54 (66.7%) had ERA and 27 (33.3%) had JPsA. At baseline, the mean Juvenile Arthritis Disease Activity Score-27 (JADAS-27) was 14.65 (SD 6.00), corresponding to a high disease activity (Calasan et al. 2014). Concomitant JIA therapies used at baseline were methotrexate in 33 (40.7%), sulfasalazine in 4 (4.9%), glucocorticoids in 9 (11.1%). Initially, the MAH stated in the SmPC that 93.8% of the ixekizumab treated patients had received at least 1 prior therapy, but these therapies included all medications, not only treatments for JIA. Thus, the MAH was asked to present the proportion of patients with any previous **JIA treatment** and the proportion of patients who were treatment naïve. The MAH provided new tables which included the number of patients with any JIA therapy and number of patients with any concomitant JIA therapy (72.8%) and updated the SmPC.

Upon CHMP request, the MAH clarified that 21/26, 80.8% of JIA treatment naïve participants did receive concomitant JIA treatment at baseline. The SmPC was also updated with the proportion of participants that were bDMARD naïve (60/81, 74.1%) and csDMARD naïve (27/81, 33.3%) (prior and/or concomitant at baseline) at study entry.

It was also noted that previous JIA therapies included NSAID, but NSAID was not included in concomitant JIA medication. Upon request, the MAH included NSAID in the definition of concomitant medications as well. The MAH included types of concomitant therapies (also including NSAID) in the SmPC as well as the proportion of patients receiving them (49.4%). The issue is considered resolved.

The use of methotrexate as concomitant therapy was less common in the adalimumab group (25%).

Statistical methods

The efficacy analysis was primarily descriptive, and no statistical test was used to compare the treatments (ixekizumab and adalimumab). However, the study had the following success criterion for the ixekizumab group: an 80% or higher estimated probability that at least 50% of ixekizumab-treated patients achieve ACR 30 response. This probability was calculated using a Bayesian statistical method, meaning that it was based on both the results of the trial (the observed ACR 30 response rate) and an assumption about the response rate prior to the trial (the assumption was that there was a 50% probability that at least 50% of ixekizumab-treated patients would achieve ACR-30 response).

The analysis described above was pre-specified in the protocol and in the statistical analysis plan, and it was endorsed by PDCO in the paediatric investigation plan (P/0049/2023). However, since no statistical test was

used, the trial has not been able to demonstrate that ixekizumab treatment leads to a statistically significant improvement in disease activity, which is expected by the CHMP guideline on juvenile idiopathic arthritis (EMA/CHMP/239770/2014 Rev. 2). Thus, even if the success criterion is reached, a conclusion regarding a beneficial effect needs to be based on extrapolation from similar diseases in adults.

All enrolled patients were included in the efficacy analyses. Only 2 of the 81 ixekizumab-treated patients had missing data in the analysis of the primary endpoint at week 16. One of these patients was imputed as a non-responder. The other patient had missing data on some components on the ACR30, and these missing components were imputed using last-observation-carried-forward. This small amount of missing data is no cause for concern.

The planned sample size was 100 patients (101 were finally enrolled in the trial). No formal sample-size calculation was performed, but the MAH calculated that recruiting 80 ixekizumab-treated patients would give the study an 80% probability of success (see the success criterion described above) and a false-positive risk of less than 1%.

Efficacy data and additional analyses

Study RHCG showed a JIA ACR30 response rate of 88.9% (72/81) in ixekizumab-treated patients. With this result, the study also met its pre-defined success criterion to show a greater than 80% estimated probability that the true JIA ACR30 response rate exceeds 50% in ixekizumab-treated patients. In addition, the response rate at week 16 was consistent across subgroups of patients who were bDMARD-naive (54/60, 90.0%) and those who were bDMARD-experienced (18/21, 85.7%). The JIA ACR50 and JIA ACR70 responses at 16 weeks were 79.0% and 64.2%, respectively, which could be considered a clinically relevant treatment effect (although in an uncontrolled open-label setting). The JIA ACR30 response rate at 16 weeks did not differ between patients with ERA (48/54, 88.9%) and JPsA (24/27, 88.9%) treated with ixekizumab. Improvements were also seen across all JIA ACR core set variables.

However, since the composite endpoint JIA includes several subjective measurements and also allows for some deterioration (in one of the 6 endpoints evaluated) the MAH was asked to also report stricter endpoints such as the number of patients with absence of active joints as well as number of patients being in clinical remission at week 16. Upon request, the MAH has clarified that 42/81 (52.5%) patients treated with ixekizumab reported absence of active joints at Week 16. The MAH points out that clinical remission implies inactive disease which has been maintained for at least 6 months on treatment or 12 months off treatment. It is acknowledged that clinical remission could not be evaluated at 16 weeks.

In patients receiving adalimumab, a JIA ACR30 response was observed at Week 16 in 19 patients (95.0%), and the JIA ACR 50 and JIA ARC 70 response rates at week 16 were 90.0% and 65.0%, respectively. Upon request, the MAH has provided the results (demographics, primary and secondary endpoints) from the 20 patients randomised to ixekizumab (90%).

An improvement of 83.1% in LEI total score during the OLT period was seen in ERA patients with baseline enthesitis (n=40) receiving ixekizumab. The change in LEI score was similar in patients receiving adalimumab, but there were few cases (n=4).

Moreover, the MAH was asked to discuss what the response rate could be expected with placebo, taking into consideration previous studies, especially studies of adalimumab in ERA/JPsA. Submitted data indicate that placebo response rate for ARC 30 can be high; however, few previous studies are available (e.g., 60% in patients with ERA in a study by Burgos-Vargas et al., Arthritis Care Res 2015;67:1503).

As stated above, the study design has limitations as it is primarily single-armed, only partly randomised in a subgroup and lacks a placebo group. The comparison with adalimumab is only descriptive. The efficacy data provided from study RHCG alone are therefore not considered robust enough to conclude a beneficial effect for the paediatric ERA/PsA patients. However, there are other data that can support the effect.

As stated in the Reflection paper on the use of extrapolation in the development of medicines for paediatrics "*For example in juvenile idiopathic arthritis medicines where a clear PK-PD relationship and therapeutic window has been established in adult arthritis models, an extrapolation plan could be based primarily on PK and dose finding studies, supported with single-arm clinical data".* The conditions ERA and JPsA are considered to be similar to the adult diseases Axial Spondyloarthritis and PsA in which ixekizumab has demonstrated efficacy both in short and long term. The MAH has shown that the observed ixekizumab trough concentrations in JIA patients in study RHCG are within the range of the adult (axSpA and PsA patients) observed data with the approved dosing regimen, both across age and across body weight (for further information see Pharmacokinetics and Discussion on clinical pharmacology). Therefore, it is reasonable to expect therapeutic benefit of ixekizumab in ERA and JPsA. In addition, the IL-17A inhibitor secukinumab, with similar mechanisms of action as ixekizumab, is already authorised for the treatment of the paediatric indications ERA and JPsA.

There remains uncertainty regarding long term effects of ixekizumab in children with ERA and JPsA. Only 16 patients had completed the OLE period and proceeded into the LTE period. To evaluate the long-term tolerability and efficacy of ixekizumab in children with ERA and JPsA, the MAH is planning to evaluate several outcomes (e.g. JIA ACR 30/50/70/90/100 and their components, flares, uveitis, low disease activity or inactive disease, growth, and development) during the OLE period (through week 104) and the LTE period (through week 264). The extension study has thus been included in the RMP as a category 3 study. This is endorsed. However, since the last patient visit for the OLT period was February 2024, one-year data became available during the procedure. The MAH was asked to provide a summary of JIA ACR responses, mean JADAS-27, and proportion of flares in the study population with ixekizumab treatment since baseline assembled also after the database lock on 02 April 2024. The MAH has provided data for ixekizumab group patients who had completed Week 56 of OLE Period by data cutoff date 11 Nov 2024 (n=79). The JIA ACR30 response rate for this cohort was more than 80% at Week 56. The result for ERA and JpSA patients was similar (82.7% and 77.8%, respectively; data not shown). None of the patients in the ixekizumab group met the protocol-defined disease flare criteria through Week 56. The MAH pointed out that clinical interpretation of the data is limited and that further evaluation of disease flare through OLE and LTE Periods will be provided in the final study report. This is acceptable.

Compared with the baseline, a reduction in mean JADAS-27 (ESR) score was observed through Week 56. Through Week 56, 27/79 (34.2%) of ixekizumab-treated patients achieved low and 32/79 (40.5%) achieved low or inactive JADAS-27 status based on the JADAS-27 (ESR) cutoffs for disease activity prespecified as per the statistical analysis plan. In addition, a figure showing JADAS-27 (ESR) from baseline up to Week 56, using the updated cutoffs published in 2021, has been presented.

No data regarding clinical remission were provided. As other measures of disease activity have been provided (i.e. JADAS-27 status), this was not further pursued by CHMP. However, data on clinical remission is expected to be provided in the long-term follow-up report.

Upon request, the MAH has provided a discussion, based on current JIA treatment guidelines, regarding treatment length, dose reduction or treatment discontinuation in a well responding patient. It is acknowledged that no guidance regarding dose reduction or discontinuation of ixekizumab can be provided based on Study RHCG, given the design and conduct of the study. The MAH recommends that these decisions are left to the physician in dialogue with the patient and parents. This is endorsed and the issues are considered resolved.

2.4.4. Conclusions on the clinical efficacy

The conditions ERA and JPsA are considered to be similar to the adult diseases Axial Spondyloarthritis and PsA in which ixekizumab has demonstrated efficacy both in short and long term. The MAH has shown that the observed ixekizumab trough concentrations in JIA patients in study RHCG are within the range of the adult (axSpA and PsA patients) observed data with the approved dosing regimen, both across age and across body weight. Therefore, it is reasonable to expect therapeutic benefit of ixekizumab in ERA and JPsA, despite the limitation of the design of the RHCG study, being an open-label single armed study, with only a descriptive comparison with adalimumab in a randomised subgroup. Upon request, the MAH has changed the wording of the indication to clarify that ixekizumab is not a first-line treatment in JIA subtypes of ERA and JPsA. The MAH has also clarified that ixekizumab may be used with or without MTX.

2.5. Clinical safety

Introduction

Study RHCG is an ongoing, multicentre, open-label, randomised, Phase 3 study of ixekizumab administered subcutaneously, with adalimumab as a reference arm (OLT Period), followed by OLE Period with ixekizumab and adalimumab in children from 2 to younger than 18 years of age with JIA subtypes of ERA (including juvenile onset ankylosing spondylitis) and JPsA. The first 40 bio-naive patients entering the study were randomised 1:1 to ixekizumab or adalimumab as mentioned earlier. The remaining patients entering the study were directly assigned to ixekizumab. Patients who received adalimumab during the OLT Period who did not attain a JIA ACR30 response at Week 16 were switched to ixekizumab in the OLE Period. Patients who received adalimumab during the OLT Period who did attain a JIA ACR30 response at Week 16 were given the option to switch or not to switch to ixekizumab in the OLE Period. At the end of OLE Period, all patients receiving adalimumab were transitioned to ixekizumab.

The safety data presented in this submission are as of the DBL date of 02 April 2024. The RHCG study includes 4 analysis sets:

- OLT Period population includes 81 ixekizumab patients with an average of 114.0 days
- OLE Period population includes 80 ixekizumab patients with an average of 316.2 days
- OLE Period - adalimumab switchers to ixekizumab (switchers), includes 9 patients with an average of 398.2 days, and
- LTE Period population includes 16 patients for an average with 81.6 days.

Patient exposure

A total of 81 patients have received at least 1 dose of ixekizumab in Study RHCG.

Overall exposure of ixekizumab during different study periods was:

- 25.28 PY in the OLT Period
- 69.25 PY in the OLE Period
- 9.81 PY in the OLE Period (adalimumab switcher to ixekizumab), and
- 3.58 PY in the LTE Period.

Table 34 ***Overall study treatment exposure.***

	ADAQ2W (N=19)	IXEQ4W (N=80)	Total (N=99)
Days of exposure, n (%)			
> 0 day	16 (84.2)	80 (100.0)	96 (97.0)
>= 7 days	16 (84.2)	80 (100.0)	96 (97.0)
>= 14 days	16 (84.2)	80 (100.0)	96 (97.0)
>= 30 days	15 (78.9)	78 (97.5)	93 (93.9)
>= 60 days	14 (73.7)	68 (85.0)	82 (82.8)
>= 90 days	13 (68.4)	68 (85.0)	81 (81.8)
>= 120 days	13 (68.4)	63 (78.8)	76 (76.8)
>= 183 days	13 (68.4)	54 (67.5)	67 (67.7)
>= 365 days	11 (57.9)	33 (41.3)	44 (44.4)
Days of exposure, n (%)			
> 0 to < 7 days	0	0	0
>= 7 to < 14 days	0	0	0
>= 14 to < 30 days	1 (5.3)	2 (2.5)	3 (3.0)
>= 30 to < 60 days	1 (5.3)	10 (12.5)	11 (11.1)
>= 60 to < 90 days	1 (5.3)	0	1 (1.0)
>= 90 to < 120 days	0	5 (6.3)	5 (5.1)
>= 120 to < 183 days	0	9 (11.3)	9 (9.1)
>= 183 to < 365 days	2 (10.5)	21 (26.3)	23 (23.2)
>= 365 days	11 (57.9)	33 (41.3)	44 (44.4)

Abbreviations: N = number of patients in the analysis population; n = number of patients in the specified category; SD = standard deviation.
See complete footnote on last page of the output.

Adverse events

Table 35. Overview of adverse events.

Parameters	OLT Safety Population		OLE Period Population			LTE Population
			OLE Period Population (Including Adalimumab Data Prior to Switch to Ixekizumab)		Adalimumab Switchers to Ixekizumab (Switchers)	
	Ixekizumab (N = 81) n (%)	Adalimumab (N = 20) n (%)	Ixekizumab (N = 80) n (%)	Adalimumab (N = 19) n (%)	Ixekizumab (N = 9) n (%)	Ixekizumab (N = 16) n (%)
All TEAEs	66 (81.5)	16 (80.0)	65 (81.3)	14 (73.7)	8 (88.9)	8 (50.0)
Treatment-related TEAEs	47 (58.0)	9 (45.0)	29 (36.3)	10 (52.6)	6 (66.7)	3 (18.8)
TEAEs by severity[a]						
Mild	37 (45.7)	6 (30.0)	33 (41.3)	3 (15.8)	3 (33.3)	5 (31.3)
Moderate	29 (35.8)	7 (35.0)	27 (33.8)	10 (52.6)	4 (44.4)	2 (12.5)
Severe	0	3 (15.0)	5 (6.3)	1 (5.3)	1 (11.1)	1 (6.3)
Death	0	0	0	0	1 (11.1)	0
SAE	3 (3.7)	3 (15.0)	9 (11.3)	2 (10.5)	1 (11.1)	1 (6.3)
AEs leading to discontinuation of study intervention	0	0	2 (2.5)	0	1 (11.1)	1 (6.3)
TEAEs of special interest						
Infections	42 (51.9)	9 (45.0)	49 (61.3)	13 (68.4)	7 (77.8)	4 (25.0)
Injection site reactions	26 (32.1)	2 (10.0)	6 (7.5)	3 (15.8)	0	1 (6.3)
Allergic reactions / hypersensitivities	25 (30.9)	6 (30.0)	26 (32.5)	6 (31.6)	3 (33.3)	2 (12.5)
Cytopenias	3 (3.7)	1 (5.0)	5 (6.3)	1 (5.3)	1 (11.1)	0
Depression	2 (2.5)	0	4 (5.0)	0	0	0
Hepatic	1 (1.2)	1 (5.0)	2 (2.5)	3 (15.8)	0	0
Inflammatory bowel disease	0	0	1 (1.3)	1 (5.3)	0	0

Table 36. Overview of adverse events by weight category.

Parameters	OLT Safety Population			OLE Period Population			OLE Period Adalimumab Switchers to Ixekizumab (Switchers)			LTE Population		
	Ixekizumab			Ixekizumab			Ixekizumab			Ixekizumab		
	10-25 kg (N = 6) n (%)	25-50 kg (N = 20) n (%)	>50 kg (N = 55) n (%)	10-25 kg (N = 6) n (%)	25-50 kg (N = 20) n (%)	>50 kg (N = 54) n (%)	10-25 kg (N = 1) n (%)	25-50 kg (N = 0) n (%)	>50 kg (N = 8) n (%)	10-25 kg (N = 4) n (%)	25-50 kg (N = 2) n (%)	>50 kg (N = 10) n (%)
All TEAEs	6 (100.0)	19 (95.0)	41 (74.5)	6 (100.0)	17 (85.0)	42 (77.8)	1 (100.0)	0	7 (87.5)	2 (50.0)	1 (50.0)	5 (50.0)
TEAEs by severity[a]												
Mild	3 (50.0)	8 (40.0)	26 (47.3)	3 (50.0)	8 (40.0)	22 (40.7)	1 (100.0)	0	2 (25.0)	2 (50.0)	0	3 (30.0)
Moderate	3 (50.0)	11 (55.0)	15 (27.3)	3 (50.0)	8 (40.0)	16 (29.6)	0	0	4 (50.0)	0	1 (50.0)	1 (10.0)
Severe	0	0	0	0	1 (5.0)	4 (7.4)	0	0	1 (12.5)	0	0	1 (10.0)
Death	0	0	0	0	0	0	0	0	1 (12.5)	0	0	0
SAE	1 (16.7)	1 (5.0)	1 (1.8)	1 (16.7)	2 (10.0)	6 (11.1)	0	0	1 (12.5)	0	0	1 (10.0)
TEAEs related to study treatment	3 (50.0)	10 (50.0)	34 (61.8)	2 (33.3)	8 (40.0)	19 (35.2)	1 (100.0)	0	5 (62.5)	1 (25.0)	0	2 (20.0)
Discontinuation from study treatment due to AE (including death)	0	0	0	0	1 (5.0)	1 (1.9)	0	0	1 (12.5)	0	0	1 (10.0)
TEAEs of special interest												
Hepatic	0	0	1 (1.8)	0	1 (5.0)	1 (1.9)	0	0	0	0	0	0
Cytopenias	0	0	3 (5.5)	0	2 (10.0)	3 (5.6)	0	0	1 (12.5)	0	0	0
Infections	5 (83.3)	11 (55.0)	26 (47.3)	6 (100.0)	13 (65.0)	30 (55.6)	1 (100.0)	0	6 (75.0)	1 (25.0)	1 (50.0)	2 (20.0)
Confirmed Opportunistic Infections	0	0	0	0	0	3 (5.6)	0	0	0	0	0	0
Allergic reactions / hypersensitivities	4 (66.7)	6 (30.0)	15 (27.3)	4 (66.7)	7 (35.0)	15 (27.8)	1 (100.0)	0	2 (25.0)	1 (25.0)	0	1 (10.0)
Injection site reactions	2 (33.3)	4 (20.0)	20 (36.4)	0	2 (10.0)	4 (7.4)	0	0	0	1 (25.0)	0	0
Depression	1 (16.7)	0	1 (1.8)	0	1 (5.0)	3 (5.6)	0	0	0	0	0	0

Inflammatory bowel disease	0	0	0	0	1 (5.0)	0	0	0	0	0	0	0

Abbreviations: n = number of patients in the specified category; N = number of patients in the analysis population; LTE = long-term extension; OLE = open-label extension; OLT = open-label treatment; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Patients with multiple occurrences of the same event are counted under the highest severity.

Sources: Table RHCG.8.69 to Table RHCG.8.72.

Common Treatment-Emergent Adverse Events

In the OLT period, the most frequently reported TEAEs (≥10%) in patients treated with ixekizumab were from the SOC categories of:

- Infections and infestations (42 [51.9%])
- General disorders and administration site conditions (33 [40.7%])
- Gastrointestinal disorders (20 [24.7%])
- Nervous system disorders (15 [18.5%])
- Respiratory, thoracic and mediastinal disorders (15 [18.5%])
- Injury, poisoning and procedural complications (14 [17.3%])
- Investigations (13 [16.0%])
- Skin and subcutaneous tissue disorders (12 [14.8%]), and
- Musculoskeletal and connective tissue disorders (11 [13.6%]).

In the OLE period the most frequently reported TEAEs (≥10%) in the patients treated with ixekizumab were from the SOC categories of:

- Infections and infestations (49 [61.2%])
- Gastrointestinal disorders (22 [27.5%])
- Respiratory, thoracic and mediastinal disorders (20 [25.0%])
- Skin and subcutaneous tissue disorders (19 [23.8%])
- Musculoskeletal and connective tissue disorders (18 [22.5%])
- Investigations (14 [17.5%])
- Injury, poisoning and procedural complications (13 [16.2%])
- General disorders and administration site conditions (12 [15.0%])
- Eye disorders (11 [13.8%]), and
- Nervous system disorders (10 [12.5%]) (Table RHCG.8.78).

OLE Period adalimumab switchers to ixekizumab (switchers)

Majority of TEAEs were from the SOC categories of:

- Infections and infestations (7 [77.8%])
- Gastrointestinal disorders (5 [55.6%])
- General disorders and administration site conditions (3 [33.3%])
- Investigations (3 [33.3%])
- Musculoskeletal and connective tissue disorders (2 [22.2%]).

All other TEAEs were reported in 1 patient in each SOC category (Table RHCG.8.79).

LTE Period

Majority of TEAEs in the patients treated with ixekizumab were from the SOC categories of Infections and infestations (4 [25.0%]) and Gastrointestinal disorders (2 [12.5%]). All other TEAEs were reported in 1 patient in each SOC category.

Table 37. Common Treatment-Emergent Adverse Events Reported in At Least 2 Patients in the Ixekizumab Group in Any Period.

Preferred Term	OLT Safety Population		OLE Period Population			LTE Population
			OLE Period Population (Including Adalimumab Data Prior to Switch to Ixekizumab)		Adalimumab Switchers to Ixekizumab (Switchers)	
	Ixekizumab (N = 81) n (%)	Adalimumab (N = 20) n (%)	Ixekizumab (N = 80) n (%)	Adalimumab (N = 19) n (%)	Ixekizumab (N = 9) n (%)	Ixekizumab (N = 16) n (%)
Patients with at least 1 TEAE	66 (81.5)	16 (80.0)	65 (81.2)	14 (73.7)	8 (88.9)	8 (50.0)
Headache	13 (16.0)	2 (10.0)	4 (5.0)	4 (21.1)	0	0
Injection site reaction	13 (16.0)	1 (5.0)	3 (3.8)	0	0	1 (6.2)
Nasopharyngitis	11 (13.6)	4 (20.0)	13 (16.2)	3 (15.8)	2 (22.2)	3 (18.8)
Injection site pain	8 (9.9)	0	1 (1.2)	3 (15.8)	0	0
Oropharyngeal pain	8 (9.9)	2 (10.0)	6 (7.5)	1 (5.3)	1 (11.1)	0
COVID-19	7 (8.6)	0	9 (11.2)	2 (10.5)	0	0
Upper respiratory tract infection	7 (8.6)	0	4 (5.0)	3 (15.8)	2 (22.2)	0
Vomiting	7 (8.6)	0	6 (7.5)	2 (10.5)	3 (33.3)	0
Diarrhoea	6 (7.4)	0	6 (7.5)	1 (5.3)	0	1 (6.2)
Pyrexia	6 (7.4)	1 (5.0)	2 (2.5)	2 (10.5)	2 (22.2)	0
Rhinitis	5 (6.2)	0	8 (10.0)	3 (15.8)	0	0
Abdominal pain upper	4 (4.9)	1 (5.0)	2 (2.5)	0	2 (22.2)	0
Eosinophil count increased	4 (4.9)	0	2 (2.5)	0	1 (11.1)	0
Tonsillitis	4 (4.9)	0	6 (7.5)	2 (10.5)	0	1 (6.2)
Arthralgia	3 (3.7)	0	9 (11.2)	0	1 (11.1)	0
Erythema	3 (3.7)	0	1 (1.2)	0	0	0
Pain in extremity	3 (3.7)	0	3 (3.8)	0	1 (11.1)	0
Viral infection	3 (3.7)	1 (5.0)	4 (5.0)	1 (5.3)	0	0
Abdominal pain	2 (2.5)	0	4 (5.0)	2 (10.5)	0	1 (6.2)
Alopecia	2 (2.5)	0	1 (1.2)	1 (5.3)	0	0
Body temperature increased	2 (2.5)	0	2 (2.5)	0	0	0
C-reactive protein increased	2 (2.5)	0	0	0	1 (11.1)	0
Contusion	2 (2.5)	1 (5.0)	1 (1.2)	1 (5.3)	0	0
Cough	2 (2.5)	1 (5.0)	9 (11.2)	2 (10.5)	1 (11.1)	1 (6.2)
Decreased appetite	2 (2.5)	0	3 (3.8)	0	0	0
Dizziness	2 (2.5)	1 (5.0)	3 (3.8)	2 (10.5)	0	0
Eczema	2 (2.5)	1 (5.0)	1 (1.2)	0	0	0
Fatigue	2 (2.5)	0	0	1 (5.3)	0	0
Gastroenteritis	2 (2.5)	1 (5.0)	4 (5.0)	1 (5.3)	0	1 (6.2)
Hand fracture	2 (2.5)	0	1 (1.2)	0	0	0
Influenza like illness	2 (2.5)	0	2 (2.5)	1 (5.3)	0	0
Injection site erythema	2 (2.5)	1 (5.0)	2 (2.5)	0	0	0
Injection site hypersensitivity	2 (2.5)	0	0	0	0	0
Injection site swelling	2 (2.5)	0	1 (1.2)	0	0	0
Muscle spasms	2 (2.5)	0	1 (1.2)	0	0	0
Nasal congestion	2 (2.5)	0	3 (3.8)	0	0	0
Nausea	2 (2.5)	2 (10.0)	6 (7.5)	4 (21.1)	0	0
Non-cardiac chest pain	2 (2.5)	0	0	0	0	0
Pharyngitis	2 (2.5)	0	2 (2.5)	0	0	0
Rash	2 (2.5)	0	4 (5.0)	1 (5.3)	0	0
Vertigo	2 (2.5)	1 (5.0)	1 (1.2)	0	0	0
Vitamin D decreased	2 (2.5)	0	0	0	0	0
Influenza	1 (1.2)	0	5 (6.2)	1 (5.3)	1 (11.1)	0
Ear pain	1 (1.2)	1 (5.0)	4 (5.0)	1 (5.3)	0	0

Preferred Term	OLT Safety Population		OLE Period Population			LTE Population
			OLE Period Population (Including Adalimumab Data Prior to Switch to Ixekizumab)		Adalimumab Switchers to Ixekizumab (Switchers)	
	Ixekizumab (N = 81) n (%)	Adalimumab (N = 20) n (%)	Ixekizumab (N = 80) n (%)	Adalimumab (N = 19) n (%)	Ixekizumab (N = 9) n (%)	Ixekizumab (N = 16) n (%)
Lower respiratory tract infection	1 (1.2)	0	4 (5.0)	0	0	0
Monocyte count decreased	1 (1.2)	1 (5.0)	4 (5.0)	1 (5.3)	1 (11.1)	0
Rhinorrhoea	0	0	4 (5.0)	1 (5.3)	0	0
Acne	0	1 (5.0)	3 (3.8)	0	0	0
Blood creatine phosphokinase increased	0	1 (5.0)	3 (3.8)	1 (5.3)	1 (11.1)	1 (6.2)
Conjunctivitis	1 (1.2)	1 (5.0)	3 (3.8)	0	0	0
Constipation	0	0	3 (3.8)	0	0	0
Dry skin	0	0	3 (3.8)	0	0	0
Juvenile idiopathic arthritis	1 (1.2)	0	3 (3.8)	0	0	0
Neck pain	0	0	3 (3.8)	0	0	0
Otitis media	1 (1.2)	0	3 (3.8)	2 (10.5)	0	0
Sinusitis	1 (1.2)	0	3 (3.8)	0	0	0
Urinary tract infection	1 (1.2)	0	3 (3.8)	0	1 (11.1)	0
Arthritis	1 (1.2)	0	2 (2.5)	0	0	0
Clavicle fracture	0	0	2 (2.5)	0	0	0
Depression	0	0	2 (2.5)	0	0	0
Dermatitis	1 (1.2)	0	2 (2.5)	0	0	1 (6.2)
Drug eruption	0	0	2 (2.5)	0	0	0
Ear infection	1 (1.2)	0	2 (2.5)	0	0	0
Gastritis	0	0	2 (2.5)	0	1 (11.1)	0
Gastrointestinal infection	1 (1.2)	0	2 (2.5)	1 (5.3)	0	0
Mite allergy	0	0	2 (2.5)	0	0	0
Musculoskeletal stiffness	1 (1.2)	0	2 (2.5)	0	0	0
Ocular hyperaemia	1 (1.2)	0	2 (2.5)	1 (5.3)	0	0
Pain	1 (1.2)	0	2 (2.5)	1 (5.3)	0	0
Protein urine present	1 (1.2)	0	2 (2.5)	0	1 (11.1)	0
Pruritus	0	0	2 (2.5)	0	0	0
Rash pruritic	1 (1.2)	1 (5.0)	2 (2.5)	0	0	0
Road traffic accident	1 (1.2)	0	2 (2.5)	0	0	0
Seasonal allergy	1 (1.2)	0	2 (2.5)	0	0	0
Suicidal ideation	0	0	2 (2.5)	0	0	0
Urticaria	0	1 (5.0)	2 (2.5)	0	0	0
White blood cells urine positive	0	0	2 (2.5)	0	1 (11.1)	0

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; LTE = long-term extension; n = number of patients in the specified category; N = number of patients in the analysis population; OLE = open-label extension; OLT = open-label treatment; TEAE = treatment-emergent adverse event.
Source: Table RHCG.8.73 to Table RHCG.8.76.

Serious adverse event/deaths/other significant events

Severe TEAEs

No severe TEAEs were reported in the patients treated with ixekizumab during the OLT Period. Six severe TEAEs were reported in 5 (6.2%) patients during the OLE Period prior to switch in the ixekizumab group. The severe TEAEs by PTs in the ixekizumab group (prior to switch) were upper respiratory tract infection, cytomegalovirus infection, sialoadenitis, ankle fracture, thrombotic thrombocytopenic purpura, and suicidal ideation.

Among the OLE Period adalimumab switchers (post switch), 1 (11.1%) patient had 3 severe TEAEs of dehydration, acute kidney injury, and haemorrhagic shock while receiving ixekizumab.

In the LTE Period, 1 (6.2%) patient had a severe TEAE of salivary gland calculus while receiving ixekizumab.

Deaths

As of database lock date of 02 April 2024, 1 patient in the OLE Period adalimumab switcher to ixekizumab died during the study. The patient was a 12-year-old female diagnosed with ERA. Patient was initially assigned to adalimumab 40 mg Q2W and received the first dose in the OLT Period on 22 December 2021. Patient switched the treatment from adalimumab to ixekizumab 80 mg Q4W on 28 July 2022. The patient was also taking concomitant methotrexate 20 mg oral once weekly for ERA since 13 May 2022. No ixekizumab PK data were available for this patient. Patient experienced vomiting for 30 days (beginning in middle of Feb 2023), followed by 10 days of severe vomiting. According to investigator, patient did not report this to parents or investigator during the course of event. Patient received the last dose of ixekizumab on 15 March 2023. On 28 March 2023, prior to the next scheduled dose of ixekizumab, the patient was hospitalised with severe dehydration, acute kidney injury, and hypertensive crisis. On 30 March 2023, the patient began with a condition at the pulmonary level (as reported), leading to alveolar haemorrhage and subsequent haemorrhagic shock that led to death on 31 March 2023. The cause of death was reported as hypovolemic shock secondary to diffuse alveolar haemorrhage. An autopsy was not performed and death certificate not available. The patient had no reported evidence of vasculitis, coagulopathy, or infection, as per the investigator. In the opinion of the study investigator, the SAEs of dehydration, acute renal failure, alveolar haemorrhage, and subsequent haemorrhagic shock that led to death were not related to ixekizumab, adalimumab, study device, or to any protocol related procedures.

Serious adverse events

Table 38. Summary of Serious Adverse Events by SOC and PT

System Organ Class Preferred Term	OLT Safety Population		OLE Period Population			LTE Population
			OLE Period Population (Including Adalimumab Data Prior to Switch to Ixekizumab)		Adalimumab Switchers to Ixekizumab (Switchers)	
	Ixekizumab (N = 81) n (%)	Adalimumab (N = 20) n (%)	Ixekizumab (N = 80) n (%)	Adalimumab (N = 19) n (%)	Ixekizumab (N = 9) n (%)	Ixekizumab (N = 16) n (%)
Patients with at least 1 SAE	3 (3.7)	3 (15.0)	9 (11.2)	2 (10.5)	1 (11.1)	1 (6.2)
Infections and infestations	2 (2.5)	1 (5.0)	3 (3.8)	0	0	0
Acute sinusitis	1 (1.2)	0	0	0	0	0
Tonsillitis	1 (1.2)	0	0	0	0	0
Cellulitis	0	1 (5.0)	0	0	0	0
Cytomegalovirus infection	0	0	1 (1.2)	0	0	0
Sialoadenitis	0	0	1 (1.2)	0	0	0
Upper respiratory tract infection	0	0	1 (1.2)	0	0	0
Musculoskeletal and connective tissue disorders	0	0	2 (2.5)	0	0	0
Joint swelling	0	0	1 (1.2)	0	0	0
Juvenile idiopathic arthritis	0	0	1 (1.2)	0	0	0
Injury, poisoning and procedural complications	1 (1.2)	0	1 (1.2)	1 (5.3)	0	0
Acetabulum fracture	1 (1.2)	0	0	0	0	0
Ankle fracture	0	0	1 (1.2)	0	0	0
Concussion	0	0	0	1 (5.3)	0	0
Blood and lymphatic system disorders	0	1 (5.0)	0	0	0	0
Bicytopenia	0	1 (5.0)	0	0	0	0
Ear and labyrinth disorders	0	1 (5.0)	0	0	0	0
Middle ear effusion	0	1 (5.0)	0	0	0	0
Hepatobiliary disorders	0	1 (5.0)	0	0	0	0
Hypertransaminasaemia	0	1 (5.0)	0	0	0	0

Immune system disorders	0	1 (5.0)	0	0	0	0
Anaphylactic reaction	0	1 (5.0)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (5.0)	1 (1.2)	0	0	0
Asthma	0	1 (5.0)	0	0	0	0
Adenoidal hypertrophy	0	0	1 (1.2)	0	0	0
Psychiatric disorders	0	0	1 (1.2)	0	0	0
Suicidal ideation	0	0	1 (1.2)	0	0	0
Surgical and medical procedures	0	0	1 (1.2)	0	0	0
Hospitalisation	0	0	1 (1.2)	0	0	0
Gastrointestinal disorders	0	0	0	1 (5.3)	0	1 (6.2)
Crohn's disease	0	0	0	1 (5.3)	0	0
Salivary gland calculus	0	0	0	0	0	1 (6.2)
Metabolism and nutrition disorders	0	0	0	0	1 (11.1)	0
Dehydration	0	0	0	0	1 (11.1)	0
Renal and urinary disorders	0	0	0	0	1 (11.1)	0
Acute kidney injury	0	0	0	0	1 (11.1)	0
Vascular disorders	0	0	0	0	1 (11.1)	0
Shock haemorrhagic	0	0	0	0	1 (11.1)	0

Abbreviations: AE = adverse event; LTE = long-term extension; n = number of patients in the specified category; N = number of patients in the analysis population; OLT = open-label treatment; OLE = open-label extension; PT = preferred term; SAE = serious adverse event; SOC = system organ class.
Sources: Table RHCG.8.82 to Table RHCG.8.85.

Adverse Events of Special Interest

The AESIs identified for ixekizumab are:
- cytopaenias (leukopaenia, neutropaenia, and thrombocytopaenia)
- liver biochemical test changes / enzyme elevations (ALT, AST, bilirubin, and ALP)
- infections
- injection site reactions
- allergic reactions / hypersensitivities
- cerebrocardiovascular events.

No TEAEs of malignancies, cerebrocardiovascular events, and interstitial lung disease were reported for any of the patients.

Cytopaenia

A total of 3 (3.7%) patients in the ixekizumab group had treatment-emergent cytopaenias in the **OLT period**, which included 1 patient with monocyte count decreased (laboratory value = 0.34x109/L) on Day 113 of the study, 1 patient with neutropaenia (laboratory value = 1.24x109/L) reported on Day 113 of the study and 1 patient with white blood cell count decreased (laboratory value = 3.69x109/L) reported on Day 114 of the study. All TEAE was considered mild in severity and none of these patients reported any associated TEAEs with cytopaenias.

Five (6.3%) patients in the ixekizumab group had treatment-emergent cytopaenias during the **OLE period**, which included 4 patients with monocyte count decreased (all cases mild, in 3 cases related to study drug) and one case with lymphopaenia (mild in severity and not related to the study drug).
None of these patients reported any associated TEAEs with cytopaenias.

OLE Period adalimumab switchers to ixekizumab (switchers). One patient had treatment-emergent cytopaenia, which included monocyte count decreased. The TEAE was considered mild in severity and related to the study drug. There were no associated TEAEs with this event.

No treatment-emergent cytopaenias were reported in the **LTE period**.

Liver Biochemical Enzyme Elevations

There was no drug-induced serious hepatotoxicity in the patients treated with ixekizumab across all periods.

One patient had hypertransaminasaemia in the ixekizumab group in the **OLT period**. The TEAE started on Day 30 of the study (ALT 108 U/L and AST 80 U/L) and resolved on Day 44. The TEAE was considered mild in severity and not related to the study drug, however ixekizumab was temporarily interrupted in this patient.

Two patients had TEAEs related to liver biochemical enzymes in the ixekizumab group in the **OLE period**: One patient had aspartate aminotransferase increased and one patient had transaminases increased. Both TEAEs were considered mild in severity and not related to the study drug.

No hepatic TEAEs were reported in switchers or in the LTE period.

Infections Including Opportunistic Infections

In the OLT Period, all the infections reported in the ixekizumab group were mild or moderate in severity. Nasopharyngitis was the only treatment-emergent infection reported in at least 10% of patients in the ixekizumab group.

Table 39. Treatment-Emergent Infections Reported in >1 Patient in the Ixekizumab Group in Any Period.

Treatment Population	OLT Safety Population		OLE Period Population			LTE Population
			OLE Period Population (Including Adalimumab Data Prior to Switch to Ixekizumab)		Adalimumab Switchers to Ixekizumab (Switchers)	
Treatment	Ixekizumab (N = 81)	Adalimumab (N = 20)	Ixekizumab (N = 80)	Adalimumab (N = 19)	Ixekizumab (N = 9)	Ixekizumab (N = 16)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with TE Infections	42 (51.9)	9 (45.0)	49 (61.2)	13 (68.4)	7 (77.8)	4 (25.0)
Nasopharyngitis	11 (13.6)	4 (20.0)	13 (16.2)	3 (15.8)	2 (22.2)	3 (18.8)
COVID-19	7 (8.6)	0	9 (11.2)	2 (10.5)	0	0
Upper respiratory tract infection	7 (8.6)	0	4 (5.0)	3 (15.8)	2 (22.2)	0
Rhinitis	5 (6.2)	0	8 (10.0)	3 (15.8)	0	0
Tonsillitis	4 (4.9)	0	6 (7.5)	2 (10.5)	0	1 (6.2)
Viral infection	3 (3.7)	1 (5.0)	4 (5.0)	1 (5.3)	0	0
Gastroenteritis	2 (2.5)	1 (5.0)	4 (5.0)	1 (5.3)	0	1 (6.2)
Pharyngitis	2 (2.5)	0	2 (2.5)	0	0	0
Influenza	1 (1.2)	0	5 (6.2)	1 (5.3)	1 (11.1)	0
Otitis media	1 (1.2)	0	3 (3.8)	2 (10.5)	0	0
Lower respiratory tract infection	1 (1.2)	0	4 (5.0)	0	0	0
Conjunctivitis	1 (1.2)	1 (5.0)	3 (3.8)	0	0	0
Gastrointestinal infection	1 (1.2)	0	2 (2.5)	1 (5.3)	0	0
Sinusitis	1 (1.2)	0	3 (3.8)	0	0	0
Urinary tract infection	1 (1.2)	0	3 (3.8)	0	1 (11.1)	0
Ear infection	1 (1.2)	0	2 (2.5)	0	0	0

Abbreviations: COVID-19 = coronavirus disease 2019; LTE = long-term extension; n = number of patients in specified category; N = number of patients; OLE = open-label extension; OLT = open-label treatment; TE = treatment emergent.

Sources: Table RHCG.8.96 to Table RHCG.8.99.

During the **OLT Period**, 2 (2.5%) patients in the ixekizumab group had serious infections, i.e. acute sinusitis and tonsillitis. Both TEAEs were considered as moderate in severity and not related to the study drug. No confirmed opportunistic infections were reported during the OLT Period and none of the patients discontinued ixekizumab due to any infection.

During the **OLE Period**, 3 (3.8%) patients in the ixekizumab group had serious infections, i.e. cytomegalovirus infection (severe and considered related to the study drug). Study drug was temporarily interrupted. Sialoadenitis (considered as severe and not related to the study drug). Upper respiratory tract infection (considered as severe and related to the study drug).

During the OLE Period, confirmed opportunistic infections were reported in 3 (3.8%) patients in the ixekizumab group: cytomegalovirus infection (the same as above), herpes zoster, oesophageal candidiasis.

None of the patients discontinued ixekizumab due to any infection during the OLE Period.

No serious infections or opportunistic infections were reported in the patients who **switched** from adalimumab to ixekizumab treatment.

No serious infections or opportunistic infection were reported during the **LTE period**.

Injection Site Reactions

All the injection site reactions reported in the ixekizumab group were mild or moderate in severity. No serious injection site reactions were reported and none of the patients discontinued ixekizumab due to injection site reactions.

Injection site reactions were reported in 26 (32.1%) patients in the ixekizumab group in the OLT period, in 6 (7.5%) patients in the ixekizumab group (before switch to ixekizumab) in the OLE period, and 1 during the LTE period.

Allergic Reactions / Hypersensitivities

Table 40. Summary of Treatment-Emergent Allergic Reactions /Hypersensitivities.

Treatment Population	OLT Safety Population		OLE Period Population			LTE Population
			OLE Period Population (Including Adalimumab Data Prior to Switch to Ixekizumab)		Adalimumab Switchers to Ixekizumab (Switchers)	
Treatment	Ixekizumab (N = 81)	Adalimumab (N = 20)	Ixekizumab (N = 80)	Adalimumab (N = 19)	Ixekizumab (N = 9)	Ixekizumab (N = 16)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patient with ≥1 TE Allergic reaction / hypersensitivity	25 (30.9)	6 (30.0)	26 (32.5)	6 (31.6)	3 (33.3)	2 (12.5)
Potential Anaphylaxis	0	0	0	0	0	0
Non-anaphylaxis	6 (7.4)	1 (5.0)	4 (5.0)	0	0	1 (6.3)
Eczema	2 (2.5)	1 (5.0)	1 (1.3)	0	0	0
Allergic respiratory disease	1 (1.2)	0	0	0	0	0
Dermatitis	1 (1.2)	0	2 (2.5)	0	0	1 (6.3)
Perioral dermatitis	1 (1.2)	0	0	0	0	0
Rash macular	1 (1.2)	0	0	0	0	0
Rash maculo-papular	1 (1.2)	0	0	0	0	0
Hypersensitivity	0	0	1 (1.3)	0	0	0

Abbreviations: n = number of patients in specified category; N = number of patients; LTE = long-term extension; OLE = open-label extension; OLT= open-label treatment; TE = treatment emergent.
Sources: Table RHCG.8.106 to Table RHCG.8.109.

Inflammatory Bowel Disease

OLT Period

No TEAEs of inflammatory bowel disease were reported in the ixekizumab group during OLT Period.

OLE Period

One patient had reported treatment-emergent inflammatory bowel disease in the ixekizumab group, and it was classified as Crohn's disease. The case was adjudicated as probable Crohn's disease. The TEAE was

considered as moderate in severity, not related to the study drug, and ixekizumab was withdrawn due to the event. The TEAE was ongoing as of data cutoff date of this report.

Depression

TEAEs related to depression and suicide, or self-injury were reported in 2 (2.5%) patients treated with ixekizumab during the OLT period, of which 1 patient reported initial insomnia (moderate severity and was considered related to the study drug) and 1 patient reported tearfulness of mild severity.

TEAEs related to depression and suicide or self-injury were reported in 4 (5.0%) patients treated with ixekizumab in the **OLE Period** prior to switch which included:

- 1 patient with depression; the event was considered mild in severity, not related to the study drug, and was ongoing at the time of cutoff date of this report;
- 1 patient with depression and suicidal ideation; both the events were considered mild in severity and not related to the study drug. The event of depression was ongoing at the time of cutoff date of this report whereas suicidal ideation was resolved;
- 1 patient with suicidal ideation; the event was considered severe, not related to study drug, and event was ongoing at the time of cutoff date of this report;
- 1 patient with depressed mood, the event was considered mild in severity, not related to the study drug, and was ongoing at the time of cutoff date of this report. This event was not suggestive of clinical depression and was retrieved due to the broad nature of the search criteria;

OLE Period adalimumab switchers to ixekizumab (switchers)
No TEAEs relevant to TEAEs related to depression and suicide or self-injury were reported.

LTE Period
No TEAEs relevant to TEAEs related to depression and suicide or self-injury were reported.

CDI-2 and C-SSRS scores

Children's Depression Inventory (CDI-2)

Depression in the paediatric patient population was assessed using 2 scales; CDI-2 and C-SSRS. CDI-2 is a 12-item self-reported scale designed to measure depressive symptoms in children and adolescents (aged 7 years and older) (Helsel and Matson 1984; Kovacs 1992; Ahlen and Ghaderi 2017). The instrument has a recall period of the past 2 weeks and responses use a 3-item Likert scale. A higher score indicates more clinically severe depression.

OLT Period
At baseline, mean (SD) CDI-2 total score was 4.47 (3.353) in the patients treated with ixekizumab. An improvement from baseline in CDI-2 total score was observed throughout the OLT Period, with maximum mean (SD) change from baseline of -1.16 (2.598) observed at Week 16.

OLE Period
CDI-2 total score was stable or improved compared to the baseline during the OLE Period (prior to switch) in the ixekizumab treated patients (with available assessment) for all visits except Week 80. Maximum mean (SD) change from baseline was -0.53 (1.885) observed at Week 104.

OLE Period adalimumab switchers to ixekizumab (switchers)
Among the adalimumab switchers, an improvement from baseline in CDI-2 score was observed in the OLE switcher population (with available assessment) up to Week 80. Maximum mean (SD) change from baseline was -1.75 (1.708) at Week 20.

LTE Period
In the LTE Period, change from baseline in CDI-2 score was stable in the LTE population up to Week 120. Maximum mean (SD) change from baseline was 2 (1.414) at Week 132.

Columbia Suicide Severity Rating Scale

C-SSRS is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behaviour during the assessment period via a questionnaire which is administered by the clinician.
The instrument is validated for use in children aged 7 to 11 (using the Children C-SSRS) as well as adults aged 12 and older (using the Adult C-SSRS form). The instrument is a composite instrument with responses being a mixture of yes / no, ordinal and nominal scales. Higher scores indicate higher suicidal ideation and behaviour. The Self-Harm Supplement Form is part of the C-SSRS instrument. It consists of 1 question and is completed at any visit, including baseline visits by the clinician. The question asked for the number of suicidal or non-suicidal self-injurious behaviours the patient experienced since last assessment and is documented in the electronic CRF.

OLT Period
Suicidal ideation was observed in 4 (5.0%) of the patients treated with ixekizumab, while suicidal behaviour was not observed. Additionally, 1 patient had self-injurious behaviour without suicidal intent. The following patients reported positive responses to suicidal ideation and behaviour (and related behaviour) on the C-SSRS during the ixekizumab treatment in the study:

- One patient reported a wish to be dead, nonspecific active suicidal thoughts and self-injurious behaviour without suicidal intent at Week 16. The patient had no past medical history of psychiatric disease. The patient discontinued the study at Week 24 asper physician decision due to flare of JIA.

- One patient reported a wish to be dead during the entire study duration, nonspecific active suicidal thoughts at screening, baseline, and on Days 30, 232, and 310. Upon completion of the follow-up form, there was active suicidal ideation with some intent to act, without specific plan on Day 310. A serious adverse event of suicidal ideation was reported, and the patient was discontinued from the study. The patient had no past medical history of psychiatric disease.

- One patient reported a wish to be dead on Day 36. The patient had no further positive responses on the C-SSRS. The patient had no past medical history of psychiatric disease. The patient continued in the study.

- One patient reported a wish to be dead at screening, and on Days 113, 261, and 554. The patient was referred to a paediatric psychiatric evaluation after Day 113. Patient reported nonspecific active suicidal thoughts on Days 261 and 554. Upon completion of the follow-up form, there were positive responses to active suicidal ideation with any methods (not plan) without intent to act and active suicidal ideation with some intent to act, without specific plan on Day 261. Patient started pregabalin on Day 294. The patient had no past medical history of psychiatric disease. The patient continued in the study.

OLE Period
In the OLE Period, suicidal ideation was observed in 2 (2.6%) of the patients treated with ixekizumab, while suicidal behaviour was not observed in the patients treated with ixekizumab.

OLE Period adalimumab switchers to ixekizumab (switchers)
Suicidal ideation or suicidal behaviour was not observed while receiving the ixekizumab.

In the **LTE Period** Suicidal ideation or suicidal behaviour was not observed while receiving ixekizumab.

Laboratory findings

Immunogenicity

Overall, 79 ixekizumab treated patients were evaluable for ADA. Of these, 1 (1.3%) patient was positive for ADA at baseline with a titre of 1:10, and no patient was positive for Nab to ixekizumab at baseline. At postbaseline, a total of 18 (22.8%) patients became TE-ADA-positive during either the OLT or OLE Periods. In the OLT Period, 7 (8.9%) patients became TE-ADA positive, and 11 (15.2%) additional patients became TE-ADA positive during the OLE Period. Of the TE-ADA positive patients, 2 (2.5%) patients were determined to be NAb negative. The remaining 16 (20.3%) patients were inconclusive for the presence of NAb, meaning that no NAb were detected at any time point during the study for these patients, but each patient had at least 1 sample with an ixekizumab concentration above the limit of drug tolerance for the NAb assay.
The maximum titres observed for TE-ADA positive patients ranged from 1:10 to 1:640. The majority of TE-ADA positive patients (14 [17.5%]) had maximum titres in the low titre category, and the remainder patients (5 [6.3%]) had maximum titres in the moderate titre category. No titre results were observed in the high titre category.

Of the 7 TE-ADA positive patients at Week 16 in the ixekizumab group, the JIA ACR30 response was observed in 6 (85.7%) patients and in TE-ADA negative patients (N = 11), JIA ACR30 response was observed in 66 (90.4%) patients, using NRI method.

In the ixekizumab group, 7 of the 18 TE-ADA positive patients reported Injection Site Reaction at any period of the study. All of them were mild or moderate in severity, and none of them were considered as SAE. None of these patients discontinued the ixekizumab due to TEAE; however, in 1 patient, treatment was temporarily interrupted.

Of the 18 patients with TE-ADA positive at any period of the study who were treated with ixekizumab, none of the patients reported Allergic Reactions / Hypersensitivity.

Safety in special populations

Pregnancy

Study RHCG protocol included strict criteria for the requirements of abstinence and/or contraception requirements for patients of childbearing potential. Pregnant and breastfeeding female study patients were excluded from entering Study RHCG. As of DBL date of 02 April 2024, no pregnancies were reported in Study RHCG.
Limited data are available on ixekizumab use in pregnant women or male partners exposed to ixekizumab to inform any drug-associated risks during pregnancy or potential effects on foetus and/or neonates. According to the MAH, 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. Similar to other low-frequency events, the potential effects of ixekizumab on pregnancy and lactation will continue to be monitored by the MAH throughout the duration of the ixekizumab clinical development programme and via routine pharmacovigilance for post-marketing data.

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

Table 41. Summary of Adverse Events Leading to Permanent Discontinuation of Study Drug.

System Organ Class Preferred Term	OLT Safety Population		OLE Period Population			LTE Population
			OLE Period Population (Including Adalimumab Data Prior to Switch to Ixekizumab)		Adalimumab Switchers to Ixekizumab (Switchers)	
	Ixekizumab (N = 81)	Adalimumab (N = 20)	Ixekizumab (N = 80)	Adalimumab (N = 19)	Ixekizumab (N = 9)	Ixekizumab (N = 16)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
AEs leading to permanent discontinuation of the study drug (patients with ≥1 AE)	0	0	2 (2.5)	0	1 (11.1)	1 (6.2)
Gastrointestinal disorders	0	0	1 (1.2)	0	0	1 (6.2)
Abdominal pain	0	0	0	0	0	1 (6.2)
Crohn's disease	0	0	1 (1.2)	0	0	0
Vascular disorders	0	0	0	0	1 (11.1)	0
Shock haemorrhagic	0	0	0	0	1 (11.1)	0
Immune system disorders	0	0	1 (1.2)	0	0	0
Hypersensitivity	0	0	1 (1.2)	0	0	0

Abbreviations: AE = adverse events; n = number of patients in specified category; N = number of patients; LTE = long-term extension; OLE = open-label extension; OLT = open-label treatment; PBO = placebo.
Sources: Table RHCG.8.87 to Table RHCG.8.89.

Post marketing experience

Ixekizumab was first authorised on 22 March 2016 in the US and on 25 April 2016 in the EU for adults with moderate-to-severe plaque psoriasis. Subsequently, ixekizumab was approved for adults with active PsA, active ankylosing spondylitis (also referred to as radiographic axSpA), and nonradiographic axSpA. Ixekizumab was also approved for use in paediatric patients aged 6 years and older with moderate-to-severe plaque psoriasis on 26 March 2020 in the US and on 26 June 2020 in the EU. In Japan, ixekizumab is also authorised for the treatment of psoriasis vulgaris, erythrodermic psoriasis, pustular psoriasis, PsA, ankylosing spondylitis, and nonradiographic axSpA in patients who have inadequate response to conventional systemic therapies. As of now, ixekizumab has been authorised in 75 countries, including those in the EU, US, Canada, Australia, Japan, Switzerland, and China.
Based on the ongoing routine surveillance activities for ixekizumab from post-marketing data since its first marketing approval, the following undesirable effects (adverse drug reactions) were identified:

- Immune system disorders
  - Anaphylaxis: Rare (≥0.01% to <0.1%)

• Infections and infestations
o Oesophageal candidiasis: Rare (≥0.01% to <0.1%).

Based on the ongoing routine safety surveillance activities, limited post- marketing data are available for use of ixekizumab in paediatric patients. According to the MAH, during routine surveillance activities, there was no significant new safety information identified in the paediatric population with the use of ixekizumab since its approval for paediatric plaque psoriasis. An additional pharmacovigilance activity in the form of an observational study (I1F-MC-B015) is ongoing to assess the long-term safety of ixekizumab treatment in paediatric patients with psoriasis.

Exposure in clinical studies is provided below.

Table 42 Cumulative exposure to ixekizumab by age group and gender in completed and ongoing studies through March 2024 subject characteristics.

Age Group; n	Male (N = 6790)	Female (N = 4172)	All LY2439821 (N = 10 962)
<18 years	134	153	287
≥18 and <65 years	6143	3627	9770
≥65 years	511	390	901
Unknown	2	2	4

Abbreviations: N = total number of subjects; n = number of subjects in the specified category.
Source: statsclstr/lillyce/prd/ly2439821/regulatory_mar2024/output/original/dsur/ly2439821_dsur_2024_demog1.rtf

During the time frame between 01 March 2021 and 29 February 2024, a total of 515 543 250 mg of ixekizumab were sold worldwide. This led to approximately 281 300 patients exposed and approximately 303 600 PY of exposure to ixekizumab in the reporting interval. Cumulatively as of 29 February 2024, there have been 754 608 520 mg of ixekizumab sold worldwide, leading to approximately 393 600 patients exposed and approximately 449 400 PY of exposure cumulatively.

2.5.1. Discussion on clinical safety

Ixekizumab was authorised on April 2016 in the EU for adults with moderate-to-severe plaque psoriasis. Subsequently, ixekizumab was approved for adults with active PsA, active ankylosing spondylitis (also referred to as radiographic axSpA), and non-radiographic axSpA. Ixekizumab was also approved for use in paediatric patients aged 6 years and older with moderate-to-severe plaque psoriasis on June 2020 in the EU.

In this submission the MAH seeks a new indication for treatment of paediatric ERA and PsA. Interim data from the ongoing open label study RHCG is submitted, that includes 81 patients treated with ixekizumab (54 ERA and 27 PsA patients). Around 25 % of these were bio-experienced. In addition, the study included 20 adalimumab treated bio-naïve patients. The study is currently ongoing and safety data are mainly from the first 16 week, however some information is also provided from patients continuing to the open label extension phase (OLE, 104 weeks) and beyond (long term extension, LTE). The study is expected to follow the patients for 5 years.

Although almost all patients have proceeded into the OLE, only 16 patients have currently completed the open label extension phase. In addition, 9 patients have switched from adalimumab to ixekizumab treatment. Up until DLP 02 April 2024, it is not fully clear how many patients that have been treated with ixekizumab for a year or longer, since the exposure tables provided by the MAH described the exposure in each period separate. Upon request, a new table was provided, showing that 41 patients (around 50%) had received treatment for more than a year up until DLP 02 April 2024.

In general, adverse events were common in all treatment groups and periods. The proportions of ixekizumab treated patients with TEAEs, treatment related TEAEs and SAEs in the OLT period were around 81%, 58% and 4%.

The most common TEAEs in the ixekizumab group are in line with the ADRs already listed in section 4.8 of the SmPC (e.g. injection site reactions, nasopharyngitis, oropharyngeal pain and upper respiratory tract infections). As seen in the paediatric psoriasis studies, the frequencies of influenza and conjunctivitis are higher (common) than reported for the adult population. In addition, rhinitis was common in the paediatric ERA/PsA population, while uncommon in other indications. This has been adequately reflected in the SmPC.

However, TEAEs in the SOC gastrointestinal disorders were more common in the ixekizumab group (24.7%) than the adalimumab group (10.0%) in the OLT period, where the most common PT was vomiting, diarrhoea and abdominal pain. In the OLE period, gastrointestinal disorders were similar in both groups period despite the fact that some of these events (vomiting and abdominal pain) are listed as very common in the adalimumab SmPC. In the ixekizumab SmPC the only GI ADRs listed are nausea (common) and inflammatory bowel disease (uncommon). In the light of the death case displayed below, which was initiated with severe vomiting, the MAH was asked to discuss whether additional gastrointestinal events should be regarded as ADRs and included in the SmPC. The MAH stated that in overall safety profile, with 9807 patients exposed to ixekizumab in the clinical trials, there were no statistical or numerical imbalance seen regarding AEs of vomiting, diarrhoea, and abdominal pain and upon medical judgment these events were not considered ADRs for ixekizumab. It is agreed that the previous studies in at least adults does not indicate any imbalances in the numbers of these events. Regarding the paediatric population, the MAH provided some additional information from the current study (data up until March 2025) and postmarketing data. The few events reported did not evoke any further concerns. Nausea is listed in the section 4.8 of the SmPC.

There were no severe TEAEs during the OLT period. In the OLE-period, 5 patients (6.2%) hade severe TEAEs, whereof 50% were due to infections. One case was however reported as thrombotic thrombocytopenic purpura and upon request additional information regarding this case were provided which indicated that an alternative cause for the TTP event was more plausible (CMV-infection).

Regarding serious events, the most common SOC were infections and infestations, followed by musculoskeletal events, however no serious event was seen in more than one patient.

There was one death during the study: A 12-year-old girl with ERA, who was on concomitant Methotrexate treatment and switched from adalimumab to ixekizumab in the OLE phase, experienced vomiting for several weeks, and severe vomiting for 10 days. The patient did not report the vomiting to parents or investigator. She was hospitalised with severe dehydration, acute kidney injury and hypertensive crisis. Two days after hospitalisation, she died due to hypovolemic shock secondary to diffuse alveolar haemorrhage, which was reported as a consequence of the renal failure. In the opinion of the study investigator, the event was not related to ixekizumab.

Adverse events of special interest (AESI) identified for ixekizumab are the following: infections, injection site reactions, allergic reactions/hypersensitivities, cytopaenias, depression, hepatic, inflammatory bowel disease, cerebrovascular events, interstitial lung disease and malignancies.

The following adverse events of special interest were not reported during the study: malignancies, cerebrovascular events, or interstitial lung disease.

As seen in the other indications, most common AESI were infections and injection site reactions. Regarding infection (51.9% in the OLT period) most were mild or moderate and the only infection occurring in more than 10% of the patients were nasopharyngitis. There were only 2 serious infections in the first 16 weeks, both considered as of moderate severity (tonsillitis and acute sinusitis) and 3 serious infections during the OLE

period, all considered severe (cytomegalovirus infection, sialoadenitis and upper respiratory tract infection). In addition to the cytomegalovirus infection, two other opportunistic infections occurred during the OLE period (herpes zoster and oesophageal candida).

Information regarding infections is adequately described in the SmPC sections 4.4 and 4.8. The number or type of events seen in the paediatric ERA and PsA population does not evoke any further concerns.

Injection reactions were very common (32.1% in the OLT period) but all reactions were mild or moderate and none led to discontinuation of ixekizumab. Information regarding injections reactions is adequately described in the SmPC section 4.8.

Regarding allergic reaction and hypersensitivities, it is noted that there were far more events reported in the paediatric ERA/PsA population (around 30%) than in previous studies (15 % at the most). Since the prevalence of these reactions were similar in the adalimumab treated group, there may be a difference in the definition of the events between the studies. Upon request the MAH confirmed an inadvertent inclusion of broad PTs under hypersensitivity SMQ and inclusion of nonspecific PTs. Correct tables of the frequencies were provided by the MAH that verified that the frequencies were in line with previous studies (7.4% for ixekizumab Q4W and 5.0% for adalimumab Q2W in the OLT Period). There was no potential anaphylaxis reported and the events of allergy/hypersensitivity were not associated with ADA positivity. The SmPC section 4.8 sates: In juvenile idiopathic arthritis (juvenile psoriatic arthritis and enthesitis-related arthritis) patients treated with ixekizumab at the recommended dosing regimen up to 104 weeks, 18 patients (22.8 %) developed anti-drug antibodies, all of which were low to moderate titre. No apparent association between the presence of anti-drug antibodies and drug concentration, efficacy, or safety was observed.

Regarding cytopaenias and liver enzyme elevation, there were few events, all considered mild in severity. However, one hepatic event, although not considered related to study drug, led to temporary interruption in ixekizumab treatment. Upon request the MAH provided additional information regarding this case and it is agreed with the MAH that alternative causes (infection and cefuroxime treatment) could explain the transient transaminase elevation in this patient.

One patient developed inflammatory bowel disease (IBD) during the study. Although there is an association with IBD and spondylopathies such as ERA/PsA, ixekizumab has been associated with IBD and information regarding this is provided in SmPC 4.4 and 4.8. No additional information is necessary based on the findings in this study.

In general, the CDI-2 total score (measuring depression) improved during the study. There are however some uncertainties regarding the information on depression/suicidal intention since the TEAEs reported are not fully in line with the suicidal intention reported with the Columbia Suicide Severity Rating Scale. There are especially concerns regarding the serious case that discontinued the study and the case were pregabalin were initiated. In both these cases, suicidal ideas were reported also at baseline. The concerns regarding depression/suicidal ideation have been previously evaluated in adult patients in the latest PSUR, were the MAH concluded that the prevalence was in line with the expected for the different populations. It was also evaluated in the paediatric psoriatic population, with the MAH conclusion that, even if the prevalence were somewhat higher in the paediatric population than adults, it seems to be in line with what to expect. Additional data provided by the MAH explained the difference in cases reported as TEAEs in this study versus the responses captured using C-SSRS. It is agreed with the MAH that no further action is needed based on the findings from this study. The MAH will continue to closely monitor reported events of depression associated with exposure to ixekizumab through ongoing routine pharmacovigilance activities, including continued assessment of long-term safety in Study RHCG and post-marketing surveillance. This is acceptable.

Although the study was to include children from 2 to 18 years, only one patient below 6 year was included. In addition, only 6 patients with weight 10-25 kg were included. Thus, the MAH restricted the indication to

patients 6 to less than 18 years old. In addition, no posology for patients in the lower weight span is included in the SmPC, instead there is a statement that" Available data do not support a posology below a body weight of 25 kg." In general, there were more TEAEs in the low weight group, especially infections, although based on low numbers. In addition, there is currently no adequate formulation for the lower dose. Thus, the MAH's suggestion to omit the lower dose is acceptable. Upon request the indication was revised to state that the treatment is for patient from 6 year and with a body weight of at least 25 kg. This is in line with the indication for paediatric plaque psoriasis and acceptable.

Since the proposed posology for the paediatric ERA/PsA population is also the same as already approved for the paediatric psoriasis patients (study included 194 patients, whereof 114 treated >1 year), information regarding short term safety in children is to some extent already known. Long term safety is however scarce and "long term safety in children" is thus already included as missing information in the RMP, together with long term data from the pivotal study in paediatric psoriatic patients. An observational registry study in psoriatic paediatric patients is ongoing. The MAH has upon request clarified that since the ERA/JPsA indication is not approved in the US, it is not possible to include this patient population in the already ongoing paediatric PASS, that are based on US claim data. This is acknowledged. Upon request, the MAH provided additional data from the RHCG study and post marketing use in paediatric population that does not evoke any further concerns. Long term paediatric data are however still limited, but it is reassuring that the ongoing PASS evaluating paediatric psoriasis patients seems to be on track to provide a final study report April 2026. The MAH has also included the ongoing LTE of study RHCG as a category 3 study in the RMP and will evaluate the feasibility for a PASS also in the JIA population within nine months of the first JIA launch in the EU. This is acceptable.

2.5.2. Conclusions on clinical safety

Since the proposed posology for the paediatric ERA/PsA population is the same as already approved for the paediatric psoriasis patients, short term safety in children is to some extent already known. No new safety findings were detected in this population. Information regarding long term safety is still limited and "long term safety in children" is already included as missing information in the RMP. The ongoing PASS evaluating paediatric psoriasis patients seems to be on track to provide a final study report April 2026. The MAH has also included the ongoing LTE of study RHCG as a category 3 study in the RMP and will evaluate the feasibility for a PASS also in the JiA population. The new indication is approvable from the safety perspective.

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 CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8.2 is acceptable.

Safety concerns

Table 43: Summary of the Safety Concerns

Summary of Safety Concerns	
Important identified risks	Inflammatory bowel disease (Crohn's disease and ulcerative colitis) Serious infections
Important potential risks	MACE[a] Malignancies[a]
Missing information	Long-term safety in adults (such as events with a low frequency and/or long latency) Use in pregnancy and lactation Use in very elderly (≥75 years of age) Long-term safety in paediatrics Use in patients with active infections Immune response to live vaccinations

Abbreviation: MACE = major adverse cerebro-cardiovascular events.

[a] In adult population.

Pharmacovigilance plan

Table 44: Summary Table of Additional Pharmacovigilance Activities

Study **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 3 – Required additional pharmacovigilance activities				
[I1F-MC-B015] Observational Post-Marketing Safety Study of Ixekizumab and Other Systemic and Non-Systemic Treatments for Pediatric Psoriasis Ongoing	• To monitor the uptake of ixekizumab in a real-world paediatric psoriasis population. • To characterise the demographic and clinical characteristics of paediatric psoriasis patients receiving ixekizumab. • To obtain information about the long-term safety pertaining to serious infections and inflammatory bowel disease.	Important identified risks: inflammatory bowel disease and serious infections Missing information: long-term safety in paediatrics (psoriasis population)	Final study report	30 April 2026[a]

Study **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 3 – Required additional pharmacovigilance activities				
I1F-MC-RHBT[b] A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care Ongoing	• To monitor the incidence rate and nature of infections, hypersensitivity reactions, inflammatory bowel disease, MACE, and malignancies in clinical practice. • To provide additional information on the long-term safety (effects which are infrequent, and/or have a longer latency period) in routine clinical practice. • To monitor the incidence and nature of AEs in the very elderly in routine clinical practice. • Signal detection • To determine if the use of ixekizumab is associated with any new adverse effects, and to confirm the safety profile in a real-world setting	Important identified risks: inflammatory bowel disease and serious infections Important potential risks: MACE and malignancy Missing information: long-term safety in adults (such as events with a low frequency and/or long latency) and use in very elderly (≥75 years of age)	Interim study report Final study report	To be initiated once the registry accrues 4000 ixekizumab exposures 31 May 2030[c]

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 3 – Required additional pharmacovigilance activities				
I1F-MC-B005 Observational Study to Assess Maternal and Foetal Outcomes Following Exposure to Ixekizumab Ongoing[d,e]	The objectives of this study are to monitor: • the uptake of ixekizumab among women of childbearing age • the incidence of maternal and foetal/infant outcomes among pregnant women with a diagnosis of PS, PsA, or axSpA exposed to ixekizumab. If sufficient exposures are identified, an additional objective is to compare maternal and foetal/infant outcomes among these pregnancies with 2 separate groups: • pregnancies treated with TNF inhibitor biologics ("TNF inhibitor cohort"), and • pregnancies with prior history of biologic treatment, but unexposed to medications indicated for PS, PsA, or axSpA in the 3 months prior to pregnancy until end of pregnancy ("unexposed cohort").	Missing information: Use in pregnancy	Interim study report Final study report	30 June 2021[d] Not yet confirmed[e]

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 – Required additional pharmacovigilance activities				
Study I1F-MC-RHCG An Open-Label Study of Ixekizumab (LY2439821) in Children with Juvenile Idiopathic Arthritis Subtypes of Enthesitis-Related Arthritis (Including Juvenile Onset Ankylosing Spondylitis) and Juvenile Psoriatic Arthritis Ongoing	The objective of the LTE period of this study is to evaluate the long-term safety, tolerability, and efficacy of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JPsA.	Missing information: Long-term safety in paediatrics	Final study report	22 July 2029

Abbreviations: AE = adverse event; ERA = enthesitis-related arthritis; JIA = juvenile idiopathic arthritis; JoAS = juvenile onset ankylosing spondylitis; JPsA = juvenile psoriatic arthritis; MACE = major adverse cardiovascular events; PMR = post-marketing requirement; PSUR = periodic safety update report; RMP = risk management plan.

a This date is anticipated and will be finalised once a data vendor is selected.

b The study is being conducted within an independent registry, the CorEvitas Psoriasis Registry. CorEvitas enrolled the first ixekizumab-exposed patient in April 2016.

c The final study report will be submitted with the PSUR/RMP and within 12 months of study completion.

d An interim analysis was not performed as sufficient pregnancy exposures had not accrued by January 2020. As per the protocol, a summary of available data was provided in PSUR 8 with reporting interval 23 March 2020 through 22 March 2021. The commitment to EMA with respect to Study B005 was deemed fulfilled.

e In May 2024, Lilly requested FDA release from Study B005 due to challenges in reaching sample size. In a response letter from the FDA dated 04 April 2025, the FDA agreed with Lilly that it is no longer feasible to meet the target sample size due to the limited number and low rate of accrual of exposed pregnancies. FDA requested a chart review of all identified pregnancies and analyses based on confirmed cases. Upon chart review, FDA will determine if the PMR is deemed fulfilled and is expected to confirm a final study report submission date. The final study report will also be provided to EMA upon fulfilment of this commitment with the FDA

Risk minimisation measures

Table 45: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	Routine risk minimisation measures: 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-General Additional pharmacovigilance activities: Study I1F-MC-RHBT: A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care (final study report due 31 May 2030) Study I1F-MC-B015: Observational Post-Marketing Safety Study of Ixekizumab and Other Systemic and Non-Systemic Treatments for Paediatric Psoriasis (final study report due 30 April 2026)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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: A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care (final study report due 31 May 2030) Study I1F-MC-B015: Observational Post-Marketing Safety Study of Ixekizumab and Other Systemic and Non-Systemic Treatments for Pediatric Psoriasis (final study report due 30 April 2026)
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 A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care (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 Additional pharmacovigilance activities: Study I1F-MC-RHBT: A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care (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 Spontaneous Follow-up Form-Cardiac Disorders Spontaneous Follow-up Form-Cerebrovascular Accident Additional pharmacovigilance activities: Study I1F-MC-RHBT: A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care (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_Paternal Spontaneous Follow-up Form-Pregnancy Outcome – Maternal_Paternal Spontaneous Follow-up Form-Breast Feeding Additional pharmacovigilance activities: Study I1F-MC-B005 – Observational Study to Assess Maternal and Foetal Outcomes Following Exposure to Ixekizumab (Final report due date is not yet confirmed[b])

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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: A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care (final study report due 31 May 2030).
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: Study I1F-MC-B015: Observational Post-Marketing Safety Study of Ixekizumab and Other Systemic and Non-Systemic Treatments for Pediatric Psoriasis (final study report due 30 April 2026) Study I1F-MC-RHCG is ongoing and has a long term extension (LTE) period of up to 5 years with a purpose of evaluating the long-term safety, tolerability, and efficacy of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JpsA (final study report due 22 Jul 2029).
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; PMR = post-marketing requirement; SmPC = summary of product characteristics.

[a] For adult population.

b In May 2024, Lilly requested FDA release from Study B005 due to challenges in reaching sample size. In a response letter from the FDA dated 04 April 2025, the FDA agreed with Lilly that it is no longer feasible to meet the target sample size due to the limited number and low rate of accrual of exposed pregnancies. FDA requested a chart review of all identified pregnancies and analyses based on confirmed cases. Upon chart review, FDA will determine if the PMR is deemed fulfilled and is expected to confirm a final study report submission date. The final study report will also be provided to EMA upon fulfilment of this commitment with the FDA.

2.7. Update of the Product information

As a result of this variation, section 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet (PL) is updated accordingly.

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 reason: 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

JIA is a heterogeneous group of diseases characterised by idiopathic arthritis that starts before the age of 16 years and persists for at least 6 weeks. JIA is the most common chronic rheumatic disease in children and a leading cause of short- and long-term disability.

ERA and JPsA are 2 of the 7 JIA subcategories defined by ILAR. ERA (including JoAS) is characterised by the association of arthritis and enthesitis and is considered as the paediatric counterpart of ankylosing spondylitis or axSpA. Other typical ERA features are:

- axial involvement
- human leukocyte antigen-B27 (HLA-B27) positivity
- acute anterior uveitis, and
- positive family history of spondyloarthritis or related conditions.

ERA accounts for about 5% to 30% of all JIA cases, with a higher prevalence in non-Western European countries.

The JPsA category by ILAR criteria requires the simultaneous presence of arthritis and psoriasis or, if psoriasis is absent, the presence of arthritis and at least 2 of the following:

- family history of psoriasis in a first-degree relative
- nail psoriasis (nail pitting or onycholysis), or
- dactylitis

JPsA represents about 1% to 7% of all JIA cases and occurs with a biphasic distribution; early peak is at 2 to 4 years and later peak at 9 to 11 years of age.

Treatment goals

The goals of JIA treatment include rapid suppression of inflammation to reduce pain, prevention of joint damage, maintenance of physical function and quality of life, and promoting normal growth and development.

3.1.2. Available therapies and unmet medical need

Treatment of juvenile idiopathic arthritis

Primary treatment

Pharmacologic first-line treatment available for patients with non-systemic JIA consists of nonsteroidal anti-inflammatory drugs, intra-articular and systemic corticosteroids, and disease-modifying antirheumatic drug (DMARD) therapy, i.e. methotrexate (MTX).

Short-term systemic use of corticosteroids may be considered in more severe cases of JIA. Persistent arthritis requires DMARD therapy. MTX is the most used conventional synthetic DMARD (csDMARD). However, a substantial proportion of patients do not achieve adequate response, may lose disease control over time, or experience tolerability problems with these treatment options.

Further line treatment

Janus kinase inhibitors tofacitinib (Xeljanz summary of product characteristics) and baricitinib (Olumiant summary of product characteristics) have been approved in the EU for the treatment of active polyarticular JIA in patients 2 years of age and older who have not responded to csDMARD treatment, with or without MTX. Specific to ERA and JPsA, tofacitinib is indicated to treat patients with JPsA while baricitinib is indicated to treat patients with ERA and JPsA.

At the time of protocol development, the current biologic treatment options for JIA included agents targeting:

- IL-17A (secukinumab) (Cosentyx summary of product characteristics)
- tumour necrosis factor (etanercept and adalimumab)
- IL-6 (tocilizumab)
- CD28 (abatacept), and
- IL-1 (anakinra and canakinumab) (Giancane et al. 2016).

At the time of protocol development, only 3 approved biologic DMARDs (bDMARDs) were available for the treatment of ERA or JPsA:

- the tumour necrosis factor inhibitors adalimumab (Humira summary of product characteristics) and etanercept (Enbrel summary of product characteristics), for the treatment of ERA, while etanercept is also approved for the treatment of JPsA, and
- an IL-17A inhibitor (secukinumab) for the treatment of ERA and JPsA (Cosentyx summary of product characteristics). Although the currently approved bDMARDs enable significant improvements in JIA, there is still a substantial proportion of patients who fail to adequately respond or do not achieve long-lasting remission (Hinze et al. 2015). Thus, there is an unmet need for novel treatments, particularly those with alternative mechanisms of action.

3.1.3. Main clinical studies

Study RHCG is an ongoing, multicentre, open-label, partially randomised, phase 3 study of ixekizumab administered subcutaneously, with adalimumab as a reference arm, in children from 2 to younger than 18 years of age with JIA subtypes of ERA and JPsA. The study was conducted in 3 treatment periods: a 16-week OLT Period followed by an OLE Period proceeding to Week 104, followed by an open-label LTE Period out to a total of 264 weeks.

Adalimumab (TNFα inhibitor) was included as an active reference arm during the OLT and OLE Periods to provide within-trial control and contextualisation of study results.

The trial had a Bayesian success criterion for ixekizumab: at least 80% probability that at least half of ixekizumab-treated patients achieve ACR 30 response at week 16. This success criterion was pre-specified in the protocol and the statistical analysis plan, and it was also endorsed by PDCO in the paediatric investigation plan.

A total of 101 patients entered the OLT Period, of these, 81 patients received ixekizumab (60 bDMARD-naive and 21 bDMARD-experienced patients), and 20 bDMARD-naive patients received adalimumab. One patient in each treatment group discontinued the study during the OLT period.

3.2. Favourable effects

Study RHCG showed a JIA ACR30 response rate of 88.9% (n=72/81) in ixekizumab-treated patients. With this result, the study also met its pre-defined success criterion. In addition, the response rate at week 16 was consistent across subgroups of patients who were bDMARD-naïve (90.0%) and those who were bDMARD-experienced (85.7%). The JIA ACR30 response rate at 16 weeks did not differ between patients with ERA (48/54, 88.9%) and JPsA (24/27, 88.9%) treated with ixekizumab.

A JIA ACR30 response was observed at Week 16 in 19 patients (95.0%) who received adalimumab.

In the ixekizumab group, the JIA ACR50 and JIA ACR70 responses at 16 weeks were 79.0% and 64.2%, respectively. In patients receiving adalimumab, the JIA ACR 50 and JIA ARC 70 response rates at week 16 were 90.0% and 65.0%, respectively.

Compared with the baseline, an improvement of 83.13% in LEI total score in ERA patients with enthesitis at baseline was observed at Week 16. For adalimumab, mean (SD) change from baseline in LEI total score in ERA patients at Week 16 was -1.50 (0.577), which is 83% improvement from baseline.

Sparse ixekizumab concentration data were collected from 81 patients up to Week 16 in study RHCG. The observed trough concentrations at steady state in JIA subjects, following administration of the proposed dosing regimen, were within the range of previously observed trough concentrations in adult patients with axSpA and PsA, following administration of the approved dosing regimen. The observed trough concentrations from paediatric patients with ERA and JPsA, respectively, are also within the range of observed trough concentrations from adult patients with axSpA and PsA, respectively.

3.3. Uncertainties and limitations about favourable effects

No fully randomised study was conducted. The adalimumab arm was included in a randomised subgroup to provide some contextualisation of the study results, but no formal statistical comparison was made. The provided efficacy data are thus regarded as descriptive only as they are derived from an uncontrolled, open-label, single-arm study. As such there are no self-standing data that demonstrate robust efficacy. Thus, efficacy data needs support from extrapolation of results seen in already approved indication in populations with a similar disease.

In adults ixekizumab is authorised for those whose disease has responded inadequately to, or who cannot tolerate, conventional therapy. For children with ERA or JPsA, conventional therapy includes NSAID, intraarticular corticosteroid injections, and sDMARD (for example methotrexate) prior to biologic agents. Upon request, the MAH has changed the wording of the indication to clarify that ixekizumab is not first-line treatment in JIA subtypes of ERA and JPsA. The MAH has also clarified that ixekizumab may be used with or without MTX.

The composite endpoint JIA ACR not only includes several subjective measurements but also allows for some deterioration, however around half of the patients (52.2%) reported absence of active joints at Week 16.

Long term effects are unknown since long term data is not yet available. The study is ongoing with an OLE Period proceeding to Week 104, followed by an open-label LTE Period out to a total of 264 weeks. At DLP (April 2024) only 16 patients had been followed up until week 104 and beyond but additional data provided with cutoff date 11 Nov 2024 (n=79) showed that none of the patients in the ixekizumab group met the protocol-defined disease flare criteria through Week 56. In addition, 32/79 (40.5%) achieved low or inactive JADAS-27 status based on the JADAS-27 (ESR) cutoffs for disease activity. Data on clinical remission are expected to be provided in the long-term follow-up report.

3.4. Unfavourable effects

Interim data from the ongoing open label study RHCG include 81 patients treated with ixekizumab (54 ERA and 27 PsA patients). Around 25 % of these were bio-experienced. In addition, the study included 20 adalimumab treated bio-naïve patients. In general, adverse events were common in all treatment groups. The proportions of ixekizumab treated patients with TEAEs, treatment related TEAEs and SAEs in the OLT period were around 81%, 58% and 4%. The most common TEAEs in the ixekizumab group are in line with the ADRs already listed in SmPC section 4.8 (e.g. injection site reactions, nasopharyngitis, oropharyngeal pain and upper respiratory tract infections). Regarding serious events, the most common SOC were infections and infestations, followed by musculoskeletal events, however no serious event was seen in more than one patient.

Most common AESI were infections and injection site reactions. Regarding infection (51.9% in the OLT period) most were mild or moderate and the only infection occurring in more than 10% of the patients were nasopharyngitis. There were 2 serious infections in the first 16 weeks, both considered of moderate severity (tonsillitis and acute sinusitis) and 3 serious infections during the OLE period, all considered severe (cytomegalovirus infection, sialoadenitis and upper respiratory tract infection). In addition to the cytomegalovirus infection, two other opportunistic infections occurred during the OLE period (herpes zoster and oesophageal candida). Information regarding infections is adequately described in the SmPC sections 4.4 and 4.8. The number or type of infectious events seen in the paediatric ERA and PsA population does not evoke any further concerns.

Injection reactions were very common (32.1% in the OLT period), however all reactions were mild or moderate and none led to discontinuation of ixekizumab. Information regarding injections reactions is adequately described in SmPC section 4.8.

3.5. Uncertainties and limitations about unfavourable effects

Although almost all patients have proceeded into the OLE, only 16 patients have currently completed the open label extension phase and only 41 patients (50%) have been treated with ixekizumab for a year or longer.

Only one patient below 6 year and only 6 patients with weight 10-25 kg were included in the study. Thus, the MAH proposed to restrict the indication to patients 6 to less than 18 years old and no posology for patients in the lower weight span was included in the SmPC. In general, there were more TEAEs in the low weight group, especially infections, although based on low numbers. In addition, there are currently no adequate formulation for the lower dose. Thus, the MAH's suggestion to omit the lower dose is acceptable. In line with the indication for paediatric plaque psoriasis it is stated that the treatment is for patient from 6 year and with a body weight of at least 25 kg**.**

Since the proposed posology for the paediatric ERA/PsA population is also the same as already approved for the paediatric psoriasis patients information regarding short term safety in children is to some extent already known. Long term safety is however scarce and "long term safety in children" is thus already included as missing information in the RMP. The final study report of the ongoing PASS evaluating paediatric psoriasis patients will be provided in April 2026. The MAH has also included the ongoing LTE of study RHCG as a category 3 study in the RMP and will evaluate the feasibility for a PASS also in the JiA population.

3.6. Effects Table

Table 46 Effects Table for Taltz in treatment of ERA and JPsA (data cut-off: 02 April 2024)

Effect	Short description	Unit	Treatment (ixekizumab)	Control (adalimumab)	References
JIA ACR	JIA ACR30, response rate at week 16	n/N, %	72/81, 88.9%	19/20, 95.0%	Study RHCG
JIA ACR	JIA ACR50, response rate at week 16	n/N, %	64/81, 79.0%	18/20, 90.0%	Study RHCG
JIA ACR	JIA ACR70, response rate at week 16	n/N, %	52/81, 64.2%	13/20, 65.0%	Study RHCG
TEAEs	TEAEs during OLT period (16 week)	N (%)	66 (81.5)	16 (80.0)	Study RHCG
SAEs	SAEs during OLT period (16 week)	N	3 (3.7)	3 (15)	Study RHCG
Infections	Infections during OLT period (16 week)		42 (51.9)	9 (45.0	Study RHCG
Injection site reactions	Injection site reactions during OLT period (16 week)		26 (32.1)	2 (10.0)	Study RHCG
GI-events	GI-events during OLT period (16 week)		20 (24.7)	2 (10.0)	Study RHCG
Depression	Depression during OLT period (16 week)		2 (2.5)	0 (0.0)	Study RHCG

Abbreviations: ACR30/50/70/90/100 = 30%/50%/70%/90%/100% improvement in American College of Rheumatology

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In study RHCG, the JIA ACR30/50/70 response rates were similar to that of adalimumab. Although the study was conducted in an open-label manner, the observed response rates are sufficiently high to be considered clinically relevant. In addition, the IL-17A inhibitor secukinumab, with similar mechanisms of action as ixekizumab, is already authorised for the treatment of ERA and JPsA.

However, no fully randomised study was conducted. The adalimumab arm was included in a randomised subgroup to provide some contextualisation of the study results, but no formal statistical comparison was made. The provided efficacy data are thus regarded as descriptive only as they are derived from an uncontrolled, open-label, single-arm study. As such there are no self-standing data that demonstrate robust efficacy. Thus, efficacy data needs support from extrapolation of results seen in already approved indication in populations with a similar disease

The MAH is applying for an extension of indication for ixekizumab (Taltz) to include treatment of active JPsA and active ERA in patients 6 to less than 18 years of age. The subtypes being applied for are recognised entities within the ILAR classification scheme for JIA. Ixekizumab is already authorised for the adult indications of axSpA (ankylosing spondylitis and non-radiographic axSpA) and PsA, and it is agreed that these entities can be considered to appropriately correlate with the proposed paediatric indications. As such, the proposed target group for the extension can be agreed. Furthermore, the observed ixekizumab trough concentrations at steady state in active JPsA and active ERA patients, following administration of the proposed posology, are within the range of observed trough concentrations in adult patients with axSpA and PsA with the approved dosing regimen. Therefore, it is reasonable to expect therapeutic benefit of ixekizumab in ERA and JPsA.

In adults ixekizumab is authorised for those whose disease has responded inadequately to, or who cannot tolerate, conventional therapy. For children with ERA or JPsA, conventional therapy includes NSAID, intraarticular corticosteroid injections, and sDMARD (for example methotrexate) prior to biologic agents. Since the efficacy result mainly are derived by extrapolation, the MAH adapted the wording of the indication to clarify that ixekizumab is not first-line treatment in JIA subtypes of ERA and JPsA, and also that it may be used with or without MTX.

Since the proposed posology for the paediatric ERA/PsA population is also the same as already approved for the paediatric psoriasis patients, short term safety in children is to some extent already known. No new safety findings were detected in this population by the MAH; concerns regarding especially gastrointestinal events have been alleviated based on the MAH's responses including data from the current study up until March 2025 and post marketing. Since a posology for patients below 25 kg could not be established, the indication is restricted to patients above this weight.

Information regarding long term safety is still limited and "long term safety in children" is thus already included as missing information in the RMP. A PASS evaluating paediatric psoriasis is currently ongoing and the LTE of study RHCG has been included as a category 3 study in the RMP. The applicant will evaluate the feasibility for a PASS also in the JiA population.

3.7.2. Balance of benefits and risks

Overall, the result from the reported study together with the extensive experience available with ixekizumab in corresponding adult indications provide adequate evidence of efficacy of ixekizumab in the treatment of patients with the ERA and JPsA subtypes of JIA. The MAH has shown that the observed

trough concentrations for JIA patients in Study I1F-MC-RHCG are within the range of the adult observed data with the approved dosing regimen, both across age and across body weight. The safety profile is in general similar as already known, and the proposed dose the same as already approved for paediatric psoriasis patients. To be in line with the corresponding adult population the wording of the indication has been changed to clarify that ixekizumab is not first-line treatment in JIA subtypes of ERA and JPsA. Information regarding long term safety in the paediatric population is still limited but the applicant has several paediatric studies ongoing to gather information post marketing.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Taltz is positive provided the conditions listed in the section Recommendation are fulfilled.

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 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 and IIIB

Extension of indication for TALTZ to include treatment alone or in combination with methotrexate, of active JPsA and ERA in patients 6 years of age and older and with a body weight of at least 25 kg, who have had an inadequate response to, or who are intolerant of, conventional therapy, based on week 16 results from study I1F-MC-RHCG. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.2 of the RMP has also been updated. Furthermore, the PI is in line with the latest QRD template version 10.4.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0049/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion "Taltz-H-C-003943-II-0053".