19 May 2022
EMA/573021/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cosentyx

International non-proprietary name: secukinumab

Procedure No. EMEA/H/C/003729/II/0079

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
ADA	Anti-drug antibody
AE	Adverse events
AIN	Secukinumab
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
ANCOVA	Analysis of covariance
AS	Ankylosing Spondylitis
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BSA	Body surface area
Cavg	Average concentration
CDC	Center for Disease Control and Prevention
CHAQ	Childhood Health Assessment Questionnaire
CI	Confidence interval
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-reactive Protein
CTCAE	Common Terminology Criteria for AEs
CV	Coefficient of variation
DMARD	Disease modifying anti-rheumatic drug
DMC	Data Monitoring Committee
EAIR	Exposure adjusted incidence rates
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicine Agency
ERA	Enthesitis-Related Arthritis
FABER	Flexion, ABduction, and External Rotation
FAS	Full analysis set
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
hCG	Human Chorionic Gonadotropin
HDL	High-density lipoprotein
HIV	Human Immunodeficiency Virus
HLA	Human leukocyte antigen
HR	Hazard ratio
IBD	Inflammatory bowel disease
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IGA	Investigators Global Assessment
ILAR	International League of Associations for Rheumatology
IMP	Investigational medicinal product

INH	Isonicotinylhydrazide
IR	Incidence rate
IRB	Institutional Review Board
IRT	Interactive Response Technology
IVR	Interactive Voice Response
JADAS	Juvenile Arthritis Disease Activity Score
JIA	Juvenile Idiopathic Arthritis
JPsA	Juvenile Psoriatic Arthritis
JSpADA	Juvenile Spondyloarthritis Disease Activity (Index)
LDL	Low-density lipoprotein
LLOQ	Lower limit of quantification
MTX	Methotrexate
MedDRA	Medical dictionary for regulatory activities
NA	Not applicable
NC	Not calculable
NSAID	Non-steroidal anti-inflammatory drug
OC/RDC	Oracle Clinical/Remote Data Capture
PFS	Prefilled Syringe
PG	Pharmacogenomics
PGA	Physician global assessment
PK	Pharmacokinetics
PPD	Purified protein derivative
PsA	Psoriatic Arthritis
PRN	As required
PRO	Patient Reported Outcome
PT	Preferred term
PUVA	Photochemotherapy
PY	Patient years
QTcF	QTc Interval by Fridericia’s equation
RA	Rheumatoid Arthritis
RBC	Red blood cell
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous(ly)
SD	Standard deviation
SGOT	Serum glutaminc oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SI	Sacroiliac (joint)
SMQ	Standard MedDRA query
SOC	System organ class
SSZ	Sulfasalazine
SUN	Standardization of Uveitis Nomenclature
TB	Tuberculosis
TBL	Serum total bilirubin
TNF	Tumour Necrosis Factor
TP1	Treatment Period 1
TP2	Treatment Period 2
TP3	Treatment Period 3
ULN	Upper limit of normal

UV	Ultraviolet
VAS	Visual Analogue Scale
WBC	White blood cell
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 16 June 2021 an application for a variation.

The following variation was requested:

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

C.I.6 (Extension of indication)
Extension of indication to include treatment of Juvenile Idiopathic Arthritis (Enthesitis-Related Arthritis and Juvenile Psoriatic Arthritis) in patients 2 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy for Cosentyx; 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 10.0 of the RMP has also been submitted.

The variation requested 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/0372/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was completed.

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 appointed by the CHMP was:

Rapporteur: Outi Mäki-Ikola

Timetable	Actual dates
Submission date	16 June 2021
Start of procedure:	17 July 2021
CHMP Rapporteur Assessment Report	10 September 2021
PRAC Rapporteur Assessment Report	16 September 2021
PRAC members comments	22 September 2021
Updated PRAC Rapporteur Assessment Report	23 September 2021
PRAC Outcome	30 September 2021
CHMP members comments	4 October 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	7 October 2021
Request for supplementary information (RSI)	14 October 2021
CHMP Rapporteur Assessment Report	21 December 2021
PRAC Rapporteur Assessment Report	3 January 2022
PRAC members comments	5 January 2022
Updated PRAC Rapporteur Assessment Report	7 January 2022
PRAC Outcome	13 January 2022
CHMP members comments	17 January 2022
Updated CHMP Rapporteur Assessment Report	20 January 2022
Request for supplementary information (RSI)	27 January 2022
CHMP Rapporteur Assessment Report	19 April 2022
PRAC Rapporteur Assessment Report	25 April 2022
PRAC members comments	26 April 2022
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	05 May 2022
CHMP members comments	10 May 2022
Updated CHMP Rapporteur Assessment Report	12 May 2022
Opinion	19 May 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Juvenile Idiopathic arthritis (JIA) is a broad term that describes a clinically heterogeneous group of arthritides of unknown cause, which begin before 16 years of age. This term encompasses several disease categories, with distinct clinical signs and symptoms, immune-pathogenesis, age at onset, gender predominance, and, in some cases, genetic background.

The MAH's initially claimed therapeutic indication was:

Juvenile idiopathic arthritis (JIA)

Enthesitis-related arthritis (ERA)

Cosentyx is indicated for the treatment of active enthesitis-related arthritis in patients 2 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.

Juvenile psoriatic arthritis (JPsA)

Cosentyx is indicated for the treatment of active juvenile psoriatic arthritis in patients 2 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.

Epidemiology

JIA is the most common rheumatic disease reported in the paediatric population (children and adolescents) in Europe and North America. A systematic review of 33 studies based on the ACR, EULAR, and ILAR classifications for JIA reported a pooled JIA incidence of 8.3 (95% CI 8.1-8.7) per 100,000 Caucasian children and adolescents. Oligoarthritis was the most frequent form (pooled incidence rate 3.7; 95% CI 3.5-3.9). The pooled incidence estimates for the other individual JIA categories were 0.4, 1.0, 0.6, 2.0 and 0.5 per 100,000 children and adolescents for RF-positive and RF-negative polyarthritis, SJIA, and the spondyloarthropathies ERA and JPsA, respectively. Gender differences are recognised in JIA, with females generally more commonly affected than males, although not in all categories. In particular, JPsA affects females slightly more frequently than males, while ERA mainly affects males.

Biologic features

Various classifications of juvenile arthritis have been proposed and used in the past. The now widely accepted ILAR classification criteria classifies JIA into 7 categories, based on predominant clinical and laboratory features, including number of joints involved, rheumatoid factor (RF) positivity, and association with psoriasis, enthesitis and other findings. The 7 JIA categories are: enthesitis-related arthritis (ERA), juvenile psoriatic arthritis (JPsA), systemic arthritis, oligoarthritis, RF positive polyarthritis, RF negative polyarthritis, and undifferentiated arthritis.

Clinical presentation, diagnosis

Of the 7 JIA categories, ERA and JPsA represent signs and symptoms of spondyloarthropathy similar to the conditions of ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-AxSpA), and psoriatic arthritis (PsA), for which secukinumab is authorised in adults.

ERA is a clinically heterogeneous group that includes children and adolescents with predominantly enthesitis, both enthesitis and arthritis, juvenile AS, anterior uveitis, or inflammatory bowel disease (IBD)-associated arthropathy. Similar to adult AS, hallmarks of the disease are pain, stiffness, and eventual loss of mobility of the back. Peripheral arthritis, also similar to adult AS, usually affects fewer joints of the lower extremities and precedes axial involvement, and arthritis of the sacroiliac joints may take years to develop. Like in adult disease, radiographic changes of the sacroiliac joint include joint space narrowing, erosions, sclerosis, osteoporosis of the pelvis, and fusion (a late finding). ERA has a strong genetic predisposition as evidenced by a positive family history and the presence of HLA-B27 in a large proportion of patients. ERA should be suspected in any child with chronic arthritis of the axial and peripheral skeleton, enthesitis, and rheumatoid factor and ANA seronegativity.

ERA accounts for approximately 3 to 11% of JIA and is more common in boys than girls. Age at onset is typically late childhood or adolescence, but some children present at a much younger age.

JPsA is an inflammatory arthritis that presents with or without psoriasis skin involvement. The current ILAR classification criteria for JPsA includes patients clinically similar to adult PsA. These children usually present with lower extremity arthritis, enthesitis, and some have axial involvement.

JPsA accounts for approximately 2 to 11% of JIA and is slightly more common in girls than boys. Age at onset has a biphasic distribution, with an early peak at 2–4 years and a later peak at 9–11 years.

Management

JIA treatment guidelines applicable to all JIA categories, including ERA and JPsA, were established by the ACR in 2011 and updated in 2019. Similar to the 2011 recommendations, the updated guidelines defined patient populations by clinical phenotype, rather than ILAR categories.

The guidelines aim to quickly control active inflammation and disease symptoms, and to prevent/minimise disease and/or treatment-related morbidities (e.g., growth disturbances, joint damage, and functional limitations). In general, the treatment goal is to control the inflammation with NSAIDs, DMARDs, corticosteroid intra-articular injections, biologic agents (either as monotherapy or in combination with other therapies), and physical and occupational therapy in patients at risk for functional limitation.

For patients with ERA and JPsA who have active enthesitis and/or sacroiliitis despite NSAID therapy, treatment options are limited. Conventional DMARDs such as methotrexate are not effective in axial disease. Tumour necrosis factor (TNF) inhibitors are recommended for patients with enthesitis and sacroiliitis if NSAIDs are not tolerated or ineffective. However, many children do not achieve disease control with currently available treatment options, including biologics. In addition, only few biologics are labelled for the use in ERA or JPsA. In the EU, etanercept is indicated for JPsA and ERA for patients aged 12 years or older, and adalimumab is indicated in ERA patients aged 6 years or older. An unmet medical need for effective treatment options exists for patients with ERA or JPsA who do not achieve disease control on currently available treatment options.

2.1.2. About the product

Secukinumab (AIN457) is a fully human immunoglobulin G1 antibody that selectively binds to and neutralises the proinflammatory cytokine IL-17A. Secukinumab (Cosentyx) was initially authorised in the EU on 15 Jan 2015 for the treatment of plaque psoriasis (PsO) in adult patients. New indications for psoriatic arthritis (PsA), ankylosing spondylitis (AS) in adult patients, non-radiographic axial spondyloarthritis (nr-axSpA) and PsO in children and adolescents from the age of 6 years were then approved. According to the MAH, secukinumab is currently authorised in over 100 countries worldwide.

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

The current approved PIP for secukinumab for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, spondyloarthritis, psoriatic arthritis and juvenile idiopathic arthritis) is EMEA-000380-PIP02-09-M04 (PIP decision number P/0372/2018, dated 07 December 2018).

2.2. Non-clinical aspects

2.2.1. Ecotoxicity/environmental risk assessment

As a monoclonal antibody, secukinumab is exempt from testing in accordance with the current CHMP guideline (CHMP/SWP/4447/00) on environmental risk assessment.

2.2.2. Discussion on non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP. During the procedure, the MAH was requested to provide an appropriate literature review from a mechanism of action viewpoint to support the safety of anti-IL-17A therapy in young children (2-<6 years), with a focus on e.g., immune function and the developing immune system, growth and maturation considering the very limited number of patients enrolled in the clinical trial and the fact that anti-IL-17 therapy are not currently indicated in this age group. The MAH has provided the requested systematic literature review of the currently available data on the immune development in children with regards to the role and function of IL-17 in the developing immune function, both from the non-clinical and clinical point of view, to further support the overall safety claims. However, the MAH withdrew their indication claim in the 2-<6 years during the procedure.

2.2.3. Conclusion on the non-clinical aspects

The available non-clinical data do not raise concern in the indication from 6-18 years.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

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

- Tabular overview of clinical studies

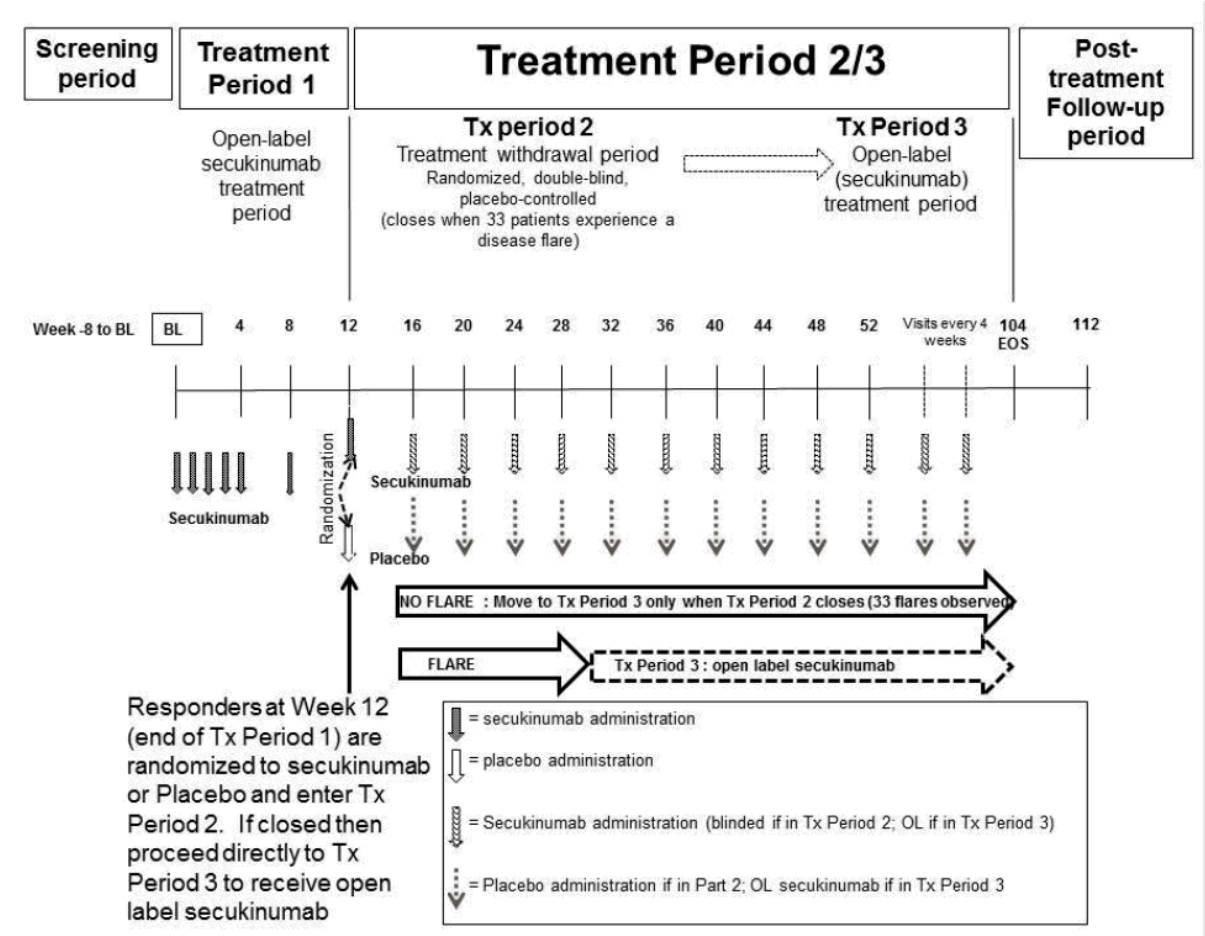
Protocol No., Countries & Study Dates	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status & Reports of Study Results
Protocol: CAIN457F2304 **Countries**: Belgium, Germany, Italy, Poland, Russia, South Africa, Spain, Turkey, United Kingdom, United States **Start**: 23-May-2017 **End**: 09-Nov-2020	**Design, purpose & population**: A three-part randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of secukinumab treatment in Juvenile Idiopathic arthritis subtypes of psoriatic and enthesitis-related arthritis	**Total**: TP1: 86 TP2: 75 **Age**: TP1: 2-17 (13.1) years TP2: 2-17 (12.8) years **Groups**: 3 TP1: 86 TP2 Group 1: 37 TP2 Group 2: 38	**Form(s)**: secukinumab PFS 150 mg/1 mL and 75 mg/0.5 mL placebo PFS matching secukinumab PFS 150 mg/1 mL and 75 mg/0.5 mL **Duration**: TP1: 12 weeks TP2/3: 92 weeks **Doses**: secukinumab 75 mg or 150 mg based on the body weight (< 50 kg or ≥ 50 kg) secukinumab 75 mg or 150 mg based on the body weight (< 50 kg or ≥ 50 kg) matching placebo	**Study Status**: complete **Report no.** **[CAIN457F2304]** full, final Report date: 12-Mar-2021 Other reports: **[dmpk rcain457f2304-ig]** **[dmpk rcain457f2304-pk]** **[dmpk rcain457f2304-pka]**

2.3.2. Pharmacokinetics

The supplied material does not contain any dedicated pharmacokinetic studies; however, the paediatric efficacy study F2304 contained a pharmacokinetic (PK) sub study based on sparse sampling. Furthermore, the sparsely sampled PK were included into a population PK model of secukinumab which included both paediatric and adult data from several indications. For this, see section 2.3.3. on population PK model.

The study treatment was secukinumab 75 mg (< 50 kg, 0.5 mL PFS) or 150 mg (≥ 50 kg, 1 mL PFS) s.c. which was the dose predicted to achieve secukinumab serum levels equivalent to adults administered a 150 mg dose regimen. All eligible subjects entered treatment phase 1 (TP1) to receive 12-weeks of open-label secukinumab. Secukinumab was administered s.c. weekly for the first 4 weeks (Baseline, Weeks 1, 2, 3, 4) and then every 4 weeks thereafter. Subjects who were a responder (JIA ACR 30) at Week 12 entered the double-blind withdrawal treatment phase 2 (TP2) and were randomized 1:1 to either secukinumab or placebo on that visit and then every 4 weeks, until either experiencing a disease flare or completion of TP2. Subjects experiencing a disease flare in TP2 immediately entered treatment phase 3 (TP3) to receive open-label secukinumab every 4 weeks until total study duration of 104 weeks for that subject was achieved. The study design is illustrated in Figure 1.

Figure 1 CAIN457F2304 study design



PK samples were obtained for all subjects, and secukinumab concentrations were assessed in serum. The PK samples were collected pre-dose at scheduled visits/ time points as indicated in the assessment schedule (Table 1). All blood samples were drawn by direct venipuncture in a forearm vein. An ELISA (enzyme-linked immunosorbent assay) method was used for bioanalytical analysis of secukinumab in serum, with LLOQs of 80 and 500 ng/mL in the two bioanalytical CRO's involved in this study.

Table 1 PK Assessment schedule

	Screening		Treatment Period 1							Treatment Period 2 / 3 (Primary Treatment Period) (Note: a patient enters Tx Period 3 in case of flare or when Tx Period 2 completes)								Unscheduled visit	Post-Treatment Safety follow-up
	1	2																
Week	**Up to -8**	**-4 to BL**	**BL**	**1**	**2**	**3**	**4**	**8**	**12/ PSW**	**16 to 20**	**24**	**28 to 48**	**52**	**56 to 72**	**76**	**80 to 100**	**104 / TD/ PSW**		**12 Weeks after last study drug dosed**
PK sampling (pre-dose)[6]			X		X		X	X	X		X		X		X		X	X[6]	X

6. PK samples should be obtained prior to study drug administration. PK sample is also obtained at any visit (scheduled or unscheduled) with a confirmed disease flare in Treatment Period 2.

Serum concentrations of secukinumab in the two different body weight categories are given in Table 2 and are visualized in Figure 2. At most time points, similar exposure was observed with the 75 mg dose level for body weights < 50 kg compared with exposure for subjects with the 150 mg dose level for body weights ≥ 50 kg. Subjects who received placebo after Week 12 until Week 104 had declining serum concentrations from Week 12 onwards with concentrations below LOQ from Week 52 onwards. Subjects

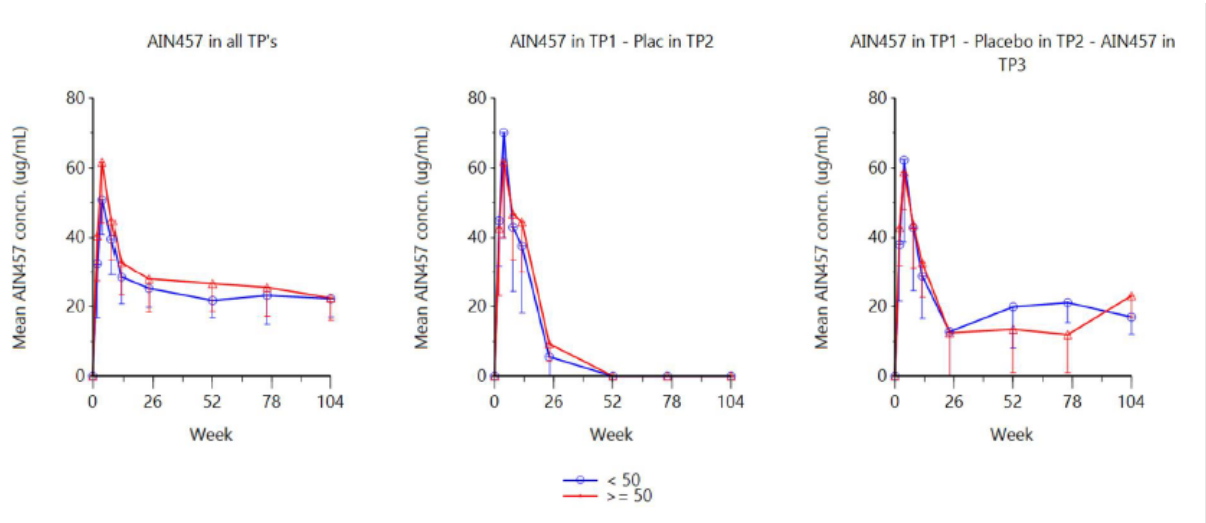
who were on placebo in TP2 and then re-started treatment had similar steady-state levels at Week 104 as subjects who stayed on the 4 weeks maintenance regimen until Week 104.

Table 2 Summary statistics for serum secukinumab concentrations (mcg/mL) by visit, body weight category and treatment period (Safety set)

		AIN457 75 mg <50kg	AIN457 150 mg ≥50kg	AIN457 75 mg <50 kg	AIN457 150 mg ≥50 kg	AIN457 75 mg <50 kg	AIN457 150 mg ≥50 kg
				AIN457 in TP1		AIN457 in TP1	
Week	Stats	AIN457 in all TP's		Placebo in TP2		Placebo in TP2 – AIN457 in TP3	
2	n	11	30	8	8	8 [1]	11
	Mean	32.5	40.4	44.8	42.6	38.0	42.7
	SD	15.8	12.9	13.2	19.5	16.5	10.8
	%CV	48.6	32.0	29.5	45.8	43.4	25.3
4	n	12	32	7	9	9	12
	Mean	50.7	61.6	70.1	61.7	62.2	58.8
	SD	9.95	17.3	30.3	21.9	23.4	10.8
	%CV	19.6	28.2	43.2	35.4	37.6	18.4
8	n	10	32	7	9	9	12
	Mean	38.3	45.4	42.9	46.7	42.8	43.6
	SD	10.3	11.0	18.6	13.2	18.3	12.4
	%CV	26.9	24.3	43.3	28.2	42.8	28.5
12	n	10	30	6	8	7	12
	Mean	28.5	32.8	37.5	44.4	28.7	32.7
	SD	7.67	9.46	19.4	14.5	12.1	10.0
	%CV	26.9	28.9	51.7	32.7	42.2	30.7
24	n	10	19	8	9	8	11
	Mean	25.2	27.9	5.56	9.33	12.8	12.4
	SD	5.45	9.57	5.92	5.06	14.5	12.4
	%CV	21.6	34.2	106.4	54.3	113.3	99.5
52	n	10	20	7	7	8	10
	Mean	21.7	26.6	0.00	0.00	19.9	13.5
	SD	5.04	7.84	0.00	0.00	11.8	12.4
	%CV	23.2	29.5	-	-	59.3	91.9
		AIN457 75 mg <50kg	AIN457 150 mg ≥50kg	AIN457 75 mg <50 kg	AIN457 150 mg ≥50 kg	AIN457 75 mg <50 kg	AIN457 150 mg ≥50 kg
				AIN457 in TP1		AIN457 in TP1	
Week	Stats	AIN457 in all TP's		Placebo in TP2		Placebo in TP2 – AIN457 in TP3	
76	n	9	20	5 [1]	8	8	9
	Mean	23.2	25.5	0.00	0.00	21.1	11.9
	SD	8.33	8.25	0.00	0.00	5.82	10.9
	%CV	35.9	32.4	-	-	27.6	91.7
104	n	7	20	6	9	6	8
	Mean	22.2	22.4	0.00	0.00	17.0	23.1
	SD	5.29	6.37	0.00-	0.00-	4.88	6.02
	%CV	23.8	28.4	-	-	28.8	26.1

n(log) is the number of subjects with non-zero concentrations.
For post-baseline visits, weight was based on dose administration actual package received at the most recent previous visit.
Subjects who received 0.5 mL (= 75 mg) pre-filled syringe were categorized as body weight < 50 kg. Subjects who received 1 mL (= 150 mg) pre-filled syringe were categorized as body weight ≥50 kg.
1) Additional patient flagged in addition to the originally flagged concentrations due to a sample outside of the time window of ± 7 days at Week 2 and ±14 days at Week 76.

Figure 2 *Mean (SD) serum trough concentrations of secukinumab in body weights <50 kg and ⩾50 kg*



2.3.3. PK/PD modelling

The dose selection for secukinumab in the JIA categories of ERA and JPsA was based on the assumption that the clinical response in paediatric patients would be similar to adult patients with similar conditions (AS and PsA) and similar exposure to secukinumab. The pediatric JIA regimen was determined to achieve similar exposure as achieved in AS and PsA adults treated with the secukinumab 150 mg. This determination was made by means of a population PK model, which predicted that the pediatric dose of 75 mg for children weighing <50 kg, and 150 mg for those weighing ≥50 kg, would achieve similar or slightly higher exposure to that achieved in adults receiving the 150 mg dose regimen. The popPK model used for the determination of the JIA regimen was developed on pooled adult RA study data over a bodyweight range of 40 to 159 kg and was considered appropriate for prediction in JIA patients given the similarity of secukinumab PK across indications.

The objectives of the current population PK analysis were

- To compare drug concentrations between JIA and pediatric psoriasis patients.
- To characterize the secukinumab PK in JIA patients.
- To compare the exposure levels expected in JIA pediatric patients receiving the proposed secukinumab regimen (75 mg s.c. < 50 kg; 150 mg s.c. ≥50 kg) with those in adult AS and PsA patients treated with the adult regimens.

The secukinumab concentrations in JIA patients in four body weight categories at Week 4 and at steady-state (Week 24, 52 and 104) from study F2304 were graphically compared to those of pediatric psoriasis patients under the same dosing regimen (studies A2310 and A2311) as well as to those of adult PsA and AS patients under the 150 and 300 mg Q4W regimens (PsA: studies F2312, F2318, F2336, and F2342; AS: study F2310). A recent population PK analysis in another pediatric population (pediatric psoriasis) indicated that pediatric patients may have higher bioavailability as compared to adults, which was not accounted for in the predicted exposure from the population PK model developed in adult RA patients. To further characterize secukinumab pharmacokinetics across five indications, including pediatric psoriasis and JIA, the entire pooled dataset was used to fit alternative models including a model with a pediatric effect on bioavailability (base model), a model with fixed allometric exponents to their theoretical values and a model with a population effect (rheumatoid arthritis) on systemic clearance.

Data from studies A2101, F2201, F2206, F2208, F2309, A2102, A2103, A2211, A2212, A2220, A2302, A2303, A2304, A2308, A2309, A2206, F2306, F2312, F2318, F2336, F2342, A2209, F2305, F2310, F2314, A2310, A2311 and F2304 were used to fit the population PK model.

The base model is the population PK model in psoriasis based on observations from adult and pediatric patients, that was originally built using observations from studies A2102, A2103, A2211, A2212, A2220, A2302, A2310, and A2311. Note that for the purpose of the current report, this model was re-estimated on those same (psoriasis) studies, and this re-estimated version of this model is referred to as "Model 0".

In Model 0, the disposition kinetics was modeled using a parameterization involving clearance (CL), central volume of distribution (V1), inter-compartmental clearance (Q), and peripheral volume of distribution (V2). A first order absorption rate constant (Ka) and bioavailability term (F) were used to characterize the rate and extent of the absorption process of the s.c. administration.

Inter-individual variabilities were included on Ka, CL, V1 and V2. Correlations between CL~V1, CL~V2 and V1~V2 were included. Body weight on CL, V1, Q, and V2 was included and estimated. Lastly, a bioavailability effect for the pediatric psoriasis population was included in the model that suggested that bioavailability was approximately 21% higher in pediatric patients.

There is no clear evidence that the development (expression, efficacy, IgG affinity, etc.) of the binding to FcRn in the various cell types in pediatric patients differs compared with adults and if there are potential differences, how they could affect the clearance of secukinumab. For this reason, no maturation process was included in Model 0.

Model 0 was re-estimated on the pool combining data from adults PsA, AS, PsO, and RA patients, as well as pediatric PsO and JIA patients. This new model, structurally identical to Model 0, is referred to as Model 1 in this report. The objective of this re-estimation was to assess the robustness of the results with respect to a wider range of weights for patients as young as 2 years of age, by incorporating a large sample size spanning across five disease populations. Model 1, like Model 0, estimated the allometric exponent coefficients.

Model 2 is similar as Model 1, but uses the theoretical allometric exponent coefficients, on the ground that those values, which are considered to have physiological basis, often provide better explanation for body weight relationships in pediatric patients.

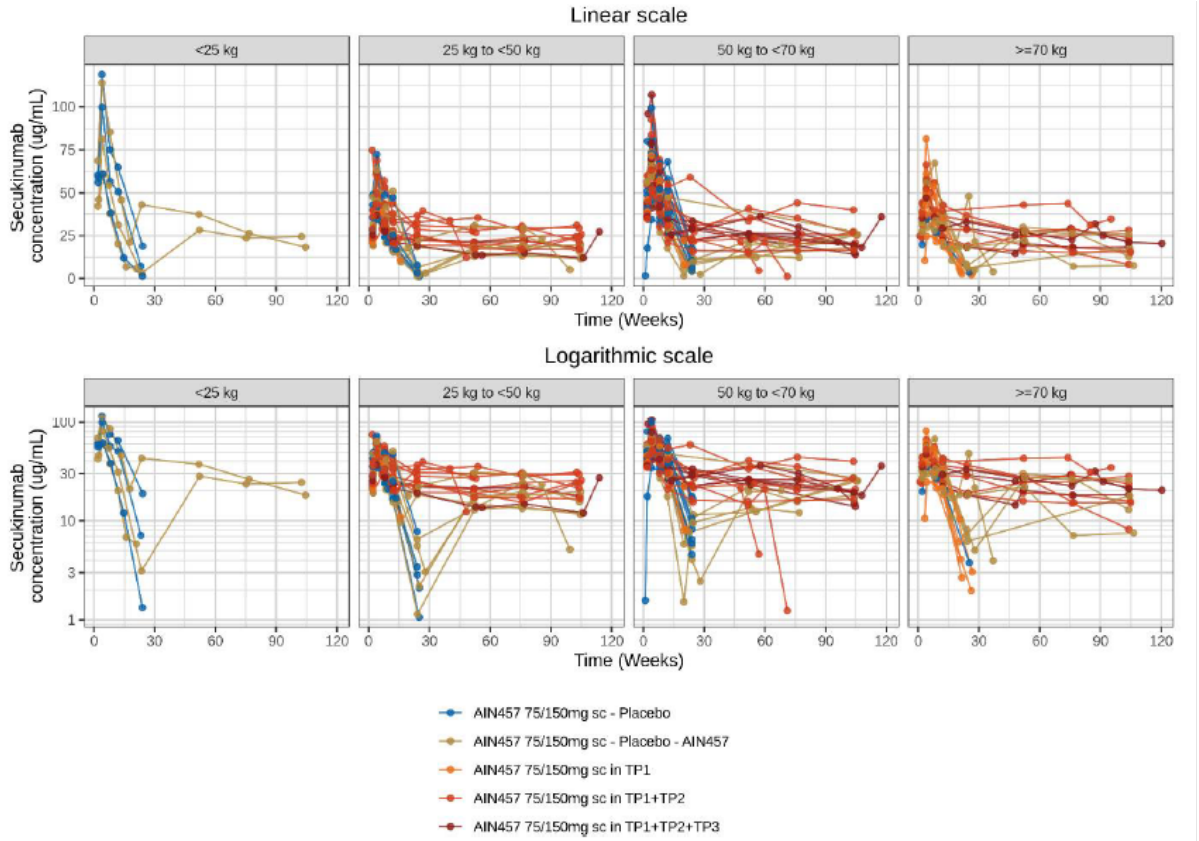
Models with disease population effects in clearance were also assessed, in order to explore potential systematic differences across disease population types. For this analysis, only effects on clearance were considered, due to the typically large shrinkage observed for the other structural parameter in previous secukinumab popPK reports. This model is referred to as Model 3 in this report.

A total of 45235 secukinumab concentrations from 7391 PsA, AS, PsO, RA, pediatric PsO and JIA patients were included in the population PK analyses. The number of concentrations by disease population and the proportion of samples below the LLOQ was less than 10% (Table 3). Figure 3 presents the 505 secukinumab concentrations above LLOQ over time in JIA study F2304.

Table 3 Number of secukinumab concentrations included in the population PK analysis, observed median (range) concentrations and proportion of samples below LOQ, by disease population

	Number of secukinumab concentrations (%)	Median (range) secukinumab concentration (ug/mL) above LOQ	Samples below LOQ (%)
Adult Psoriasis	17295 (38.2)	18 (0.0821-627)	1.4
Ankylosing Spondylitis	5157 (11.4)	18.6 (0.0854-525)	4.9
Juvenile Idiopathic Arthritis	505 (1.1)	30.9 (1.14-119)	2.1
Pediatric Psoriasis	1098 (2.4)	42.4 (1.21-236)	1.0
Psoriatic Arthritis	14049 (31.1)	21.4 (0.404-731)	5.5
Rheumatoid Arthritis	7131 (15.8)	13.7 (0.08-601)	5.6
Overall	**45235 (100)**	**19.1 (0.08-731)**	**3.8**

Figure 3 Secukinumab serum concentrations versus time in study F2304



*AIN457 75/150 mg s.c.- Placebo: Patients receiving secukinumab in TP1 and randomized to placebo at Week 12

**AIN457 75/150 mg s.c. - Placebo - AIN457: Patients receiving secukinumab in TP1, randomized to placebo at Week 12 and switched to open-label secukinumab after experiencing a disease flare.

***AIN457 75/150 mg s.c. in TP1 - Patients receiving secukinumab in TP1 only (non-responders at end of TP1 who discontinued from the study).

****AIN457 75/150 mg s.c. in TP1 + TP2 - Patients receiving secukinumab in TP1, randomized to active treatment in TP2 and never experienced a disease flare after randomization into TP2 and reaches a total study duration of 104 weeks.

*****AIN457 75/150 mg s.c. in TP1 + TP2 + TP3 - Patients receiving secukinumab in TP1, randomized to active treatment in TP2 and entered TP3 after experiencing a disease flare.

The parameter estimates of the population PK models are shown in Table 4.

Table 4 ***Population PK models parameter estimates***

Parameter	Model 0 (Original Model - Fixed parameters)	Model 1 (Model 0 with re-estimated parameters)	Model 2 (Model 0 with allometric coefficients fixed to standard values)	Model 3 (Model 1 with RA effect on CL)
-2LL	331295*	295594	295881	295133
Structural parameters				
CL (L/day)	0.2	0.2 (1%)	0.19 (<1%)	0.19 (1%)
F (fraction)	0.77	0.79 (1%)	0.79 (<1%)	0.79 (1%)
Ka (1/day)	0.17	0.22 (2%)	0.22 (2%)	0.24 (2%)
Q (L/day)	0.3	0.25 (3%)	0.26 (1%)	0.24 (3%)
V1 (L)	3.8	4.5 (1%)	4.5 (1%)	4.6 (1%)
V2 (L)	3	1.8 (3%)	2 (3%)	1.7 (3%)
Between-subject variability, standard deviations				
IIV CL	0.32	0.35 (1%)	0.35 (1%)	0.34 (1%)
IIV Ka	0.35	0.39 (5%)	0.4 (4%)	0.45 (4%)
IIV V1	0.27	0.38 (2%)	0.37 (2%)	0.36 (2%)
IIV V2	0.22	0.99 (2%)	0.95 (2%)	1 (2%)
IIV V1-CL	0.66	0.65 (2%)	0.62 (2%)	0.66 (2%)

IIV V2-CL	-0.007	-0.46 (3%)	-0.44 (4%)	-0.44 (4%)
IIV V2-V1	0.75	-0.72 (2%)	-0.67 (3%)	-0.7 (2%)
Covariate effects				
CL~Weight***	0.89	0.81 (2%)	0.75 (FIX)	0.86 (2%)
CL~RA**				0.22 (5%)
F~Ped**	0.24	0.19 (7%)	0.15 (8%)	0.16 (9%)
Q~Weight***	0.74	0.39 (19%)	0.75 (FIX)	0.5 (17%)
V1~Weight***	0.88	0.73 (4%)	1 (FIX)	0.73 (4%)
V2~Weight***	0.69	0.99 (7%)	1 (FIX)	1 (8%)
Residual variability				
Additive error (ug/mL)	0.0265	0.026 (4%)	0.025 (4%)	0.026 (4%)
Proportional error (%)	0.19	0.25 (<1%)	0.25 (<1%)	0.25 (<1%)

Parameters are presented as Point Estimates (%RSE). Parameters that were fixed during the estimation are followed by (FIX). Only point estimates are presented for Model 0, as it was used for evaluation only.

Abbreviations: %RSE: percent relative standard error of the estimate (SE/parameter estimate * 100); CL: clearance; V1: volume of central compartment; Q: inter-compartmental clearance; V2: volume of peripheral compartment; Ka: absorption rate constant; F: bioavailability; IIV: interindividual variability; WT: bodyweight; RA: Rheumatoid Arthritis; Ped: pediatric. Fixed parameters, i.e., not estimated, are followed by FIX.

* The OFV of the original model (Model 0) was recalculated based on the updated pool (including study F2304), to allow a comparison with the OFV of the other models (Model 1 – 3).

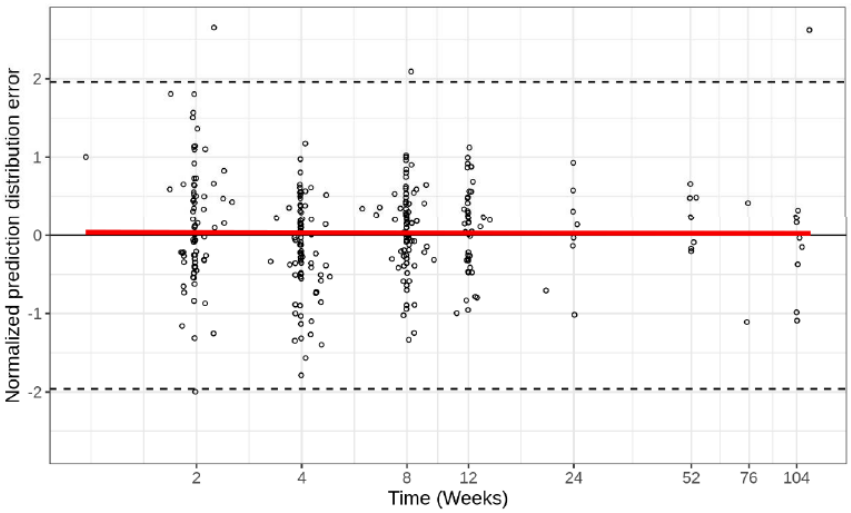
** The pediatric and rheumatoid arthritis population effects F and CL, respectively, represent relative difference from the population estimate in the log-space (i.e. $\log(P_s) = \log(P_{pop}) + beta$, where P_s is the estimate for the subpopulation, P_{pop} is the population parameter estimate and beta is the deviation from P_{pop} for the sub-population). The bioavailability estimate for adult patients was equal to 77% for Model 0 and 79% for Models 1, 2, and 3. The bioavailability estimate for pediatric patients was equal to 98%, 96%, 92%, and 93% for Models 0, 1, 2, and 3 respectively. The CL estimate for the adult RA patients in Model 3 was 0.24 L/day.

*** The reference population is a 90 kg adult patient.

The proposed SmPC contained no population PK-derived information. The aim of the current population PK modelling exercise is to justify that the proposed dose leads to a both safe and effect concentration range, i.e. that the paediatric doses are within the therapeutic window if the exposure-efficacy-safety relationships are assumed to be same for children and adults. The NPDE versus time in JIA patients (Study F2304) for the final population PK model (Model 3) are presented in Figure 4. Overall, the model captured the observed concentrations adequately. The distributions of individual CL, Ka, V1 and V2 random effects by disease population type are presented in Figure 5, respectively. The EBEs for CL, Ka, V1 and V2 were generally symmetrically distributed around zero across disease populations. Regarding the JIA population specifically, the EBE distribution for CL, Ka, V1 and V2 was symmetrically distributed around zero, both overall, and when stratified across the ERA and JPsA categories.

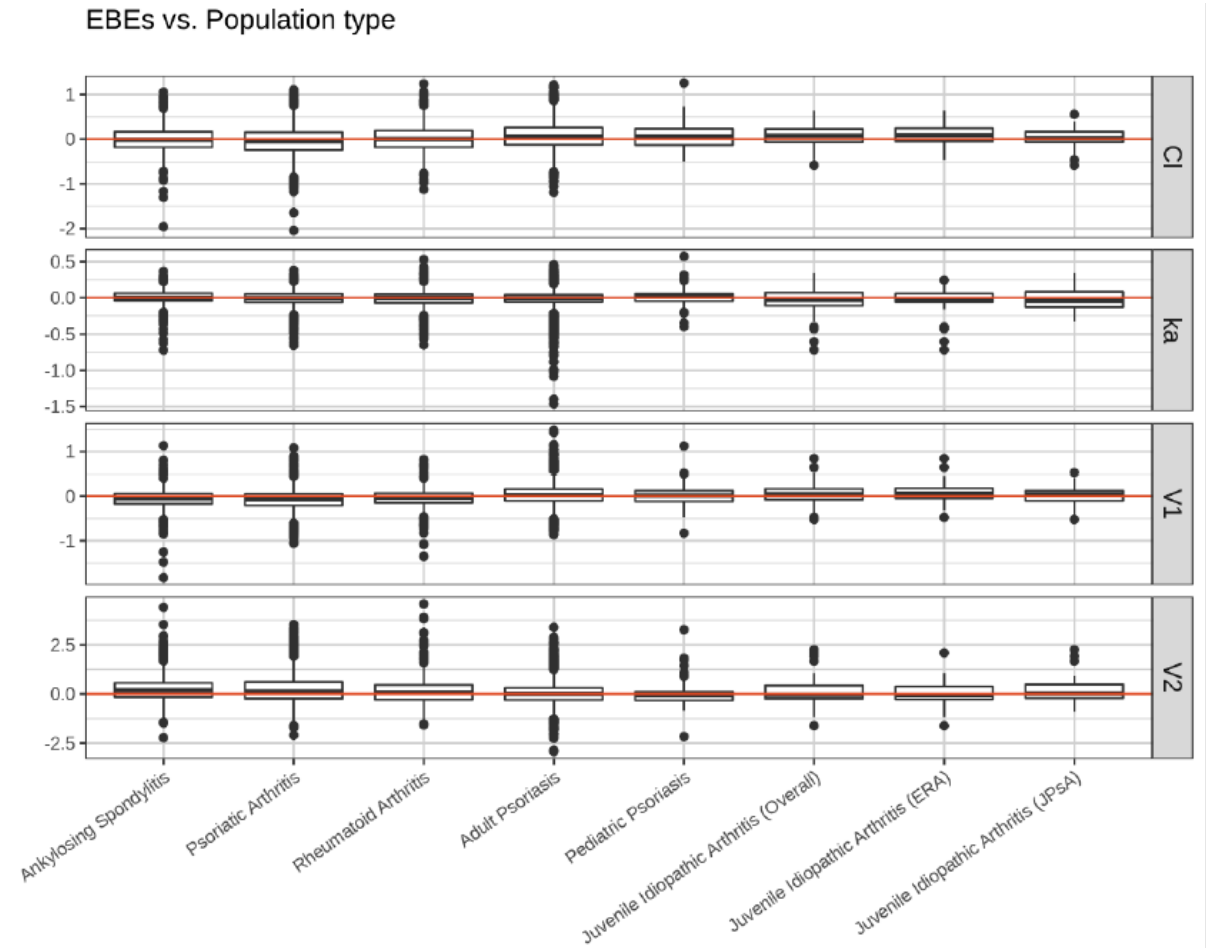
Figure 6 presents the post-hoc EBEs for CL versus body weight. Figure 7 presents the NPDE versus weight in the two pediatric populations and in adult patients. The NPDE was normally distributed and no trend for bias across weight could be detected.

Figure 4 NPDE versus time in JIA patients (Study F2304) - Model 3



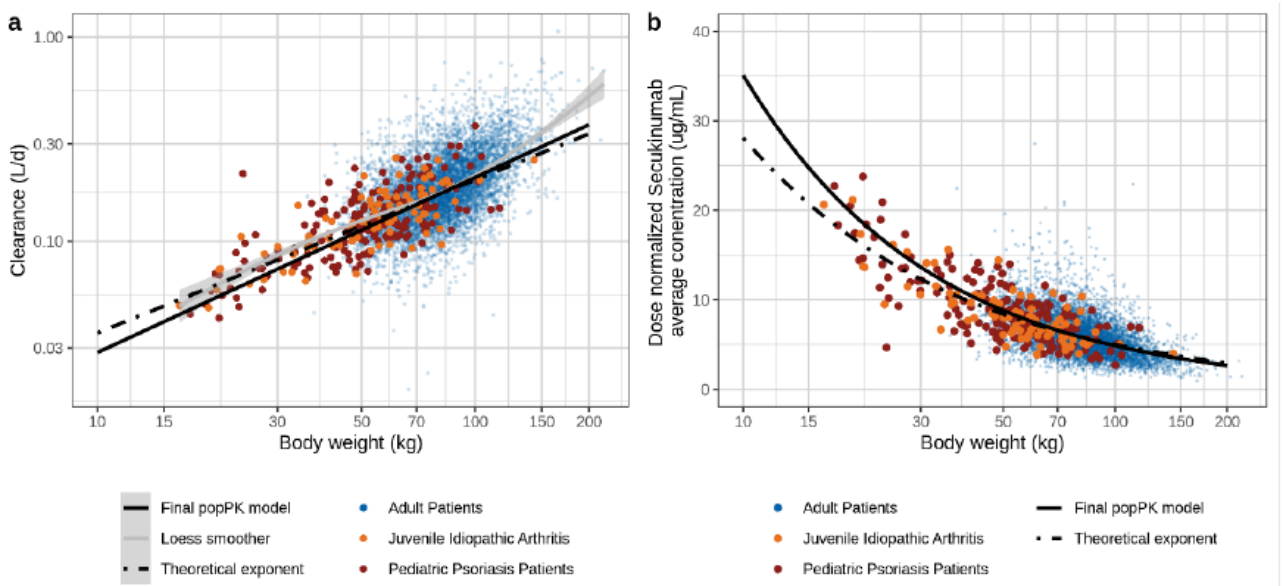
The red line through the points is a linear regression. Note the logarithmic x-axis scale.

Figure 5 *Distribution of individual CL, Ka, V1 and V2 random effects by population type – Model 3*



The lower and upper ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers extend to the 1.5 time the interquartile range (IQR) beyond the box or the more extreme values whichever is closer to the box. Dots represent the outliers. The EBE distribution for the JIA population in Study F2304 is presented both overall, and stratified across the ERA and JPsA categories.

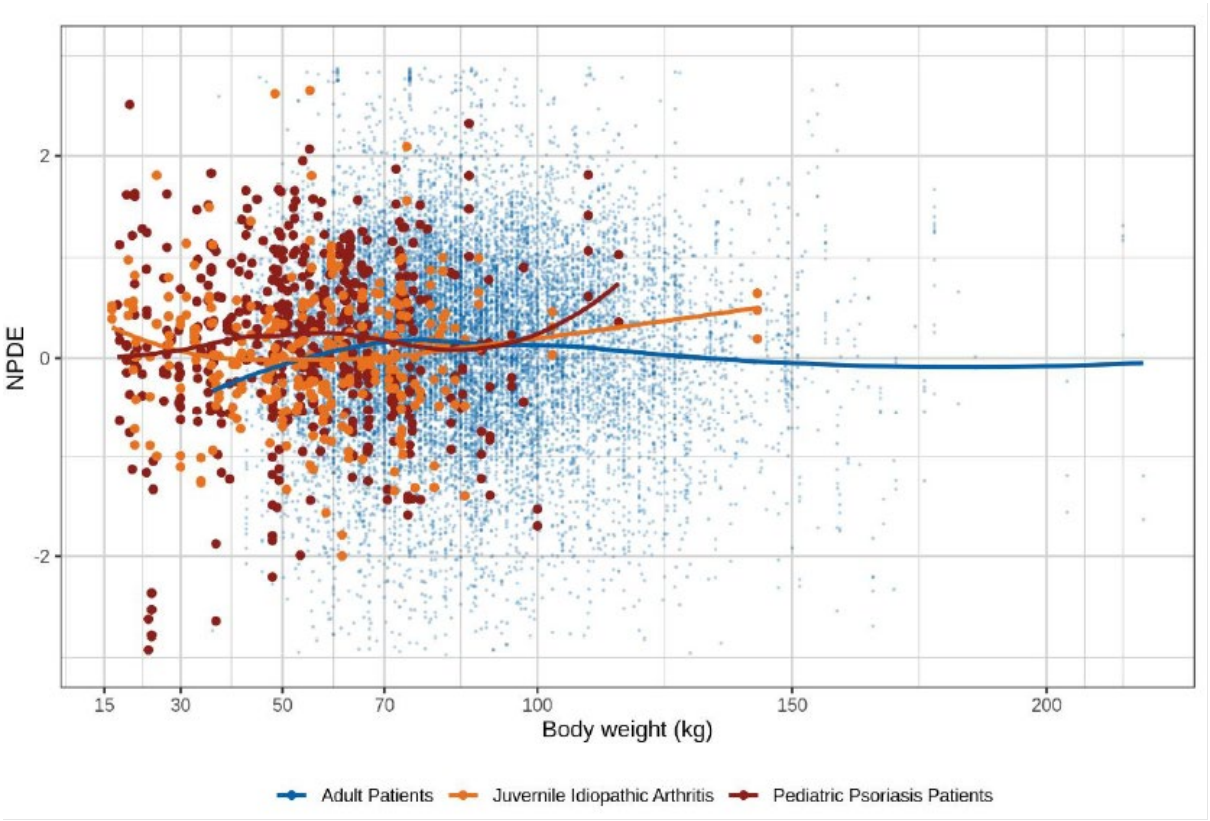
Figure 6 *Individual clearance and dose normalized secukinumab average concentrations versus body weight – Model 3*



Points represent individual post-hoc EBEs for clearance (a) and dose-normalized secukinumab steady state concentrations (b).

The solid black lines represent the relationship between individual estimates and body weight for the Final popPK model. The dashed black line represents the relationship between individual estimates and body weight for a model with the same structure as the Final popPK model and the allometric coefficients fixed to their theoretical values (Model R1, exponents fixed to 0.75 and 1 for clearance processes and volumes of distribution, respectively). The solid grey line (Panel (a) only) represents a smooth regression line for the individual post-hoc EBEs for Clearance versus body weight.

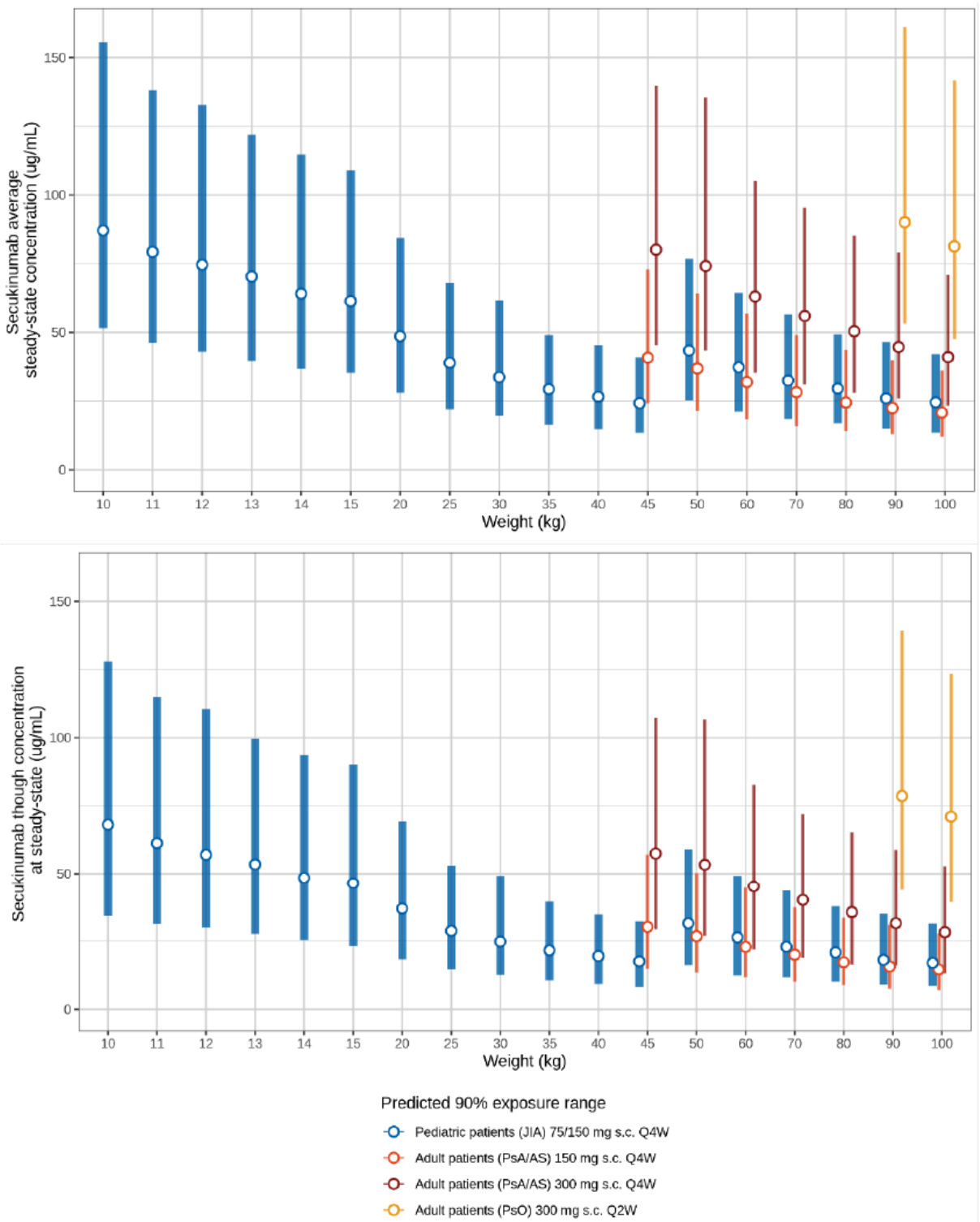
Figure 7 *NPDE versus time in JIA patients and versus weight in pediatric and adult patients – Model 3*



The colored lines through the points in each plot is a local regression (loess in R). Dots are normalized prediction distribution errors.

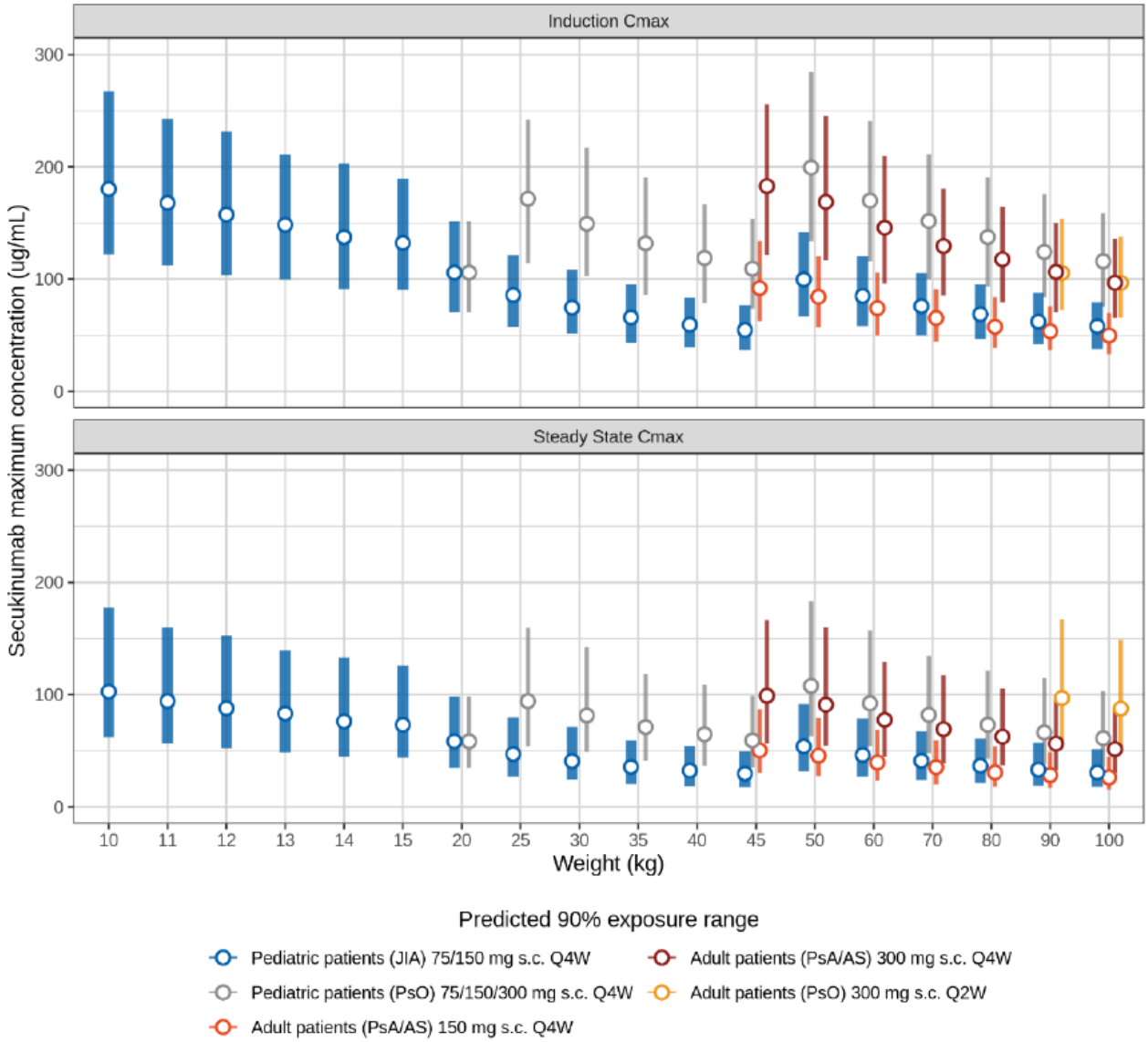
Model simulations were performed using Model 3 to assess the expected distribution of the trough (Cmin) and average concentration at steady state (Cavg,ss) in pediatric subjects treated with secukinumab 75 mg s.c. (<50 kg) or 150 mg s.c. (≥ 50 kg), for specific weights relevant to the 2 to 18 years old children. For comparison purpose, additional simulations were performed for AS and PSA adults treated with 150 mg Q4W and 300 mg Q4W, both for specific adult weights as well as averaged across the empirical weight distribution of the AS and PsA studies. Similar simulations were performed for heavy weight (≥ 90 kg) adult PsO patients treated with 300 mg Q2W. Model simulations (Figure 8) suggest that the current pediatric regimen will maintain exposure levels similar to those observed in adults at the 150 mg dose for JIA patients weighting 25 kg or above. In an RSI response, the MAH also provided a figure of Cmax predictions for paediatric subjects and adult subjects (Figure 9).

Figure 8 *Average and trough secukinumab concentrations at steady-state over body weight – Model 3*



Open dots: median of simulated average and trough concentrations at steady-state; Bars: 90% model-based prediction intervals (PIs). All predictions are based on Model 3, and account for PK differences in pediatric and adult patients.

Figure 9 *Maximum secukinumab steady-state concentration over body weight during induction and at steady state*



Open dots: median of simulated maximum concentrations during induction and at steady-state; Bars: 90% model-based prediction intervals (PIs). All predictions are based on the Final popPK model, and account for PK differences in paediatric and adult patients.

MAH interpretation of the PK results in terms of adequateness of the selected pediatric regimen

The secukinumab dosing regimen that was administered in Study F2304 was determined based on the population PK model developed on pooled adult rheumatoid arthritis (RA) study data over a bodyweight range of 40 to 159 kg, such that the pediatric concentrations would be in the range of that of ≤ 90 kg adults treated with the 150 or the 300 mg regimens.

In presence of a pediatric population-specific bioavailability, originally identified in a population PK analysis incorporating data from adult and pediatric PsO patients, that was not accounted for in the popPK RA model, the expected steady-state concentrations were higher as compared to the original predictions. The pediatric effect, in combination with a disease specific effect indicating an approximately 21% higher clearance for adult RA patients as compared to other disease populations included in the

analysis, led to expected concentrations that are higher than the original predictions, especially for low weight pediatric JIA patients.

One explanation for this higher bioavailability could be the difference in body composition between adults and children. Indeed, it has been seen in healthy volunteers that secukinumab systemic exposure is higher after administration in the thigh than in the less lean, more adipose abdominal region. This difference increases with bodyweight. Therefore, one can hypothesize that children, having relatively less adipose tissue than adults, show somewhat higher exposure due to higher absorption into the systemic circulation after s.c. administration in "leaner" subcutaneous tissue.

Model simulations suggest that dose adjustments for body weights < 50 kg and ≥ 50 kg pediatric patients are expected to maintain exposure levels similar to those in adults at the 150 mg dose for JIA patients weighting 25 kg or above. Higher exposure levels are expected for JIA patients with body weight below 25 kg, which are in the range of those in adult AS and PsA patients weighing between 45-100 kg and treated with the efficacious and safe secukinumab 300 mg Q4W regimen, which has already been approved, as well as of those in heavy weight adult PsO patients treated with the 300 mg Q2W regimen, which showed a safety profile consistent with the known safety profile of secukinumab.

The MAH states that overall, the selected secukinumab dosing regimen in JIA is expected to lead to adequate exposure to ensure efficacious treatment across all weights relevant for pediatric development, while maintaining exposure levels within those expected in previously treated adult populations where secukinumab was found to be well tolerated, thus supporting the dosing recommendation in JIA patients.

The MAH concluded that:

- The secukinumab concentrations of the JIA patients from Study F2304 were similar across the two JIA categories ERA and JPsA, and were similar to those observed in pediatric psoriasis patients of same weight and treated with the same pediatric regimen.
- The secukinumab concentrations were well characterized by a 2-compartment population PK model based on a large patient pool including adult ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, and psoriasis patients, as well as pediatric psoriasis and JIA patients. There was a tendency for slightly increased concentrations in both pediatric indications (pediatric psoriasis and JIA) as compared to adults, which could be attributed to an approximately 15% higher bioavailability in pediatric patients as compared to adults.
- The pediatric concentrations in JIA patients were generally consistent with the predictions from the population PK model based on adult and pediatric psoriasis data, regardless of the patient weight.
- Model simulations suggest that JIA patients weighting 25 kg or above and treated with the F2304 regimen would achieve exposure levels at steady-state similar to those achieved in PsA and AS adults treated with the 150 mg regimen. The expected distribution of average secukinumab concentration at steady-state in patients weighing 10 to 25 kg and receiving 75 mg Q4W was in the range of those achieved in adult AS and PsA patients weighing between 45-100 kg and treated with the efficacious and safe secukinumab 300 mg Q4W regimen, which has already been approved.
- Overall, the selected JIA dosing regimen (75 mg s.c. < 50 kg; 150 mg s.c. ≥ 50 kg) is expected to lead to adequate exposure to ensure efficacious treatment across all weights relevant for pediatric development, while maintaining exposure levels within those expected in previously treated adult and pediatric populations where secukinumab was found to be safe, thus supporting the dosing recommendation in JIA patients.

2.3.4. Discussion on clinical pharmacology

The MAH has taken sparse PK samples within the clinical efficacy study F2304. A separate analysis and discussion of raw PK data was provided, and the PK data from JIA patients has also been combined with a very large set of secukinumab PK data in both adults and children. After the population PK model was fitted, it was used to predict secukinumab exposure by bodyweight, and this is indeed a relevant application of the model; because of sample size limitations and the presence of between-subject variability, the raw data alone do not very well inform about secukinumab exposure in the smallest children. PK modelling is used to fill this gap in knowledge.

Study F2304 PK data consists of trough PK samples taken over the study duration of two years. Trough samples are mainly informative of bioavailability and clearance, and these two parameters determine the average secukinumab concentration at steady state. Trough PK samples are not informative of absorption rate, and slightly informative of distribution processes. Thus, trough PK samples will mainly inform about secukinumab steady-state concentrations, and they will not necessarily inform much about Cmax.

Population PK modelling has been conducted on the basis of 27 secukinumab clinical studies; an extensive PK dataset. A change in parameter estimates has been noted when expanding the PK model from psoriasis data to cover multiple indications (Model 0 versus Models 1 to 3, Table 4). Most importantly, the absorption rate increases, peripheral volume decreases, between-subject variability of peripheral volume greatly increases, the negative correlation between individual estimates of clearance and peripheral volume increases, and the correlation between central and peripheral volume of distribution is reversed from positive to negative. No physiological reason could be identified for these changes in parameter values. If the population PK model on the whole would be necessary to support the current type II variation, then the MAH would likely need to investigate what is the cause of the discrepant results. However, for the purposes of the current type II variation, it is sufficient that the model predicts accurately for JIA patient population, and no issues have been raised with regard to the parameter value discrepancies, unless they are supplemented by inaccurate PK predictions for JIA patients. The model diagnostics suggest that the population PK model predicts accurately for JIA patients on average (Figure 4 to Figure 6) and therefore the CHMP considered the model fit for the purpose of predicting secukinumab exposures in the JIA patient population.

The current model suggests a higher bioavailability for children versus adults. One could further speculate that not only the extent, but also the rate of absorption differs between adults and children. If this is true, then children will have a higher Cmax due to faster absorption of secukinumab, and it is possible that this trend would not be captured by the population PK model due to trough samples not being informative of absorption rate. In an RSI response, the MAH acknowledged that a difference in absorption rate between children and adults is indeed possible; however, any reasonable change in absorption rate constant will have negligible effects on the Cmax. The CHMP considered that this issue is solved.

The population PK model predicts the highest exposures for the smallest children (Figure 8 and Figure 9) which may present a problem for the extrapolation of safety from adults to children. In a second RSI, the MAH was requested to further justify that the amount of available adult safety data contains sufficient information to support extrapolation of safety from adults. In their response, the MAH restricted the indication to children aged six years and older; hence, this issue is solved.

2.3.5. Conclusions on clinical pharmacology

The MAH has characterized the PK of secukinumab in JIA patients by PK sampling of trough concentrations in paediatric clinical efficacy study F2304. The trough concentrations have been combined into an extensive population PK dataset, and a population PK analysis has been conducted.

ERA and JPsA patients (2 to less than 18 years of age) were administered secukinumab at the recommended paediatric dosing regimen. At week 24, patients weighing <50 kg, and weighing ≥50 kg had a mean ± SD steady-state trough concentration of 25.2±5.45 µg/ml (n=10) and 27.9±9.57 µg/ml (n=19), respectively.

The CHMP considered that the clinical pharmacology package was sufficient to support the following dosing recommendations in JIA patients 6 years of age and older:

The recommended dose is based on body weight and administered by subcutaneous injection at weeks 0, 1, 2, 3, and 4, followed by monthly maintenance dosing. Each 75 mg dose is given as one subcutaneous injection of 75 mg. Each 150 mg dose is given as one subcutaneous injection of 150 mg.

Recommended dose for juvenile idiopathic arthritis

Body weight at time of dosing	*Recommended dose*
<50 kg	*75 mg*
≥50 kg	*150 mg*

2.4. Clinical efficacy

2.4.1. Dose response studies

No separate dose response studies were conducted for secukinumab in JIA patients. Based on the expectation that paediatric patients with JIA (ERA and JPsA) would respond similarly to adults with similar conditions (AS, nr-axSpA and PsA) and similar exposure to secukinumab, dose selection for the main study was based on a population PK model that utilised trial data from adult indications to predict exposure of secukinumab according to body weight in children. Model simulations suggested that dosing based on weight categories < 50 kg and ≥ 50 kg would maintain exposure levels similar to those observed in adults at the 150 mg dose.

2.4.2. Main study

Study F2304: Three-part randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of secukinumab treatment in Juvenile Idiopathic arthritis subtypes of psoriatic and enthesitis-related arthritis

Methods

Study F2304 was a double-blind, placebo-controlled, event-driven randomised withdrawal study, consisting of a screening period of up to 8 weeks, 3 treatment periods plus a post-treatment follow-up period.

In Treatment Period 1 (TP1), all subjects received open-label secukinumab at baseline and every week for the first 4 weeks (loading dose period) and at Week 8. Subjects who were responders (minimum JIA ACR 30 response) at the end of TP1 (Week 12) received a dose of secukinumab or placebo and advanced to TP2; non-responders were not dosed and entered the post-treatment follow-up period.

A randomised, double-blind, withdrawal design was used for Treatment Period 2 (TP2). Responding subjects were randomised 1:1 to either continue secukinumab or switch to placebo in a blinded fashion, with randomisation stratified by JIA category (ERA and JPsA). Subjects who experienced a disease flare (as per JIA ACR flare definition) entered Treatment Period 3 (TP3) to receive open-label secukinumab until end of study (last dose at Week 100). Subjects who did not experience a flare could continue in TP2 until end of study, without entering TP3.

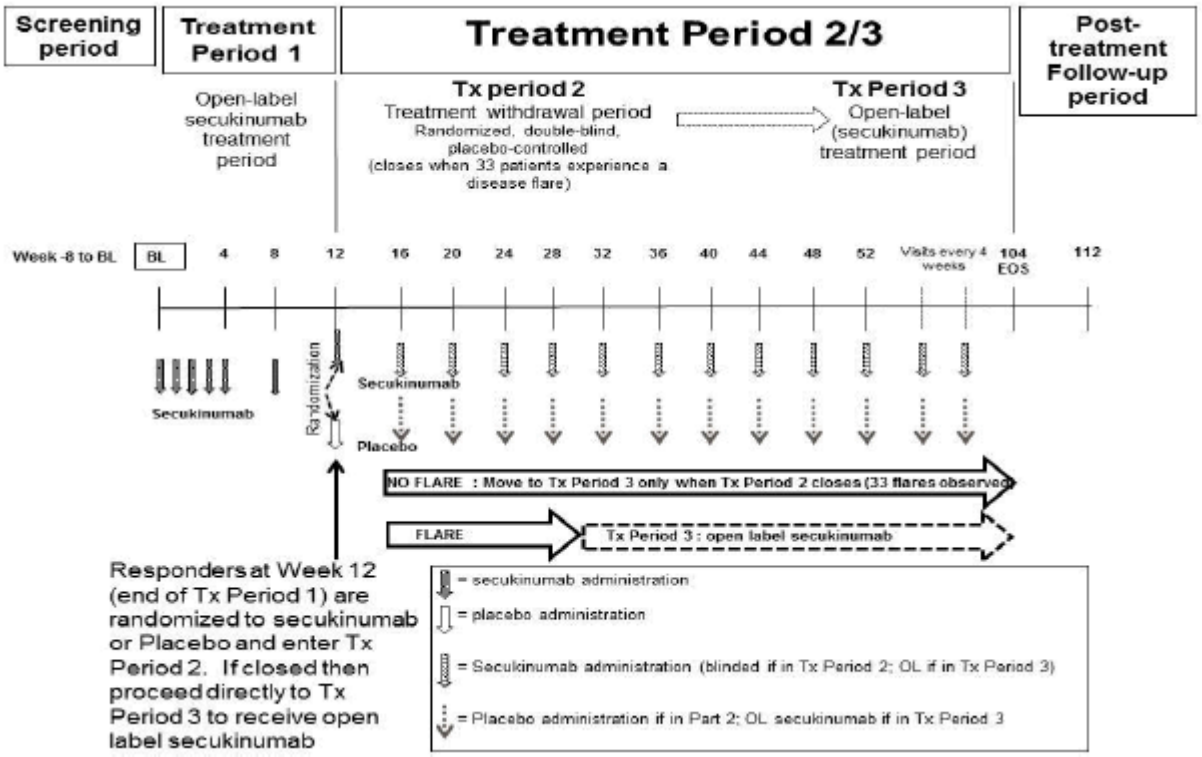
TP2 was event-driven. Per protocol, TP2 was to end either when 33 subjects had experienced a disease flare, or when all subjects had reached end of study (Week 104) or discontinued, whichever occurred first. The study closed after all subjects had reached Week 104 or discontinued, with a total of 31 flare events observed.

The key elements of study F2304 are outlined in Table 5, and the study design is graphically depicted in Figure 10.

Table 5 ***Key elements of study F2304***

Study Phase	**Phase III**
Design	Double-blind, randomized, controlled, secukinumab vs placebo in target JIA population (ERA and JPsA). Randomization in TP2 stratified by JIA categories (ERA and JPsA)
Main purpose	To determine the efficacy and safety of treatment with secukinumab vs placebo in pediatric patients with JIA category ERA and JPsA, who were biologic treatment naïve and had active disease despite current or previous NSAID and DMARD therapy
Population	Male and female patients aged ≥ 2 years to < 18 years at screening who were diagnosed with either ERA or JPsA based on fulfilling a modified ILAR JIA classification criteria
Study treatment	Secukinumab or matching placebo Dosing: 75 mg in patients weighing < 50 kg, 150 mg in patients weighing ≥ 50 kg given subcutaneously
Doses of secukinumab	TP1: Open-label secukinumab at baseline, Weeks 1, 2, 3, 4, and 8 TP2: Treatment withdrawal (double-blind) Responders (minimum JIA ACR30) randomized 1:1 at Week 12 to receive either secukinumab or placebo every 4 weeks until disease flare or Week 100 TP3: Open-label secukinumab every 4 weeks until Week 100
Number of patients enrolled	Total: 86 patients including: ERA: 52 patients JPsA: 34 patients
Study status	Completed; Last patient last visit: 09-Nov-2020

Figure 10 Study design for study F2304



Study participants

The following main eligibility criteria were applied in study F2304:

Main inclusion criteria:

- Written informed consent from parent or legal guardian of the child and written informed assent from the child
- Male or female, ≥ 2 years old and <18 years old at the time of screening
- Confirmed diagnosis of ERA according to the ILAR classification criteria or JPsA according to the modified ILAR classification criteria at least 6 months prior to Screening. ILAR diagnostic criteria for JPsA were modified to include HLAB27-positive males whose symptoms began after their 6th birthday, as well as patients who had AS, ERA, sacroiliitis with IBD, reactive arthritis, acute anterior uveitis, or a history of any of these disorders in a first-degree relative.
- Active disease (ERA or JPsA) defined as:
    - ≥ 3 active joints (swollen or if not swollen must be both tender and limited range of motion) at Baseline, and
    - ≥ 1 site of active enthesitis at Baseline or documented by history.
- Inadequate response (≥ 1 month) or intolerance to ≥ 1 NSAID.
- Inadequate response (≥ 2 months) or intolerance to ≥ 1 DMARD.
- No concomitant use of second line agents such as disease-modifying and/or immunosuppressive drugs (specific wash-out periods were defined in the protocol), with the exception of the following agents which must remain at stable dose during trial TP1 and TP2:

- Stable dose of methotrexate (maximum of 20 mg/m2 BSA/week) for at least 4 weeks prior to the Baseline visit, and folic/folinic acid supplementation (according to standard medical practice of the centre)
- Stable dose of sulfasalazine (ERA subjects only) < 50 mg/kg/day with max of 3000 mg/day for at least 4 weeks prior to the Baseline visit
- Stable dose of an oral corticosteroid at a prednisone equivalent dose of < 0.2 mg/kg/day or up to 10 mg/day maximum, whichever was less, for at least 7 days prior to Baseline
- Stable dose of no more than one NSAID for at least 1 week prior to Baseline

- Negative QuantiFERON test. Negative Purified Protein Derivative (PPD) test was also acceptable if either required by local guidelines or if the subject was < 5 years of age.

Main exclusion criteria:

- Use of other investigational drugs within 4 weeks or 5 half-lives of Baseline, or until the expected pharmacodynamic effect had returned to baseline, whichever was longer.
- History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes.
- Subjects with active uncontrolled inflammatory bowel disease or active uncontrolled uveitis.
- Subjects who had ever received biologic immunomodulating agents, including but not limited to TNFα inhibitors, T-cell costimulatory, Anti-IL6, Anti-IL1, cell-depleting therapies including but not limited to anti-CD20 (e.g., alemtuzumab, anti-CD4, anti-CD5, anti-CD3, and anti-CD19), secukinumab or other biologic drugs directly targeting IL-17 or IL-17 receptor or any investigational immunomodulating agent.
- Subjects taking any non-biologic DMARD except for methotrexate (or sulfasalazine for ERA subjects only).
- Subjects fulfilling any ILAR diagnostic JIA category other than ERA or JPsA.
- Subjects taking medications prohibited by the protocol (e.g., topical corticosteroids or ultraviolet (UV) therapy at screening).
- Subjects taking high potency opioid analgesics (morphine equianalgesic or higher) including but not limited to methadone, hydromorphone and morphine.
- Any intramuscular/intravenous/intra-articular corticosteroid treatment within 4 weeks before Baseline.
- Active or recurrent bacterial, fungal or viral infection including known infection with Human Immunodeficiency Virus (HIV), Hepatitis B, and Hepatitis C at Baseline.
- History or evidence of active TB or evidence of latent TB (positive QuantiFERON or Purified Protein Derivative at screening) but unwilling or unable to complete a minimum of 4 weeks of latent TB treatment before initiating treatment with secukinumab.
- History or current diagnosis of Electrocardiogram (ECG) abnormalities indicating significant risk of safety for subjects participating in the study such as:
    - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second- or third-degree AV block without a pacemaker

    - History of familial long QT syndrome or known family history of Torsades de Pointes
- Pregnant or nursing (lactating) females.
- Female subjects (< 18 years of age) of childbearing potential (menarchal or becoming menarchal during the study) who did not agree to abstinence or, if sexually active, did not agree to the use of contraception as defined in the protocol
- Active ongoing inflammatory diseases other than JPsA / ERA that might confound the evaluation of the benefit of secukinumab therapy.
- Underlying metabolic, haematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the Investigator, immunocompromises the subject and/or places the subject at unacceptable risk for participation in a study with an immunomodulatory treatment.
- Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension and uncontrolled diabetes (could be discussed on a case-by-case basis with the MAH).
- History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as AST/SGOT, ALT/SGPT, alkaline phosphatase, or serum bilirubin. The Investigator was guided by the following criteria:
    - Any single parameter not exceeding 2 × ULN. A single parameter elevated up to and including 2 × ULN were re-checked once more as soon as possible, and in all cases, at least prior to baseline, to rule out lab error.
    - If the TBL concentration was increased above 2 × ULN, total bilirubin was differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin should not exceed the value of 1.6 mg/dL (27 µmol/L).
- Screening total WBC count < 3000/µL, or platelets < 100000/µL or neutrophils < 1500/µL or haemoglobin < 8.5 g/dL (85 g/L).
- History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that had been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that had been removed).
- Plans for administration of live vaccines during the study period or within 6 weeks preceding Baseline.

Treatments

The following study treatments were used:

Investigational drug:

- Secukinumab pre-filled syringe (PFS), available as 150 mg in 1.0 mL and as 75 mg in 0.5 mL

Reference therapies:

- Secukinumab placebo, available as 1 mL and 0.5 mL PFS, in a form to match secukinumab PFS.

Secukinumab 75 mg/0.5 mL and 150 mg/1 mL PFS and matching placebos PFS were provided in a double-blind fashion and had identical appearance. Administration of study treatment was to occur at

the study site for the whole study duration (104 weeks); in response to the COVID-19 pandemic/epidemic, shipment of IMP and home administration was permitted in contingency situations from June 2020 (Protocol Amendment 2).

Treatment arms:

- **TP1 open-label:** Secukinumab 75 mg or 150 mg based on the body weight (< 50 kg or ≥ 50 kg) was administered s.c. at Baseline, Weeks 1, 2, 3, 4, and 8. The end of TP1 visit at Week 12 was determined based on subject's response to the study drug administered (responders entered TP2 and non-responders entered post-treatment follow-up).
- **TP2 treatment withdrawal:** Subjects who were responders (minimum JIA ACR 30) at the end of TP1 visit at Week 12, entered into TP2 at the same visit and were randomized 1:1 to receive blinded secukinumab (75 mg/ 0.5 mL or 150 mg/ 1.0 mL, based on body weight) or matching placebo. Subjects then continued to receive secukinumab or placebo every 4 weeks until either experiencing a disease flare or completion of TP2 (i.e. 33 disease flares observed in the overall study population) or completion of 104 weeks of total study duration in TP2.
- **TP3 open-label:** All subjects who experienced a flare in TP2 entered TP3 at the visit where the flare was confirmed. In TP3, secukinumab 75 mg or 150 mg s.c. (based on body weight) was administered every 4 weeks until Week 100 was reached.

Concomitant treatments:

The use of other JIA medications during the study was restricted to stable doses of methotrexate, sulfasalazine (ERA patients only), oral corticosteroids and no more than one NSAID. Other therapies for JIA had to be discontinued prior to randomisation, and wash-out periods for different classes were defined in the study protocol.

Objectives and endpoints

The purpose of study F2304 was to demonstrate the efficacy and safety of secukinumab treatment in paediatric patients ≥ 2 to < 18 years with active JPsA and ERA and to demonstrate the sustained efficacy of secukinumab by using a flare prevention design in the double-blind placebo-controlled treatment withdrawal part of the trial. The stated objectives of study F2304 along with their associated endpoints are listed in Table 6.

Table 6 ***Objectives and endpoints for study F2304***

Objectives	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure
Primary objective	
To demonstrate that the time to flare in TP2 is longer with secukinumab for combined ERA and JPsA groups than with placebo	Time to disease flare (active vs. control) Timeframe: TP2
Secondary objectives	
To evaluate the effect of secukinumab treatment for all subjects and each JIA category in TP1 up to Week 12 (end of TP1) with respect to: • JIA ACR 30/50/70/90/100 and inactive disease status • Each JIA ACR core component • Change from baseline JADAS score • Total enthesitis count • Total dactylitis count	JIA ACR 30/50/70/90/100 inactive disease status JIA ACR core components JADAS score Total enthesitis count Total dactylitis count Timeframe: TP1
To evaluate withdrawal effect of secukinumab treatment for all subjects and each JIA category during and at the end of TP2 with respect to: • JIA ACR 30/50/70/90/100 and inactive disease status	JIA ACR 30/50/70/90/100 inactive disease status Timeframe: TP2
To evaluate PK of secukinumab and confirm the predicted dose in TP1	Secukinumab serum concentrations and derived PK parameters Timeframe: TP1
To evaluate the safety/tolerability and immunogenicity of secukinumab	AEs, laboratory values, vital signs, Anti-Drug Antibodies (ADA) Timeframe: Entire study
Exploratory objectives	
To explore time to flare for ERA and JPsA categories individually in TP2	Time to disease flare Timeframe: TP2
To evaluate withdrawal effect of secukinumab treatment for all subjects and each JIA category during and at the end of TP2 with respect to: • Each JIA ACR core component • JADAS score • Total enthesitis count • Total dactylitis count • Swollen joint count • Tender joint count • Overall back pain (VAS) in ERA subset only • Nocturnal back pain (VAS) in ERA subset only • Psoriasis global assessment (IGA Mod 2011) in JPsA subset only • % total BSA affected by psoriasis in JPsA subset only • Modified Schober's Test	• JIA ACR core components • JADAS score • Total enthesitis count • Total dactylitis count • Swollen joint count • Tender joint count • Overall back pain VAS • Nocturnal back pain VAS • IGA Mod 2011 • % total BSA affected by psoriasis • Modified Schober's test Timeframe: TP2
To explore the effect of secukinumab treatment with respect to the JSpADA Index for all subjects and each JIA category at Weeks 12, 52, 104 and at time of disease flare in TP2	JSpADA index Timeframe: Entire study
To explore the correlations of JSpADA Index with JADAS, PGA of disease activity (VAS), and the CHAQ.	• JSpADA index • PGA of disease activity VAS • CHAQ Timeframe: Entire study
To evaluate effect of secukinumab treatment in TP3 after a subject experiences a disease flare in TP2.	• JIA ACR 30/50/70/90/100 • Inactive disease status • JIA ACR components Timeframe: TP3
To explore the effect of secukinumab treatment for all subjects over time	JIA ACR 30/50/70/90/100 Timeframe: Entire study
To explore the time to inactive disease with secukinumab treatment for all subjects and each JIA category	Inactive disease Timeframe: Entire study
To explore the effect of secukinumab treatment for all subjects and each JIA category by proportion achieving clinical remission on drug (≥ 6 months inactive disease)	Inactive disease status Timeframe: Entire study
To identify potential proteomic biomarkers associated with treatment response to secukinumab	Timeframe: Entire study

The following endpoint definitions were applied:

JIA ACR response criteria

Standard ACR paediatric Criteria (JIA ACR criteria) consists of 6 core components. JIA ACR 30/50/70/90/100 were defined as 30%, 50%, 70%, 90% and 100% improvement from baseline respectively in a minimum of three variables in the core set with no more than one variable worsening more than 30% as defined in the JIA ACR criteria.

The 6 core components variables are:

- Physician global assessment of disease activity on a 0 - 100 mm VAS from 0 mm = no disease activity to 100 mm = very severe disease activity
- Parent or subject's (if appropriate in age) Global Assessment of Subject's overall wellbeing on a 0-100 mm VAS from 0 mm = very well to 100 mm = very poor.
- Functional ability: Childhood Health Assessment Questionnaire (CHAQ; an instrument completed by the parent (for subjects 18 years and older, completed by the subject and parent together), consisting of multiple choice and VAS items concerning difficulty in performing eight common activities of daily living; dressing and grooming, arising, eating, walking, reaching, personal hygiene, gripping and activities).
- Number of active joints using the ACR definition (any joint with swelling or in the absence of swelling, limitation of motion accompanied by either pain on motion or tenderness not due to deformity)
- Number of joints with limited range of motion
- Laboratory measure of inflammation: C-reactive Protein (CRP)

The core components were used to determine ACR Paediatric response, Juvenile Arthritis Disease Activity Score (JADAS) and inactive disease status. JIA ACR response, responder status at Week 12, and flare occurrence in TP2 were determined by a central vendor.

Clinical inactive disease definition was adapted from the JIA ACR criteria. All of the following were required to be met:

- No joints with active arthritis
- No uveitis
- CRP value within normal limits for the laboratory where tested or, if elevated, not attributable to JIA
- Physician's global assessment of disease activity score $\leq$ 10mm
- Duration of morning stiffness attributable to JIA $\leq$15 min

Clinical remission on medication was defined as $\geq$ 6 consecutive months of inactive disease while the subject was on medication.

Flare definition

Both criteria 1 and 2 must be fulfilled to meet the definition of a disease flare. Criteria changes described are relative to the End of TP1 (Week 12 visit).

1. $\geq$ 30% worsening in at least 3 of the 6 ACR response variables
    - Physician global assessment of overall disease activity
    - Parent or patient global assessment of overall well-being

- Functional ability (CHAQ)
- Number of joints with active arthritis
- Number of joints with limited range of motion
- Index of inflammation: CRP

2. ≥ 30% improvement in no more than 1 of the 6 ACR response variables

Contingencies:

- if the Physician or Parent Global Assessment is one of the 3 response variables used to define flare, worsening of ≥ 20 mm (1-100mm visual analogue scale) must be present;
- if the number of active joints or joints with limitation of motion is one of the 3 response variables used to define flare, worsening in ≥ 2 joints must be present;
- if CRP is one of the 3 response variables to define flare it must be above normal range

Joint and enthesitis counts

Tender joint counts were based on assessment of 75 joints, swollen joint counts on 68 joints, and counts of joints with limitation of motion on 69 joints. Enthesitis count was based on assessment of tenderness in 16 entheseal sites.

Juvenile Arthritis Disease Activity Score (JADAS)

Juvenile Arthritis Disease Activity Score (JADAS) is a composite disease activity score consisting of 4 components:

- Physician global assessment of disease activity
- parent/subject global assessment of overall well-being
- active joint count
- CRP

JADAS-27 (Juvenile Arthritis Disease Activity Score in 27 joints) ranges from 0 to 57 and JADAS-71 ranges from 0 to 101, with higher scores indicating more disease activity.

Sample size

For the sample size calculation, the MAH assumed that the Flare-free time follows an exponential distribution with a constant hazard ratio.

The hazard ratio of flare events for the secukinumab group relative to placebo group was estimated to be 0.32 in TP2. The hazard ratio of 0.32 was used to establish the sample size necessary in TP2 and consequently TP1 (derived from the median time to disease flare for etanercept and placebo in children with polyarticular Juvenile Rheumatoid Arthritis, as reported in a publication by Lovell et. al. 2000).

With the hazard ratio assumed to be 0.32, 33 flares were necessary to detect a statistically significant difference between secukinumab and placebo, assuming 90% power and a 1-sided significance level of 0.025. No data were available to estimate the placebo hazard rate beyond 6-months. Given that uncertainty and a maximum 21-month follow-up in TP2, the total sample size necessary to achieve 33 flares in TP2 was estimated to be at least 60 and at most 80 subjects. Assuming approximately 70% to 85% of subjects responded in TP1, the estimated minimum number of subjects treated in TP1 was between 70 and 86. Under the assumption of 12 months of accrual duration, the total maximum expected

study duration is 33 months. The expected number of flare events was 12 and 21 respectively, for secukinumab and placebo group in TP2.

Randomisation

At the Week 12 visit, all responders were eligible to enter TP2 where they were randomised via Interactive Response Technology (IRT) to one of the two treatment arms in a 1:1 ratio: active as secukinumab 75 or 150 mg based on their weight at that visit, or matching placebo.

The randomisation was stratified by each JIA category (strata: JPsA and ERA) so that approximately an equal number from each category were to receive either active or placebo.

In terms of the IRT process, the Investigator or his/her delegate contacted the IRT after confirming that the subject fulfilled the response criteria. The IRT assigned a randomisation number to the subject, which was used to link the subject to a treatment arm and specified a unique medication number for the first package of study drug to be dispensed to the subject. The randomisation number was not communicated to the caller.

The randomisation numbers were generated using the following procedure to ensure that treatment assignment was unbiased and concealed from subjects/parents and Investigator staff. A subject randomisation list was produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomisation numbers. These randomisation numbers were linked to the different treatment arms and to study strata, which in turn were linked to medication numbers. A separate medication list was produced by or under the responsibility of the MAH's Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Blinding (masking)

Subjects/parents, Investigator staff, persons performing the assessments, and data analysts remained blinded to the identity of the treatment (TP2) from the time of randomisation until the primary endpoint analysis/final analysis database lock, using the following methods:

1. Randomisation data were kept strictly confidential until the time of unblinding, and were not accessible by anyone else involved in the study with the exception of the bioanalyst, independent statistician, programmer and DMC members.
2. The identity of the treatments was concealed by use of study drug with identical packaging, labeling, schedule of administration, administration route and appearance for both secukinumab and placebo.

Unblinding only occurred in the case of subject emergencies and after the primary efficacy analysis/final analysis.

Statistical methods

The following analysis set were used for the efficacy summaries:

- The Full Analysis Set (FAS) for Treatment Period 1 (Full Analysis Set 1) will consist of all patients who received at least one dose of study drug in Treatment Period 1.
- The FAS for Treatment Period 2 (Full Analysis Set 2) will consist of all randomized patients who received at least one dose of study drug in Treatment Period 2. Following the intent-to-treat

principle, patients will be analysed according to the treatment they were assigned to at randomization in Treatment Period 2.

- The FAS for Treatment Period 3 (Full Analysis Set 3) will consist of all patients who received at least one dose of study drug in Treatment Period 3.

Primary efficacy endpoint: time to flare

The primary efficacy endpoint was time to disease flare in TP2, defined as the interval between the date of randomization to the date of first occurrence of a disease flare event. Subjects who did not experience a flare event at the end of TP2 or discontinued prematurely before the end of TP2 for reasons other than experiencing a disease flare were censored at the date of the last efficacy evaluation in TP2. The two treatment groups were compared using a one-sided stratified log-rank test with the stratification factor of JIA category (ERA or JPsA) and MTX use at baseline (yes/no) at the 2.5% level of significance. Hazard ratios and their associated 95% confidence intervals were estimated based on a Cox proportional hazards model with treatment and analysis factors JIA category (ERA or JPsA) and MTX use at baseline as explanatory variables. Of note, the plan to stratify the analysis by MTX use at baseline or as an additional explanatory variable in the model represents a change in the protocol-defined analysis plan but was pre-planned in the SAP.

Sensitivity analyses were planned e.g. to consider a scenario where patients discontinuing the study treatment prematurely for any reason will be considered as having flared at the time of study treatment discontinuation.

Pre-specified subgroup analyses for the primary endpoint evaluated the consistency of the effect by JIA category (ERA and JPsA), and methotrexate use at baseline. Additional subgroup analyses of the primary endpoint were conducted by age, gender and weight categories.

Secondary and exploratory endpoints

The secondary and exploratory efficacy objectives and respective endpoints are listed in Table 6. The secondary variables were summarised descriptively only using FAS of the respective treatment period using observed data only. The analyses were done to evaluate

- effect of secukinumab treatment in Treatment Period 1 up to Week 12 (end of Treatment period 1)
- withdrawal effect of secukinumab treatment during and at the end of Treatment Period 2

on the efficacy measures for all patients and each JIA category.

The analysis of exploratory endpoints included descriptive evaluation of the effect of secukinumab treatment in Treatment Period 3 after a patient experiences a disease flare in Treatment Period 2.

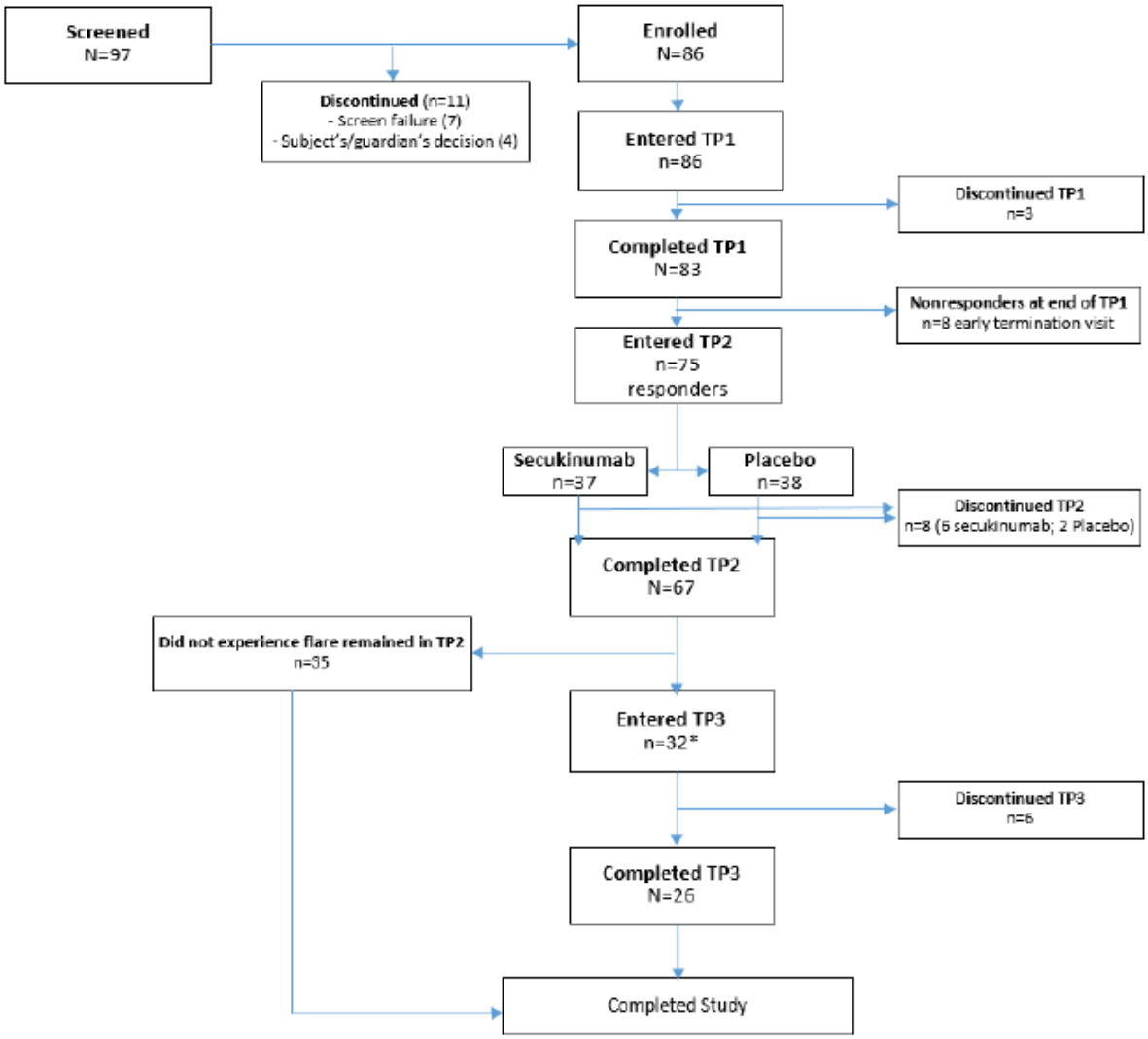
Results

Participant flow

A total of 97 subjects were screened, of which 86 were enrolled into TP1. Of these 86 subjects, 83 completed TP1, and 75 were deemed responders eligible for randomisation into TP2. A total of 67 subjects completed TP2, and 61 subjects completed the entire study.

Subject disposition in study F2034 is outlined in Figure 11, and reasons for discontinuation are displayed in Table 7.

Figure 11 Subject disposition in study F2304 – TP1, TP2, and TP3 (Safety Set)



*The 32 patients who entered into TP3 included 2 patients (Patient and Patient) who were erroneously switched into TP# but had not experienced any flare at TP2. These 2 patients were considered as not having flared for efficacy analysis.
One other patient (Patient) experienced a flare at the discontinuation visit in TP2. The patient was discontinued due to SAE and did not enter TP3. For correct reporting, this patient was considered as having flared for efficacy analysis for time to flare.
As a result, 32 flare events are included in the efficacy analysis for time to flare.

Table 7 ***Subject disposition and reasons for discontinuation – Treatment periods 1, 2 and 3 (Safety Set)***

Disposition/Reason	Period 1	Period 2			Period 3		
	AIN457 N=86 n (%)	AIN457 N=37 n (%)	Placebo in TP2 N=38 n (%)	Total N=75 n (%)	AIN457 N=11 n (%)	Placebo in TP2 N=21 n (%)	Total N=32 n (%)
Completed treatment period	83 (96.5)	31 (83.8)	36 (94.7)	67 (89.3)	10 (90.9)	16 (76.2)	26 (81.3)
Continued to Period 2	75 (87.2)	NA	NA	NA	NA	NA	NA
Continued to Period 3	0	11 (29.7)	21 (55.3)	32 (42.7)	NA	NA	NA
Discontinued during or at the end of the treatment period*	3 (3.5)	6 (16.2)	2 (5.3)	8 (10.7)	1 (9.1)	5 (23.8)	6 (18.8)
Primary reason for discontinuing							
AE	0	1 (2.7)	2 (5.3)	3 (4.0)	0	3 (14.3)	3 (9.4)
Death	0	0	0	0	0	0	0
Lack of efficacy	3 (3.5)	1 (2.7)	0	1 (1.3)	0	1 (4.8)	1 (3.1)
Non-compliance with study treatment	0	0	0	0	0	0	0
Pregnancy	0	0	0	0	0	0	0
Protocol deviation	0	0	0	0	0	0	0
Study terminated by sponsor	0	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0	0
Technical problems	0	0	0	0	0	0	0
Physician decision	0	1 (2.7)	0	1 (1.3)	0	1 (4.8)	1 (3.1)
Subject/guardian decision	0	3 (8.1)	0	3 (4.0)	1 (9.1)	0	1 (3.1)

AIN457: all patients who did not take any placebo before or during the period.
Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s.
Patients who were mistakenly switched from TP2 to TP3 were counted as having completed TP2.
* Includes patients who completed the given period and discontinued prematurely from the study treatment on the same date.
NA = Not applicable.

Recruitment

The study was conducted in 32 Investigator sites across 10 countries: 3 centres in Belgium (n=4), 4 centres in Germany (n=16), 2 centres in Italy (n=2), 1 centre in Poland (n=4), 5 centres in Russia (n=18), 2 centres in South Africa (n=5), 2 centres in Spain (n=6), 4 centres in Turkey (n=17), 5 centres in the United Kingdom (n=8), and 4 centres in the United States (n=6).

Conduct of the study

The original protocol for the study had an effective date of 24 October 2016; first subject first visit took place on 23 May 2017, and last subject last visit took place on 09 November 2020.

The protocol was amended on two occasions. In Amendment 1, dated 06 April 2017 (i.e., before enrolment of the first subject), some clarifications and corrections were made into the ILAR diagnostic criteria; it was also clarified that subjects discontinuing prior to Week 12 visit may be replaced. Study completion, post-study treatment and eligibility to enter into extension study was clarified, and the suggested order of assessments was amended in order to minimise delays during visits.

Amendment 2, dated 04 June 2020, was issued to adapt the protocol to COVID-19 -related challenges, most importantly permitting shipment of IMP to the subjects as well as its administration at home (under caregiver supervision, as appropriate). Study visits were also permitted to be replaced with phone calls or virtual contacts in contingency situations.

Overall, 64.0% (55/86) subjects had at least one protocol deviation, among them 64.6% (31/48) subjects in secukinumab group and 63.2% (24/38) subjects in the placebo group. The most common cause of protocol deviation was 'prohibited concomitant medication' reported in 25.6% subjects overall (25.0% in secukinumab group and 26.3% in placebo in TP2 group). This includes protocol deviations attributed to prohibited medications, incorrect dose of a concomitant medication or use of biologics during the study follow-up period. According to the MAH, the majority of such protocol deviations were related to the dose of a corticosteroid, oral DMARD or NSAID that was not maintained stable since baseline, with most of these deviations representing discontinuations or dose reductions. The deviations were balanced between TP2 treatment groups.

Protocol deviation 'selection criteria not met' was reported in 23.3% subjects overall. The majority of these protocol deviations were related to missing lab results or lab results that were not available before randomisation, or were related to the use of second line concomitant medications either not listed in the protocol as acceptable or not at a stable dose per protocol. Within the category 'treatment deviation' (20.9%), the majority was associated with subjects missing a visit and therefore missing a dose.

The categories of protocol deviations were generally balanced between the treatment groups and are displayed in Table 8.

Table 8 ***Protocol deviations by deviation category – Entire treatment period (Safety Set)***

Protocol deviation	AIN457 N=48 n (%)	Placebo in TP2 N=38 n (%)	Total N=86 n (%)
Subjects with at least one protocol deviation	**31 (64.6)**	**24 (63.2)**	**55 (64.0)**
Selection Criteria Not Met	11 (22.9)	9 (23.7)	20 (23.3)
Treatment Deviation	11 (22.9)	7 (18.4)	18 (20.9)
Prohibited Concomitant Medication	12 (25.0)	10 (26.3)	22 (25.6)
Other Deviation	4 (8.3)	6 (15.8)	10 (11.6)

AIN457: all subjects who did not take any placebo. Placebo in TP2: all subjects who took placebo in TP2 and AIN457 in other period/s.
A subject with multiple occurrences of a protocol deviation category is counted only once in the protocol deviation category.
Subjects may have protocol deviations in more than one protocol deviation category.

In total, 9 subjects had protocol deviations, mostly missed doses and/or missed assessments, related to COVID-19 pandemic. According to the MAH, due to the limited number of protocol deviations related to COVID-19 pandemic and as judged from the results of sensitivity analyses for COVID-19 impact, there seemed to be at most a minimal impact on the primary efficacy results.

In September 2020, the MAH was informed by one of its service providers of a cyber security attack that mandated a shutdown of the provider's entire network. However, a subsequent incident analysis by the MAH indicated no impact with respect to study F2304.

Baseline data

The mean age of subjects enrolled in the study was 13.1 years (range: 2 to 17 years). There were 3 subjects (1 ERA, 2 JPsA) in the 2-<6 years age group, 22 subjects in the 6-<12 years age group, and 61 subjects in the 12-<18 years age group. The majority of subjects were male (66.3%) and

predominantly White (95.3%), with mean weight and height of 56.0 kg and 158.0 cm, respectively. The mean BMI was approximately 21.7 kg/m2. There were 6 subjects with a body weight of <25 kg, 24 subjects with a body weight of 25 to <50 kg, and 56 subjects with a body weight of 50 kg or higher at baseline. Among subjects enrolled, 52 subjects (60.5%) had ERA and 34 subjects (39.5%) had JPsA.

Apart from a different gender distribution for subjects with ERA and JPsA (ERA: male 78.8%; JPsA: male 47.1%), the demographic and baseline characteristics of subjects were generally comparable between the treatment groups and by JIA category. The demographic characteristics are summarised in Table 9.

Table 9 ***Subject demographics, all subjects (Safety Set)***

Demographic characteristics	Treatment Period 1	Treatment Period 2		
	AIN457 N=86	AIN457 N=37	Placebo in TP2 N=38	Total N=75
JIA category: Total				
Age (years)				
n	86	37	38	75
Mean	13.1	13.6	12.0	12.8
SD	3.13	2.74	3.45	3.20
Median	14.0	14.0	13.0	14.0
Min – Max	2 – 17	6 – 17	2 – 17	2 – 17
Sex – n (%)				
Male	57 (66.3)	24 (64.9)	27 (71.1)	51 (68.0)
Female	29 (33.7)	13 (35.1)	11 (28.9)	24 (32.0)
Race – n (%)				
White	82 (95.3)	36 (97.3)	35 (92.1)	71 (94.7)
Black or African American	0	0	0	0
Asian	1 (1.2)	0	1 (2.6)	1 (1.3)
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Unknown	0	0	0	0
Other	3 (3.5)	1 (2.7)	2 (5.3)	3 (4.0)
Ethnicity – n (%)				
Hispanic or Latino	5 (5.8)	3 (8.1)	1 (2.6)	4 (5.3)
Not Hispanic or Latino	67 (77.9)	25 (67.6)	35 (92.1)	60 (80.0)
Unknown	5 (5.8)	4 (10.8)	1 (2.6)	5 (6.7)
Not Reported	9 (10.5)	5 (13.5)	1 (2.6)	6 (8.0)
Weight (kg)				
n	86	37	38	75
Mean	55.99	57.42	49.03	53.17
SD	20.886	16.454	20.278	18.845
Median	56.10	58.50	50.45	55.40
Min - Max	16.5 - 143.2	25.3 - 88.5	16.5 - 103.0	16.5 - 103.0
Height (cm)				
n	86	37	38	75
Mean	158.03	161.22	153.49	157.31
SD	17.986	15.479	21.511	19.054
Median	162.00	163.30	160.50	162.00
Min - Max	95.0 - 190.0	126.1 - 190.0	95.0 - 181.2	95.0 - 190.0
BMI(kg/m²)				
n	86	37	38	75
Mean	21.695	21.706	19.807	20.744
SD	5.6079	4.3315	4.3871	4.4345
Median	20.735	21.050	18.780	19.830
Min - Max	13.33 - 50.32	15.45 - 33.27	13.33 - 32.88	13.33 - 33.27
Smoking status at baseline – n (%)				
No	82 (95.3)	34 (91.9)	37 (97.4)	71 (94.7)
Yes	4 (4.7)	3 (8.1)	1 (2.6)	4 (5.3)

AIN457: all patients who did not take any placebo before or during the period.
Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s.
N = Number of patients in the Safety Set from the overall JIA population, including ERA and JPsA categories combined.
Weight and height are taken from the last evaluation on the day of or prior to study treatment start.

At baseline, mean JADAS-27 score was 15.072 (SD 7.129, range 3.3 – 35.3), mean total enthesitis count was 2.6 (SD 2.51, range 0 – 13), and mean total dactylitis count was 1.0 (SD 2.15, range 0 – 11). Baseline disease characteristics were generally comparable between the TP2 treatment groups as well as between JIA subtypes; mean total enthesitis count was slightly higher in subjects with ERA than subjects with JPsA (2.7 vs. 2.3), whereas mean total dactylitis count was higher in subjects with JPsA than subjects with ERA (1.8 vs. 0.4). Mean CRP at baseline was 23.96 mg/l (SD 38.76, range 0 – 185.16) in subjects with ERA, compared to 10.52 mg/l (SD 13.97, range 0.34 – 55.24) in subjects with JPsA.

Some 65% of subjects with either subtype in TP1 was using methotrexate at baseline; within the two subtypes, MTX was used by 33/52 (63%) of ERA subjects in TP1 (15/22 (68%) for secukinumab in TP2 and 14/22 (64%) for placebo in TP2), and by 23/34 (68%) of JPsA subjects in TP1 (11/15 (73%) for secukinumab in TP2 and 11/16 (69%) for placebo in TP2). Among ERA subjects, concomitant use of sulfasalazine was reported for 12/52 (23%) subjects enrolled in TP1 and 8/44 (18%) subjects randomised in TP2, with 5 on secukinumab and 3 on placebo. Baseline disease characteristics are summarised in Table 10.

Table 10 ***Disease history and background characteristics, all subjects (Safety Set)***

Disease characteristics	Treatment period 1 AIN457 N=86	Treatment Period 2 AIN457 N=37	Placebo in TP2 N=38	Total N=75
JIA category (ERA/JPsA) - n (%)				
ERA	52 (60.5)	22 (59.5)	22 (57.9)	44 (58.7)
JPsA	34 (39.5)	15 (40.5)	16 (42.1)	31 (41.3)
Time since diagnosis(years)				
n	86	37	38	75
Mean (SD)	1.97	1.77	2.25	2.01
SD	1.969	1.847	2.048	1.953
Median	1.09	0.95	1.29	1.09
Min – Max	0.5 – 9.3	0.5 – 7.7	0.5 – 9.3	0.5 – 9.3
JADAS-27 score				
n	86	37	38	75
Mean	15.072	15.244	15.647	15.448
SD	7.1288	8.0685	6.8995	7.4507
Median	14.019	13.733	14.850	14.400
Min - Max	3.30 - 35.30	3.90 - 31.80	3.30 - 35.30	3.30 - 35.30
JADAS-71 score				
n	86	37	38	75
Mean	18.293	18.650	18.805	18.728
SD	10.1995	11.0165	10.6484	10.7584
Median	15.850	18.000	16.157	17.014
Min - Max	4.90 - 67.30	4.90 - 47.18	5.30 - 67.30	4.90 - 67.30
Total enthesitis count				
n	85	37	37	74
Mean	2.6	2.7	2.5	2.6
SD	2.51	2.89	2.34	2.61
Median	2.0	2.0	2.0	2.0
Min - Max	0 - 13	0 - 13	0 - 10	0 - 13
Total dactylitis count				
n	82	37	37	74
Mean	1.0	1.2	1.0	1.1
SD	2.15	2.22	2.29	2.24
Median	0.0	0.0	0.0	0.0
Min - Max	0 - 11	0 - 8	0 - 11	0 - 11
Physician global assessment of disease activity (0-100 mm)				
n	86	37	38	75
Mean	47.3	44.7	46.4	45.5
SD	21.17	21.93	19.77	20.74
Median	43.5	40.0	44.0	40.0
Min - Max	8 - 100	19 - 100	8 - 80	8 - 100
Overall well-being score (0-100 mm)				
n	86	37	38	75
Mean	48.5	46.7	51.8	49.3
SD	28.25	30.26	27.90	29.01
Median	54.0	46.0	58.0	57.0
Min - Max	0 - 100	0 - 100	0 - 100	0 - 100

Disease characteristics	Treatment period 1	Treatment Period 2		
	AIN457 N=86	AIN457 N=37	Placebo in TP2 N=38	Total N=75
Childhood Health Assessment Questionnaire (CHAQ)				
n	86	37	38	75
Mean	0.7587	0.6993	0.8553	0.7783
SD	0.61560	0.60843	0.63754	0.62316
Median	0.6875	0.5000	0.8750	0.7500
Min - Max	0.000 – 3.000	0.000 – 1.750	0.000 – 3.000	0.000 – 3.000
Number of joints with active arthritis using the ACR definition				
n	86	37	38	75
Mean	7.7	8.3	7.8	8.1
SD	7.54	7.14	8.71	7.93
Median	5.0	5.0	5.0	5.0
Min - Max	2 – 54	3 – 30	3 – 54	3 – 54
Number of joints with limitation of motion				
n	86	37	38	75
Mean	5.5	5.8	6.0	5.9
SD	4.74	3.34	5.88	4.77
Median	4.0	5.0	4.0	5.0
Min - Max	0 – 29	1 – 14	0 – 29	0 – 29
CRP (mg/L)				
n	86	37	38	75
Mean	18.644	20.471	20.470	20.471
SD	31.9505	33.6371	34.3400	33.7647
Median	5.715	5.990	6.0000	5.990
Min - Max	0.00 – 185.16	0.06 – 145.20	0.00 – 185.16	0.00 – 185.16
MTX use - n (%)				
Yes	56 (65.1)	26 (70.3)	25 (65.8)	51 (68.0)
No	30 (34.9)	11 (29.7)	13 (34.2)	24 (32.0)

AIN457: all patients who did not take any placebo before or during the period.

Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s.

N = Number of patients in the Safety Set.

Disease history, background characteristics and methotrexate use were assessed at baseline.

JADAS-27 (Juvenile Arthritis Disease Activity Score in 27 joints) ranges from 0 to 57 and JADAS-71 ranges from 0 to 101 (higher scores indicate more disease activity). Total enthesitis count ranges from 0 to 16. Total dactylitis count ranges from 0 to 20. Physician's Global Assessment of disease activity ranges from 0-100 mm. Overall well-being score ranges from 0-100 mm.

Numbers analysed

The overall Full Analysis Set (FAS; all subjects who received at least one dose of study drug) and overall Safety Set (all subjects who received at least one dose of study drug in the study) were identical and comprised all 86 subjects enrolled into the study (Table 11). No subjects were excluded from the analysis sets.

In TP2, subjects were randomised via a 1:1 stratified randomisation design to either secukinumab or placebo treatment. As a result in TP2, there were 22 subjects with ERA receiving treatment with

secukinumab, 22 subjects with ERA receiving treatment with placebo, 15 subjects with JPsA receiving treatment with secukinumab (40.5%), and 16 subjects with JPsA receiving treatment with placebo.

Table 11 ***Analysis Sets – TP1, TP2, and TP3 (Safety Set 1)***

	Period 1	Period 2			Period 3		
Analysis set	**AIN457 n (%)**	**AIN457 n (%)**	**Placebo in TP2 n (%)**	**Total n (%)**	**AIN457 n (%)**	**Placebo in TP2 n (%)**	**Total n (%)**
Randomized Set	NA	37 (43.0)	38 (44.2)	75 (87.2)	NA	NA	NA
	FAS1	FAS2			FAS3		
Full Analysis Sets	86 (100)	37 (43.0)	38 (44.2)	75 (87.2)	11 (12.8)	21 (24.4)	32 (37.2)
	Safety Set 1	Safety Set 2			Safety Set 3		
Safety Sets	86 (100)	37 (43.0)	38 (44.2)	75 (87.2)	11 (12.8)	21 (24.4)	32 (37.2)

AIN457: all patients who did not take any placebo before or during the period.
Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s.
Full Analysis Set 1/3 (FAS1/3) consists of all patients who received at least one dose of study drug in TP1/3. FAS1 is equivalent to the entire treatment period FAS.
Full Analysis Set 2 (FAS2) consists of all randomized patients who received at least one dose of study drug in TP2.
Safety Set 1/2/3 consists of all patients who received at least one dose of study drug in TP1/2/3. Safety Set 1 is equivalent to the entire treatment period Safety Set.
N = Number of patients in the Safety Set 1. NA = Not Applicable.

Outcomes and estimation

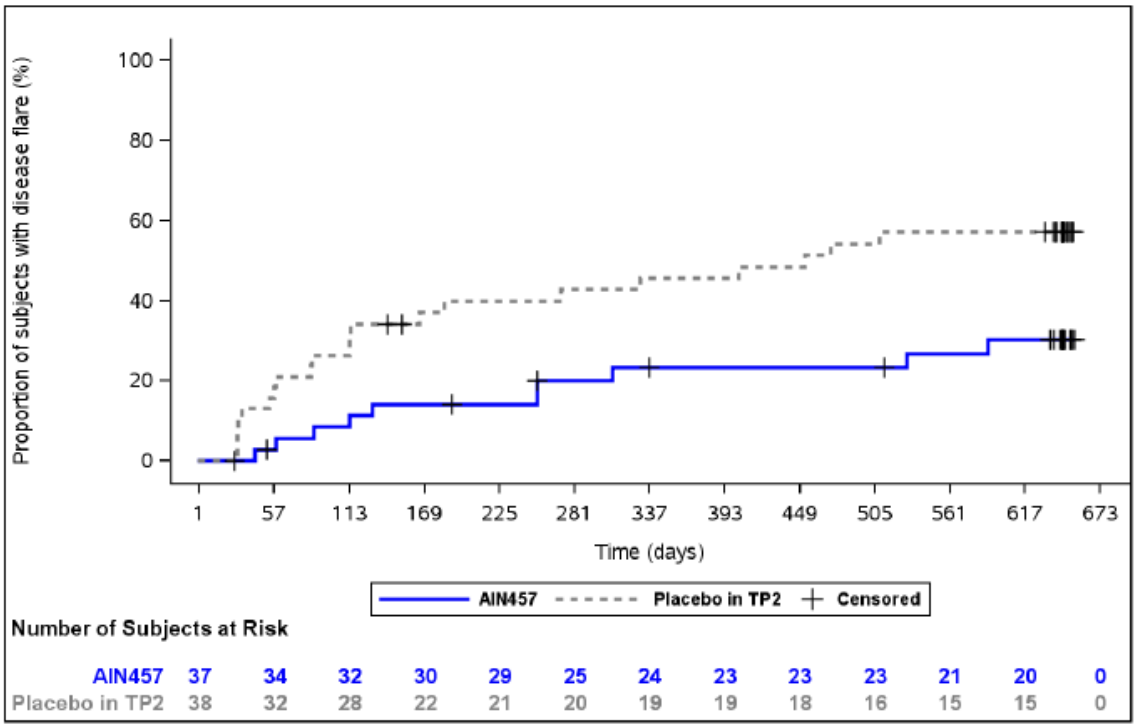
Primary endpoint – time to flare in TP2

Study F2304 met its primary endpoint: for the combined ERA and JPsA categories, the time to flare in TP2 was statistically significantly longer in the secukinumab group compared to the placebo group (hazard ratio of flare event, HR = 0.28, 95% CI: 0.13 to 0.63, p<0.001). The risk of flare was reduced by 72% for subjects on secukinumab compared with subjects on placebo in TP2.

During TP2, there were a total of 21 flare events in the placebo group compared to 10 flare events in the secukinumab group. At 1 year, the flare-free rate was 76.7% (95% CI: 58.7, 87.6) in the secukinumab group and 54.3% (95% CI: 37.1, 68.7) in the placebo group. By the end of TP2, median time to disease flare was not reached in the secukinumab group and was 453 days in the placebo group.

Kaplan-Meier estimates of time to disease flare are graphically depicted in Figure 12, and the survival analysis is summarised in Table 12.

Figure 12 Kaplan-Meier estimates of the time to disease flare – TP2 (FAS2)



AIN457: all patients who did not take any placebo. Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s.
Day 1 = date of randomization. Disease flare was derived relative to the end of Treatment Period 1 (Week 12 visit).
Patients who did not experience a flare in TP2, were censored at the date of their last non-missing flare evaluation in TP2.
Patients at risk = patients in TP2 who did not have flare and were not censored before or at the start of the specified day.

Table 12 ***Survival analysis of time to disease flare – TP2 (FAS2)***

	AIN457 N=37	Placebo in TP2 N=38
Number of flare events at the end of TP2 – n (%)	10 (27.0)	21 (55.3)
Kaplan-Meier estimates		
Median, in days (95% CI)	NC (NC, NC)	453.0 (114.0, NC)
Flare-free rate (95% CI)		
6 months	85.8 (69.2, 93.8)	60.1 (42.7, 73.7)
12 months	76.7 (58.7, 87.6)	54.3 (37.1, 68.7)
18 months	73.2 (54.6, 85.1)	42.9 (26.7, 58.1)
Hazard ratio to placebo		
Estimate (95% CI)	0.28 (0.13, 0.63)	
p-value	<0.001**	

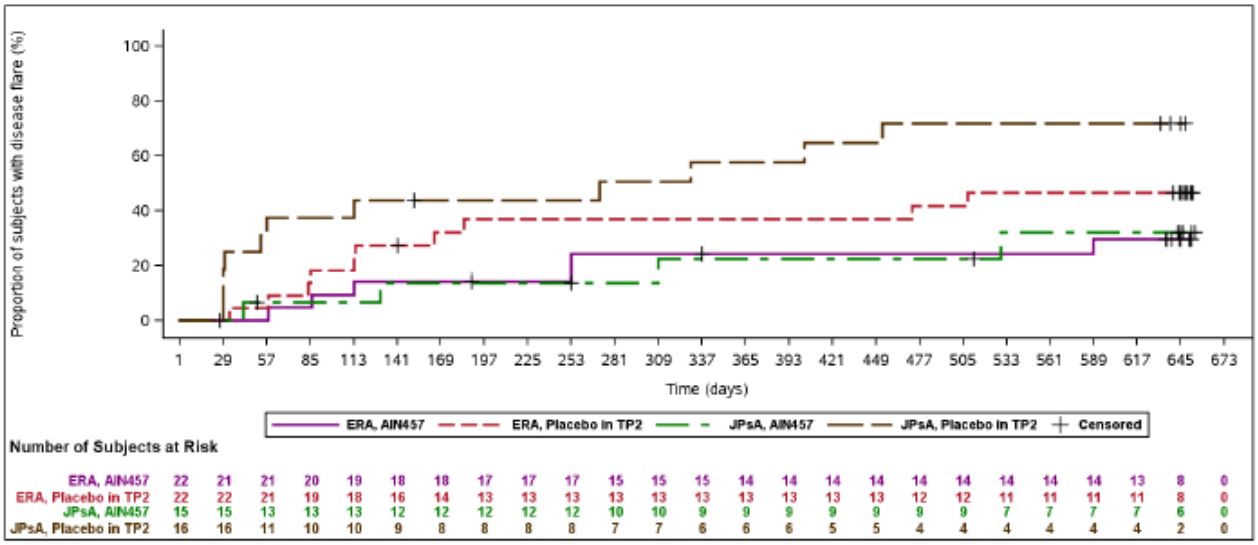
AIN457: all patients who did not take any placebo. Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s.
NC = Not calculable.
Disease flare was derived relative to the end of TP1 (Week 12 visit). Patients who did not experience a disease flare in TP2, were censored at the date of their last non-missing flare evaluation in TP2 (including patients who discontinued prematurely for reasons other than experiencing a disease flare, patients mistakenly switched to TP3 and patients who completed TP2 without a flare).
Flare-free rate(%) = (Probability that a patient will be flare-free until the end of the specified interval) x 100.
Hazard ratios and associated 95% confidence intervals are based on a Cox proportional hazards model with treatment and analysis factors JIA category (ERA or JPsA) and MTX use at baseline as explanatory variables.
Log-rank test is adjusted for analysis factors JIA category (ERA or JPsA) and MTX use at baseline.
** = Statistically significant on one-sided significance level 0.025.

A tipping point analysis with a worst-case scenario was conducted to examine the potential effects of missing data on the results of the primary endpoint. For the worst-case scenario, subjects in the secukinumab arm who discontinued prematurely in TP2 for any reason were considered as having a flare at the date of TP discontinuation, while subjects in the placebo arm in TP2 were considered as censored at 645 days. Results of this sensitivity analysis estimated a 51% relative reduction in risk of disease flare for subjects treated with secukinumab compared to placebo in TP2 (HR=0.49, 95% CI: 0.25 to 0.97, p=0.021).

Prolongation in time to disease flare in TP2 was observed in both JIA categories for subjects treated with secukinumab compared to placebo. In the ERA subgroup, there was an estimated 55% relative reduction in risk of disease flare for subjects treated with secukinumab compared to placebo in TP2 (HR=0.45, 95% CI: 0.16 to 1.28), and the estimated flare-free rate at 1-year post randomisation was 75.6% (95% CI: 50.9, 89.1) for secukinumab vs. 63.0% (95% CI: 39.4, 79.5) for placebo. In the JPsA subgroup, there was an estimated 85% relative reduction in risk of disease flare for subjects treated with secukinumab compared to placebo in TP2 (HR=0.15, 95% CI: 0.04 to 0.57), and the estimated flare-free rate at 1-year post randomisation was 77.5% (95% CI: 44.8, 92.3) for secukinumab vs 42.2% (95% CI: 18.1, 64.6) for placebo.

Kaplan-Meier estimates of time to disease flare for the subtypes are shown in Figure 13, and the survival analyses for the subtypes are summarised in Table 13.

Figure 13 Kaplan-Meier estimates of time to disease flare, by ERA and JPsA JIA category – TP2 (FAS2)



AIN457: all patients who did not take any placebo. Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s.

Day 1 = Date of randomization. Disease flare was derived relative to the end of Treatment Period 1 (Week 12 visit).

Patients who did not experience a disease flare in Treatment Period 2, were censored at the date of their last non-missing flare evaluation in Treatment Period 2.

Patients at risk = patients in TP2 who did not have flare and were not censored before or at the start of the specified day.

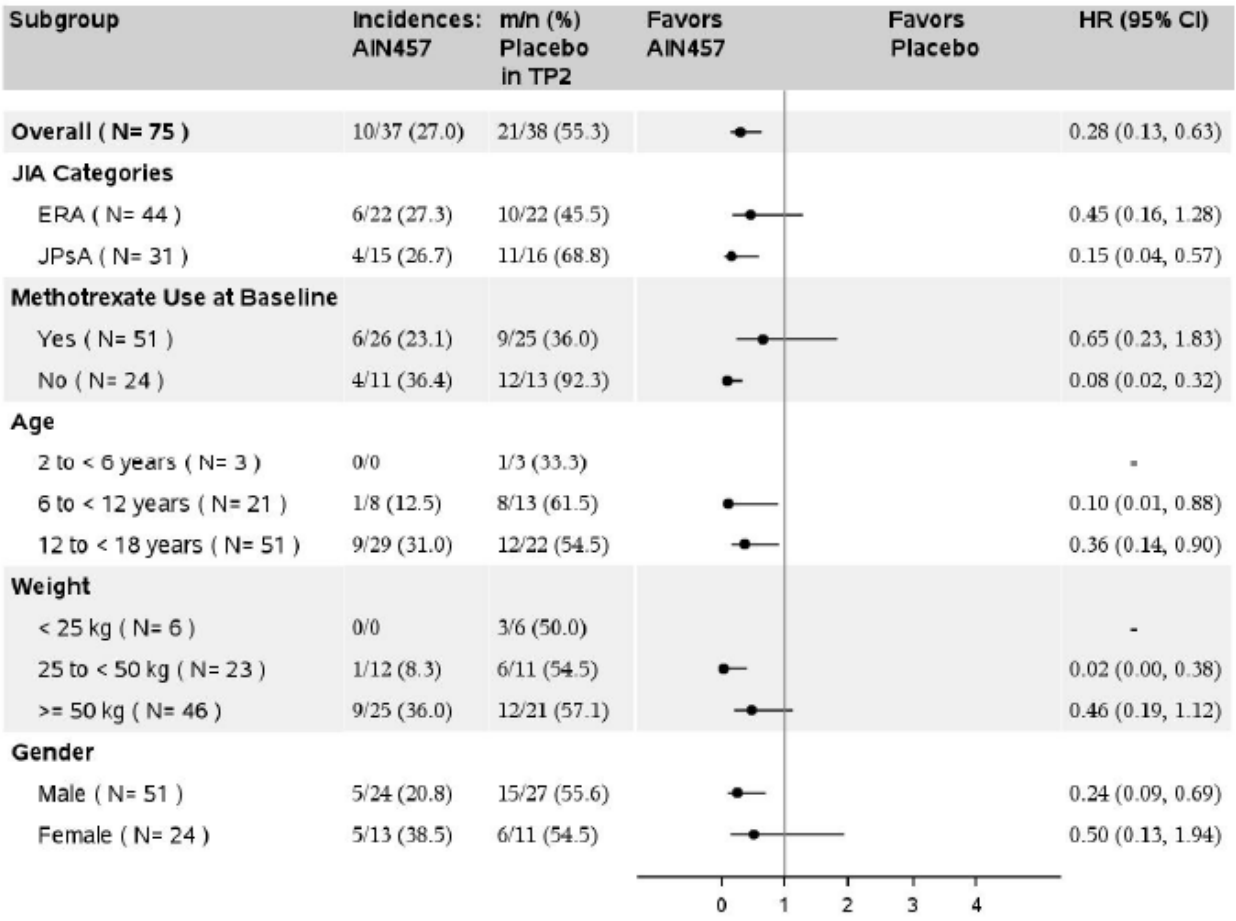
Table 13 ***Survival analysis of time to disease flare by ERA and JPsA JIA category – TP2 (FAS2)***

	ERA		JPsA	
	AIN457 N=22	Placebo in TP2 N=22	AIN457 N=15	Placebo in TP2 N=16
Number of flare events at the end of TP2 – n (%)	6 (27.3)	10 (45.5)	4 (26.7)	11 (69.0)
Kaplan-Meier estimates				
Median, in days (95% CI)	NC (589.0, NC)	NC (114.0, NC)	NC (309.0, NC)	271.0 (30.0, NC)
Flare-free rate (95% CI)				
6 months	85.7 (62.0, 95.2)	63.0 (39.4, 79.5)	86.2 (55.0, 96.4)	56.3 (29.5, 76.2)
12 months	75.6 (50.9, 89.1)	63.0 (39.4, 79.5)	77.5 (44.8, 92.3)	42.2 (18.1, 64.6)
18 months	75.6 (50.9, 89.1)	53.3 (30.6, 71.6)	67.8 (34.4, 86.9)	28.1 (8.9, 51.4)
Hazard ratio to placebo				
Estimate (95% CI)	0.45 (0.16, 1.28)		0.15 (0.04, 0.57)	

AIN457: all patients who did not take any placebo. Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s.
NC = Not calculable.
Disease flare was derived relative to the end of TP1 (Week 12 visit). Patients who did not experience a disease flare in TP2, were censored at the date of their last non-missing flare evaluation in TP2 (including patients who discontinued prematurely for reasons other than experiencing a disease flare, patients mistakenly switched to TP3 and patients who completed TP2 without a flare).
Flare-free rate(%) = (Probability that a patient will be flare-free until the end of the specified interval) x 100.
Hazard ratios and associated 95% confidence intervals are based on a Cox proportional hazards model with treatment and analysis factor MTX use at baseline as explanatory variables.
Log-rank test is adjusted for analysis factor MTX use at baseline.

In descriptive subgroup analyses based on age, weight, gender and methotrexate use at baseline, point estimates for hazard ratios were in favour of secukinumab across all subgroups (Figure 14).

Figure 14 Hazard ratio for time to disease flare by subgroup—TP2 (FAS2)



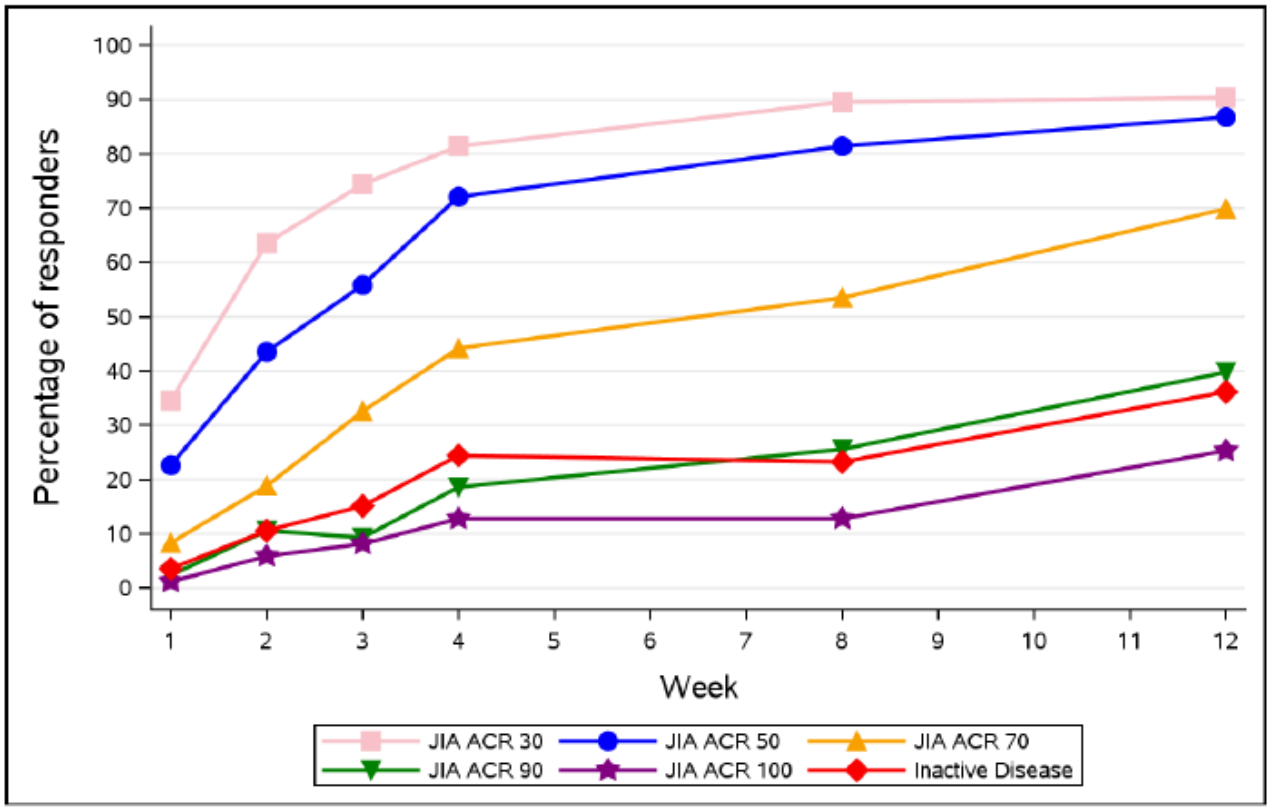
n : Number of patients in FAS2
m : Number of events at the end of TP2
m/n : Proportion of patients with disease flare in TP2

Secondary endpoints – TP1 (open-label secukinumab)

During open-label secukinumab treatment in TP1, disease activity improvements were observed already during the first weeks. At Week 12, a JIA ACR 30 response was achieved by 75/83 subjects (90.4%) completing TP1, and they were thereby eligible for randomisation into TP2. A JIA ACR 70 response was achieved by 58/83 subjects (69.9%), and inactive disease status was achieved by 30/83 subjects (36.1%). JIA ACR responses during TP1 for all subjects are shown in Figure 15, and Week 12 responses by disease subtype are shown in Table 14.

Improvements were seen across all JIA ACR core components, with the largest improvements seen on active joint count (79.3%) and physician's global assessment (77.4%), and the smallest improvement (13.6%) seen on median CRP.

Figure 15 JIA ACR 30/50/70/90/100 response and inactive disease for all subjects by visit – TP 1 (FAS1)



JIA ACR 30/50/70/90/100, ≥30%/50%/70%/90%/100% improvement in the American College of Rheumatology Juvenile Idiopathic Arthritis response criteria. JIA ACR response was derived relative to baseline. Patients with non-missing values were included in the analysis.

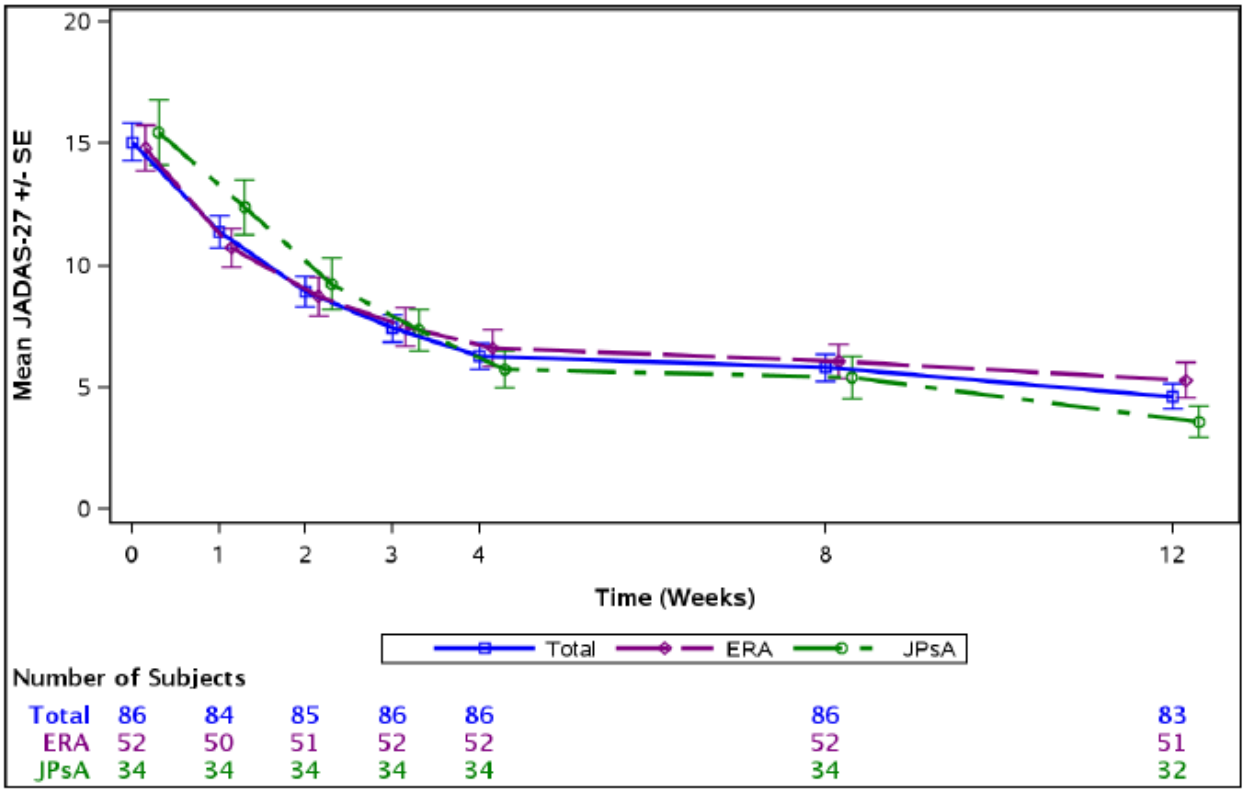
Table 14 ***JIA ACR response rates by JIA category at Week 12 (FAS1)***

	Total		ERA		JPsA	
	n/m (%)	95% CI	n/m (%)	95% CI	n/m (%)	95% CI
JIA ACR 30	75/83 (90.4)	(81.4, 95.4)	44/51 (86.3)	(73.1, 93.8)	31/32 (96.9)	(82.0, 99.8)
JIA ACR 50	72/83 (86.7)	(77.1, 92.9)	41/51 (80.4)	(66.5, 89.7)	31/32 (96.9)	(82.0, 99.8)
JIA ACR 70	58/83 (69.9)	(58.7, 79.2)	34/51 (66.7)	(52.0, 78.9)	24/32 (75.0)	(56.2, 87.9)
JIA ACR 90	33/83 (39.8)	(29.4, 51.1)	17/51 (33.3)	(21.1, 48.0)	16/32 (50.0)	(32.2, 67.8)
JIA ACR 100	21/83 (25.3)	(16.7, 36.2)	14/51 (27.5)	(16.3, 42.0)	7/32 (21.9)	(9.9, 40.4)
Inactive disease status	30/83 (36.1)	(26.1, 47.5)	20/51 (39.2)	(26.2, 53.9)	10/32 (31.3)	(16.7, 50.1)

n = Number of patients with response.
m = Number of patients with non-missing value.

Decreases in JADAS scores, indicating decreasing disease activity, were seen in TP1 starting from the first weeks of treatment, with a well established effect being observed from Week 4. For all subjects in TP1, the mean JADAS-27 score decreased from a baseline score of 15.07 (SD 7.13) to 4.64 (SD 4.72) at Week 12 (Figure 16); mean decrease from baseline to Week 12 was -10.49 (SD 7.23). Total enthesitis and dactylitis counts decreased from baseline to Week 12 among subjects with either disease subtype (Table 15).

Figure 16 *JADAS-27 absolute values (mean +/- SE) for all subjects and each JIA category by visit – TP1 (FAS1)*



JADAS-27 (Juvenile Arthritis Disease Activity Score in 27 joints) ranges from 0 to 57 (higher scores indicate more disease activity).
For each visit, only patients with a value at both baseline and the respective post-baseline visit are included.
SE=SD/sqrt(n)

Table 15 ***Change from baseline in enthesitis count and dactylitis count by JIA category at Week 12 (FAS1)***

		Total			ERA			JPsA		
		n	mean	SD	n	mean	SD	n	mean	SD
Total enthesitis count	Baseline	85	2.6	2.51	52	2.7	2.16	33	2.3	2.99
	Week 12	82	0.7	1.73	51	0.5	1.16	31	1.2	2.35
	Change	82	-1.8	2.31	51	-2.2	1.87	31	-1.2	2.83
Total dactylitis count	Baseline	82	1.0	2.15	48	0.4	1.44	34	1.8	2.69
	Week 12	78	0.3	1.01	46	0.2	0.98	32	0.4	1.04
	Change	78	-0.8	1.83	46	-0.2	0.79	32	-1.5	2.53

Total enthesitis count ranges from 0 to 16. Total dactylitis count ranges from 0 to 20.

In descriptive subgroup analyses based on age and weight group, gender and methotrexate use at baseline, JIA ACR 30 response rates ranging from 82.8% to 100%, and JIA ACR 50 response rates ranging from 79.3% to 100% were seen across the different subgroups (Table 16). Notably, all 6 subjects in the <25 kg weight band were also JIA ACR 70 responders at Week 12; this group includes all 3 subjects aged <6 years.

Table 16 ***JIA ACR 30 and JIA ACR 50 response rates at Week 12 by subgroups (FAS1)***

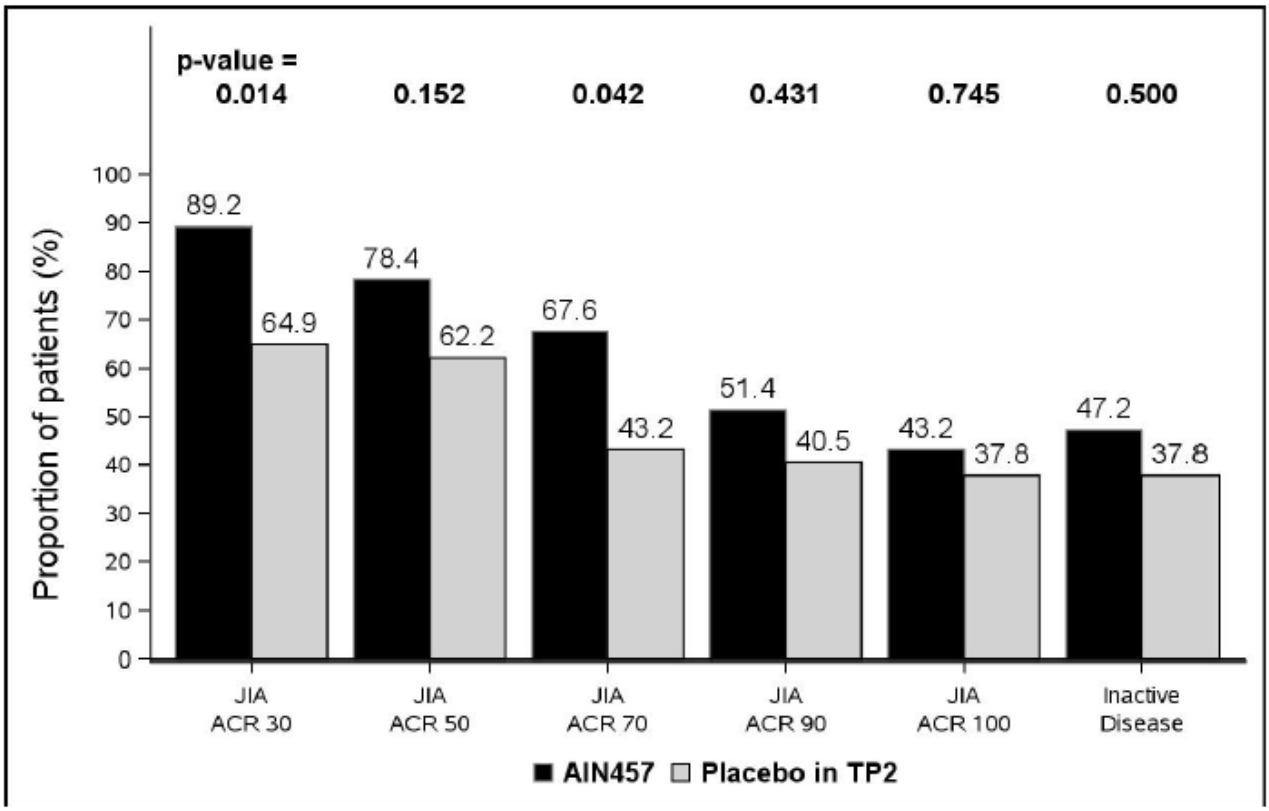
Subgroup	JIA ACR 30 response n/m (%)	JIA ACR 50 response n/m (%)
Overall (N=86)	75/83 (90.4)	72/83 (86.7)
JIA categories		
ERA (N=52)	44/51 (86.3)	41/51 (80.4)
JPsA (N=34)	31/32 (96.9)	31/32 (96.9)
Methotrexate use at baseline		
Yes (N=56)	51/54 (94.4)	49/54 (90.7)
No (N=30)	24/29 (82.8)	23/29 (79.3)
Age		
2 to <6 years (N=3)	3/3 (100)	3/3 (100)
6 to <12 years (N=22)	21/22 (95.5)	20/22 (90.9)
12 to <18 years (N=61)	51/58 (87.9)	49/58 (84.5)
Weight		
<25 kg (N=6)	6/6 (100)	6/6 (100)
25 to <50 kg (N=24)	23/23 (100)	23/23 (100)
≥50 kg (N=56)	46/54 (85.2)	43/54 (79.6)
Gender		
Male (N=57)	51/57 (89.5)	48/57 (84.2)
Female (N=29)	24/26 (92.3)	24/26 (92.3)

N = Number of patients in FAS1; n = Number of patients with response; m = number of patients with non-missing value.

Secondary endpoints – TP2 and TP3

The proportion of subjects who, at the end of TP2, had a JIA ACR response or met the criteria for inactive disease was higher among subjects randomised to continue secukinumab compared to those randomised to placebo in TP2 (Figure 17). Of note, due to the event-driven design of the study, the end of TP2 is based on each individual subject's last visit for TP2.

Figure 17 JIA ACR 30/50/70/90/100 response and inactive disease at the end of TP2 (FAS2)

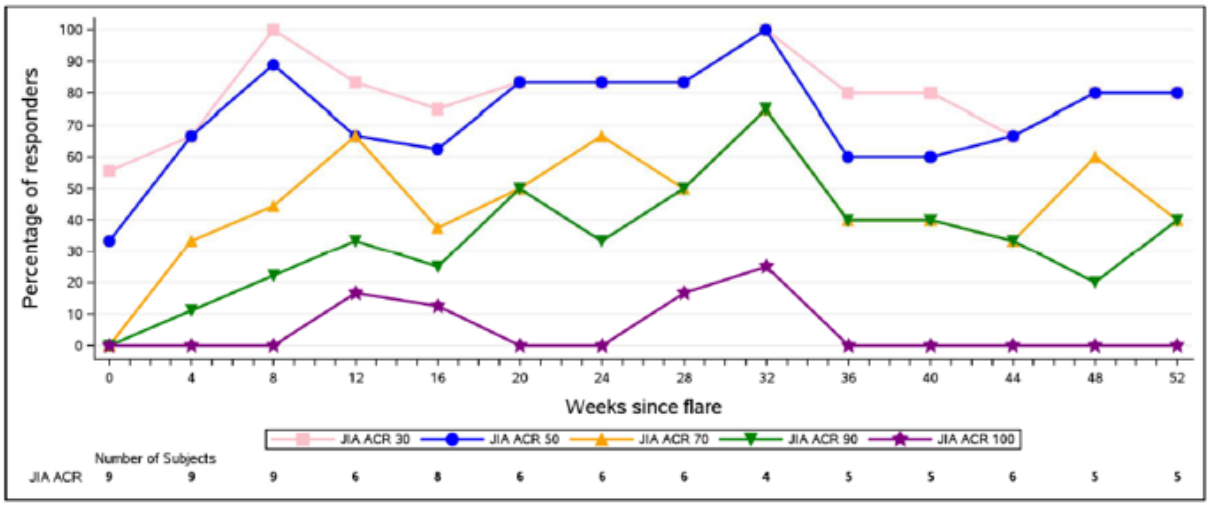


AIN457: all patients who did not take any placebo. Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s.
Due to the event driven design of the study, the end of TP2 is based on individual patient's last visit at TP2.
JIA ACR 30/50/70/90/100, ≥30%/50%/70%/90%/100% improvement in the ACR JIA response criteria. JIA ACR response was derived relative to baseline.
P-values are from the Cochran-Mantel-Haenszel (CMH) test, adjusted for analysis factors JIA category (ERA or JPsA) and methotrexate use at baseline without adjustment for multiplicity of testing.

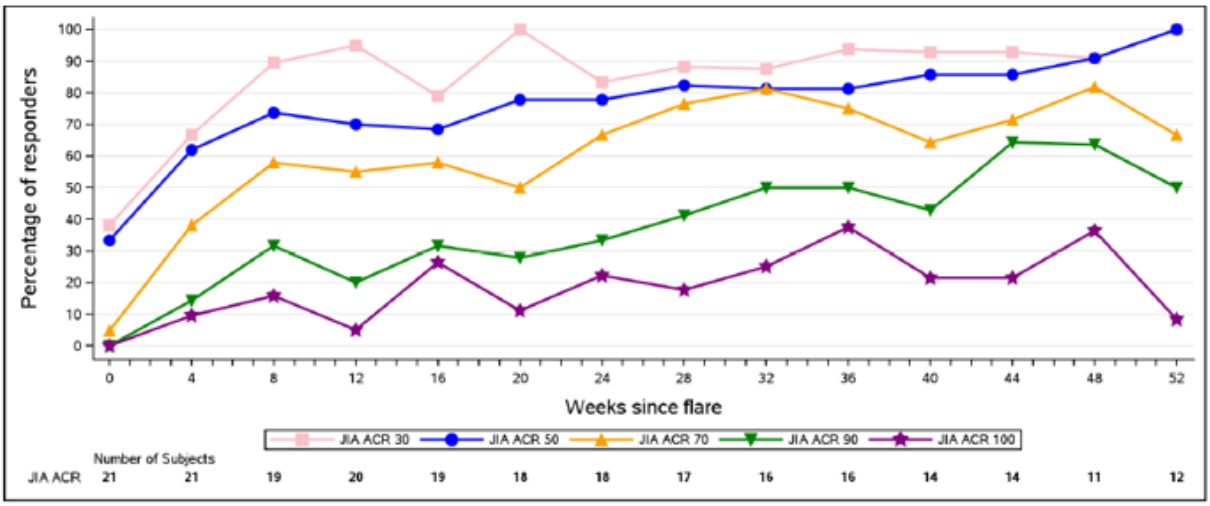
Per the study protocol, subjects who flared during TP2 transitioned into TP3 in which they received open-label secukinumab. The proportions of subjects developing different grades of JIA ACR responses after entering TP3 are displayed in Figure 18.

Figure 18 Proportion of subjects achieving JIA ACR response in TP3 - Subjects who flared in TP2

Treatment: AIN457



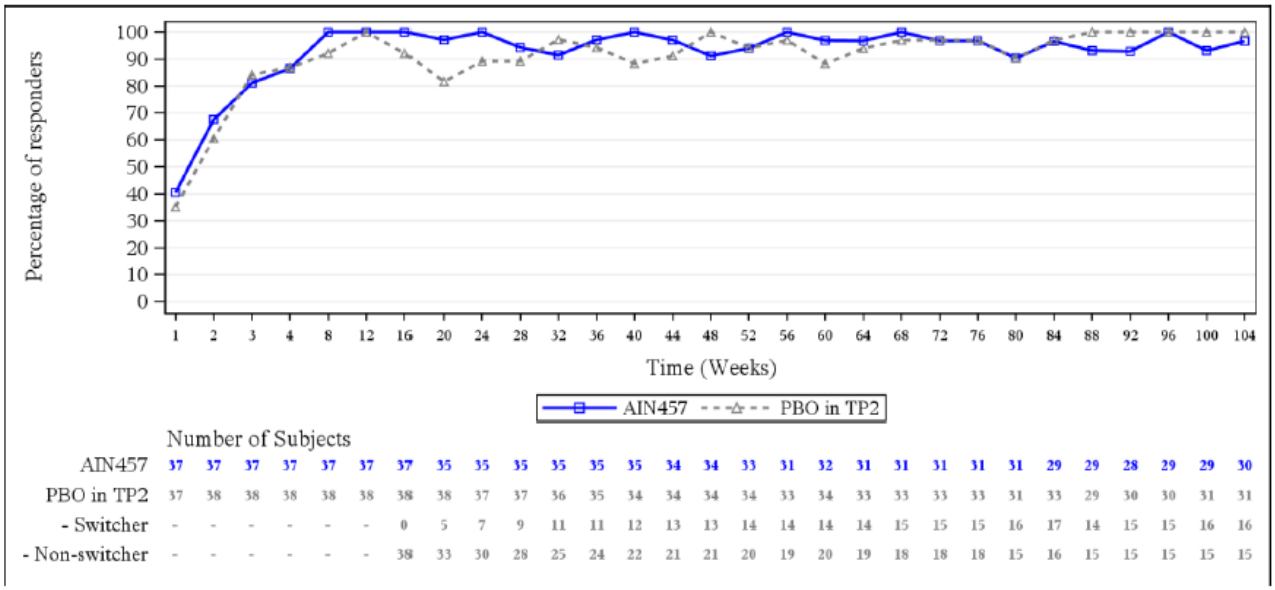
Treatment: Placebo in TP2



- AIN457: all subjects who did not take any placebo. Placebo in TP2: all subjects who took placebo in TP2 and AIN457 in other period/s.
- JIA ACR 30/50/70/90/100, >=30%/50%/70%/90%/100% improvement in the American College of Rheumatology Juvenile Idiopathic Arthritis response criteria. JIA ACR response was derived relative to baseline.
- Data for up to 1 year after flare is displayed. Only subjects in full analysis set 3 who flared in treatment period 2 are included.

To further elucidate the time course of disease activity in a population for whom the treatment strategy would correspond to "treatment withdrawal followed by retreatment as needed" as compared to chronic continuous treatment, and consequently to enable an informal comparison of these longer-term treatment strategies, the MAH was requested to provide a summary of JIA ACR responses and mean JADAS-27 in the entire study population through Week 104, i.e. combining subjects with and without a flare. The results are summarised in Figure 19 through Figure 23.

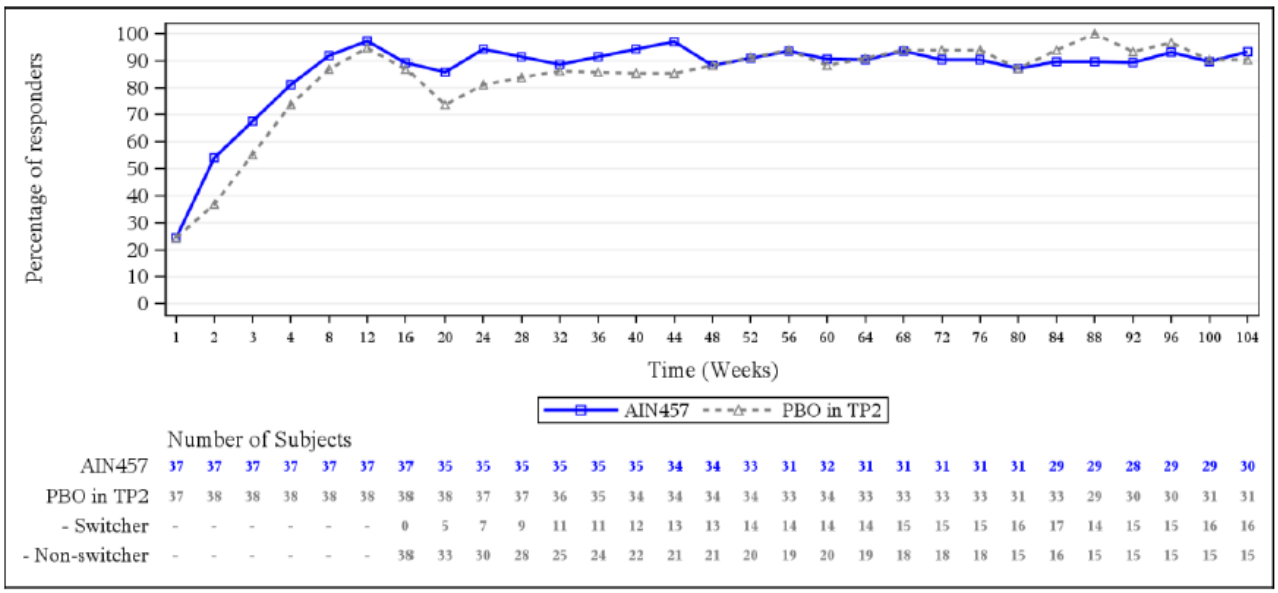
Figure 19 JIA ACR30 up to Week 104 using observed data (Full Analysis Set 2)



Patients in PBO in TP2 group took AIN457 up to Week 12 (Treatment Period 1).

From Week 16 to Week 104, PBO in TP2 included patients who switched to AIN457 after experiencing flare (Switcher) and patients who stayed on placebo in TP2 (Non-switcher).

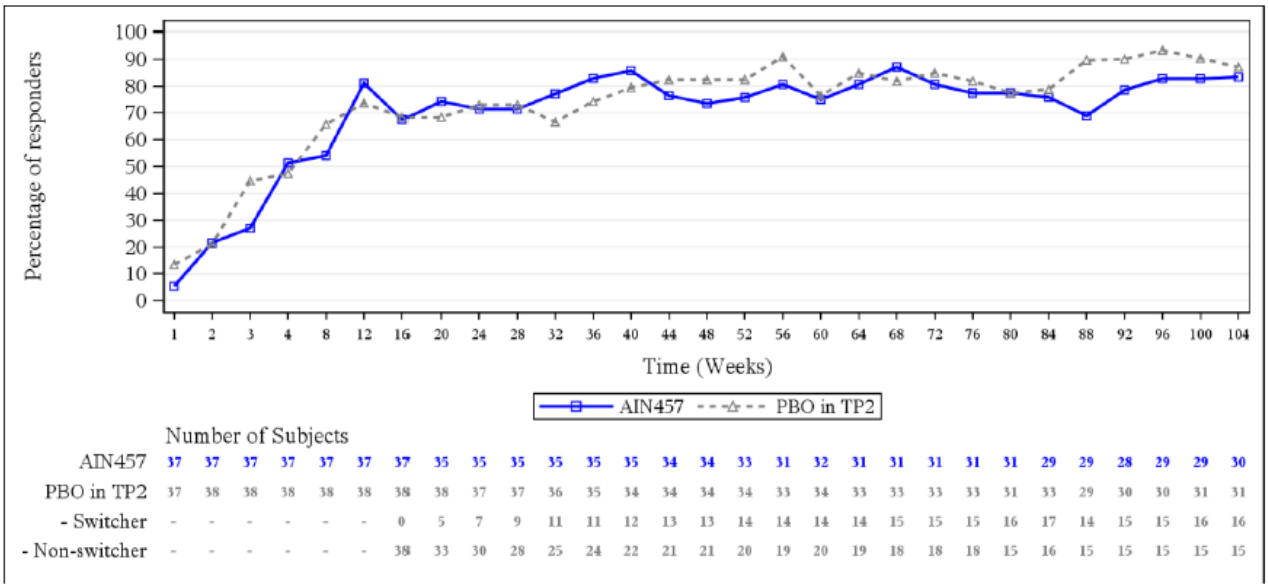
Figure 20 JIA ACR50 up to Week 104 using observed data (Full Analysis Set 2)



Patients in PBO in TP2 group took AIN457 up to Week 12 (Treatment Period 1).

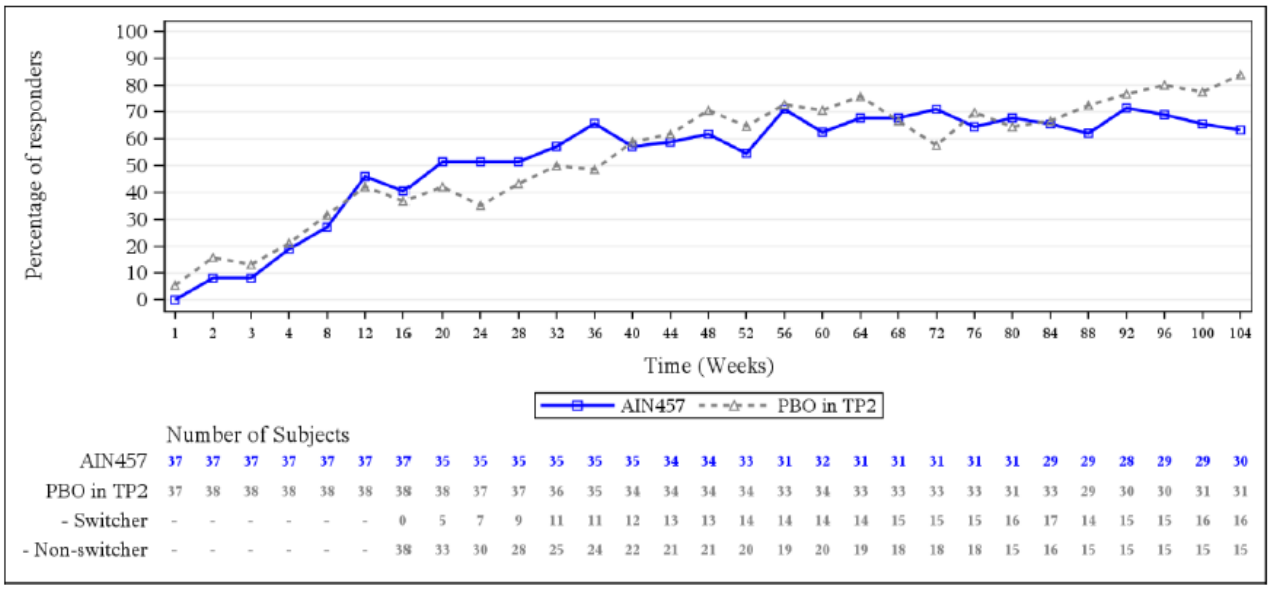
From Week 16 to Week 104, PBO in TP2 included patients who switched to AIN457 after experiencing flare (Switcher) and patients who stayed in Placebo in TP2 (Non-switcher).

Figure 21 JIA ACR70 up to Week 104 using observed data (Full Analysis Set 2)



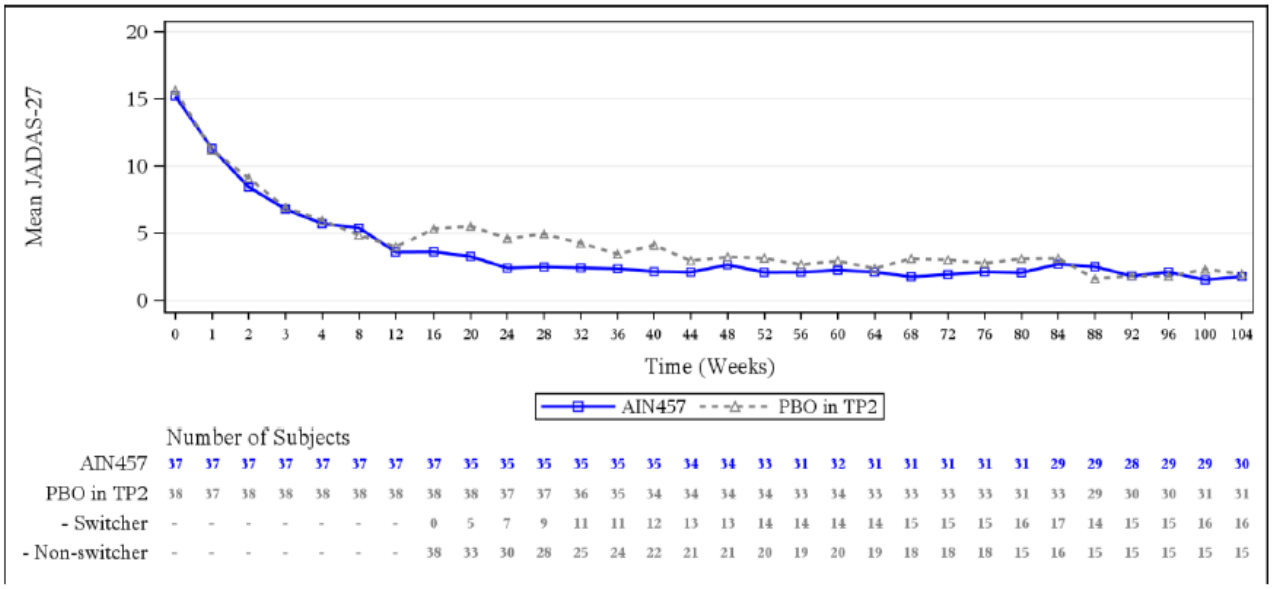
Patients in PBO in TP2 group took AIN457 up to Week 12 (Treatment Period 1).
From Week 16 to Week 104, PBO in TP2 included patients who switched to AIN457 after experiencing flare (Switcher) and patients who stayed in Placebo in TP2 (Non-switcher).

Figure 22 JIA ACR90 up to Week 104 using observed data (Full Analysis Set 2)



Patients in PBO in TP2 group took AIN457 up to Week 12 (Treatment Period 1).
From Week 16 to Week 104, PBO in TP2 included patients who switched to AIN457 after experiencing flare (Switcher) and patients who stayed in Placebo in TP2 (Non-switcher).

Figure 23 Mean JADAS-27 score up to Week 104 using observed data (Full Analysis Set 2)



Patients in PBO in TP2 group took AIN457 up to Week 12 (Treatment Period 1).
From Week 16 to Week 104, PBO in TP2 included patients who switched to AIN457 after experiencing flare (Switcher) and patients who stayed in Placebo in TP2(Non-switcher).

Summary of main study

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

Table 17 ***Summary of efficacy for trial CAIN457F2304***

Title: A three-part randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of secukinumab treatment in Juvenile Idiopathic Arthritis subtypes of psoriatic and enthesitis-related arthritis		
Study identifier	Protocol Number: CAIN457F2304 EudraCT Number: 2016-003761-26	
Design	Multicentre, double-blind, placebo-controlled, event-driven, randomised withdrawal (RW) study	
	Duration of main (RW) phase: Treatment Period 2 (TP2): Treatment Period 3 (TP3) (for subjects with a flare only) Duration of open-label phase (TP1): Duration of Extension phase:	 92 weeks or until disease flare From disease flare until Week 104 12 weeks None
Hypothesis	Superiority over placebo in TP2.	
Treatment groups (TP1)	Open-label Secukinumab PFS, available as 150 mg in 1.0 mL and as 75 mg in 0.5 mL	Secukinumab 75 mg (<50 kg) or 150 mg (≥50 kg) s.c. injections at Weeks 0, 1, 2, 3, 4, and 8, N = 86 (all enrolled subjects)

Treatment groups (TP2)	Secukinumab PFS, available as 150 mg in 1.0 mL and as 75 mg in 0.5 mL		Secukinumab 75 mg (<50 kg) or 150 mg (≥50 kg) s.c. injections Q4W from Week 12 to Week 100 or until disease flare, N = 37
	Placebo, available as 1 mL and 0.5 mL PFS, in a form to match secukinumab PFS		Placebo, s.c. injections Q4W from Week 12 to Week 100 or until disease flare, N = 38
Treatment groups (Treatment Period 3)	For subjects with a flare only; open-label Secukinumab PFS, available as 150 mg in 1.0 mL and as 75 mg in 0.5 mL		Secukinumab 75 mg (<50 kg) or 150 mg (≥50 kg) s.c. injections Q4W, from flare until Week 100, N = 32
Endpoints and definitions	Primary endpoint	Time to Disease Flare	The primary efficacy endpoint was the time to disease flare event in TP2, which was defined as the interval between the date of randomization to the date of first occurrence of disease flare event. The analysis of the primary efficacy endpoint was based on the full analysis set TP2.
	Secondary endpoint	JIA ACR 30/50/70/90/100 over time up to Week 12 (TP1)	Standard ACR pediatric Criteria (JIA ACR criteria) consists of 6 core components. JIA ACR 30/50/70/90/100 were defined as 30%, 50%, 70%, 90% and 100% improvement from baseline respectively in a minimum of three variables in the core set with no more than one variable worsening more than 30% as defined in the JIA ACR criteria.
	Secondary endpoint	Inactive Disease Status over time up to Week 12 (TP1)	Clinical inactive disease definition was adapted from the JIA ACR criteria. All were required to be met: • No joints with active arthritis • No uveitis • CRP value within normal limits for the laboratory where tested or, if elevated, not attributable to JIA • Physician's global assessment of disease activity score ≤ 10mm • Duration of morning stiffness attributable to JIA ≤15 min
	Secondary endpoint	JIA ACR Components over time up to Week 12 (TP1)	Six ACR components: • Physician global assessment of disease activity on a 0 - 100 mm VAS from 0 mm = no disease activity to 100 mm = very severe disease activity • Parent or subject's (if appropriate in age) Global Assessment of Subject's overall well-being on a 0-100 mm VAS from 0 mm = very well to 100 mm = very poor. • Functional ability: (CHAQ) • Number of active joints using the ACR definition (any joint with swelling or in the absence of swelling, limitation of motion accompanied by either pain on motion or tenderness not due to deformity) • Number of joints with limited range of motion Laboratory measure of inflammation: CRP (mg/L)

	Secondary endpoint	JASDAS Score over time up to Week 12 (TP1)	Juvenile Arthritis Disease Activity Score (JADAS) composite disease activity score for juvenile idiopathic arthritis (JIA) consists of 4 components: • physician global assessment of disease activity; • parent/subject global assessment of overall well-being; • active joint count; • CRP (local) JADAS-27 (Juvenile Arthritis Disease Activity Score in 27 joints) ranges from 0 to 57 and JADAS-71 ranges from 0 to 101 (higher scores indicate more disease activity).
	Secondary endpoint	Total Enthesitis Count over time up to Week 12 (TP1)	The following 16 entheseal sites were assessed for the presence or absence of tenderness (enthesitis) on each side of the body: • Anterior Entheses: Greater trochanter of the Femur; Medial condyle of the femur; Lateral condyle of the femur • Posterior Entheses: Greater tuberosity of humerus; medial epicondyle of humerus; lateral epicondyle of humerus, Achilles tendon; and calcaneal insertion of the plantar fascia.
	Secondary endpoint	Total Dactylitis Count over time up to Week 12 (TP1)	The dactylitis count was the number of fingers and toes presenting with dactylitis, with a range of 0-20
	Secondary endpoint	JIA ACR 30/50/70/90/100 over time Week 12 up to Week 104 (TP2)	Standard ACR pediatric Criteria (JIA ACR criteria) consists of 6 core components. JIA ACR 30/50/70/90/100 were defined as 30%, 50%, 70%, 90% and 100% improvement from baseline respectively in a minimum of three variables in the core set with no more than one variable worsening more than 30% as defined in the JIA ACR criteria.
	Secondary endpoint	Inactive Disease Status over time Week 12 up to Week 104 (TP2)	Clinical inactive disease definition was adapted from the JIA ACR criteria. All were required to be met: • No joints with active arthritis • No uveitis • CRP value within normal limits for the laboratory where tested or, if elevated, not attributable to JIA • Physician's global assessment of disease activity score ≤ 10mm • Duration of morning stiffness attributable to JIA ≤15 min
	Secondary endpoint	Secukinumab serum concentration / PK parameters TP1	To evaluate PK of secukinumab and confirm the predicted dose in TP1, PK samples were obtained for all subjects, and secukinumab concentrations were assessed in serum.

	Secondary endpoint	Safety and tolerability of secukinumab, entire study.	Entire study.
Database lock	Clinical Lock: 10 December 2020		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set 2, Treatment Period 2.		
	The primary objective is to demonstrate that the time to flare in Treatment Period 2 is longer with secukinumab for combined ERA and JPsA groups than with placebo.		
Descriptive statistics and estimate variability	Treatment group[a]	Secukinumab	Placebo in TP2
	Number of subjects	37	38
	Number of Events	10	21
	Proportion of Events	0.27	0.55
	Kaplan-Meier estimate Median (days) and 95% CI	NC (NC, NC)	453.0(114.0, NC)
Effect estimate per comparison	Primary endpoint	Comparison groups	*Secukinumab vs. Placebo in TP2*
		Hazard ratio to Placebo Estimate	0.28
		Hazard ratio to Placebo 95% CI	(0.13, 0.63)
		Stratified log-rank test-One-sided P-value	<0.001**
Notes	- [a] Secukinumab: all subjects who did not take any placebo. Placebo in TP2: all subjects who took placebo in TP2 and Secukinumab in other period/s.		
	- Hazard ratios and associated 95% confidence intervals are based on a Cox proportional hazards model with treatment and analysis factors JIA category (ERA or JPsA) and MTX use at baseline as explanatory variables.		
	- Log-rank test is adjusted for analysis factors JIA category (ERA or JPsA) and MTX use at baseline. ** = Statistically significant on one-sided significance level 0.025.		

	- Disease flare was derived relative to the end of TP1 (Week 12 visit). Subjects who did not experience a disease flare in TP2, were censored at the date of their last non-missing flare evaluation in TP2 (including subjects who discontinued prematurely for reasons other than experiencing a disease flare, subjects mistakenly switched to TP3 and subjects who completed TP2 without a flare).		
Analysis description	**Secondary analysis: JIA ACR 30/50/70/90/100 and inactive disease status at Week 12**		
Analysis population and time point description	Full Analysis Set 1, 12 weeks		
Descriptive statistics and estimate variability	Treatment group	Secukinumab	
	Endpoints	Number of Responders/ Number of subjects	95% CI
	JIA ACR 30	75/83 (90.4)	(81.4, 95.4)
	JIA ACR 50	72/83 (86.7)	(77.1, 92.9)
	JIA ACR 70	58/83 (69.9)	(58.7, 79.2)
	JIA ACR 90	33/83 (39.8)	(29.4, 51.1)
	JIA ACR 100	21/83 (25.3)	(16.7, 36.2)
	Inactive disease	30/83 (36.1)	(26.1, 47.5)
Analysis description	**Secondary analysis: change from baseline in JIA ACR core components at Week 12**		
Analysis population and time point description	Full Analysis Set 1, 12 weeks		
Descriptive statistics and estimate variability	Treatment group	Secukinumab	
	Endpoints	Number of subject	Mean/Median* and SD for change from baseline to Week 12 (*C-reactive protein is shown as median change from baseline, due to outliers of C-reactive protein values.)
	Physician global assessment of disease activity	83	-34.7 (16.90)

	Parent or subject global assessment of overall well-being	83	-28.4 (28.41)
	Functional ability (CHAQ)	83	-0.467 (0.5231)
	Number of joints with active arthritis	83	-6.3 (7.23)
	Number of joints with limited range of motion	83	-4.3 (4.41)
	C-reactive protein standardized value (mg/L)	83	-0.600 (31.5034)
Analysis description	**Secondary analysis: Change from baseline in Juvenile Arthritis Disease Activity Score (JADAS-27 and JADAS-71)**		
Analysis population and time point description	Full Analysis Set 1, 12 weeks		
Descriptive statistics and estimate variability	Treatment group	Secukinumab	
	Endpoints	Number of subjects	Mean and SD for change from baseline
	JADAS-27	83	-10.487 (7.2262)
	JADAS-71	83	-13.403(9.7300)
Analysis description	**Secondary analysis: Change from baseline in total enthesitis count**		
Analysis population and time point description	Full Analysis Set 1, 12 weeks		
Descriptive statistics and estimate variability	Treatment group	Secukinumab	
	Endpoint	Number of subjects	Mean and SD for change from baseline
	Total enthesitis count	82	-1.8 (2.31)
Analysis description	**Secondary analysis: Change from baseline in total dactylitis count**		

Analysis population and time point description	Full Analysis Set 1, 12 weeks		
Descriptive statistics and estimate variability	Treatment group	Secukinumab	
	Endpoint	Number of subjects	Mean and SD for change from baseline
	Total dactylitis count	78	-0.8 (1.83)
Analysis description	**Secondary analysis: JIA ACR 30/50/70/90/100 and inactive disease status at the end of Treatment Period 2**		
Analysis population and time point description	Full Analysis Set 2, At the end of Treatment Period 2		
Descriptive statistics and estimate variability	Treatment group	Secukinumab	Placebo in TP2
	JIA ACR 30	33/37 (89.2)	24/37 (64.9)
	JIA ACR 50	29/37 (78.4)	23/37 (62.2)
	JIA ACR 70	25/37 (67.6)	16/37 (43.2)
	JIA ACR 90	19/37 (51.4)	15/37 (40.5)
	JIA ACR 100	16/37 (43.2)	14/37 (37.8)
	Inactive Disease	17/36 (47.2)	14/37 (37.8)

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH has conducted a double-blind, placebo-controlled, event-driven randomised withdrawal study (study F2304) evaluating the efficacy and safety of secukinumab in 86 paediatric patients aged 2 to < 18 years with JIA subtypes of ERA or JPsA.

According to the CHMP Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (EMA/CHMP/239770/2014 Rev. 2), randomised placebo-controlled withdrawal design trials can be considered acceptable in JIA for products where efficacy and safety have been established in adults. Furthermore, an event driven approach is recommended to be considered to

avoid the risk that the withdrawal part is too short to show a difference in the flare rate between the placebo and the new drug. Considering the extensive clinical experience accumulated with secukinumab to date, the general design of the study is considered consistent with the Guideline. The responder and flare definitions used in the study are well established. The study was also compliant with the Key Binding Elements of the respective Paediatric Investigation Plan for secukinumab.

In principle, the eligibility criteria were consistent with the proposed indication. However, the inclusion criteria required an inadequate response (≥ 1 month) or intolerance to ≥ 1 NSAID, as well as an inadequate response (≥ 2 months) or intolerance to ≥ 1 DMARD, whereas the MAH's initially proposed indication only stated that secukinumab would be indicated for ERA or JPsA patients who have responded inadequately to, or who cannot tolerate, conventional therapy (which could be understood as implying NSAIDs only). At the CHMP's request, the MAH added a cross-reference to Section 5.1 where the population enrolled into study F2304 is described in sufficient detail. The indication was also amended to specify that secukinumab may be used with or without MTX which was considered acceptable to the CHMP.

The secukinumab dosing regimen was based on modelling and simulation from adult studies; separate dose response studies in paediatric patients were not performed. The weight-tiered regimen is the same as the one that has already been authorised for paediatric psoriasis.

The assessment instruments used in the study are in accordance with relevant guidance, and the selected endpoints permit a comprehensive characterisation of the efficacy of secukinumab in patients with the applicable subtypes of JIA. According to the CHMP Guideline, given the well-known bias of the withdrawal trial toward responders, every effort should be made to report a meaningful outcome over time such as ACR Pedi 70, 90, minimal disease activity or inactive disease / remission at 1 and 2 years. These outcomes were included among the secondary endpoints of the study.

The MAH has adapted the definition of 'inactive disease' from the JIA ACR criteria, and the definition is also largely consistent with the definition provided in the CHMP Guideline. However, some operationalisations have been made, i.e., the MAH has operationalised "normal physician's global assessment of disease activity" as "Physician's global assessment of disease activity score ≤ 10mm". Also, "absence of morning stiffness" was operationalised as "Duration of morning stiffness attributable to JIA ≤15 min" and no information was given on how morning stiffness duration was measured. In principle, other parties may apply slightly different operationalisations, in which case the results would not be fully comparable. Therefore, whereas it can be agreed that results for 'inactive disease' can be presented in a context where the corresponding exact definition is available, their inclusion in the SmPC, where a condensed presentation is required, is not supported. At the CHMP's request, the MAH agreed to remove this information from the SmPC.

As stated in the CHMP Guideline, JIA is a fluctuating, flaring disease, and for some forms of JIA, the risk of flares decreases with aging. Thus, once patients are stabilised in remission, lower maintenance dosages and even drug withdrawal may be appropriate. Dose-reduction or dose-interruption and re-treatment at relapse should be addressed within the clinical programme, and controlled clinical study designs are preferred. While not directly addressing this aspect of treatment, study F2304 allows a limited opportunity to address the need for continued maintenance treatment in a well responding patient.

The event-driven sample size is found adequate for detecting a clinically relevant effect and statistically significant effect. The randomisation and blinding procedures are considered adequate.

Log-rank test, stratified by JIA category and MTX use, is a robust statistical method for comparing the distribution of event times and considered fit for purpose. In terms of effect size, the hazard ratio estimated by the specified Cox proportional hazards model is conventional. Here it measures the

immediate risk of observing a disease flare among those that have not been observed to experience flare at earlier visits post Week 12. Provision of a single hazard ratio as a measure of treatment effect can be criticised for its inherent selection bias (as the immediate risk of flare is compared between groups that are affected by post-randomisation selection, i.e. those that have not flared under their randomised treatment) which may also lead to the hazard ratio as not being constant. The estimated proportions of subjects that experience flare by selected timepoints may be better understood and can be retrieved from the analyses conducted by the MAH. Of note, the trial did not reach the number of observed flares required for the primary analysis and thus continued until all subjects reached all Week 104. Therefore, no administrative censoring needed to be done before, approximately, Week 104. The reasons for non-administrative censoring of data should always be evaluated and sensitivity analyses done, especially if the proportion of non-administratively censored observations is large because censoring might be predictive of flare. To this end, the MAH planned a sensitivity analysis where subjects discontinuing the study treatment prematurely for any reason are considered as having flared at the time of study treatment discontinuation.

The efficacy summaries provided for TP1 are descriptive. In the absence of a blinded comparator, it is impossible to assess the extent to which the responses and improvements in disease activity may reflect an effect of the treatment.

The descriptive summaries of observed data by TP2 visit and randomised treatment reflect the disease activity among those that have not been observed to experience a disease flare following 'response' at Week 12. Given that subjects are excluded from TP2 and the data summaries in question, and no adjustments are done to account for this selection process, these summaries have no causal interpretation concerning the effect of withdrawal from active treatment.

The summary of JIA response at the time of observed disease flare and at subsequent evaluations help understand the disease state relative to study baseline and whether disease activity is improved following re-treatment (for subjects receiving placebo in TP2), although these data are open-label and lack a control arm. The summaries also shed light on the robustness of the flare definition as an endpoint and as a criterion guiding treatment decisions.

Overall, the data analyses provided are adequate for meeting the primary objective. While a comparison of benefits and risks between potential alternative treatment strategies beyond the primary endpoint was not included among the stated objectives of the study, the study design in itself would not seem to preclude also such comparisons.

The original protocol for the study had an effective date of 24 October 2016; first subject first visit took place on 23 May 2017, and last subject last visit took place on 09 November 2020. The highest number of subjects were enrolled in Russia (18), Turkey (17) and Germany (16). Almost 50% of subjects were recruited within EU Member States.

The study protocol was amended on two occasions. The amendments do not jeopardise the reliability or integrity of the study, and COVID 19 -related challenges in study conduct appear to have been appropriately managed.

A protocol deviation implying inappropriate use of prohibited or non-acceptable medications was reported in a high proportion of subjects. As these have not been further commented on in the CSR, the MAH was requested to clarify the nature of these medications and discuss their potential implications regarding the efficacy analyses. In its response, the MAH clarified that the majority of such protocol deviations were related to the dose of a corticosteroid, oral DMARD or NSAID that was not maintained stable since baseline, with most of these deviations representing discontinuations or dose reductions. The deviations were balanced between TP2 treatment groups, and according to the MAH, are not believed to have an impact on the efficacy analyses. The clarification is considered acceptable to the CHMP.

Considering the length of the study, overall attrition during the study was moderate, with over 70% of subjects completing the planned 2 years of treatment. There was no particular clustering with respect to reasons for discontinuation.

The majority of subjects were in the higher age and body weight ranges; only 3 subjects under 6 years of age, and 6 subjects with a body weight of less than 25 kg body weight at baseline were enrolled into the study. Demographic and baseline characteristics were generally comparable between the treatment groups; whereas slight differences between the disease subtypes could be observed, these do not raise concerns with respect to the validity of the results.

Efficacy data and additional analyses

Study F2304 met its primary endpoint, demonstrating a statistically significant prolongation of time to flare with secukinumab compared to placebo in TP2 (HR of flare event = 0.28, 95% CI: 0.13 to 0.63, p<0.001). The primary analysis was appropriately supported with a tipping point analysis, confirming robustness of the results with respect to censoring of data during the 92-week follow-up. A prolongation of time to flare with secukinumab compared to placebo was observed in both ERA and JPsA subjects; in ERA subjects, the risk of a disease flare with placebo was lower when compared to JPsA subjects. Other descriptive subgroup analyses (based on age, weight, gender and methotrexate use at baseline) yielded HR's <1 for all subgroups; notably, the effect of secukinumab was more pronounced among subjects who were not using methotrexate, but it can be agreed that incremental efficacy is seen both with and without methotrexate. During the procedure, the indication was amended to specify that secukinumab may be used with or without MTX which was considered acceptable to the CHMP. From an efficacy perspective, the results do not point to particular concerns regarding any of the subgroups analysed, but it should be noted that all subjects in the 2-<6-year age range were randomised to placebo in TP2; as such, an assessment of efficacy based on the primary endpoint in this age group is not possible.

During TP1, improvements in disease activity were rapid, and over 90% of subjects completing TP1 achieved a JIA ACR 30 response. Almost 70% of subjects achieved a JIA ACR 70 response, and 36% achieved inactive disease status which – although in an uncontrolled open-label setting - can be considered suggestive of a clinically relevant treatment effect. The following statement is currently included in the SmPC and was considered adequate to the CHMP also as it would pertain to JIA: "Available data suggest that a clinical response is usually achieved within 16 weeks of treatment. Consideration should be given to discontinuing treatment in patients who have shown no response by 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks."

Improvements were seen in both disease subtypes and across all analysed subgroups; a JIA ACR 70 response at Week 12 was seen in all 6 subjects in the <25 kg weight band (with this group also including all 3 subjects aged 2-<6 years). However, even from an efficacy perspective, the evidence base for inclusion of the 2-<6-year age group in the initially proposed indication was considered very limited.

Since actual clinical experience in the youngest patients initially proposed to be included in the therapeutic indication was very limited, the MAH revised the indication during the procedure to exclude children from 2 to less than 6 years of age.

The separation in Kaplan-Meier curves mostly occurred during the first 4-5 months after randomisation into TP2, suggesting that the risk of flare varies among the patients and that those who are in the highest need for continued therapy tend to flare during the first months after discontinuation of secukinumab. Also, only 55% of subjects withdrawing to placebo had experienced a flare event at the end of TP2; thus, in the clinical setting, a substantial proportion of patients with an early response to secukinumab could incur longer-term treatment benefit even with a short treatment course.

Moreover, at the time of the observed flare event, subjects' disease activity levels were often better than at baseline, with a third (7/21) of subjects still meeting JIA ACR50 response in the placebo group. Whether the predefined flare events on placebo were indicative of further decline in subjects' - and thereby populations' - clinical state is not possible to tell since subjects were switched to open-label secukinumab immediately when a flare was observed. However, among subjects who met the flare criteria on continued secukinumab, the subsequent JIA ACR response profiles appeared not very different as compared with subjects who did not have flare event, with e.g. JIA ACR 50 response rates varying around 80% following flare vs. 90% in subjects with no flare observed. This suggests that the flare definition may not have been a specific indicator of a permanent loss of response. Given the retreatment with open-label secukinumab, it is not possible to conduct a comprehensive comparison of outcomes between populations whose secukinumab is continued vs. discontinued at Week 12. In order to better assess the benefit of long-term treatment, a longer-term placebo control would be required.

Given these observations, there remains uncertainty regarding the appropriate length of treatment; it may be that any "lost opportunity" could be quite limited if a treatment strategy is applied whereby treatment in a well responding patient is interrupted and restarted in case of a flare.

To elucidate the time course of disease activity in a population for whom the treatment strategy would correspond to "treatment withdrawal followed by retreatment as needed" as compared to chronic continuous treatment, and consequently to enable an informal comparison of these longer-term treatment strategies, the MAH was requested to provide a summary of JIA ACR responses and mean JADAS-27 in the entire study population through Week 104, i.e. combining subjects with and without a flare, and provide a discussion.

In its response, the MAH argued that the study was not designed to assess individualised treatment durations nor the possibilities to attempt dose reduction or discontinuation in a well-responding patient. Rather, the goal was to maximise the benefit to patients, and the study results support the need for continuous (monthly) treatment with secukinumab s.c. for the prevention of flares. The MAH further argued that assessments within the study were primarily symptomatic and may not represent the complete assessment of inflammation for each patient, and that increased joint or structural damage could still be occurring even in the absence of symptoms. Therefore, the MAH considered that it cannot make standardised recommendations to discontinue treatment within this multi-faceted and fluctuating disease that would apply to all patients and proposed that it is best for any decisions to that effect to be left to the treating physician, following a full assessment of the patients' disease burden.

The CHMP agreed that an evaluation of different long-term treatment strategies was not among the stated objectives of study F2304; nevertheless, the design and the collected data do in fact provide an opportunity to evaluate the merits of different approaches in this respect, and the results would seem to support the notion that overall, similar longer-term outcomes on the group level can be achieved with a relapse-retreatment strategy compared to chronic treatment.

The demonstration of treatment benefit with secukinumab in study F2304 is not disputed, and it can also be agreed that the results are not sufficiently robust to formalise different long-term treatment recommendations into the SmPC. Furthermore, the lack of information regarding different longer-term treatment strategies is not viewed as critical to the benefit-risk balance. Consequently, the issue is not pursued further within the current variation procedure. Nevertheless, considering that the current posology in principle outlines a potentially life-long treatment for a paediatric population, less demanding long-term treatment approaches, e.g. less frequent dosing schemes or indeed dose interruptions in well-responding patients, would very likely translate into decreased treatment burden and could even increase compliance. As such, the MAH is strongly recommended to study the effectiveness and usability of different long-term treatment strategies in JIA patients, including strategies involving a "treatment withdrawal followed by retreatment as needed" approach in the post-authorisation setting.

2.4.4. Conclusions on the clinical efficacy

Secukinumab was studied in a double-blind, placebo-controlled, event-driven randomised withdrawal study in 86 paediatric patients aged 2 to < 18 years with ERA or JPsA subtypes of JIA. The study met its primary endpoint, demonstrating a statistically significant and clinically relevant prolongation in time to disease flare. During the open-label Treatment Period 1, improvements in disease activity were rapid, and at Week 12, almost 70% of subjects had achieved a JIA ACR 70 response and 36% had achieved inactive disease status which – although in an uncontrolled open-label setting - can be considered as further supporting a clinically relevant treatment effect.

Since actual clinical experience in the youngest patients initially proposed to be included in the therapeutic indication was very limited (total N=3), the MAH revised their claim during the procedure to exclude children from 2 to less than 6 years of age from the indication.

The MAH is recommended to study the effectiveness and usability of different long-term treatment strategies in JIA patients, including strategies involving a "treatment withdrawal followed by retreatment as needed" approach in the post-marketing setting.

The CHMP considered that the efficacy data available supports the following indication:

Juvenile idiopathic arthritis (JIA)

Enthesitis-related arthritis (ERA)

Cosentyx, alone or in combination with methotrexate (MTX), is indicated for the treatment of active enthesitis-related arthritis in patients 6 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy (see section 5.1).

Juvenile psoriatic arthritis (JPsA)

Cosentyx, alone or in combination with methotrexate (MTX), is indicated for the treatment of active juvenile psoriatic arthritis in patients 6 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy (see section 5.1).

2.5. Clinical safety

Introduction

This safety analysis is primarily based on data from Study F2304. The safety population included all patients who were exposed to study treatment (N=86).

Safety evaluations consisted of evaluation of AEs and SAEs, laboratory abnormalities, findings on ECGs and vital signs, immunogenicity, and important compound- and class-related risks including infections and infestations, inflammatory bowel disease, malignant or unspecified tumours, suicidal ideation and behaviour, and hepatitis B reactivation.

AEs are presented as absolute and relative frequencies and as exposure-adjusted incidence rates per 100 patient-years (PY) of exposure.

The focus of the safety presentation is on the overall population over the entire study period (TP1 +TP2 + TP3). The randomized withdrawal study design limits comparison of safety between the randomized treatment groups (secukinumab vs placebo in TP2), since given that all patients received secukinumab in TP1, a carry-over effect into TP2 cannot be excluded for patients randomized to placebo.

The safety population thus comprises:

- patients who received secukinumab in TP1 only (up to Week 12)
- patients who received secukinumab in TP1, were randomized to placebo in TP2, and remained on placebo until end of study
- patients who received secukinumab in TP1, were randomized to placebo in TP2, and switched to open-label secukinumab in TP3
- patients who received secukinumab throughout the entire study period (TP+ TP2 + TP3)

To assess the consistency of safety across different baseline characteristics, subgroup analyses were performed on intrinsic factors of age, gender and weight and the extrinsic factor of concomitant methotrexate use.

In addition, a cross study comparison of safety data from study F2304 with pooled data from the pediatric psoriasis studies study A2310 and study A2311 was performed by means of side-by-side presentation of AEs (crude incidence and exposure-adjusted AEs). This analysis included data from those patients who received the same weight-based dosing regimen and treatment duration (12 weeks) across all 3 studies.

Study A2310 was a multicenter, randomized, double-blind, parallel group, placebo- and active (etanercept)-controlled study to demonstrate the superiority of secukinumab (low and high dose) in pediatric patients aged 6 years to less than 18 years with severe chronic plaque psoriasis with respect to both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared to placebo (Study A2310 Week 52).

Study A2311 was an open-label, parallel group, two-arm, multi-center trial in pediatric patients aged 6 years to less than 18 years with moderate to severe chronic plaque psoriasis with respect to PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared to placebo (historical control) [Study A2311 Week 24].

The MAH also refers to the large safety database across all indications (cumulative exposure of 35,241 patient-years from 21,159 patients and healthy volunteers) in clinical trials, and 680,470 patient-years of post-marketing exposure [PSUR (26-Dec-2019 to 25-Dec-2020)].

Patient exposure

All patients received secukinumab in TP1 and TP3 and either placebo or secukinumab in TP2. Overall, the mean duration of exposure to study treatment (secukinumab or placebo) during the study period (TP1 + TP2 + TP3) was 601 days, with a patient-time of 141.5 PY (Table 18).

In TP2, the mean duration of exposure was longer in the secukinumab group (456 days) compared to the placebo in TP2 group (358 days), which reflects that a higher proportion of patients randomized to placebo exited TP2 due to a flare.

A maximum of 29 SC doses for the secukinumab treatment group could be administered for the entire treatment period (last dose at Week 100). During the entire treatment period, 23/48 patients (47.9%) in the secukinumab group and 10/38 patients (26.3%) in the Placebo in TP2 group received the maximum number of study treatment injections (i.e., secukinumab in TP1 and TP3 and Placebo in TP2).

Table 18 Duration of exposure to study treatment – Entire treatment period (Safety set)

Duration of exposure	AIN457* N=48	Placebo in TP2 N=38	Total N=86
Exposure in days			
Mean	542.7	674.5	601.0
SD	269.72	148.33	232.67
Median	728.5	729.5	729.0
Min - Max	56-803	197-788	56-803
Patient years	71.3	70.2	141.5

AIN457: all patients who did not take any placebo before or during the period. Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s. *The shorter mean duration in exposure in the secukinumab group is influenced by the inclusion of the short exposure time of the patients who were only in TP1 (12 weeks), in addition to the exposure time in TP1+TP2 and TP1+TP2+TP3 Duration of exposure to study treatment is defined as the number of days on the study treatment during the considered period. Patient-years is calculated as a sum of individual patient durations in days divided by 365.25.

Table 19 Patient disposition – TP1, TP2, and TP3 (Safety set)

	Period 1	Period 2			Period 3		
Disposition/Reason	AIN457 N=86 n (%)	AIN457 N=37 n (%)	Placebo in TP2 N=38 n (%)	Total N=75 n (%)	AIN457 N=11 n (%)	Placebo in TP2 N=21 n (%)	Total N=32 n (%)
Completed treatment period	83 (96.5)	31 (83.8)	36 (94.7)	67 (89.3)	10 (90.9)	16 (76.2)	26 (81.3)
Continued to Period 2	75 (87.2)	NA	NA	NA	NA	NA	NA
Continued to Period 3	0	11 (29.7)	21 (55.3)	32 (42.7)	NA	NA	NA
Discontinued during or at the end of the treatment period*	3 (3.5)	6 (16.2)	2 (5.3)	8 (10.7)	1 (9.1)	5 (23.8)	6 (18.8)
Primary reason for discontinuing							
AE	0	1 (2.7)	2 (5.3)	3 (4.0)	0	3 (14.3)	3 (9.4)
Death	0	0	0	0	0	0	0
Lack of efficacy	3 (3.5)	1 (2.7)	0	1 (1.3)	0	1 (4.8)	1 (3.1)
Non-compliance with study treatment	0	0	0	0	0	0	0
Pregnancy	0	0	0	0	0	0	0
Protocol deviation	0	0	0	0	0	0	0
Study terminated by sponsor	0	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0	0
Technical problems	0	0	0	0	0	0	0
Physician decision	0	1 (2.7)	0	1 (1.3)	0	1 (4.8)	1 (3.1)
Subject/guardian decision	0	3 (8.1)	0	3 (4.0)	1 (9.1)	0	1 (3.1)

AIN457: all patients who did not take any placebo before or during the period. Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s. Patients who were mistakenly switched from TP2 to TP3 were counted as completed Period 2. *Includes patients who completed the given period and discontinued prematurely from the study treatment on the same date. NA = Not applicable.

Concomitant medications or treatments

The study design and eligibility criteria included lack of response or intolerance to ≥ 1 NSAID and DMARD and allowed for continued use and stable dose of NSAID, methotrexate, sulfasalazine (ERA patients only), and/or corticosteroids during TP1 and TP2. This should be taken into consideration for the interpretation of the data on use of concomitant medications.

The treatment groups in the entire treatment period refer to the secukinumab (all patients who did not take any placebo) and the placebo (all patients who took placebo in TP2 and secukinumab in other period/s) groups and are presented as secukinumab and Placebo in TP2 groups in this SCS. Treatment comparisons between secukinumab and Placebo in TP2 groups have not been made since due to the study design, the exposure times for these groups were different over the entire treatment period. In addition, it cannot be ruled-out that events occurring in TP2 under placebo are due to a spill-over effect by the previous secukinumab treatment in TP1.

During the entire treatment period, concomitant medications were used by more than 98% of patients (secukinumab: 97.9% [47/48 patients]; Placebo in TP2: 100% [38/38 patients]) and were well-balanced between the treatment groups. In general, the 5 most commonly used medications were folic acid, methotrexate, paracetamol, ibuprofen and naproxen. As per ATC class, the 5 most commonly used concomitant medications categories included Musculoskeletal system (secukinumab: 97.9% [47/48 patients]; Placebo in TP2: 92.1% [35/38 patients]), Genitourinary system and sex hormones (secukinumab: 87.5% [42/48 patients]; Placebo in TP2: 81.6% [31/38 patients]), Alimentary tract and metabolism (secukinumab: 83.3% [40/48 patients]; Placebo in TP2: 81.6% [31/38 patients]), Sensory organs (secukinumab: 77.1% [37/48 patients]; Placebo in TP2: 76.3% [29/38 patients]) and Blood and blood forming organs (secukinumab: 70.8% [34/48 patients]; Placebo in TP2: 73.7% [28/38 patients]).

In the entire treatment period, concomitant medical procedures and significant non-drug therapies were used by 41.9% of patients (secukinumab: 41.7% [20/48 patients]; Placebo in TP2: 42.1% [16/38 patients]). The most commonly used disease-specific therapy categories included Surgical and medical procedures (secukinumab: 31.3% [15/48 patients]; Placebo in TP2: 23.7% [9/38 patients]) and Investigations (secukinumab: 18.8% [9/48 patients]; Placebo in TP2: 26.3% [10/38 patients]).

Adverse events

Considering that the randomized withdrawal study design limits comparisons between the randomized treatment groups, the section below focuses on presentation of AEs over the entire treatment period (TP1 + TP2 + TP3).

Common adverse events

Adverse events by system organ class and preferred term

Treatment-emergent AEs were reported by 79 patients (91.9%) in the entire treatment period (Table 20). The 3 most common reported SOCs reported in the total population were Infections and infestations (79.1%), Gastrointestinal disorders (52.3%) and Musculoskeletal and connective tissue disorders (37.2%) (Table 20).

The AE incidence in Infections and infestations was mainly driven by events of nasopharyngitis, upper respiratory tract infection and pharyngitis, while diarrhoea, nausea and vomiting were the most frequent AEs in the Gastrointestinal disorders SOC. Arthralgia was the most frequently reported AE in the Musculoskeletal and connective tissue disorders SOC (Table 20, Table 21). All of these reported AEs were mild or moderate in severity.

Table 20 Absolute and relative frequencies for treatment emergent AEs by primary system organ class – Entire treatment period (Safety Set)

Primary system organ class	AIN457 N=48 n (%)	Placebo in TP2 N=38 n (%)	Total N=86 n (%)
Any primary system organ class	44 (91.7)	35 (92.1)	79 (91.9)
Infections and infestations	38 (79.2)	30 (78.9)	68 (79.1)
Gastrointestinal disorders	24 (50.0)	21 (55.3)	45 (52.3)
Musculoskeletal and connective tissue disorders	17 (35.4)	15 (39.5)	32 (37.2)
Respiratory, thoracic and mediastinal disorders	16 (33.3)	9 (23.7)	25 (29.1)
Skin and subcutaneous tissue disorders	14 (29.2)	16 (42.1)	30 (34.9)
Investigations	11 (22.9)	10 (26.3)	21 (24.4)
General disorders and administration site conditions	10 (20.8)	12 (31.6)	22 (25.6)
Injury, poisoning and procedural complications	10 (20.8)	15 (39.5)	25 (29.1)
Nervous system disorders	6 (12.5)	9 (23.7)	15 (17.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (10.4)	0	5 (5.8)
Ear and labyrinth disorders	4 (8.3)	3 (7.9)	7 (8.1)
Eye disorders	4 (8.3)	2 (5.3)	6 (7.0)
Renal and urinary disorders	4 (8.3)	0	4 (4.7)
Blood and lymphatic system disorders	3 (6.3)	7 (18.4)	10 (11.6)
Cardiac disorders	2 (4.2)	0	2 (2.3)
Immune system disorders	2 (4.2)	0	2 (2.3)
Metabolism and nutrition disorders	2 (4.2)	3 (7.9)	5 (5.8)
Psychiatric disorders	2 (4.2)	4 (10.5)	6 (7.0)
Reproductive system and breast disorders	2 (4.2)	4 (10.5)	6 (7.0)
Congenital, familial and genetic disorders	1 (2.1)	1 (2.6)	2 (2.3)
Hepatobiliary disorders	1 (2.1)	1 (2.6)	2 (2.3)
Social circumstances	1 (2.1)	0	1 (1.2)
Vascular disorders	1 (2.1)	1 (2.6)	2 (2.3)

AIN457: all patients who did not take any placebo. Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s. N= number of total patients; n= number of patients with events Primary system organ classes are sorted in descending order of frequency in the AIN457 column. A patient with multiple AEs within a primary system organ class is counted only once in the row. MedDRA version 23.1 was used for reporting. Source: [Study F2304-Table 14.3.1-1.2]

Overall, the most commonly reported AEs (≥15%) by PT were nasopharyngitis (27 patients, 31.4%), diarrhoea (17 patients, 19.8%), nausea (19 patients, 22.1%), upper respiratory tract infection (19 patients, 22.1%) and cough (13 patients, 15.1%) (Table 21).

Table 21 Treatment emergent AEs by PT (at least 3% in Total) in descending frequency – Entire treatment period (Safety Set)

Preferred term	AIN457 N=48 n (%)	Placebo in TP2 N=38 n (%)	Total N=86 n (%)
-Any preferred term	44 (91.7)	35 (92.1)	79 (91.9)
Nasopharyngitis	16 (33.3)	11 (28.9)	27 (31.4)
Diarrhoea	11 (22.9)	6 (15.8)	17 (19.8)
Nausea	11 (22.9)	8 (21.1)	19 (22.1)
Upper respiratory tract infection	10 (20.8)	9 (23.7)	19 (22.1)
Arthralgia	8 (16.7)	4 (10.5)	12 (14.0)
Cough	8 (16.7)	5 (13.2)	13 (15.1)
Oropharyngeal pain	7 (14.6)	5 (13.2)	12 (14.0)
Headache	6 (12.5)	6 (15.8)	12 (14.0)
Pharyngitis	6 (12.5)	3 (7.9)	9 (10.5)
Pyrexia	6 (12.5)	6 (15.8)	12 (14.0)
Influenza	5 (10.4)	0	5 (5.8)
Vomiting	5 (10.4)	4 (10.5)	9 (10.5)
Alanine aminotransferase increased	4 (8.3)	0	4 (4.7)
Aphthous ulcer	4 (8.3)	1 (2.6)	5 (5.8)
Back pain	4 (8.3)	3 (7.9)	7 (8.1)
Tonsillitis	4 (8.3)	4 (10.5)	8 (9.3)
Abdominal pain upper	3 (6.3)	2 (5.3)	5 (5.8)
Aspartate aminotransferase increased	3 (6.3)	1 (2.6)	4 (4.7)
Conjunctivitis	3 (6.3)	2 (5.3)	5 (5.8)
Haematuria	3 (6.3)	0	3 (3.5)
Ligament sprain	3 (6.3)	3 (7.9)	6 (7.0)
Paronychia	3 (6.3)	1 (2.6)	4 (4.7)
Pneumonia	3 (6.3)	1 (2.6)	4 (4.7)
Rhinitis	3 (6.3)	5 (13.2)	8 (9.3)
Sinusitis	3 (6.3)	0	3 (3.5)
Skin papilloma	3 (6.3)	0	3 (3.5)
Abdominal pain	2 (4.2)	6 (15.8)	8 (9.3)
Arthropod bite	2 (4.2)	2 (5.3)	4 (4.7)
Contusion	2 (4.2)	4 (10.5)	6 (7.0)
Dyspepsia	2 (4.2)	2 (5.3)	4 (4.7)

Eczema	2 (4.2)	1 (2.6)	3 (3.5)
Gastroenteritis	2 (4.2)	2 (5.3)	4 (4.7)
Injection site pain	2 (4.2)	1 (2.6)	3 (3.5)
Musculoskeletal stiffness	2 (4.2)	1 (2.6)	3 (3.5)
Neutropenia	2 (4.2)	2 (5.3)	4 (4.7)
Pain in extremity	2 (4.2)	4 (10.5)	6 (7.0)
Pruritus	2 (4.2)	2 (5.3)	4 (4.7)
Rash	2 (4.2)	2 (5.3)	4 (4.7)
Respiratory disorder	2 (4.2)	1 (2.6)	3 (3.5)
Skin abrasion	2 (4.2)	1 (2.6)	3 (3.5)
Tracheitis	2 (4.2)	1 (2.6)	3 (3.5)
Vertigo	2 (4.2)	1 (2.6)	3 (3.5)
Acne	1 (2.1)	5 (13.2)	6 (7.0)
Alopecia	1 (2.1)	2 (5.3)	3 (3.5)
Ear pain	1 (2.1)	2 (5.3)	3 (3.5)
Fatigue	1 (2.1)	2 (5.3)	3 (3.5)
Gastrointestinal infection	1 (2.1)	2 (5.3)	3 (3.5)
Impetigo	1 (2.1)	3 (7.9)	4 (4.7)
Joint injury	1 (2.1)	4 (10.5)	5 (5.8)
Oral herpes	1 (2.1)	2 (5.3)	3 (3.5)
Otitis media	1 (2.1)	3 (7.9)	4 (4.7)
Respiratory tract infection	1 (2.1)	4 (10.5)	5 (5.8)
Transaminases increased	1 (2.1)	2 (5.3)	3 (3.5)
Urticaria	1 (2.1)	2 (5.3)	3 (3.5)
Psoriasis	0	4 (10.5)	4 (4.7)
Radius fracture	0	3 (7.9)	3 (3.5)

AIN457: all patients who did not take any placebo. Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s. N= number of total patients; n= number of patients with events. Preferred terms are sorted in descending order of frequency in the AIN457 column. A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. MedDRA version 23.1 was used for reporting.

Exposure adjusted incidence rates

In total, the EAIR (expressed as per 100 PY) of treatment-emergent AEs by any primary SOC in the entire treatment period was 290.7 in all patients. The EAIRs of the most commonly reported SOCs with AEs were: Infections and infestations (134.2/100 PY), Gastrointestinal disorders (50.4/100 PY) and Musculoskeletal and connective tissue disorders (31.0/100 PY), respectively.

Treatment periods

Overall, 56 out of 86 subjects (65.1%) experienced incidence of treatment-emergent AEs in any SOC in TP1. The 3 most commonly reported AEs by SOC were Infections and infestations (38.4%), Gastrointestinal disorders (17.4%) and Skin and subcutaneous tissue disorders (12.8%) in TP1.

The overall incidence of treatment-emergent AEs in TP2 in any SOC was 84.0% (63/75 subjects) (secukinumab: 34/37 subjects, 91.9%; placebo: 29/38 subjects, 76.3%). The 3 most commonly reported AEs by SOC in the TP2 in both treatment groups were Infections and infestations (secukinumab 73.0%; placebo 44.7%), Gastrointestinal disorders (secukinumab 48.6%; placebo 28.9%) and Musculoskeletal and connective tissue disorders (secukinumab 29.7%; placebo 23.7%).

Overall, 23 out of 32 subjects (71.9%) experienced incidence of treatment-emergent AEs in any SOC over TP3. The 3 most commonly reported AEs by SOC in TP3 were Infections and infestations (62.5%), Gastrointestinal disorders (40,6%) and Musculoskeletal and connective tissue disorders (34.4%) in TP3.

Potential relationship of adverse events to study treatment

Treatment-emergent AEs possibly related to study treatment by the investigator were reported in 32/86 patients (37.2%) in the entire treatment period. These AEs were most commonly reported in the SOCs of Infections and infestations (12.8%, mainly due to nasopharyngitis), Gastrointestinal disorders (8.1%, mainly due to diarrhoea and aphthous ulcer), and General disorders and administration site conditions (8.1%, mainly due to injection site pain and injection site pruritus).

Severity of adverse events

The majority of treatment-emergent AEs in the entire treatment period were either mild (40/86 patients, 46.5%) or moderate in severity (37/86 patients, 43.0%). Severe AEs occurred at a low frequency (2/86 patients, 2.3%).

The severe AEs of aphthous ulcer and joint effusion were reported in one patient each in TP1. Both AEs were non-serious events. The aphthous ulcer AE was considered related to study treatment by the investigator, secukinumab dose was not changed and the event resolved with treatment. The joint effusion AE was considered unrelated to secukinumab by the investigator, resolved with treatment and the study treatment was withdrawn. There were no severe events in the Placebo in TP2 group.

Side-by-side display of adverse events in JIA categories ERA and JPsA and paediatric psoriasis (low dose group)

A side-by-side display of AEs up to Week 12 from the low dose group (secukinumab 75 mg [< 50 kg]; secukinumab 150 mg [≥ 50 kg,]) of the pooled psoriasis paediatric studies (Study A2310 Week 52 DBL data and Study A2311 Week 24 DBL data) and final core study DBL data from Study F2304 in TP1 for all patients and by body weight group is presented below.

Treatment-emergent AEs were reported in 56 patients (65.1%) in Study F2304 and in 42 patients (51.2%) in the secukinumab group from the pooled paediatric psoriasis studies (Study A2310 and Study A2311). Majority of the reported AEs in Study F2304 were mild or moderate in severity.

In both Study F2304 and the pooled paediatric psoriasis studies, AEs by SOC were most commonly reported in Infections and infestations, and this AE pattern was observed across all the body weight categories (< 25 kg, 25 - < 50 kg and ≥ 50 kg), followed by Gastrointestinal disorders and Skin and general disorders (in the body weight categories of 25 - < 50 kg and ≥ 50 kg). As expected for the JIA population, AEs in the Musculoskeletal disorders SOC were reported in a higher number of patients [9 patients (10.5%); 5 patients in the body weight category of 25 - < 50 kg and 4 patients in the ≥ 50 kg category] in Study F2304 vs. only 1 patient (1.2%) in the ≥ 50 kg category in the paediatric psoriasis studies (Table 22).

Table 22 Absolute and relative frequencies for treatment-emergent AEs by primary SOC for CAIN457F2304 and pooled psoriasis paediatric studies up to week 12

	CAIN457F2304		Pooled psoriasis paediatric studies			
	AIN457 N=86		AIN457 low dose* N=82		Placebo N=41	
Primary system organ class	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
-Any primary system organ class	56(65.1)	(54.0, 74.9)	42(51.2)	(40.0, 62.3)	22(53.7)	(37.6, 69.0)
Infections and infestations	33(38.4)	(28.3, 49.5)	26(31.7)	(22.1, 43.0)	16(39.0)	(24.6, 55.5)
Gastrointestinal disorders	15(17.4)	(10.4, 27.5)	7(8.5)	(3.8, 17.3)	7(17.1)	(7.7, 32.6)
Skin and subcutaneous tissue Disorders	11(12.8)	(6.9, 22.1)	8(9.8)	(4.6, 18.8)	3(7.3)	(1.9, 21.0)
General disorders and administration site Conditions	10(11.6)	(6.0, 20.8)	6(7.3)	(3.0, 15.8)	3(7.3)	(1.9, 21.0)
Musculoskeletal and connective tissue Disorders	9(10.5)	(5.2, 19.4)	1(1.2)	(0.1, 7.5)	1(2.4)	(0.1, 14.4)
Respiratory, thoracic mediastinal Disorders	7(8.1)	(3.6, 16.6)	3(and 3.7)	(0.9, 11.1)	3(7.3)	(1.9, 21.0)
Investigations	5(5.8)	(2.2, 13.7)	2(2.4)	(0.4, 9.4)	2(4.9)	(0.8, 17.8)
Nervous system disorders	5(5.8)	(2.2, 13.7)	3(3.7)	(0.9, 11.1)	5(12.2)	(4.6, 27.0)
Injury, poisoning and procedural complications	3(3.5)	(0.9, 10.6)	3(3.7)	(0.9, 11.1)	2(4.9)	(0.8, 17.8)
Blood and lymphatic system disorders	2(2.3)	(0.4, 8.9)	4(4.9)	(1.6, 12.7)	1(2.4)	(0.1, 14.4)
Ear and labyrinth disorders	2(2.3)	(0.4, 8.9)	1(1.2)	(0.1, 7.5)	0(0.0)	(0.0, 10.7)
Psychiatric disorders	2(2.3)	(0.4, 8.9)	0(0.0)	(0.0, 5.6)	1(2.4)	(0.1, 14.4)
Reproductive system and breast disorders	2(2.3)	(0.4, 8.9)	2(2.4)	(0.4, 9.4)	1(2.4)	(0.1, 14.4)
Eye disorders	1(1.2)	(0.1, 7.2)	1(1.2)	(0.1, 7.5)	1(2.4)	(0.1, 14.4)
Metabolism and nutrition disorders	1(1.2)	(0.1, 7.2)	0(0.0)	(0.0, 5.6)	0(0.0)	(0.0, 10.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1(1.2)	(0.1, 7.2)	0(0.0)	(0.0, 5.6)	0(0.0)	(0.0, 10.7)
Renal and urinary disorders	0(0.0)	(0.0, 5.3)	2(2.4)	(0.4, 9.4)	2(4.9)	(0.8, 17.8)
Vascular disorders	0(0.0)	(0.0, 5.3)	1(1.2)	(0.1, 7.5)	0(0.0)	(0.0, 10.7)

A patient with multiple adverse events within a primary system organ class is counted only once. System organ classes are presented in descending frequency in AIN457 group from Study CAIN457F2304. The pooled psoriasis paediatric studies includes AIN457A2310 week 52 DBL data and AIN457A2311 week 24 DBL data. *For AIN457 low dose group, patients weighing < 50 kg received 75 mg and patients weighing ≥ 50 kg received 150 mg (the same dose regimen as Study F2304). MedDRA Version 22.1 has been used for the reporting of adverse events in Pooled psoriasis paediatric studies. MedDRA Version 23.1 has been used for the reporting of adverse events in CAIN457F2304 DBL.

The PTs for AEs (for all patients and by body weight category) were also more frequently reported from the Infections and infestations SOC (commonly reported PTs included upper respiratory tract infection and nasopharyngitis).

Serious adverse event/deaths/other significant events

Deaths

No deaths were reported in the study (Table 23).

Other serious or clinically relevant adverse events

Treatment emergent SAEs were reported for 11 patients (12.8%) overall, and all were reported in patients receiving secukinumab. By treatment period, SAEs were reported for 2 patients in TP1, 5 patients in TP2 (all were randomized to secukinumab), and 5 patients in TP3. The most frequently reported SAEs were Infections and infestations (SOC; 7 patients, 8.1%). There was no trend or pattern with respect to type of SAE reported, and SAEs were reported in both JIA categories (ERA: 4 patients, JPsA: 7 patients).

One of the SAEs led to discontinuation of study drug; this was an SAE of Crohn's disease also mentioned below.

SAEs considered related to study treatment by the investigator were reported for 2 patients:

- In TP2, Crohn's disease was reported as an SAE in a JPsA patient randomized to secukinumab. Study medication was discontinued due to the event.
- In TP3, a JPsA patient who was randomized to placebo in TP2 experienced a flare that was reported as an SAE (juvenile PsA). Study medication (secukinumab) was continued.

Adverse events requiring dose interruption or discontinuation of study drug

Overall, few patients required interruption of dosing or discontinuation of study drug due to an AE.

AEs leading to discontinuation of study treatment were reported for 8 patients (9.3%). By SOC, the most frequent events were Musculoskeletal and connective tissue disorders (3 patients, 3.5%; the events were joint effusion and enthesopathy) and Skin and subcutaneous tissue disorder (2 patients, 2.3%; the events were psoriasis, and urticaria). The remaining AEs were pneumonia, epilepsy, and the SAE of Crohn's disease mentioned above. In two patients, these AEs occurred during placebo treatment in TP2 (enthesopathy, psoriasis); the remaining AEs occurred during secukinumab treatment in TP1 (joint effusion), TP2 (Crohn's disease, pneumonia) and TP3 (enthesopathy, epilepsy, urticaria).

AEs leading to interruption of study drug were reported for 7 patients (8.1%); by SOC, the most frequent such AEs were Infections and infestations (4 patients, 4.7%). The remaining AEs were diarrhea, food poisoning, nonalcoholic fatty liver disease, transaminase increased, and blood alkaline phosphatase increased, all reported in single patients each.

AEs leading to study drug discontinuation were reported in both JIA categories (ERA: 3 patients, JPsA: 5 patients). Similarly, AEs leading to interruption of study drug were also reported in both JIA categories (ERA: 3 patients, JPsA: 4 patients).

Table 23 Overview of deaths and other serious or significant events – Overall (Safety Set)

	AIN457 N=48 n (%)	Placebo in TP2 N=38 n (%)	Total N=86 n (%)
Number of patients with any AE	44 (91.7)	35 (92.1)	79 (91.9)
Number of patients with serious or other significant events			
Death	0	0	0
SAE	7 (14.6)	4 (10.5)	11 (12.8)
Discontinued study treatment due to AE	3 (6.3)	5 (13.2)	8 (9.3)
Dose interruption due to AE	5 (10.4)	2 (5.3)	7 (8.1)

AIN457: all patients who did not take any placebo. Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s. A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. MedDRA version 23.1 was used for reporting Source: [Study F2304-Table 12-3], [Study F2304-Table 14.3.1-6.2]

Table 24 Absolute and relative frequencies of treatment-emergent SAEs by PTs – Entire treatment period (Safety set)

Preferred term	AIN457 N=48 n (%)	Placebo in TP2 N=38 n (%)	Total N=86 n (%)
Any preferred term	7 (14.6)	4 (10.5)	11 (12.8)
Abdominal injury	1 (2.1)	0	1 (1.2)
Appendicitis	1 (2.1)	0	1 (1.2)
Cholesteatoma	1 (2.1)	0	1 (1.2)
Crohn's disease	1 (2.1)	0	1 (1.2)
Folliculitis	1 (2.1)	0	1 (1.2)
Food poisoning	1 (2.1)	0	1 (1.2)
Pilonidal cyst	1 (2.1)	0	1 (1.2)
Acute sinusitis	0	1 (2.6)	1 (1.2)
Adenoidal hypertrophy	0	1 (2.6)	1 (1.2)
Juvenile psoriatic arthritis	0	1 (2.6)	1 (1.2)
Pneumonia	0	1 (2.6)	1 (1.2)
Postoperative wound infection	0	1 (2.6)	1 (1.2)
Tonsillitis	0	1 (2.6)	1 (1.2)

AIN457: all patients who did not take any placebo. Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s. N= number of total patients; n= number of patients with events Preferred terms are sorted in descending order of frequency in the AIN457 column. A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. MedDRA version 23.1 was used for reporting.

Exposure adjusted incidence rates

The EAIR (per 100 PY) of treatment-emergent SAEs by any primary SOC in the entire treatment period was 8.2 in all patients. The most commonly reported SAEs were in the SOCs of Infections and infestations and Gastrointestinal disorders (EAIR: 5.1/100 PY and 1.4/100 PY, respectively) (Table 25).

*Table 25 Exposure adjusted incidence rates for **treatment-emergent SAEs**, by primary system organ class – Entire treatment period (Safety Set)*

	AIN457 N=48		Placebo in TP2 N=38		Total N=86	
Primary System organ class	**n/EX**	**(IR)**	**n/EX**	**(IR)**	**n/EX**	**(IR)**
-Any primary system organ class	7/67.4	(10.4)	4/67.3	(5.9)	11/134.7	(8.2)
Infections and infestations	3/70.5	(4.3)	4/67.7	(5.9)	7/138.2	(5.1)
Gastrointestinal disorders	2/70.2	(2.8)	0/70.2	(0.0)	2/140.4	(1.4)
Injury, poisoning and procedural complications	1/71.0	(1.4)	0/70.2	(0.0)	1/141.1	(0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1/69.6	(1.4)	0/70.2	(0.0)	1/139.8	(0.7)
Musculoskeletal and connective tissue disorders	0/71.3	(0.0)	1/69.5	(1.4)	1/140.8	(0.7)
Respiratory, thoracic and mediastinal disorders	0/71.3	(0.0)	1/69.6	(1.4)	1/140.9	(0.7)

AIN457: all patients who did not take any placebo. Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s.
N= number of total patients; n= number of patients with events. Primary system organ classes are sorted in descending order of frequency in the AIN457 column. A patient with multiple events within a primary system organ class is counted only once in the row. EX = Exposure in PY. IR = Incidence rate per 100 PY. For patients with event, exposure time is censored at time of first event.
MedDRA version 23.1 was used for reporting.

Laboratory findings

Criteria for clinically notable laboratory abnormalities were based on CTCAE grades for the following parameters: haemoglobin, platelets, WBC, neutrophils, lymphocytes, creatinine, TBL, GGT, ALT, AST, ALP, glucose, cholesterol, and TG.

Hematology

All newly occurring or worsening laboratory abnormalities in the entire treatment were either CTCAE Grade 1 or 2, with the exception of 2 cases of CTCAE Grade 3 decreases in neutrophil count in the secukinumab group. There were no CTCAE Grade 4 abnormalities observed in the entire treatment period (Table 26).

CTCAE Grade 3 abnormalities in neutrophil count during the entire treatment period were as follows.

- 2 out of 85 patients (2.4%) with AE of neutropenia experienced a shift in absolute neutrophil levels (<1.0-0.5 x10e9/L) from no grade at Week 12 to Grade 3 by Week 88 (11-year-old male weighing 32.7 kg with Grade 3 abnormality at this single visit) and Week 44 (9-year-old male weighing 30 kg with Grade 3 abnormality at this single visit). These Grade 3 abnormalities were observed in TP2 in the secukinumab treatment group and were not associated with any infections.

Most of the patients had normal hematology values at baseline and also at post-baseline during the entire treatment period.

Table 26 Hematology: number and percentage of patients with newly occurring or worsening after baseline CTCAE grades – Entire treatment period (Safety Set)

Variable Criterion	AIN457 N=48 n/m (%)	Placebo in TP2 N=38 n/m (%)	Total N=86 n/m (%)
Hemoglobin (g/L)			
< LLN - 100 g/L (Grade 1)	11/ 43 (25.6)	2/ 30 (6.7)	13/ 73 (17.8)
< 100 - 80 g/L (Grade 2)	1/ 48 (2.1)	1/ 37 (2.7)	2/ 85 (2.4)
< 80 g/L (Grade 3)	0/ 48	0/ 37	0/ 85
Platelets (10e9/L)			
< LLN - 75 x10e9/L (Grade 1)	3/ 47 (6.4)	4/ 37 (10.8)	7/ 84 (8.3)
< 75 - 50 x10e9/L (Grade 2)	0/ 48	0/ 37	0/ 85
< 50 - 25 x10e9/L (Grade 3)	0/ 48	0/ 37	0/ 85
< 25 x10e9/L (Grade 4)	0/ 48	0/ 37	0/ 85
WBC (10e9/L)			
< LLN - 3.0 x10e9/L (Grade 1)	4/ 46 (8.7)	8/ 35 (22.9)	12/ 81 (14.8)
< 3.0 - 2.0 x10e9/L (Grade 2)	4/ 48 (8.3)	3/ 37 (8.1)	7/ 85 (8.2)
< 2.0 - 1.0 x10e9/L (Grade 3)	0/ 48	0/ 37	0/ 85
< 1.0 x10e9/L (Grade 4)	0/ 48	0/ 37	0/ 85
Neutrophils (10e9/L)			
< LLN - 1.5 x10e9/L (Grade 1)	7/ 47 (14.9)	3/ 37 (8.1)	10/ 84 (11.9)
< 1.5 - 1.0 x10e9/L (Grade 2)	5/ 48 (10.4)	5/ 37 (13.5)	10/ 85 (11.8)
< 1.0 - 0.5 x10e9/L (Grade 3)	2/ 48 (4.2)	0/ 37	2/ 85 (2.4)
< 0.5 x10e9/L (Grade 4)	0/ 48	0/ 37	0/ 85
Lymphocytes (10e9/L)			
< LLN - 0.8 x10e9/L (Grade 1)	3/ 46 (6.5)	2/ 36 (5.6)	5/ 82 (6.1)
< 0.8 - 0.5 x10e9/L (Grade 2)	1/ 46 (2.2)	2/ 37 (5.4)	3/ 83 (3.6)
< 0.5 - 0.2 x10e9/L (Grade 3)	0/ 48	0/ 37	0/ 85
< 0.2 x10e9/L (Grade 4)	0/ 48	0/ 37	0/ 85

AIN457: all patients who did not take any placebo. Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s. There were no CTCAE Grade 4 abnormalities for hemoglobin (Life-threatening consequences; urgent intervention indicated). LLN = Lower limit of normal. n = Number of patients with most extreme value meeting the criterion post-baseline and that is newly occurring or worsening compared to baseline. m = Number of patients with evaluable criterion who did not meet the criterion at baseline. A patient with multiple variable measurements is counted only once under the worst condition. Newly occurring means missing at baseline and 'grade x' after baseline and worsening means 'less than grade x' at baseline and worsened to 'grade x' post-baseline where $1 \leq x \leq 4$.

Treatment Periods

Most of the newly occurring or worsening abnormalities in haematology parameters in TP2 were CTCAE Grade 1 or 2. Occurring at the highest frequencies among all haematology parameters was haemoglobin decrease in TP2. Differences were observed for newly occurring or worsening abnormalities between the secukinumab treatment group and placebo for Grade 1 haemoglobin decrease (< LLN - 100 g/L: secukinumab 18.8% and placebo 6.7%) and neutrophil decrease (< LLN - 1.5 x109/L: secukinumab 16.2% and placebo 2.7%). As stated earlier in entire treatment period, 2 CTCAE Grade 3 abnormalities were observed in secukinumab treatment group only for absolute neutrophils (<1.0-0.5 x10e9/L) in 2 subjects in TP2. The majority of subjects had values within normal range in TP2 with low frequencies of subjects shifting to CTCAE Grade 1 or Grade 2 from Week 12 within TP2.

Clinical chemistry

Newly occurring or worsening abnormalities in clinical chemistry parameters in the entire treatment period were mostly of CTCAE Grade 1 or 2 (Table 27). CTCAE Grade 3 abnormalities in the entire treatment period were as follows:

- Serum aspartate aminotransferase (> 5.0-20.0 x ULN) was noted in 1 patient (1.2%) (Table 27). The Grade 3 abnormality was observed in TP3 in Patient in the secukinumab treatment group.
- Serum alanine aminotransferase (> 5.0-20.0 x ULN) were noted in 2 patients (2.3%) (27). These Grade 3 abnormalities were observed in TP2 in Patient and Patient in the secukinumab treatment group.

There were no CTCAE Grade 4 abnormalities reported during the entire treatment period.

Additional details about the hepatic transaminase elevations are provided in the hepatic enzymes section.

Table 27 Chemistry: number and percentage of patients with newly occurring or worsening after baseline CTCAE grades – Entire treatment period (Safety Set)

Variable Criterion	AIN457 N=48 n/m (%)	Placebo in TP2 N=38 n/m (%)	Total N=86 n/m (%)
Creatinine (umol/L), Plasma/Serum			
> ULN - 1.5 x ULN (Grade 1)	3/ 48 (6.3)	1/ 38 (2.6)	4/ 86 (4.7)
> 1.5 - 3.0 x ULN (Grade 2)	0/ 48	0/ 38	0/ 86
> 3.0 - 6.0 x ULN (Grade 3)	0/ 48	0/ 38	0/ 86
> 6.0 x ULN (Grade 4)	0/ 48	0/ 38	0/ 86
Bilirubin (umol/L), Serum			
> ULN - 1.5 x ULN (Grade 1)	5/ 46 (10.9)	3/ 37 (8.1)	8/ 83 (9.6)
> 1.5 - 3.0 x ULN (Grade 2)	3/ 47 (6.4)	3/ 38 (7.9)	6/ 85 (7.1)
> 3.0 - 10.0 x ULN (Grade 3)	0/ 48	0/ 38	0/ 86
> 10.0 x ULN (Grade 4)	0/ 48	0/ 38	0/ 86
Gamma Glutamyl Transferase (U/L), Serum			
> ULN - 2.5 x ULN (Grade 1)	1/ 45 (2.2)	1/ 36 (2.8)	2/ 81 (2.5)
> 2.5 - 5.0 x ULN (Grade 2)	1/ 48 (2.1)	0/ 37	1/ 85 (1.2)
> 5.0 - 20.0 x ULN (Grade 3)	0/ 48	0/ 38	0/ 86
> 20.0 x ULN (Grade 4)	0/ 48	0/ 38	0/ 86
Alanine Aminotransferase (U/L), Serum			
> ULN - 3.0 x ULN (Grade 1)	12/ 40 (30.0)	13/ 34 (38.2)	25/ 74 (33.8)
> 3.0 - 5.0 x ULN (Grade 2)	3/ 48 (6.3)	3/ 38 (7.9)	6/ 86 (7.0)
> 5.0 - 20.0 x ULN (Grade 3)	2/ 48 (4.2)	0/ 38	2/ 86 (2.3)
> 20.0 x ULN (Grade 4)	0/ 48	0/ 38	0/ 86
Aspartate Aminotransferase (U/L), Serum			
> ULN - 3.0 x ULN (Grade 1)	12/ 46 (26.1)	11/ 37 (29.7)	23/ 83 (27.7)
> 3.0 - 5.0 x ULN (Grade 2)	3/ 48 (6.3)	0/ 38	3/ 86 (3.5)
> 5.0 - 20.0 x ULN (Grade 3)	1/ 48 (2.1)	0/ 38	1/ 86 (1.2)
> 20.0 x ULN (Grade 4)	0/ 48	0/ 38	0/ 86
Alkaline Phosphatase (U/L), Serum			
> ULN - 2.5 x ULN (Grade 1)	5/ 46 (10.9)	3/ 32 (9.4)	8/ 78 (10.3)

Variable Criterion	AIN457 N=48 n/m (%)	Placebo in TP2 N=38 n/m (%)	Total N=86 n/m (%)
> 2.5 - 5.0 x ULN (Grade 2)	1/ 48 (2.1)	0/ 38	1/ 86 (1.2)
> 5.0 - 20.0 x ULN (Grade 3)	0/ 48	0/ 38	0/ 86
> 20.0 x ULN (Grade 4)	0/ 48	0/ 38	0/ 86
Fasting glucose increased (mmol/L), Serum			
> ULN - 8.9 mmol/L (Grade 1)	15/ 44 (34.1)	16/ 31 (51.6)	31/ 75 (41.3)
> 8.9 - 13.9 mmol/L (Grade 2)	0/ 47	0/ 38	0/ 85
> 13.9 - 27.8 mmol/L (Grade 3)	0/ 48	0/ 38	0/ 86
> 27.8 mmol/L (Grade 4)	0/ 48	0/ 38	0/ 86
Fasting glucose decreased (mmol/L), Serum			
< LLN - 3.0 mmol/L (Grade 1)	10/ 47 (21.3)	3/ 38 (7.9)	13/ 85 (15.3)
< 3.0 - 2.2 mmol/L (Grade 2)	0/ 48	3/ 38	3/ 86
< 2.2 - 1.7 mmol/L (Grade 3)	0/ 48	0/ 38	0/ 86
< 1.7 mmol/L (Grade 4)	0/ 48	0/ 38	0/ 86
Cholesterol (mmol/L), Serum			
> ULN - 7.75 mmol/L (Grade 1)	9/ 32 (28.1)	6/ 30 (20.0)	15/ 62 (24.2)
> 7.75 -10.34 mmol/L (Grade 2)	0/ 38	0/ 36	0/ 74
> 10.34-12.92 mmol/L (Grade 3)	0/ 38	0/ 36	0/ 74
> 12.92 mmol/L (Grade 4)	0/ 38	0/ 36	0/ 74
Triglycerides (mmol/L), Plasma/Serum			
1.71 - 3.42 mmol/L (Grade 1)	7/ 38 (18.4)	3/ 32 (9.4)	10/ 70 (14.3)
> 3.42 - 5.7 mmol/L (Grade 2)	1/ 38 (2.6)	0/ 35	1/ 73 (1.4)
> 5.7 - 11.4 mmol/L (Grade 3)	0/ 38	0/ 36	0/ 74
> 11.4 mmol/L (Grade 4)	0/ 38	0/ 36	0/ 74

AIN457: all patients who did not take any placebo. Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s. LLN = Lower limit of normal, ULN = Upper limit of normal. n = Number of patients with most extreme value meeting the criterion post-baseline and that is newly occurring or worsening compared to baseline. m = Number of patients with evaluable criterion who did not meet the criterion at baseline. A patient with multiple variable measurements is counted only once under the worst condition. Newly occurring means missing at baseline and 'grade x' after baseline and worsening means 'less than grade x' at baseline and worsened to 'grade x' post-baseline where $1 \leq x \leq 4$.

Hepatic enzymes

The incidence of liver enzyme abnormalities was low in the entire treatment period. Increases in ALT > 3 x ULN were detected in 8 patients (9.3%). Two patients (4.2%) were noted with ALT increase > 5 x ULN in the secukinumab treatment group while AST levels > 3 x ULN were noted in 4 patients (8.3%) and > 5 x ULN in 1 patient (2.1%) in the secukinumab treatment group. There were no patients who met the laboratory criteria of Hy's Law (Table 28).

Details of hepatic transaminases elevations (> 3 x ULN) are provided below

1. Patient A had normal ALT (17 U/L) at baseline (Day 1). Following multiple Grade 1 elevations in ALT from Day 113 onwards, an AE of recurrent increase of ALT (moderate in severity, unrelated to study treatment) was reported. On Day 617, an AE of non-alcoholic fatty liver disease (moderate in severity, unrelated to study treatment) was reported. On Day 645, ALT continued to be elevated at 139 U/L (> 3 x ULN) with concomitant AST elevation at 52 U/L and an AE of transaminases increased (moderate, unrelated to study treatment, study treatment interrupted) was reported on the same day. On Day 672, the patient was noted with a Grade 3 elevation (ALT increase > 5 x ULN)

accompanied by AST elevation. The patient had received oral methotrexate (20 mg) once weekly for ERA from Day -92 to Day 427. At the time of last reporting (Day 729), the AEs of non-alcoholic fatty liver disease and transaminases increased were ongoing with ALT at 136 U/L (> 3 x ULN) and with AST at 54 U/L.

2. Patient B was reported with normal ALT levels at baseline and noted to have a single instance of Grade 3 elevation in ALT (242 U/L: ALT increase > 8 x ULN) on Day 209 after a Grade 1 elevation on Day 29. On Day 209 (Week 28). AST on the same day was 115 U/L (> 3 x ULN). Mild AEs of ALT and AST increase (both unrelated to study treatment) were reported on Day 209 which were considered resolved on Day 244 for ALT increase and Day 245 for AST increase (Day 244: ALT: 41 U/L and AST: 26 U/L). The patient had been receiving 20 mg methotrexate once weekly (as 2 mL SC injections each) for ERA from Day -74 onwards.
3. Patient C in TP3 on Day 478 experienced a single instance of AST elevation (299 U/L, > 8 x ULN) accompanied by elevated ALT (81 U/L). An AE of AST increase (moderate in severity, suspected to be related to study treatment) was reported on Day 479. Treatment included ursodeoxycholic acid and AST and ALT levels normalized on Day 510 (ALT: 13 U/L; AST: 20 U/L). The patient had been receiving 15 mg methotrexate weekly (as SC injections) for ERA from Day -592 onwards.

Table 28 Chemistry: number and percentage of patients with newly occurring or worsening after baseline abnormalities in liver enzymes – Entire treatment period (Safety Set)

Criteria	AIN457 N=48 n/m (%)	Placebo in TP2 N=38 n/m (%)	Total N=86 n/m (%)
ALT > 3 x ULN	5/48 (10.4)	3/38 (7.9)	8/86 (9.3)
ALT > 5 x ULN	2/48 (4.2)	0/38	2/86 (2.3)
ALT > 8 x ULN	1/48 (2.1)	0/38	1/86 (1.2)
ALT > 10 x ULN	0/48	0/38	0/86
ALT > 20 x ULN	0/48	0/38	0/86
AST > 3 x ULN	4/48 (8.3)	0/38	4/86 (4.7)
AST > 5 x ULN	1/48 (2.1)	0/38	1/86 (1.2)
AST > 8 x ULN	1/48 (2.1)	0/38	1/86 (1.2)
AST > 10 x ULN	0/48	0/38	0/86
AST > 20 x ULN	0/48	0/38	0/86
ALT or AST > 3 x ULN	6/48 (12.5)	3/38 (7.9)	9/86 (10.5)
ALT or AST > 5 x ULN	3/48 (6.3)	0/38	3/86 (3.5)
ALT or AST > 8 x ULN	2/48 (4.2)	0/38	2/86 (2.3)
ALT or AST > 10 x ULN	0/48	0/38	0/86
ALT or AST > 20 x ULN	0/48	0/38	0/86
TBL > 1.5 x ULN	3/47 (6.4)	3/38 (7.9)	6/85 (7.1)
TBL > 2 x ULN	0/48	1/38 (2.6)	1/86 (1.2)
TBL > 3 x ULN	0/48	0/38	0/86
ALP > 2 x ULN	1/48 (2.1)	0/37	1/85 (1.2)
ALP > 3 x ULN	0/48	0/38	0/86
ALP > 5 x ULN	0/48	0/38	0/86
ALT or AST > 3 x ULN & TBL > 2 x ULN	0/48	0/38	0/86
ALT or AST > 5 x ULN & TBL > 2 x ULN	0/48	0/38	0/86
ALT or AST > 10 x ULN & TBL > 2 x ULN	0/48	0/38	0/86
ALP > 3 x ULN & TBL > 2 x ULN	0/48	0/38	0/86

Criteria	AIN457 N=48 n/m (%)	Placebo in TP2 N=38 n/m (%)	Total N=86 n/m (%)
ALP > 5 x ULN & TBL > 2 x ULN	0/48	0/38	0/86
ALT or AST > 3 x ULN & TBL > 2 x ULN & ALP < 2 x ULN (Hy's Law laboratory criteria)	0/48	0/38	0/86

AIN457: all patients who did not take any placebo. Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s. ULN = Upper limit of normal. Newly occurring: patients not meeting criterion at baseline and meeting criterion post-baseline. n = Number of patients who meet the designated criterion. m = Number of patients with evaluable criterion who did not meet the criterion at baseline. A patient with multiple variable measurements is counted only once under the worst condition.

Treatment Periods

Most of the newly occurring or worsening abnormalities in haematology parameters in TP2 were CTCAE Grade 1 or 2. Occurring at the highest frequencies among all haematology parameters was haemoglobin decrease in TP2. Differences were observed for newly occurring or worsening abnormalities between the secukinumab treatment group and placebo for Grade 1 haemoglobin decrease (< LLN - 100 g/L: secukinumab 18.8% and placebo 6.7%) and neutrophil decrease (< LLN - 1.5 x10^9/L: secukinumab 16.2% and placebo 2.7%). As stated earlier in entire treatment period, 2 CTCAE Grade 3 abnormalities were observed in secukinumab treatment group only for absolute neutrophils (<1.0-0.5 x10e9/L) in 2 subjects in TP2. The majority of subjects had values within normal range in TP2 with low frequencies of subjects shifting to CTCAE Grade 1 or Grade 2 from Week 12 within TP2.

Lipid profile

Overall, the frequency of newly occurring or worsening after baseline abnormalities in lipid parameters was low for the entire treatment period.

Urinalysis

Small improvements post-baseline were seen in a few parameters at various timepoints during the entire treatment period, but overall, no trends were noted.

Vital signs, physical findings, and other observations related to safety

Overall, there were only a few cases of changes in vital signs reported during the entire treatment period, which included 11 patients (12.8%) with newly occurring high sitting pulse rate and 4 patients each (4.7%) with newly occurring notable abnormalities of high systolic and high diastolic blood pressure, respectively. These were not considered clinically meaningful. Interpretation is focused on the total population for the entire study since it cannot be ruled-out that events occurring in TP2 under placebo are due to a spill-over effect by the previous secukinumab treatment in TP1 (Table 29).

Table 29 Vital signs: newly occurring notable abnormalities – Entire treatment period (Safety Set)

Vital Sign	Abnormal Category	AIN457 N=48 n/m (%)	Placebo in TP2 N=38 n/m (%)	Total N=86 n/m (%)
Systolic Blood Pressure (mmHg)	High	4/48 (8.3)	0/38	4/86 (4.7)
Diastolic Blood Pressure (mmHg)	High	2/48 (4.2)	2/38 (5.3)	4/86 (4.7)
Sitting Pulse Rate (bpm)	Low only	0/48	0/38	0/86
	High only	9/48 (18.8)	2/38 (5.3)	11/86 (12.8)
	Low and High	0/48	0/38	0/86

AIN457: all patients who did not take any placebo. Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s. Patients meeting the following criteria are considered to be patients with newly occurring abnormalities; High: >ULN (Upper limit of normal) and increased >20 (mmHg/bpm) in change from baseline; Low: <LLN (Lower limit of normal) and decreased >20 (bpm) in change from baseline. m = Number of patients at risk for an abnormality with a non-missing value at baseline and post-baseline.
n = Number of patients who meet the designated criterion. A patient with multiple variable measurements is counted only once under the worst condition.

Physical development

The changes in height and weight in these pediatric patients over the entire treatment period were similar in the secukinumab and Placebo in TP2 treatment groups, and the patients continued to grow (height and weight) over time up to the end of study.

Electrocardiograms

Overall, the incidence of newly occurring notable abnormalities in ECG parameters was low in the entire treatment period (Table 30).

Table 30 Number and percentage of patients with notably abnormal ECG parameters after baseline – Entire treatment period (Safety Set)

Criterion	AIN457 N=48 n/m (%)	Placebo in TP2 N=38 n/m (%)	Total N=86 n/m (%)
QTcF > 500 msec	0/46 (0.0)	0/38 (0.0)	0/84 (0.0)
QTcF > 480 msec	1/46 (2.2)	0/38 (0.0)	1/84 (1.2)
QTcF > 450 msec	1/46 (2.2)	0/38 (0.0)	1/84 (1.2)
QTcF changes from baseline > 30 msec	3/46 6.5)	4/38 (10.5)	7/84 (8.3)
QTcF changes from baseline > 60 msec	0/46 (0.0)	1/38 (2.6)	1/84 (1.2)
PR interval > 250 msec	0/46 (0.0)	0/38 (0.0)	0/84 (0.0)

AIN457: all patients who did not take any placebo. Placebo in TP2: all patients who took placebo in TP2 and AIN457 in other period/s. n = Number of patients with most extreme value meeting the criterion post-baseline and that is newly occurring or worsening compared to baseline. m = Number of patients with evaluable criterion. A patient with multiple variable measurements is counted only once under the worst condition.

Safety topics of interest

Safety considerations that arose from prior experience with secukinumab in psoriasis, PsA, AS, and nr-axSpA, and that may be relevant in the JIA categories of ERA and JPsA, are identified risks of infections and infestations, potential risks of malignant or unspecified tumours, IBD, hepatitis B reactivation, and

suicidal ideation and behaviour. These safety topics of interest were evaluated using standardized groupings of terms defined on a project level.

Infections and infestations (by SOC) were reported in 68 patients (79.1%). All events were mild or moderate in intensity. With the exception of one case of pneumonia, none led to discontinuation of study treatment.

AEs related to the identified risks of hypersensitivity (SMQ) (narrow) were reported in 18 patients (20.9%). All were non-serious, mild or moderate in severity, and with the exception of one case of urticaria (which occurred on secukinumab treatment in TP3 and led to withdrawal of study drug), none led to any change in study treatment. No injection site reactions were reported.

AEs related to the identified risk of neutropenia (NMQ) (narrow) were reported in 6 patients (7.0%). Four patients were receiving secukinumab at the time of the event, and 2 patients were on placebo. All events were single occurrences, non-serious, not associated with infections, and did not require treatment or interruption of study drug. One neutropenia AE was moderate, all other AEs were mild in intensity. The events were ongoing at last report in 3 patients, and resolved in 3 patients.

The search for IBD retrieved one case; this was Crohn's disease in a patient randomized to secukinumab in TP2, the event was an SAE and led to discontinuation of study drug.

No cases of MACE, mycobacterial infections, hepatitis B reactivation, or malignancy were reported.

Intentional self-injury was reported in one patient during TP3 (SMQ: suicide/self-injury); this was a case of self-inflicted injury in a patient randomized to placebo in TP2. The patient completed the study and entered the extension study. No other cases related to the risk of suicidal ideation or behaviour were reported.

Table 31 Absolute and relative frequencies for risk management plan (RMP) risks based on treatment-emergent AEs – Entire treatment period (Safety Set)

Risk category Risk name Level 1	AIN457 N=48 n (%)	Placebo in TP2 N=38 n (%)	Total N=86 n (%)
Compound and class related risk	3 (6.3)	0	3 (3.5)
Infections (Fungal) Fungal infectious disorders (HLGT)			
Infections (Herpes viral) Herpes viral infections (HLT)	2 (4.2)	2 (5.3)	4 (4.7)
Infections (Infectious pneumonia) Infectious pneumonia (NMQ) (broad)	3 (6.3)	2 (5.3)	5 (5.8)
Infections (Skin structure) Infections of skin structures (NMQ)	15 (31.3)	6 (15.8)	21 (24.4)
Infections (Staphylococcal) Staphylococcal infections (HLT)	0	1 (2.6)	1 (1.2)
Important identified risk			
Hypersensitivity Hypersensitivity (SMQ) (narrow)	8 (16.7)	10 (26.3)	18 (20.9)
Infections Infections and infestations (SOC)	38 (79.2)	30 (78.9)	68 (79.1)
Neutropenia Neutropenia (NMQ) (narrow)	3 (6.3)	3 (7.9)	6 (7.0)
Important potential risk			
Inflammatory Bowel Disease_PS Inflammatory bowel disease (NMQ) (narrow)	1 (2.1)	0	1 (1.2)
Suicidal ideation and behavior			

Suicide/self-injury (SMQ)	0	1 (2.6)	1 (1.2)

AIN457: all subjects who did not take any placebo. Placebo in TP2: all subjects who took placebo in TP2 and AIN457 in other period/s.
N= number of total subjects; n= number of subjects with events. A subject with multiple occurrences of a level under one treatment is counted only once for the same risk for that treatment.

Exposure-adjusted incidence rates over entire treatment period

The most frequent EAIR (per 100 PY) over the entire treatment period were reported in the category of Infections and infestations (SOC) for all treatment groups (135.9/100 PY). Infection of skin structures (NMQ) was the second most frequent category reported (18.0/100 PY). Other AEs with notable EAIRs (>5 per 100 PY) included Hypersensitivity (SMQ) (14.5/100 PY).

Treatment periods

In TP1, the SOC of Infections and infestations (33/86 subjects, 38.4%) was the most frequently reported AE among all risks from the RMP. In line with observations in entire treatment period, the SOC of Infections and infestations (45/75 subjects, 60.0%) represented the most frequently reported AE among all risks from the RMP in TP2 (secukinumab: 28/37 subjects, 75.7%; placebo: 17/38 subjects, 44.7%). In TP2, the other 2 most frequently reported risks were observed for Infections of skin structures (NMQ) (total: 16/75 subjects, 21.3%; secukinumab: 13/37 subjects, 35.1%; placebo: 3/38 subjects, 7.9%) and Hypersensitivity (SMQ, narrow search) (total: 8/75 subjects, 10.7%; secukinumab: 3/37 subjects, 8.1%; placebo: 5/38 subjects, 13.2%) in TP2. In TP3, the SOC of Infections and infestation was the most frequently reported AE among all risks from the RMP.

Subgroups of study population

Subgroup analyses by age, gender, weight and concomitant methotrexate use were performed for disposition, demographics, treatment exposure, treatment-emergent AEs, SAEs and important risks in Study F2304. Treatment-emergent AEs were also analyzed by JIA category (ERA and JPsA).

The results of these analyses were consistent with those of the overall population and did not reveal any safety concerns specific to any of the subgroups. Key safety results by age and weight groups are highlighted in Table 32 and Table 33, respectively.

Of note, analysis of safety revealed no indication of an increased safety concern in the age group of 2 to <6 years (3 patients) or the lowest weight group (<25 kg, 6 patients), as compared to the overall population (the <25 kg weight group also includes the 3 patients from the 2 to <6-year-old group). One of these patients (2-years-old at study entry, weight <25 kg), experienced an SAE of tonsillitis in TP1, and an SAE of adenoidal hypertrophy in TP3; neither event was considered related to study treatment (secukinumab) and the patient recovered from both events with no treatment interruption.

Table 32 Key safety findings by age for the entire treatment period (Safety Set)

	Total N=86	**2 to <6** N=3	**6 to <12** N=22	**12 to <18** N=61
Exposure				
Duration of exposure – days *				
Mean (SD)	601.0 (232.67)	726.7 (5.51)	659.0 (180.31)	573.8 (250.07)
Patient-years	141.5	6.0	39.7	95.8
Key safety events – n (%)				
AEs	79 (91.9)	3 (100)	20 (90.9)	56 (91.8)
Deaths	0	0	0	0

	Total	2 to <6	6 to <12	12 to <18
	N=86	N=3	N=22	N=61
SAEs	11 (12.8)	1 (33.3)	1 (4.5)	9 (14.8)
Key risks				
Infections	68 (79.1)	2 (66.7)	16 (72.7)	50 (82.0)
Suicide/self-injury	1 (1.2)	0	1 (4.5)	0
Inflammatory bowel disease	1 (1.2)	0	0	1 (1.6)
Malignant tumors	0	0	0	0
Hepatitis B reactivation	0	0	0	0

* Exposure is expressed in relation to exposure to study treatment, i.e., patients randomised to placebo in TP2 were exposed to placebo for some part of the whole duration

Table 33 Key safety findings by weight for the entire treatment period (Safety Set)

	Total	<25 kg	25 to <50 kg	≥50 kg
	N=86	N=6	N=24	N=56
Exposure				
Duration of exposure – days *				
Mean (SD)	601.0 (232.67)	572.7 (239.95)	689.3 (148.88)	566.1 (253.83)
Patient-years	141.5	9.4	45.3	86.8
Key safety events – n (%)				
AEs	79 (91.9)	5 (83.3)	23 (95.8)	51 (91.1)
Deaths	0	0	0	0
SAEs	11 (12.8)	1 (16.7)	1 (4.2)	9 (16.1)
Key risks				
Infections	68 (79.1)	4 (66.7)	18 (75.0)	46 (82.1)
Suicide/self-injury	1 (1.2)	0	0	1 (1.8)

* Exposure is expressed in relation to exposure to study treatment, i.e., patients randomised to placebo in TP2 were exposed to placebo for some part of the whole duration

Immunogenicity and immunological events

In study F2304 there were no patients with treatment-emergent ADAs (i.e., negative at baseline and positive during treatment). One patient in the Placebo in TP2 group was reported having ADAs at baseline only. This patient was reported to have an immunogenicity-related mild AE of urticaria on Day 326, which was considered unrelated to the study treatment; no action was taken with study treatment, and the event was considered resolved with treatment on Day 328.

Safety related to drug-drug interactions and other interactions

No new information regarding drug interactions was generated in Study F2304.

Live vaccines should not be given concurrently with secukinumab. The immunomodulatory nature of secukinumab may reduce immune responses to live attenuated vaccines or may render a recipient prone to infectious manifestations (including secondary transmission) resulting from attenuated live vaccines. Patients receiving secukinumab may receive concurrent inactivated or non-live vaccinations.

Data from study CAIN457A2224 suggest that secukinumab does not suppress the humoral immune response to the meningococcal or influenza vaccines.

Population results in PsA and AS patients with secukinumab do not suggest that methotrexate has an impact on the disposition of secukinumab.

Discontinuation due to adverse events

AEs leading to discontinuation

In study F2304 the incidence of AEs leading to discontinuation was low and reported in 8/86 patients (9.3%) in the entire treatment period. These AEs as per SOC were reported in no more than 1-2 patients in either treatment group and were non-serious, with the exception of Crohn's disease. AEs leading to discontinuation were reported in both JIA categories (ERA: 3 patients, JPsA: 5 patients).

Treatment periods

In TP1, 1 out of 86 subjects had joint effusion AE causing study drug discontinuation. During TP2, a similar proportion of subjects in both treatment groups had AEs leading to study drug discontinuation (secukinumab: 2/37 subjects, 5.4%; placebo: 2/38 subjects, 5.3%). All AEs (pneumonia, enthesopathy, psoriasis) were reported as non-serious except for the SAE of Crohn's disease. In TP3, 3 out of 32 subjects had enthesopathy, epilepsy and urticaria AEs respectively, which led to study drug discontinuation.

AEs leading to dose interruption or adjustment

In study F2304 the incidence of AEs leading to dose interruption was low and reported in 7/86 patients (8.1%) in the entire treatment period. AEs leading to dose interruption were reported in both JIA categories (ERA: 3 patients, JPsA: 4 patients).

Treatment Periods

Over TP1, 3 out of 86 subjects had AEs leading to temporary dose interruption. One subject each had AEs by PT pharyngotonsillitis, upper respiratory tract infection, blood alkaline phosphatase increased. Two out of 37 subjects (5.4%) in the secukinumab treatment group only had AEs leading to temporary dose interruption (1 subject each: diarrhoea and transaminases increased) in TP2. AEs leading to dose adjustments or temporary interruption were reported by 3 of 32 subjects (9.4%; majority were in SOC Infection and infestations) in TP3.

Post marketing experience

No post-marketing data is available for ERA and JPsA, the paediatric JIA categories under assessment.

2.5.1. Discussion on clinical safety

Safety is based on a single phase 3 study F2304 in the target population. In addition, cross study comparative tabulation of the safety results of this single study in the current target indication and the pooled data from two previous (recently approved) paediatric psoriasis clinical trials are presented. The

MAH also refers to the large safety data set in adults, which includes post marketing safety data. In addition, an updated population PK model of secukinumab, utilising paediatric and adult data from several indications, has been provided to support the submission.

Exposure

Overall, a single study F2304 with the mean duration of exposure to study treatment (secukinumab or placebo) during the study period (TP1 + TP2 + TP3) of 601 days, with a patient-time of 141.5 PY could, in principle, be considered adequate. However, the CHMP raised objections since the safety data in 2 - <6 years of age are limited to 3 subjects. Furthermore, all of these subjects were randomised to receive placebo in TP2, and even though they are continuing on open-label secukinumab in the long-term extension study, long-term safety data will be, at best, only available from these three patients. The MAH revised their claim during the procedure to exclude children from 2 to less than 6 years of age from the indication.

Safety results in Study F2304

- TEAE

Infections and infestations represented the most frequently reported safety topic of interest driven by mild to moderate events of nasopharyngitis and upper respiratory tract infections. There were no reported cases of MACE, mycobacterial infections, hepatitis B reactivation, or malignancy.

In study F2304 the majority of subjects experienced TEAEs during the study. Overall (N = 86 patients), the reported TEAEs were most frequently categorized in the SOCs Infections and Infestations (68 patients, 71.1%), Gastrointestinal disorders (45 patients, 52.3%) and Musculoskeletal and connective tissue disorders (32 patients, 37.2%).

The most frequently reported TEAEs overall by PT (those occurring in ≥15 % of subjects) were nasopharyngitis (27 patients, 31.4%), diarrhoea (17 patients, 19.8%), nausea (19 patients, 22.1%), upper respiratory tract infection (19 patients, 22.1%) and cough (13 patients, 15.1%).

By SOC the frequencies of TEAEs in the category Respiratory, thoracic and mediastinal disorders were higher in the secukinumab treatment arm, 16 (33.3%) vs 9 (23.7%) in the placebo and Neoplasms benign, malignant and unspecified (including cysts and polyps), 5 (10.4%) in the IMP arm vs none in the placebo arm. In the placebo arm TEAEs were more numerous in the SOC category Skin and subcutaneous tissue disorders 14 (29.25%) vs 16 (42.15%) and Nervous system disorders 6 (12.5) vs 9 (23.7%) and Blood and lymphatic system disorders 3 (6.3) vs 7 (18.4), in the secukinumab and placebo arms, respectively.

By PT the frequencies of TEAEs were more numerous in the IMP treatment arm for the PT of Diarrhoea 11 (22.9) vs 6 (15.8), Arthralgia 8 (16.7%) vs 4 (10.5%), Pharyngitis 6 (12.5%) vs 3 (7.9%) and Influenza 5 (10.4%) vs 0. The frequencies were quite similar between the treatment arms for Nasopharyngitis 16 (33.3%) vs 11 (28.9%), Nausea 11 (22.9%) vs 8 (21.1%) and Upper respiratory tract infection 10 (20.8) vs 9 (23.7%) in the IMP and placebo arms, respectively.

The AE incidence in Infections and infestations was mainly driven by events of nasopharyngitis, upper respiratory tract infection and pharyngitis, while diarrhoea, nausea and vomiting were the most frequent AEs in the Gastrointestinal disorders SOC. Arthralgia was the most frequently reported AE in the Musculoskeletal and connective tissue disorders SOC.

Most TEAEs in the entire treatment period were either mild or moderate: 40 (46.5%) patients reported only mild AEs, while 37 (43.0%) patients reported AEs up to moderate in severity. Severe AEs occurred at a low frequency: 2 patients (2.3%) reported a severe AE, both of which (joint effusion and aphthous ulcer) occurred in TP1. No severe events occurred in TP2 or TP3.

- SAEs

No deaths were reported in the study.

Treatment emergent SAEs were reported for 11 patients (12.8%) overall, and all were reported in patients receiving secukinumab. The SAE were mainly single occurrences in both treatment arms and did not show any trends or clustering.

By treatment period, SAEs were reported for 2 patients in TP1, 5 patients in TP2 (all were randomized to secukinumab), and 5 patients in TP3. The most frequently reported SAEs were Infections and infestations (SOC; 7 patients, 8.1%). There was no trends or patterns or clustering with respect to type of SAE reported, and SAEs were reported in both JIA categories (ERA: 4 patients, JPsA: 7 patients). One of the SAEs led to discontinuation of study drug; this was an SAE of Crohn's disease also mentioned hereafter. SAEs considered related to study treatment by the investigator were reported for 2 patients: In TP2, the Crohn's disease was reported as an SAE in a JPsA patient. Study medication was discontinued due to the event. In addition, in TP3, a JPsA patient who was randomized to placebo in TP2 experienced a flare that was reported as an SAE and study medication (secukinumab) was continued.

- Safety issues of special interest

Based on previous experience, identified risks of infections and infestations, potential risks of malignant or unspecified tumours, IBD, hepatitis B reactivation, and suicidal ideation and behaviour were taken to be putatively also relevant for the JIA categories of ERA and JPsA. The safety results appeared, in general, to be consistent with the known safety profile of secukinumab.

- Malignancies

No malignancies were observed in the study. However, in the SOC Neoplasms benign, malignant and unspecified (including cysts and polyps), a discrepancy between the treatment arms was seen, with an incidence of 5 (10.45%) in the secukinumab treatment arm in comparison with none in the placebo arm. The MAH discussed in more detail this finding and the possible reasons for the observed discrepancy and based on the provided data, malignancies appear not to be a safety concern, in short term, for this target paediatric population.

- Laboratory results

Evaluation of laboratory results, vital signs, ECGs, and other physical findings did not identify any new safety concerns. Most of the newly occurring or worsened haematology and clinical chemistry abnormalities were CTCAE grade 1 or grade 2. Of note is, that 2 patients with an AE of neutropenia randomized to secukinumab in TP2 developed a grade 3 decrease in neutrophil count. These were, however, single occurrences, resolved without interruption of study drug, and importantly, were not associated with infections. The incidence of liver abnormalities was low, and there were no patients who met the laboratory criteria of Hy's Law.

- Growth and maturation

No evidence of growth retardation was observed, based on changes in height and weight measured during the study. The changes observed were similar in the secukinumab and placebo groups in TP2, and the patients continued to grow over time up to the end of study. As no assessment of Tanner staging of pubertal development was performed in this study, the MAH referred to data from the paediatric PsO study A2310 (reviewed as part of procedure EMEA/H/C/003729/II/0057). The results suggest that secukinumab did not have any effect on sexual maturation of the paediatric PsO patients treated in the study. Some residual uncertainly may remain, as no data in the target indication itself are available; however, this issue was not further pursued by the CHMP in the 6-18 years subgroup. In

the 2-<6 years subgroup, the CHMP expressed concerns during the assessment regarding the development of the immune system, growth and maturation in children in this youngest age group. The MAH revised their claim during the procedure to exclude children from 2 to less than 6 years of age from the indication.

- Immunogenicity

There were no patients with treatment-emergent anti-drug antibodies in the study.

- Subgroup analysis

Subgroup analyses by age (2 - < 6 years, 6 - < 12 years and 12 - < 18 years) and weight (< 25 kg, 25 - <50 kg, ≥ 50 kg) for incidence rate of TEAEs in TP1 did not reveal any safety concerns and did not show increased incidence rates for the lower age (2 - < 6 years) and lower weight (< 25 kg) groups. However, the CHMP raised objections on the small numbers in the lowest age and weight categories, which hampers firm conclusions. The MAH revised their claim during the procedure to exclude children from 2 to less than 6 years of age from the indication.

Subgroup analyses by gender, concomitant methotrexate use, for baseline characteristics of disposition, background and demographics, duration of exposure, crude incidence and EAIR per 100 PY of treatment-emergent AEs, SAEs and safety issues of special interest AEs, did not reveal any safety concerns.

In the course of the study F2304 the patients received, in addition to the IMPs methotrexate (and/or other DMARDs). This was not included in the initial indication claim. As indicated in the efficacy section, the MAH revised the indication claim during the procedure to indicate that secukinumab may be used alone or in combination with methotrexate.

- Discontinuations due to AEs

Discontinuations due to AEs were not numerous. There were none in the TP1, 1 (2.7%) in TP2 and none in the TP3 in the secukinumab treatment arm. The respective incidences were only slightly higher in the placebo arm: 2 (5.3%) in TP2 and 3 (14.3) in TP3 (placebo in TP2).

- Long-term data

Study F2304 is a 2-year study (core phase) with an additional extension study to assess the efficacy and safety in the JIA categories of ERA and JPsA. Safety data are available for all patients who received at least one dose of study drug up to final core study DBL (with the above-mentioned limitations in the smallest of children). Data from the ongoing extension study (Study F2304E1) was not included in this application, and the MAH has committed to submitting these data (see RMP section 2.6).

Clinical data in the youngest (2 - < 6 years) age group is scarce, especially long-term data (at best will be available only for the 3 patients currently participating in the long-term extension study F2304E1). As there are no other ongoing or planned studies in JIA or other paediatric patients that could provide relevant additional efficacy or safety data, the MAH was requested during the procedure to discuss in detail and propose a plan of possible means whereby the long-term safety, in this youngest age group, could be followed-up.

The MAH has, with due diligence, investigated the feasibility of accruing these and concluded that a long-term safety assessment was considered not feasible due to limited sample size, complexity of pooling data from different origins, difficulty to account for previous exposure or confounders, and ultimately limited precision of estimates. Therefore, based upon these considerations the MAH has determined that it is not feasible to obtain sufficient data in JPsA or ERA patients aged 2 to <6 years-old using a

combination registry approach i.e. to conduct a registry-based PASS in this subset of patients aged 2 to 6 years old. The MAH withdrew the indication claim in the 2-<6 years subgroup during the procedure.

Extrapolation

It is further noted, that tabulated cross study comparative data with pooled paediatric psoriasis studies study A2310 and study A2311 were presented and the MAH refers also to the large Cosentyx adult safety set, including post-marketing data. The safety profile for secukinumab observed in study F2304 was comparable to that of secukinumab in the pooled psoriasis paediatric studies and adult safety data. However, considering that there may be age-related differences e.g. in comorbidities, the strategy and adequacy of extrapolation from these sources is not considered ideal, as the paucity of actual data among patients aged 2 - <6 years limits possibilities to qualify the extrapolation model. This was acknowledged by the MAH. During the procedure, the MAH revised their indication claim to children 6 years of age and older.

Overall, the safety profile of secukinumab in study F2304 in a population of paediatric patients, six years and older, in the JIA categories of ERA and JPsA, appeared consistent with the known safety profile of secukinumab, and appeared not to show any new or unexpected safety signals.

2.5.2. Conclusions on clinical safety

The safety profile of secukinumab in the single phase 3 study F2304 of the paediatric population, 6 years and older, with the juvenile idiopathic arthritis categories of psoriatic arthritis and enthesitis-related arthritis shows no new or unexpected safety signals. The safety data appeared broadly consistent with the overall safety profile of secukinumab based on the existing extensive adult safety data across multiple indications, including psoriasis, PsA, and axial SpA (both non-radiographic axial SpA and AS) and also with that of the patients with the recently approved indication of paediatric psoriasis.

The main uncertainty and safety concern was related to the very limited experience in children under 6 years of age, particularly as the target population for secukinumab (or any anti-IL-17 therapy) would have been extended to this age group for the first time. Addressing this limitation e.g. through an appropriately designed post-authorisation safety study was not considered feasible, and the MAH decided to exclude this age group from the therapeutic indication during the procedure.

The CHMP concluded that the safety profile of secukinumab in treatment of paediatric patients, 6 years and older, with the juvenile idiopathic arthritis categories of psoriatic arthritis and enthesitis-related arthritis is considered acceptable.

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 version 10.2 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 10.2 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

Important identified risks	Infections and infestations Hypersensitivity
Important potential risks	Malignant or unspecified tumors Major Adverse Cardiovascular Events (MACE) Hepatitis B reactivation Suicidal ideation and behavior
Missing information	Fetal exposure in utero Long-term safety data

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances.				
None				
Category 3 - Required additional pharmacovigilance activities.				
Corrona Psoriasis Registry Ongoing	The primary goal of the registry is to assess the incidence and nature of malignancies in a real-world population of moderate-to-severe psoriasis patients (including PsA patients) on secukinumab therapy.	Malignant or unspecified tumors Long-term safety, Suicidal ideation and behavior	Final study report submission	June-2033
CAIN457F2304E1 Secukinumab longterm efficacy, safety and tolerability in JPsA and ERA up to 4 Years Ongoing	The primary objective of this study is to evaluate the long-term efficacy of subcutaneously administered secukinumab (provided as pre-filled syringes) with respect to JIA ACR30 response over time up to Week 308 visit in patients with active JPsA and ERA subtypes of JIA and who completed the Phase III study CAIN457F2304.	Long-term safety	Final study report submission	15-Jul-2025

Risk minimisation measures

Safety concern	Routine risk minimization activities
	• None **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine.
Suicidal ideation and behavior	**Routine risk communication:** • No specific measures are required for patients receiving secukinumab - standard of care is adequate. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine.
Missing information	
Fetal exposure in utero	**Routine risk communication:** • SmPC Section 4.6. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine.
Long-term safety data	**Routine risk communication:** • No risk minimization measure is considered necessary at this time. Routine risk minimization (standard of care for the target population) is considered sufficient. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine.

2.7. Update of the Product information

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

In addition, an editorial change was made in the Section 4.2 of the SmPC for the 150/300 mg solution for injection to delete a duplicate paragraph.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- The MAH has performed satisfactory user consultations of Cosentyx PL in context of original MA application (plaque psoriasis) and extension of indication procedures (PsA, AS and paediatric plaque psoriasis).

- Both adult and adolescent users have been included into the readability testing. For children, it is expected that the PL would be read by adult caregivers.

- Given that the proposed PL changes related to the new indication of juvenile idiopathic arthritis

are not extensive, a new user consultation is not deemed necessary.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The JIA categories ERA and JPsA are chronic conditions with decreased health-related quality of life and risk of permanent joint damage. JIA may persist into adulthood, causing ongoing significant morbidity and impaired quality of life and imposing a significant burden on patients, their parents, and society.

ERA and JPsA, as defined by the ILAR classification, represent paediatric correlates of the adult conditions for which secukinumab is approved, i.e., AS, nr-axSpA, and PsA. While JPsA includes patients with conditions similar to adult PsA, many paediatric patients with spondyloarthritis-like conditions are classed as ERA (as well as sometimes JPsA).

ERA is considered a form of undifferentiated spondyloarthritis. Although patients with ERA may not have signs of axial disease at their time of diagnosis, many of these children later develop sacroiliitis and evolve into spondyloarthropathies in adulthood. Similarities between ERA and adult spondyloarthritis include enthesitis, arthritis, and inflammatory back pain, and a shared genetic susceptibility through the HLA-B27 risk allele linked to activation of the IL-23 / IL-17 axis. Another common feature is inflammatory bowel disease, present in a subset of ERA and adult spondyloarthritis patients. While adults experience predominantly inflammatory back pain, common presenting features of juvenile-onset disease are localized more to hips and peripheral joints. Sacroiliitis, if present, can also be clinically silent in children with ERA.

3.1.2. Available therapies and unmet medical need

The goal of therapy in all forms of JIA, including ERA and JPsA, is to achieve an inactive disease state, prevent disability and damage, and ensure the age-appropriate development of affected children and adolescents.

NSAIDs are the first-line of treatment in ERA and JPsA. They provide symptomatic relief, but are not disease-modifying and do not alter disease progression; in addition, some patients respond poorly to NSAIDs. Intra-articular corticosteroid injections are widely used to induce rapid relief of inflammatory symptoms and for functional improvement, and they play an important part in the prevention of deformities secondary to joint contractures; however, corticosteroids should not be used long-term. Methotrexate, which is the most widely used synthetic DMARD in JIA, does not improve axial disease, and the ACR JIA guidelines advise against methotrexate monotherapy in children with sacroiliitis and enthesitis.

TNF inhibitors are recommended for patients with enthesitis and/or sacroiliitis who do not achieve disease control on NSAIDs. However, many children, including patients with ERA and JPsA, do not respond to TNF therapy. Furthermore, whereas other classes of biologic agents have become available or are being studied for certain types of JIA, there are currently no medicinal products authorised in the EU for use in both ERA and JPsA. There is thus an unmet need for new therapies with high efficacy and a favourable safety and tolerability profile for these conditions in children and adolescents.

3.1.3. Main clinical studies

The main clinical study to support the current variation application (study F2304) was a double-blind, placebo-controlled, event-driven randomised withdrawal study, evaluating the efficacy and safety of secukinumab in 86 paediatric patients aged 2 to < 18 years with JIA subtypes of ERA or JPsA. During Treatment Period 1, all subjects received open-label secukinumab for 12 weeks. At the end of TP1, subjects with a JIA ACR 30 response were randomised to continue on secukinumab or switch to placebo (Treatment Period 2 [TP2]). Follow-up continued until the subject developed a flare, or for a maximum of 100 weeks. The primary endpoint was time to flare during TP2.

3.2. Favourable effects

Study F2304 met its primary endpoint: for the combined ERA and JPsA categories, the time to flare in TP2 was statistically significantly longer in the secukinumab group compared to the placebo group (hazard ratio of flare event, HR = 0.28, 95% CI: 0.13 to 0.63, p<0.001). The risk of flare was reduced by 72% for subjects on secukinumab compared with subjects on placebo in TP2. Robustness of the primary analysis was appropriately supported by a tipping point analysis with a worst-case scenario.

During TP2, there were a total of 21 flare events in the placebo group compared to 10 flare events in the secukinumab group. At 1 year, the flare-free rate was 76.7% (95% CI: 58.7, 87.6) in the secukinumab group and 54.3% (95% CI: 37.1, 68.7) in the placebo group. By the end of TP2, median time to disease flare was not reached in the secukinumab group and was 453 days in the placebo group.

Prolongation in time to disease flare in TP2 was observed in both JIA categories (ERA: HR=0.45, 95% CI: 0.16 to 1.28; JPsA: HR=0.15, 95% CI: 0.04 to 0.57). In descriptive subgroup analyses based on age, weight, gender and methotrexate use at baseline, a favourable effect of secukinumab was seen across all analysed subgroups. The difference between treatment groups was more pronounced among subjects who were not using methotrexate.

During TP1 (i.e., when all subjects were receiving open-label secukinumab), improvements in disease activity was observed already during the first weeks. At Week 12, a JIA ACR 30 response was achieved by 75/83 subjects (90.4%) completing TP1, a JIA ACR 70 response was achieved by 58/83 subjects (69.9%), and inactive disease status was achieved by 30/83 subjects (36.1%).

Improvements were seen across all JIA ACR core components, with the largest improvements seen on active joint count (79.3%) and physician's global assessment (77.4%), and the smallest improvement (13.6%) seen on median CRP.

In descriptive subgroup analyses for TP1 based on age and weight group, gender and methotrexate use at baseline, JIA ACR 30 response rates ranging from 82.8% to 100%, and JIA ACR 50 response rates ranging from 79.3% to 100% were seen across the different subgroups. Although based on descriptive statistics only, the results were consistent across the subgroups analysed.

During TP1, mean JADAS-27 score decreased from 15.07 (SD 7.13) at baseline to 4.64 (SD 4.72) at Week 12; mean decrease from baseline to Week 12 was -10.49 (SD 7.23).

3.3. Uncertainties and limitations about favourable effects

Actual clinical experience in the youngest patients initially proposed for inclusion in the indication and posology (i.e., patients 2 - <6 years of age) was limited to 3 subjects; furthermore, all of these subjects were randomised to receive placebo in TP2, further limiting the opportunity for conclusions

regarding longer-term effects. All of these subjects developed at least a JIA ACR 70 response at the end of TP1, but the experience in these youngest children was still considered very limited. The MAH decided to exclude this age group from the indication.

At the end of TP2, only 55% of subjects withdrawing to placebo had experienced a flare event; thus, in the clinical setting, a substantial proportion of patients with an early response to secukinumab could incur longer-term treatment benefit even with a short treatment course. While the available results are not considered sufficiently robust to formalise different long-term treatment recommendations into the SmPC, these aspects are considered of potentially substantial clinical relevance, and the MAH is recommended to study the effectiveness and usability of different long-term treatment strategies in JIA patients, including strategies involving a "treatment withdrawal followed by retreatment as needed" approach in the post-authorisation setting.

3.4. Unfavourable effects

In study F2304 the majority of subjects experienced TEAEs during the study. Overall (N = 86 patients), the reported TEAEs were most frequently categorized in the SOCs Infections and Infestations (68 patients, 71.1%), Gastrointestinal disorders (45 patients, 52.3%) and Musculoskeletal and connective tissue disorders (32 patients, 37.2%).

By SOC the frequencies of TEAEs in the category Respiratory, thoracic and mediastinal disorders were higher in the secukinumab treatment arm, 16 (33.3%) vs 9 (23.7%) in the placebo and Neoplasms benign, malignant and unspecified (including cysts and polyps), 5 (10.4%) in the IMP arm vs none in the placebo arm. In the placebo arm TEAEs were more numerous in the SOC category Skin and subcutaneous tissue disorders 14 (29.25%) vs 16 (42.15%) and Nervous system disorders 6 (12.5) vs 9 (23.7%) and Blood and lymphatic system disorders 3 (6.3) vs 7 (18.4), in the secukinumab and placebo arms, respectively.

The most frequently reported TEAEs overall by PT (those occurring in ≥15 % of subjects) were nasopharyngitis (27 patients, 31.4%), diarrhoea (17 patients, 19.8%), nausea (19 patients, 22.1%), upper respiratory tract infection (19 patients, 22.1%) and cough (13 patients, 15.1%).

By PT, the frequencies of TEAEs were higher in the IMP treatment arm in comparison with placebo for the PTs of Diarrhoea 11 (22.9) vs 6 (15.8), Arthralgia 8 (16.7%) vs 4 (10.5%) and Pharyngitis 6 (12.5%) vs 3 (7.9%). The frequencies were similar between the treatment arms for Nasopharyngitis 16 (33.3%) vs 11 (28.9%), Nausea 11 (22.9%) vs 8 (21.1%) and Upper respiratory tract infection 10 (20.8) vs 9 (23.7%) in the IMP and placebo arms, respectively.

The AE incidence in Infections and infestations was mainly driven by events of nasopharyngitis, upper respiratory tract infection and pharyngitis, while diarrhoea, nausea and vomiting were the most frequent AEs in the Gastrointestinal disorders SOC. Arthralgia was the most frequently reported AE in the Musculoskeletal and connective tissue disorders SOC.

Most TEAEs in the entire treatment period were either mild or moderate: 40 (46.5%) patients reported only mild AEs, while 37 (43.0%) patients reported AEs up to moderate in severity. Severe AEs occurred at a low frequency: 2 patients (2.3%) reported a severe AE, both of which (joint effusion and aphthous ulcer) occurred in TP1. No severe events occurred in TP2 or TP3.

No deaths were reported in the study.

Treatment emergent SAEs were reported for 11 patients (12.8%) overall, and all were reported in patients receiving secukinumab. By treatment period, SAEs were reported for 2 patients in TP1, 5 patients in TP2 (all were randomized to secukinumab), and 5 patients in TP3. The most frequently

reported SAEs were Infections and infestations (SOC; 7 patients, 8.1%). There was no trends or patterns or clustering with respect to type of SAE reported, and SAEs were reported in both JIA categories (ERA: 4 patients, JPsA: 7 patients). One of the SAEs led to discontinuation of study drug. SAEs considered related to study treatment by the investigator were reported for 2 patients: In TP2, the Crohn's disease was reported as an SAE in a JPsA patient. Study medication was discontinued due to the event. In addition, in TP3, a JPsA patient who was randomized to placebo in TP2 experienced a flare that was reported as an SAE and study medication (secukinumab) was continued.

Subgroup analyses based on age and weight group, gender and concomitant methotrexate use were performed for treatment-emergent AEs, SAEs and important risks in Study F2304. Treatment-emergent AEs were also analysed by JIA category. The results of these analyses were consistent with those of the overall population and did not reveal any safety concerns specific to any of the subgroups.

3.5. Uncertainties and limitations about unfavourable effects

Overall, a single study F2304 with the mean duration of exposure to study treatment (secukinumab or placebo) during the study period (TP1 + TP2 + TP3) of 601 days, with a patient-time of 141.5 PY could, in principle, be considered adequate for the assessment of B/R of the newly proposed indications. However, a concern was that the safety data on patients 2 - <6 years of age are limited to 3 subjects. Furthermore, all of these subjects were randomised to receive placebo in TP2, and even though they are continuing on open-label secukinumab in the long-term extension study, long-term safety data will be, at best, only available from these three patients.

At the CHMP's request, the MAH provided a detailed review of the currently available scientific information on the immune development in children with regard to the role and function of IL-17 in the developing immune function, both from the non-clinical and clinical point of view (including both non-clinical and clinical systematic reviews of the available peer reviewed literature), to further support the overall safety claims in the youngest patient age group. In addition, as there are no other ongoing or planned studies in JIA or other paediatric patients that could provide relevant additional efficacy or safety data, the MAH was requested during the procedure to discuss in detail and propose a plan of possible means whereby the long-term safety, in this youngest age group, could be followed-up. The MAH has, with due diligence, investigated the feasibility of accruing these and concluded that a long-term safety assessment was considered not feasible due to limited sample size, complexity of pooling data from different origins, difficulty to account for previous exposure or confounders, and ultimately limited precision of estimates. Therefore, based upon these considerations the MAH has determined that it is not feasible to obtain sufficient data in JPsA or ERA patients aged 2 to <6 years-old using a combination registry approach i.e. to conduct a registry-based PASS in this subset of patients aged 2 to 6 years old and ultimately withdrew the indication claim in the 2-<6 years patients during the procedure.

3.6. Effects Table

Table 34 *Effects Table for Cosentyx in treatment of ERA and JPsA (study F2304 (data cut-off: 10 Dec 2020)*

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Flare	Time to flare, TP2	HR	secukinumab vs. placebo: 0.28		95% CI: 0.13 to 0.63, p<0.001	F2304
	Number of flare events, TP2	n/N, %	10/37, 27.0%	21/38, 55.3%		F2304
JIA ACR	JIA ACR 30 response rate, TP1	n/N, %	75/83, 90.4%		95% CI: 81.4%, 95.4%	F2304
	JIA ACR 70 response rate, TP1	n/N, %	58/83, 69.9%		95% CI: 58.7%, 79.2%	F2304
	JIA ACR 90 response rate, TP1	n/N, %	33/83, 39.8%		95% CI: 29.4%, 51.1%	F2304
	Inactive disease, TP1	n/N, %	30/83, 36.1%		95% CI: 26.1%, 47.5%	F2304
JADAS-27	JADAS-27 score at Week 12	Mean (SD)	4.64 (4.72)			F2304
	JADAS-27, mean change BL to Week 12	Mean (SD)	-10.49 (7.23)			F2304
Unfavourable Effects						
Number of patients, all		N	86		Safety Analysis set	Study F2304
Any TEAEs, by SOC	Number of patients	n (%)	44 (91.7)	35 (92.1)	Single phase 3 with small numbers in lowest age and weight categories, limited and pending long term data.	Study F2304
Any related TEAE	Number of patients	n (%)	32 (37.2)		same concerns	Study F2304
Infections and infestations	Number of patients	n (%)	38 (79.2)	30 (78.9)	same concerns	Study F2304
Gastrointestinal disorders, All	Number of patients	n (%)	24 (50.0)	21 (55.3)	same concerns	Study F2304
Musculoskeletal and connective tissue disorders, All	Number of patients	n (%)	17 (35.4)	15 (39.5)	same concerns	Study F2304
Skin and cutaneous tissue disorders	Number of patients	n (%)	14 (29.2)	16 (42.1)	same concerns	Study F2304
Respiratory, thoracic and		n (%)	16 (33.3)	9 (23.7)	same concerns	Study F2304

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
mediastinal disorders						
Any Grade 3 TEAEs	Number of patients	n (%)	2	0	same concerns	Study F2304
Any Grade 4 TEAEs	Number of patients	n (%)	0	0	same concerns	Study F2304
Any Grade 5 TEAEs	Number of patients	n (%)	0	0	same concerns	Study F2304
Any SAE	Number of patients	n (%)	12.8%	0	same concerns	Study F2304
Any Related SAE	Number of patients	n (%)	1	1	same concerns	Study F2304
Discontinuations related to AE	Number of patients	n (%)	TP1:0 TP2:1 (2.7) TP3: 0	TP2:2 (5.3) TP3:3 (14.3)	same concerns	Study F2304
Deaths, All	Number of patients	n (%)	0	0	same concerns;	Study F2304

Abbreviations: ACR, American College of Rheumatology; AE, adverse event; CI, confidence interval; ERA, Enthesitis related arthritis; HR, hazard ratio; JADAS-27, Juvenile Arthritis Disease Activity Score based on 27 joints; JIA, Juvenile Idiopathic Arthritis; JPsA, Juvenile Psoriatic Arthritis; n = number of responders; N = number of subjects; PP, per protocol; SAE, serious adverse event; TEAE, treatment emergent adverse event; TP, treatment period

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The MAH initially applied for a new indication for secukinumab (Cosentyx) to include treatment of Juvenile Idiopathic Arthritis (Enthesitis-Related Arthritis and Juvenile Psoriatic Arthritis) in patients 2 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy. The subtypes being applied for are recognised entities within the ILAR classification scheme for JIA. Furthermore, secukinumab is already authorised for the adult indications of axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis) and psoriatic arthritis, and it is agreed that that these entities can be considered to appropriately correlate with the proposed paediatric indications.

Whereas medicinal products are available for the treatment of JIA, these are mostly authorised for polyarticular JIA, and a dearth of therapies still exists for other subtypes, including ERA and JPsA. Secukinumab in the proposed target groups can therefore be considered to address a clinically relevant unmet need.

In study F2304, a statistically significant treatment effect was shown for secukinumab in respect to time to flare in the randomised withdrawal phase. Furthermore, although TP1 was conducted in an open-label manner, the observed response rates are sufficiently high to be considered evidence of a drug effect. The demonstrated effects can be considered clinically relevant and thus generally supportive of the new indication.

From the safety perspective, acknowledging the limitations of cross study comparisons, the safety profile observed for secukinumab in the single phase 3 study F2304 appeared, so far, broadly similar to what has previously been reported for secukinumab.

The main uncertainty and safety concern was related to the very limited experience in children under 6 years of age, particularly as the target population for secukinumab (or any anti-IL-17 therapy) would

have been extended to this age group for the first time. Addressing this limitation e.g. through an appropriately designed post-authorisation safety study was not considered feasible, and the MAH decided to exclude this age group from the therapeutic indication during the procedure.

3.7.2. Balance of benefits and risks

Overall, the reported study is considered to provide adequate evidence of efficacy of secukinumab in the treatment of patients with the ERA and JPsA subtypes of JIA in patients aged 6-18 years, and the observed safety profile is largely consistent with extensive experience gained in adult patients. The extensive experience available with secukinumab in corresponding adult indications can also be considered supportive of a beneficial benefit-risk profile.

3.8. Conclusions

The overall B/R of Cosentyx is positive in the following indication:

Juvenile idiopathic arthritis (JIA)

Enthesitis-related arthritis (ERA)

Cosentyx, alone or in combination with methotrexate (MTX), is indicated for the treatment of active enthesitis-related arthritis in patients 6 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy (see section 5.1).

Juvenile psoriatic arthritis (JPsA)

Cosentyx, alone or in combination with methotrexate (MTX), is indicated for the treatment of active juvenile psoriatic arthritis in patients 6 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy (see section 5.1).

4. Recommendations

Outcome

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

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

C.I.6 (Extension of indication)
Extension of indication to include treatment of Juvenile Idiopathic Arthritis (Enthesitis-Related Arthritis and Juvenile Psoriatic Arthritis) in patients 6 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy for Cosentyx alone or in combination with methotrexate; 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 10.2 of the RMP has been approved.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and

to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to 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/0372/2018 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 EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion "Cosentyx EMEA/H/C/003729/II/0079".

Attachments

1. SmPC and Package Leaflet (changes highlighted) as adopted by the CHMP on 19 May 2022