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CLINICAL SCIENCE

Secukinumab in enthesitis-related arthritis and juvenile psoriatic arthritis: a randomised, double-blind, placebo-controlled, treatment withdrawal, phase 3 trial

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ABSTRACT

Background Treatment options in patients with enthesitis-related arthritis (ERA) and juvenile psoriatic arthritis (JPsA) are currently limited. This trial aimed to demonstrate the efficacy and safety of secukinumab in patients with active ERA and JPsA with inadequate response to conventional therapy.

Methods In this randomised, double-blind, placebo-controlled, treatment-withdrawal, phase 3 trial, biologic-naïve patients (aged 2 to <18 years) with active disease were treated with open-label subcutaneous secukinumab (75/150 mg in patients <50/≥50 kg) in treatment period (TP) 1 up to week 12, and juvenile idiopathic arthritis (JIA) American College of Rheumatology 30 responders at week 12 were randomised 1:1 to secukinumab or placebo up to 100 weeks. Patients who flared in TP2 immediately entered open-label secukinumab TP3 that lasted up to week 104. Primary endpoint was time to disease flare in TP2.

Results A total of 86 patients (median age, 14 years) entered open-label secukinumab in TP1. In TP2, responders (ERA, 44/52; JPsA, 31/34) received secukinumab or placebo. The study met its primary end point and demonstrated a statistically significant longer time to disease flare in TP2 for ERA and JPsA with secukinumab versus placebo (27% vs 55%, HR, 0.28; 95% CI 0.13 to 0.63; $p < 0.001$). Exposure-adjusted incidence rates (per 100 patient-years (PY), 95% CI) for total patients were 290.7/100 PY (230.2 to 362.3) for adverse events and 8.2/100 PY (4.1 to 14.6) for serious adverse events in the overall JIA population.

Conclusions Secukinumab demonstrated significantly longer time to disease flare than placebo in children with ERA and JPsA with a consistent safety profile with the adult indications of psoriatic arthritis and axial spondyloarthritis.

Trial registration number NCT03031782.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Treatment options for patients with the juvenile idiopathic arthritis (JIA) subtypes of enthesitis-related arthritis (ERA) and juvenile psoriatic arthritis (JPsA) are limited. Conventional synthetic disease-modifying antirheumatic drugs (DMARDs), glucocorticoids and non-steroidal anti-inflammatory drugs provide limited efficacy with safety issues with long-term use. Studies have shown the efficacy of biologic DMARD (bDMARD) anti-TNF agents in patients with ERA or JPsA, but many patients continue to experience uncontrolled disease or experience treatment-related side effects.

WHAT THIS STUDY ADDS

⇒ In this double-blind, randomised, placebo-controlled, event-driven treatment withdrawal phase 3 study, the time to JIA disease flare was statistically longer in patients treated with secukinumab compared with placebo-treated patients from week 12 up to week 104 (27% vs 55%, HR, 0.28; 95% CI 0.13 to 0.63; $p < 0.001$).
⇒ Improvements in JIA American College of Rheumatology (ACR) responses, JIA ACR-inactive disease, JIA ACR core set components, Juvenile Arthritis Disease Activity Score were reported in patients treated with secukinumab up to 12 weeks.
⇒ No new safety signals were reported with secukinumab for up to 2 years.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of inflammatory disorders that includes patients with arthritis of unknown aetiology that starts before the age of 16 years and persists for 6 or more weeks.¹ Enthesitis-related arthritis (ERA) and juvenile psoriatic arthritis (JPsA) are two

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results from this study support that secukinumab, a fully human monoclonal antibody that inhibits IL-17A, is an effective and safe bDMARD in the treatment of patients with ERA and JPsA categories of JIA. Safety profile of secukinumab in JIA categories was consistent with reported adult indications of psoriatic arthritis and axial spondyloarthritis.

categories of JIA that represent paediatric counterparts of adult non-radiographic axial spondyloarthritis (nr-axSpA) and psoriatic arthritis (PsA), respectively.^{1,2}

Non-steroidal anti-inflammatory drugs (NSAIDs) and conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) are considered first-line agents in JPsA, while NSAIDs and sulphasalazine are considered for ERA. Although the current treatment strategies for ERA and JPsA help to relieve pain, these medications often provide limited efficacy on the underlying disease.³ This necessitates initiation of more intensive therapy, including the introduction of biologic (b)DMARDs, of which very few are approved for ERA and JPsA treatments.^{4,5}

The interleukin (IL)-17A pathway plays an important role in the pathogenesis of ERA and JPsA. Compared with controls, increased levels of IL-17A were reported in patients with JIA, especially in the setting of active disease.⁶ Progression of structural damage is mediated by the IL-17 pathway in inflammatory arthritis.⁷ Secukinumab, a fully human monoclonal antibody that directly inhibits IL-17A, has demonstrated efficacy and safety in adult patients with psoriasis (PsO), PsA, ankylosing spondylitis (AS) and nr-axSpA.^{8–11} This phase 3 study demonstrated the efficacy and safety of secukinumab in patients with active ERA and JPsA.

METHODS**Study design and participants**

This was a 2-year, randomised, double-blind, placebo-controlled, event-driven, treatment-withdrawal, phase 3 study that consisted of three treatment periods (TPs): open-label (OL) secukinumab TP1 (up to 8 weeks); a randomised, double-blind, placebo-controlled, withdrawal period (up to week 104) TP2; OL secukinumab TP3 and a post-treatment follow-up period (online supplemental figure S1). The study was planned to be continued until 33 flare events had occurred or randomised patients had completed 104 weeks in the study. In this event-driven, treatment-withdrawal study, the patients were treated first in an OL manner with the study drug for 12 weeks, and responders (JIA American College of Rheumatology (ACR)30 responders) were randomised to the study drug or placebo in a double-blind manner. In this phase of treatment, occurrence of a protocol-defined disease flare led to withdrawal from the double-blind treatment phase and patients were retreated with the study drug in an OL fashion.¹²

Key inclusion criteria included patients aged ≥ 2 to < 18 years at screening, classified according to the International League of Associations for Rheumatology JIA classification criteria as either ERA or JPsA, disease duration of ≥ 6 months with inadequate response to ≥ 1 csDMARDs or NSAIDs. Eligible patients were naïve to bDMARDs and had active disease. Key exclusion criteria included active uncontrolled inflammatory bowel disease (IBD) or uncontrolled uveitis. Detailed inclusion and exclusion criteria are provided in online supplemental appendix (Section S2).

Eligible patients entered TP1 and received OL subcutaneous secukinumab in prefilled syringes (75/150 mg in patients $< 50/\geq 50$ kg). During TP1, secukinumab was administered weekly up to week 4, followed by every 4 weeks (Q4W). At week 12 (end of TP1), JIA ACR30 responders entered TP2 and were randomised 1:1 to continue secukinumab or receive placebo Q4W until a disease flare, or up to week 100. JIA ACR30 non-responders at week 12 were discontinued from the study. All patients who experienced a disease flare in TP2 or completed TP2 without a disease flare entered TP3 to again receive OL secukinumab Q4W up to week 100.

The study protocol was reviewed and approved by the respective ethics committee or institutional review board of each centre. The study was conducted according to the International Council for Harmonization Good Clinical Practice guidelines.

Randomisation

Eligible patients were randomised (1:1) to continue secukinumab or newly start placebo in TP2. Randomisation was performed centrally using an Interactive Response Technology system and was stratified by JIA category (ERA, JPsA) (Section S3, online supplemental appendix).

Procedures

Secukinumab was administered subcutaneously in prefilled syringes (75/150 mg in patients $< 50/\geq 50$ kg). Study visits and study drug administration were scheduled at baseline and weeks 1, 2, 3 and 4, followed by 4 weekly visits through week 104 with study drug administration until week 100. Patients could continue stable background therapies with NSAIDs, methotrexate,¹³ sulfasalazine and oral glucocorticoids (Section S4, online supplemental appendix). Efficacy outcomes and adverse events (AEs) were assessed at each study visit.

Outcomes and assessments

All study outcomes are listed in the study protocol, which is provided in the online supplemental appendix (Section S5). At each planned visit, data for the six validated JIA ACR core set variables (CRVs) were recorded.¹⁴ The JIA ACR30 response as per the JIA ACR response criteria is defined as $\geq 30\%$ improvement in three or more of six CRVs, with no more than one of the remaining CRVs worsening by $> 30\%$.¹⁴ The primary end point was time to JIA flare in TP2, defined as per the Pediatric Rheumatology Collaborative Study Group/Paediatric Rheumatology International Trials Organisation JIA flare criteria as $\geq 30\%$ worsening from baseline in at least three of the six CRVs with no more than one of the remaining CRVs with $> 30\%$ improvement relative to the end of TP1 (week 12).¹⁵ Key secondary efficacy end points included JIA ACR30/50/70/90/100 responses, inactive disease (JIA ACR-ID) status,¹⁶ JIA ACR CRVs, Juvenile Arthritis Disease Activity Score (JADAS)-27-C reactive protein and total enthesitis and dactylitis counts at week 12 in TP1, and JIA ACR30/50/70/90/100 responses and JIA ACR-ID status at the end of TP2.

Safety analyses were conducted for the entire study period (TP1–TP3) in the overall JIA population. Safety assessments included all AEs coded as per the *Medical Dictionary for Regulatory Activities* (V.23.1), serious AEs (SAEs), treatment-emergent AEs (TEAEs), injection site reactions and antiseckinumab antibody development (immunogenicity).

Statistical analysis

For sample size estimation, the HR of flare events for the secukinumab group relative to the placebo group was estimated to be 0.32 in TP2.¹⁷ Thirty-three flares (12 for secukinumab, 21 for placebo) were estimated to detect a statistically significant difference between secukinumab and placebo to achieve 90% power by an one-sided significance level of 0.025. With an event-driven approach, the study was to be either stopped once 33 disease flares were detected or last patient's last visit over the study is achieved. We expected that a maximum 92 weeks of TP2 was necessary to observe 33 disease flares. Assuming approximately 85% of the patients respond at JIA ACR30 levels in TP1, we estimated that at most 94 patients needed to be enrolled into the study to allow for a sufficient number of patients to be randomised into TP2.

To show the superiority of secukinumab over placebo on the primary end point of time to disease flare in the two treatment groups, an one-sided stratified log-rank test was used with treatment, stratification variable of JIA category (ERA or JPsA) and methotrexate use as explanatory variables. HR and their associated 95% CIs were estimated based on a Cox proportional hazards model. Kaplan-Meier estimates (95% CI) of the probability of disease flare by treatment groups were calculated. Patients either experienced a disease flare or were censored in TP2. Subgroup analyses for time to disease flare were performed for the stratification variable of JIA category (ERA or JPsA). The intention-to-treat principle was applied for all primary and key secondary efficacy analyses.

The safety data analysis was conducted on the safety set that included all patients who received at least one dose of secukinumab. Exposure-adjusted incidence rates (per 100 patient-years (PY) of follow-up) were calculated for AEs and SAEs. An independent data safety monitoring board was responsible for ongoing monitoring of the safety of patients in the study.

Patient and public involvement

Patients or the public were not involved in the design or conduct of the trial. Written informed consent was obtained from parents or legal guardians of each patient at screening.

RESULTS

Patient characteristics

Between 23 May 2017 and 9 November 2020, among 97 patients screened for eligibility, 86 patients (88.7%) entered TP1 to receive OL secukinumab (online supplemental figure S2). There were 52 patients (60.5%) diagnosed with ERA and 34 (39.5%) with JPsA.

At baseline, there was a male preponderance in the ERA group (78.8%, 41/52) and a slight female majority in the JPsA group (52.9%, 18/34) (table 1). Of the 86 patients enrolled in TP1, 75 patients (87.2%) with a JIA ACR30 response at week 12 (end of TP1) were allowed to enter TP2. The baseline characteristics and clinical features of patients who entered TP2 were comparable to those of the overall study cohort (online supplemental table S1).

Overall, 75 patients (ERA/JPsA, 44/31) entered TP2 to be randomised 1:1 to continue secukinumab or newly receive placebo, with 67 patients completing TP2 and 26 completing TP3 (online supplemental figure S2). The most common reason for patients to discontinue the study early was lack of efficacy.

Time to JIA flare (primary endpoint)

The study was completed with last patient's last visit achieved. A total of 31 JIA flares had occurred, and all 67 remaining patients had reached week 104 (in TP2/TP3). In TP2, flare events occurred in 10/37 (27%) in the secukinumab group versus 21/38 (55%) in the placebo group. The median time to flare was not reached for the secukinumab group and was 453 (95% CI 114 to not calculable) days for the placebo group. The

Table 1 Baseline demographics and clinical characteristics of all JIA patients and each JIA category in TP1

Variable	JIA (N=86)	ERA (N=52)	JPsA (N=34)
Age (years), mean (SD)	13.1 (3.1)	13.7 (2.6)	12.2 (3.7)
Male, n (%)	57 (66.3)	41 (78.8)	16 (47.1)
Race, n (%)			
White	82 (95.3)	51 (98.1)	31 (91.2)
Other*	4 (4.7)	1 (1.9)	3 (8.8)
Ethnicity, n (%)			
Hispanic or Latino	5 (5.8)	2 (3.8)	3 (8.8)
Caucasian	67 (77.9)	42 (80.8)	25 (73.5)
Unknown†	14 (16.3)	8 (15.4)	6 (17.6)
JADAS-27 score, mean (SD)	15.1 (7.1)	14.8 (6.7)	15.5 (7.8)
Physician global assessment of disease activity (VAS 0–100 mm), mean (SD)	47.3 (21.1)	47.2 (20.2)	47.4 (22.9)
Parent/patient global assessment of overall well-being (VAS 0–100 mm), mean (SD)	48.5 (28.3)	50.0 (27.6)	46.3 (29.5)
Childhood Health Assessment Questionnaire–Disability Index, mean (SD)	0.8 (0.6)	0.8 (0.6)	0.8 (0.7)
Number of joints with active arthritis, mean (SD)	7.7 (7.5)	6.2 (3.4)	10.0 (10.6)
Number of joints with limited range of motion, mean (SD)	5.5 (4.7)	4.9 (3.3)	6.6 (6.3)
C-reactive protein standardised value (mg/L), mean (SD)	18.6 (32.0)	24.0 (38.8)	10.4 (14.0)
Total enthesitis count, mean (SD)	2.6 (2.5); n=85	2.7 (2.2); n=52	2.3 (3.0); n=33
Total dactylitis count, mean (SD)	1.0 (2.2); n=82	0.4 (1.4); n=48	1.8 (2.7); n=34
MTX use, n (%) yes	56 (65.1)	33 (63.5)	23 (67.6)

*Asian and other races.

†ethnicity not reported or unknown.

ERA, enthesitis-related arthritis; JADAS, Juvenile Arthritis Disease Activity Score; JIA, juvenile idiopathic arthritis; JPsA, juvenile psoriatic arthritis; MTX, methotrexate; TP, treatment period; VAS, visual analogue scale.

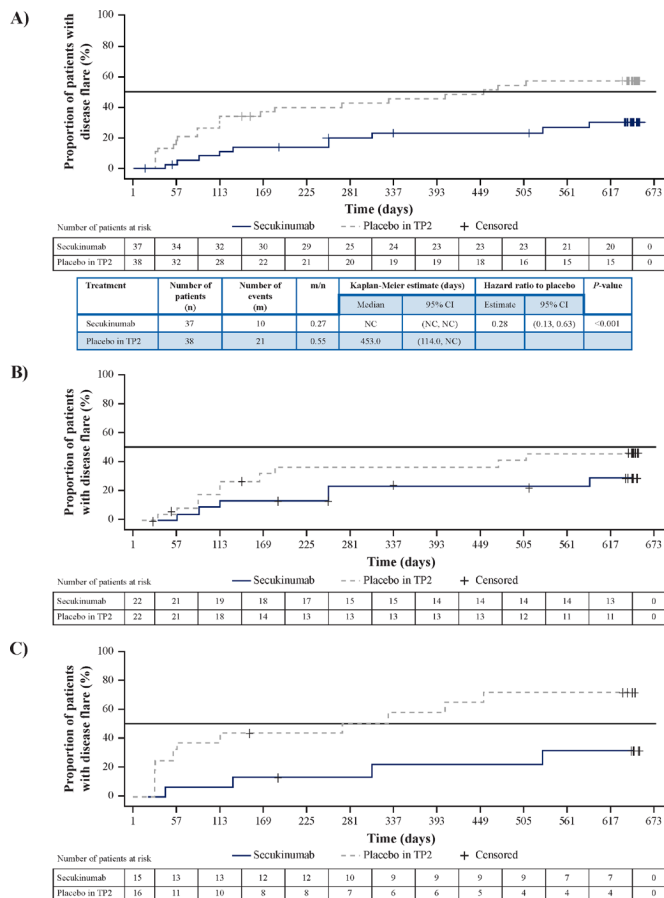


Figure 1 Time to disease flare in (A) overall JIA population and JIA subcategories of (B) ERA and (C) JPsA in TP2. A) JIA: 72% flare risk reduction; HR, 0.28; 95% CI, 0.13 to 0.63; $p < 0.001$. B) ERA: 55% flare risk reduction; HR, 0.45; 95% CI, 0.16 to 1.28; $p = 0.075$. C) JPsA: 85% flare risk reduction; HR, 0.15; 95% CI, 0.04 to 0.57; $p < 0.001$. HR and associated 95% CIs were 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 was adjusted for analysis factors JIA category (ERA or JPsA) and methotrexate use at baseline. SEC: all patients who did not take any placebo. Placebo in TP2: all patients who took placebo in TP2 and SEC in other period/s. Day 1: date of randomisation. 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. Patients at risk: patients in TP2 who did not have flare and were not censored before or at the start of the specified day. ERA, enthesitis-related arthritis; JIA, juvenile idiopathic arthritis; JPsA, juvenile psoriatic arthritis; m/n, proportion of patients with disease flare in TP2; NC, not calculable; SEC, secukinumab; TP, treatment period.

study met its primary end point and demonstrated a statistically significant prolongation in time to disease flare in TP2 for the combined JIA categories of ERA and JPsA in the secukinumab group compared with the placebo group (HR, 0.28 (95% CI 0.13 to 0.63), $p < 0.001$) (figure 1A). The estimated mean time to disease flare in the placebo group was 453 days and could not be formally calculated for the secukinumab group as fewer than 50% of patients in this group had flared at the time of study completion. Based on Kaplan-Meier estimation, the probability of remaining free of disease flares after 1 year was 76.7% (95% CI 58.7 to 87.6) for the secukinumab group versus 54.3% (95% CI 37.1 to 68.7) for the placebo group (figure 1A). Subgroup analysis by JIA category also showed that time to disease flare

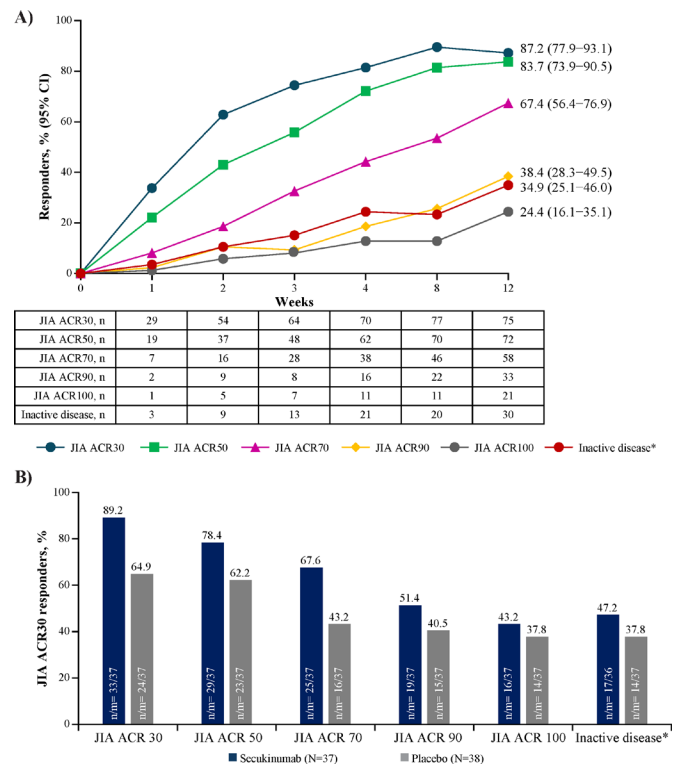


Figure 2 Improvement in ACR responses from baseline with open-label secukinumab in TP1 (A), and improvement from baseline at the end of TP2 (B). *Inactive disease status. 95% CI are from NRI analysis of ACR response derived relative to baseline. N=86 N, number of patients in the full analysis set; n, number of patients with response (B). *Inactive disease status. NRI analysis. ACR, American College of Rheumatology; JIA, juvenile idiopathic arthritis; m, total number of patients with an assessment at the end of TP2; N, total number of patients in the treatment group; n, number of patients who satisfy the criteria; NRI, non-responder imputation; TP, treatment period.

was longer in secukinumab treatment versus placebo for ERA (HR, 0.45 (95% CI 0.16 to 1.28)) (figure 1B) and JPsA (HR, 0.15 (95% CI 0.04 to 0.57)) (figure 1C).

Key secondary end points

Onset of JIA ACR30 response occurred as early as week 1 (33.7%) and increased to 87.2% (75/86) at week 12. A total of 67.4% (58/86) of patients achieved a JIA ACR70 response while 34.9% (30/86) achieved JIA ACR-ID status at week 12 (non-responder imputation analysis) (figure 2A). During TP2, compared with patients randomised to placebo, a higher proportion of patients receiving secukinumab achieved JIA ACR30/50/70/90/100 response and JIA ACR-ID status at the end of TP2, which refers to each patient's last assessment in TP2 (figure 2B). Rates of JIA patients who reported inactive disease in the secukinumab group were higher than placebo group (47.2% vs 37.8%).

In the overall JIA population, with OL secukinumab, a notable reduction of mean JADAS-27 was observed up to week 12 reaching moderate disease activity and reached minimal disease activity in both secukinumab and placebo groups in TP2 (figure 3). In ERA and JPsA categories, JADAS-27 reached moderate and minimal disease activity, respectively, with OL secukinumab in TP1. In TP2, the scores reached minimal disease activity with secukinumab treatment in ERA and inactive disease in JPsA, whereas with placebo, the scores reached moderate and

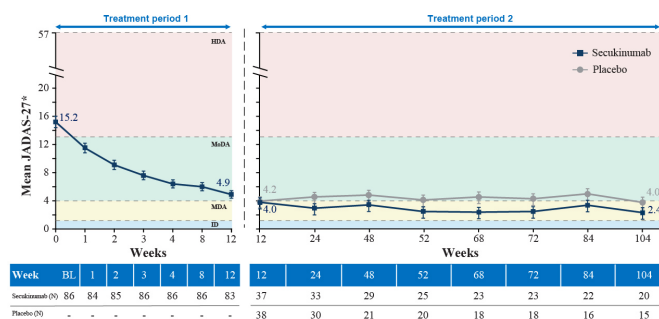


Figure 3 Mean JADAS-27 in TP1 and TP2 in the overall JIA population Full analysis set. MMRM analysis. *Least square mean values. JADAS-27 ranges from 0 to 57 (higher scores indicate more disease activity). HDA, high disease activity; ID, inactive disease; JADAS-27, Juvenile Arthritis Disease Activity Score in 27 joints; JIA, juvenile idiopathic arthritis; MDA, minimal disease activity; MMRM, mixed-effect model repeated measure; MoDA, moderate disease activity; N, total number of patients in the treatment group; TP, treatment period

minimal disease activity in ERA and JPsA categories, respectively (online supplemental figure S3).

Safety

Safety data were available for a total of 141.5 PY over the entire treatment period (secukinumab, 71.3 PY; placebo in TP2, 70.2 PY). During the study, 79 patients (91.1%) reported at least one AE in the entire TP (table 2). Eight patients (9.3%) discontinued the study due to AEs (secukinumab, 3 (6.3%); placebo, 5 (13.2%)) and 11 (12.8%) patients reported SAEs. The most frequent TEAEs were nasopharyngitis (27 (31.4%)), nausea (19 (22.1%)), upper respiratory tract infection (19 (22.1%)) and diarrhoea (17 (19.8%)).

One patient with ERA had a medical history of uveitis that was non-recurring during the study. Two ERA patients, both aged 16 years, reported AE of acute anterior uveitis of mild or moderate severity that was not considered related to the study drug by the investigators and resolved with topical therapy; hence, the dose of study drug remains unchanged, and both the patients

recovered and completed the study. One JPsA patient (2.7%) in the secukinumab group newly reported Crohn's disease during the study. There was no family history of IBD. The patient experienced disease flare and discontinued the study drug due to Crohn's disease on Day 127, entered post-treatment follow-up period and completed the same. The investigator suspected a causal relationship to secukinumab/placebo. There were no cases of mycobacterial infections, hepatitis B reactivation, malignancy or deaths. Only one patient reported injection-site reaction. No treatment-emergent antidrug antibodies were detected in any sample of patients treated with secukinumab during the study.

DISCUSSION

Secukinumab is a monoclonal antibody targeting IL-17A that was found to result in rapid improvement of arthritis, dactylitis and enthesitis in children with ERA and JPsA. This study met its primary end point and demonstrated that time to disease flare in TP2 was significantly longer with secukinumab treatment than placebo in the overall JIA population. At the tested weight-stratified dosages, secukinumab markedly decreased the flare risk by 72% compared with placebo, and there was no new safety signal.

There remains a high unmet medical need for therapies indicated for ERA and JPsA as there is a dearth of tested therapies.¹⁸ In order to limit or even avoid the negative impact of ERA and JPsA on patient development, QoL or disease-associated joint damage, rapid and sustained control of disease signs and symptoms is recommended,^{19 20} which can be achieved with early initiation of anti-inflammatory treatment in JIA.²¹ Current treatment guidelines recommend initial bDMARD treatment for patients with risk factors, high disease activity and those who are intolerant to csDMARDs.^{21 22}

We consider secukinumab an important new treatment option for children with ERA and JPsA as secukinumab resulted in a rapid and profound improvement of signs and symptoms of both ERA and JPsA in this study, including the resolution of dactylitis and enthesitis. The achievement of inactive disease, a preferred treatment target for JIA, was achieved in over 30% of patients by week 12, and in over 40% of patients who

Table 2 Safety summary for the entire treatment period (safety set)

Safety events	TP1	TP2		Entire secukinumab exposure period
	Secukinumab, N=86	Secukinumab, N=37	Placebo, N=38	Total, N=86
AEs, n (%) (PT)	56 (65.1)	34 (91.9)	29 (76.3)	79 (91.9)
SAE, n (%) (PT)	2 (2.3)	5 (13.5)	0	11 (12.8)
AEs leading to study discontinuation	1 (1.2)	2 (5.4)	5 (13.2)	8 (9.3)
Death	0	0	0	0
Most frequent TEAEs, n (%) (PT)				
Nasopharyngitis	5 (5.8)	14 (37.8)	6 (15.8)	27 (31.4)
Nausea	6 (7.0)	7 (18.9)	3 (7.9)	19 (22.1)
Upper respiratory tract infection	6 (7.0)	6 (16.2)	6 (15.8)	19 (22.1)
Diarrhoea	1 (1.2)	9 (24.3)	2 (5.3)	17 (19.8)
Cough	1 (1.2)	7 (18.9)	4 (10.5)	13 (15.1)
Arthralgia	2 (2.3)	6 (16.2)	3 (7.9)	12 (14.0)
Oropharyngeal pain	5 (5.8)	4 (10.8)	2 (5.3)	12 (14.0)
Headache	5 (5.8)	3 (8.1)	3 (7.9)	12 (14.0)
Fever	2 (2.3)	6 (16.2)	2 (5.3)	12 (14.0)

Secukinumab and placebo in TP2 groups have not been compared as the study design and the exposure times for these groups were different over the entire TP. 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.

AE, adverse event; IR, incidence rate per 100 subject years; PT, preferred term; SAE, serious adverse event; SOC, primary system organ class; TEAEs, treatment emergent AEs; TP, treatment period.

received secukinumab throughout the entire study. Resolution of enthesitis is highly impactful given the known profound detrimental effects of enthesitis, including pain, in both adults and children.²³

The responses in children with JPsA receiving secukinumab in this study are consistent with the findings from studies in patients with PsA where secukinumab has demonstrated sustained improvements in ACR responses, in resolution of enthesitis and dactylitis, in skin clearance with sustained improvement across the six key manifestations of PsA through 5 years.^{24–26} ERA is considered the paediatric counterpart of nr-axSpA² and children with ERA also experienced a profound improvement of signs and symptoms of their disease. The role of IL-17A in spondyloarthritis manifestations of skin, joints and entheses is well known, and profound improvement with secukinumab was reported in patients with PsO, PsA and AS.^{11 27}

Prior bDMARD exposure was an exclusion criterion for study participation. Earlier studies in JIA support that exposure to prior bDMARDs decreases the response rate to subsequent treatments in medication trials.^{28 29} Although this trial does not provide information about secukinumab efficacy in the setting of prior bDMARD exposure, we note that a retrospective study in patients with ERA who failed anti-TNF treatment reported significant improvement in JIA disease activity as measured by JADAS with secukinumab treatment.³⁰ Consistent with this finding, patients in this study experienced a rapid, profound, and sustained decrease in disease activity as measured by JADAS-27 for up to 2 years.

There was only one reported injection-site reaction during the study, and no antiseckinumab antibodies were detected. Indeed, secukinumab was generally well tolerated, and its safety profile in this study population of patients with ERA or JPsA was consistent with that observed in adult patients with axial spondyloarthritis and PsA.^{8 9 25}

There was one reported case of Crohn's disease that was categorised as an important potential risk, consistent with prior reports in the medical literature based on a postmarketing study in Vigibase.³¹ Anterior chronic non-infectious uveitis is quite common, especially with early onset of JPsA,³² but was not observed in this study. On the contrary, two cases of new acute anterior uveitis were reported, both regarded unrelated to the study treatment by the treating physicians, and a patient with a history of acute anterior uveitis prior to baseline did not experience reactivation of uveitis during the study.

Limitations of the trial must be considered. Secukinumab efficacy was assessed indirectly by the occurrence of JIA flares. Owing to the large number of placebo-treated patients who met flare criteria in TP2 and who stopped placebo when entering TP3, observed differences in efficacy between secukinumab versus placebo may be blunted. The trial population was relatively small and predominantly white but was in line with other JIA trials. Thus, it was not possible to detect rare AEs. Another limitation of this study is the lack of data on skin manifestations, especially in JPsA patients, although it has been acknowledged that secukinumab demonstrated sustained efficacy across various skin outcomes in previously reported randomised trials in paediatric patients with PsO.³³

In conclusion, secukinumab demonstrated efficacy and safety in the JIA categories of ERA and JPsA. The significantly longer time to disease flare in TP2 and improvement in disease activity observed establish secukinumab as a candidate in the treatment of patients with ERA and JPsA.

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Secukinumab in Enthesitis-Related Arthritis and Juvenile Psoriatic Arthritis: a randomised, double-blind, placebo-controlled, treatment withdrawal, phase 3 trial

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Supplementary Appendix

Inclusion and exclusion criteria

Inclusion criteria

1. Male or female patients in the age range of ≥ 2 years to < 18 years at screening
2. Confirmed diagnosis of enthesitis-related arthritis (ERA) according to the International League of Associations for Rheumatology (ILAR) classification criteria or juvenile psoriatic arthritis (JPsA) according to the modified ILAR criteria that had occurred at least 6 months prior to screening
3. Active disease defined as:
 - ≥ 3 active joints (swollen or if not swollen must be tender with limited range of motion) at baseline and
 - ≥ 1 site of active enthesitis at baseline or documented history
4. Inadequate response to ≥ 1
 - nonsteroidal anti-inflammatory drugs (NSAIDs) for ≥ 1 month or
 - disease modifying anti-rheumatic drugs (DMARDs) for ≥ 2 months
5. No concomitant use of second line disease-modifying and/or immunosuppressive drugs except the stable doses of
 - methotrexate (maximum of 20 mg/m^2 body surface area/week) for at least 4 weeks prior to baseline visit, and folic/folinic acid supplementation
 - sulfasalazine (ERA patients only) $< 50 \text{ mg/kg/day}$ with a maximum of 3000 mg/day for at least 4 weeks prior to baseline visit

- 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
 - not more than one NSAID for at least 1 week prior to baseline
6. Negative results for
- QuantiFERON test or
 - purified protein derivative (PPD) test if required by local guidelines or if the patient was <5 years of age
 - positive PPD was defined as >15 mm induration in children >4 years and >10 mm for children <4 years
 - patients with positive PPD results participated in the study if further work up established that the patient had no evidence of active tuberculosis (TB). In presence of latent TB, treatment was initiated according to local country guidelines for a minimum of 4 weeks before baseline
7. Signed and written informed consent from parent/legal guardian of the child prior to any study related activity or assessment

Exclusion criteria

1. 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
2. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes
3. Patients with active uncontrolled inflammatory bowel disease or uveitis
4. Patients who had received biologic immunomodulating agents, including but not limited to tumor necrosis factor (TNF) α inhibitors, T-cell costimulatory, anti-IL6, anti-

IL1, cell-depleting therapies (alemtuzumab, anti-CD4, anti-CD5, anti-CD3, and anti-CD19), secukinumab or other biologic drugs directly targeting interleukin (IL)-17 or IL-17 receptor or any investigational immunomodulating agent

5. Patients taking any non-biologic DMARD except for methotrexate or sulfasalazine (for ERA patients)
6. Patients fulfilling any ILAR diagnostic juvenile idiopathic arthritis (JIA) category other than ERA or JPsA
7. Patients taking medications prohibited by the protocol
8. Patients taking high potency opioid analgesics (morphine equianalgesic or higher) including but not limited to methadone, hydromorphone and morphine
9. Any intramuscular/intravenous/intra-articular corticosteroid treatment within 4 weeks before baseline
10. Patients with active or recurrent bacterial, fungal or viral infection including known infection with HIV, Hepatitis B, and Hepatitis C at baseline
11. Patients with active TB or latent TB who are unwilling or unable to complete a minimum of 4 weeks of latent TB treatment before initiating treatment with secukinumab
12. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients 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
13. Pregnant or lactating females (pregnancy defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin laboratory test)
 14. Female patients (<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
 15. Active ongoing inflammatory diseases other than JPsA/ERA that might confound the benefit of secukinumab therapy
 16. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which immunocompromises the patient and/or places the patient at unacceptable risk for participation in a study
 17. Significant medical problems or diseases, including but not limited to uncontrolled hypertension and uncontrolled diabetes
 18. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, or serum bilirubin. The criteria for diagnosis included:
 - any single parameter not exceeding 2× upper limit of normal (ULN). A single parameter elevated up to 2× ULN were re-checked again prior to baseline, to rule out lab error

- if the total bilirubin concentration increased above 2× ULN, it was differentiated into the direct and indirect reacting bilirubin; with serum bilirubin not exceeding 1.6 mg/dL (27 µmol/L) in either case
19. Patients with total WBC count <3000/µL, or platelets <100000/µL or neutrophils <1500/µL or hemoglobin <8.5 g/dL (85 g/L) at screening
 20. History of lymphoproliferative disease or any known malignancy within the past 5 years (except for treated basal cell carcinoma or actinic keratoses with no evidence of recurrence in the past 3 months and carcinoma in situ of the cervix or non-invasive malignant colon polyps that had been removed)
 21. Current severe progressive or uncontrolled disease rendering the patient unsuitable for the trial
 22. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins)
 23. Any medical or psychiatric condition that would preclude the participant from adhering to the protocol or completing the study per protocol
 24. History or evidence of ongoing alcohol or drug abuse, within the last 6 months before baseline
 25. Plans for administration of live vaccines during the study period or within 6 weeks preceding baseline

Further details on patient randomisation and masking

Patients eligible to enter treatment period (TP)² were randomised 1:1 to continue secukinumab or newly start placebo. Allocation of patients to the treatment arms was performed using an Interactive Response Technology (IRT) system. TP² was blinded to the parents/patients,

investigators, and sponsor. Randomisation in TP2 was stratified by JIA category (ERA, JPsA).

The site personnel (study coordinator or specified designee) were required to enter or select information including but not limited to the user's identification and password, protocol number, patient number, and patient's date of birth. The site personnel were then provided with a treatment assignment and dispensable unit or container number when drug was being supplied via the IRT system.

Additional details on drug administration and procedures

Secukinumab was administered subcutaneously in pre-filled syringes of 75 mg for patients with body weight of <50 kg or 150 mg for patients with body weight $\geq$ 50 kg. During TP1, five weekly loading doses of secukinumab were administered up to week 4, followed by 4-weekly injections thereafter. Patients could continue stable background therapies with NSAIDs, methotrexate ($\leq$ 20 mg/m²/week),¹ sulfasalazine (ERA patients only; $\leq$ 50 mg/kg/day or 3 g/day, whichever was lower), and oral glucocorticoids ($\leq$ 0.2 mg/kg/day of prednisone equivalent or $\leq$ 10 mg/day, whichever was lower). Intra-articular glucocorticoid injections were not permitted within 4 weeks prior to baseline, during TP1 or TP2; but patients were allowed to receive injections in up to four joints per 24-week period during TP3.

Study endpoints, outcomes and assessments

Primary endpoint

- Time to disease flare during TP2

Secondary endpoints

- Efficacy of secukinumab treatment for all subjects and each JIA category in TP1 measured using:

- JIA American College of Rheumatology (ACR)30/50/70/90/100
- Inactive disease status
- JIA ACR core components
- Juvenile Arthritis Disease Activity Score (JADAS)
- Total enthesitis count
- Total dactylitis count
- Withdrawal effect of secukinumab treatment for all subjects and each JIA category in TP2 assessed by:
 - JIA ACR30/50/70/90/100
 - Inactive disease status
- Secukinumab serum concentrations and derived pharmacokinetic parameters in TP1
- Safety/tolerability:
 - Evaluation of adverse events/serious adverse events
 - Laboratory values
 - Vital signs
- Immunogenicity assessment
 - Anti-drug antibodies

Exploratory endpoints

- Time to disease flare for ERA and JPsA in TP2
- Withdrawal effect of secukinumab treatment for all subjects and each JIA category in TP2 assessed by:
 - JIA ACR core components
 - JADAS

- Total enthesitis count
- Total dactylitis count
- Swollen joint count
- Tender joint count
- Overall back pain (using visual analog scale [VAS]) in ERA subset only
- Nocturnal back pain (using VAS) in ERA subset only
- Psoriasis (PsO) global assessment (Investigator's Global Assessment [2011 modified version (IGA (Mod 2011))] in JPsA subset only
- Percentage of total body surface area affected by PsO
- Modified Schober's test
- Juvenile Spondyloarthritis Disease Activity Index (JSpADA) at weeks 12, 52, 104 and at time of disease flare in TP2
- Correlations of JSpADA³ with JADAS, patient global assessment of disease activity (VAS) and the Child Health Assessment Questionnaire (CHAQ) during entire study period
- Efficacy of secukinumab in TP3 after experiencing disease flare in TP2 measured by:
 - JIA ACR 30/50/70/90/100
 - Inactive disease status
 - JIA ACR core components
- Efficacy of secukinumab in entire study period measured by:
 - JIA ACR30/50/70/90/100
 - Inactive disease
 - Proportion of patients achieving clinical remission

- Potential proteomic biomarkers associated with treatment response to secukinumab in entire study period

Assessment of JIA ACR core set variables and other efficacy assessments

The six validated JIA ACR core set variables that were assessed are as follows:⁴ physician's global evaluation of overall disease activity (VAS 0–100 mm); patient/parent assessment of overall well-being (VAS 0–100 mm); number of joints with active arthritis, i.e. with swelling or in the absence of swelling, limitation in range of motion accompanied by either joint tenderness or pain on motion; number of joints with limitation of motion; cross-culturally adapted and validated version of Childhood Health Assessment Questionnaire-Disability Index (CHAQ-DI)⁵ as a measure of physical ability; and C-reactive protein (CRP) as a measure of systemic inflammation.

The following efficacy assessments were assessed and confirmed in real-time, according to validated criteria, by independent evaluators at the PRINTO/PRCSG centralized coordinating centers: JIA core set variables by certified joint assessors; JIA ACR30/50/70/90/100 response; JIA flare; JIA ACR-ID and JADAS-27 CRP scores and disease status. The JADAS-27 cutoffs published in 2021 were used: high (>13.0), moderate (4.1–13.0), minimal (1.5–4.0) and inactive disease (JADAS-ID) (≤ 1.4).⁶

Additional results of other key endpoints

At the end of TP1 and TP2, all JIA ACR core set variables improved from baseline, including >50% improvement in patient-reported outcomes (CHAQ-DI, parent/patient-reported assessment of overall well-being) (Fig. S4 and Table S2).

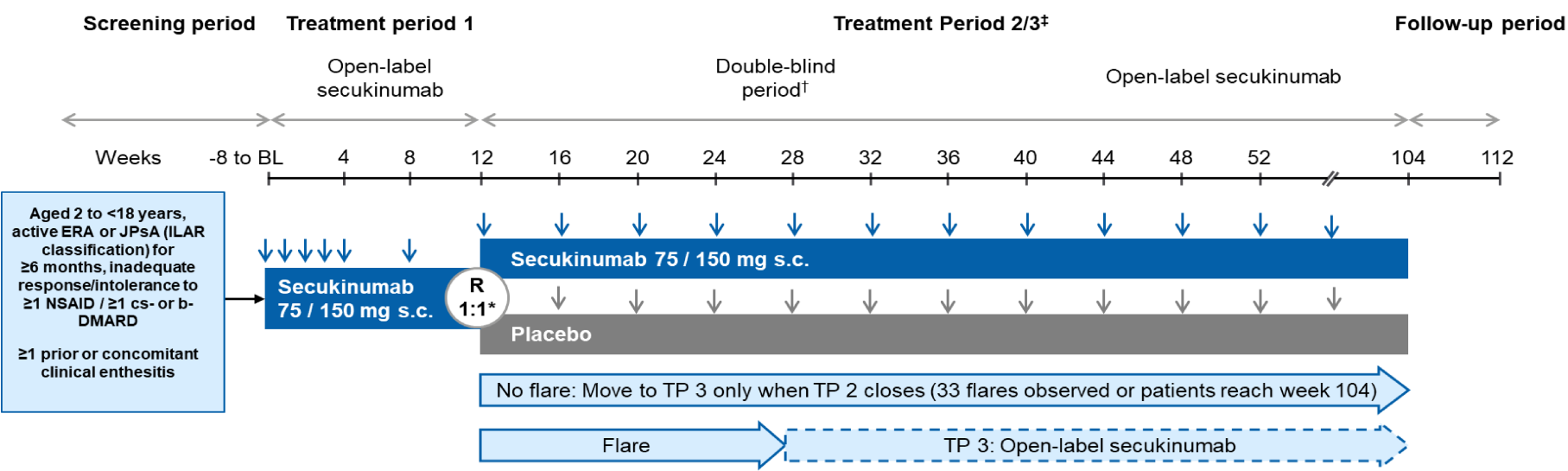
In patients with enthesitis or dactylitis at baseline (N=71 or N=22, respectively), resolution of enthesitis or dactylitis was reported in 69.0% and 59.1% patients, respectively, using non-

responder imputation analysis for missing data (Fig. S5). Among 31 patients with enthesitis and 12 patients with dactylitis at baseline who entered TP2 and were randomised to receive secukinumab during TP2, 45.2% and 25% of patients, respectively, showed sustained resolution of enthesitis and dactylitis for six or more months. Similar results were observed in patients with ERA and JPsA (Table S2).

Additional results on safety

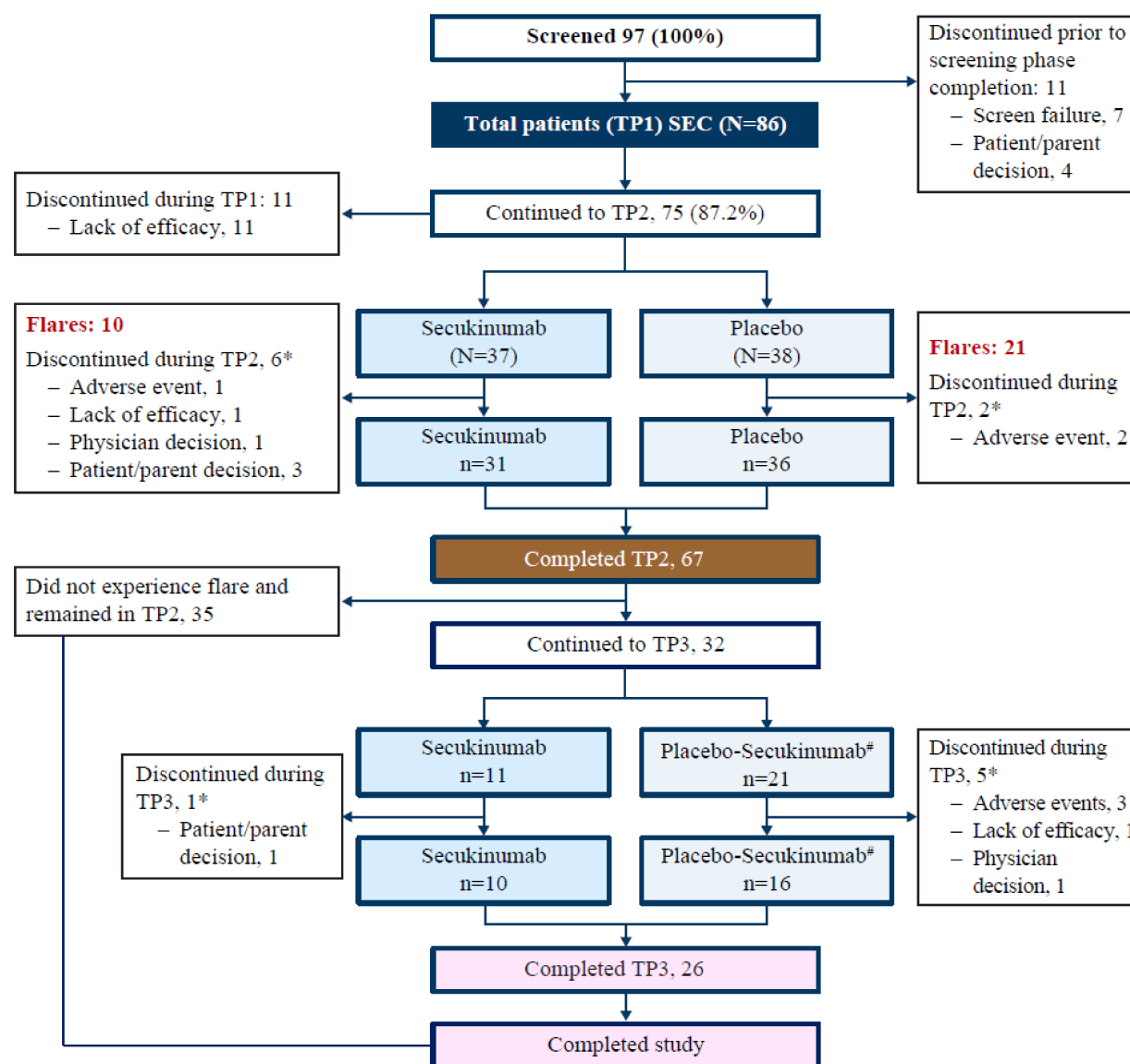
For the entire study (N=86), the exposure-adjusted incidence rates (IRs) (95% CI) for AEs per 100 patient-years (PY) of follow-up was 290.7 (230.2 to 362.3). The IR was 355.4 (258.2 to 477.1) for secukinumab patients who did not take any placebo throughout the study (N=48), and 236.6 (164.8 to 329.1) for all patients who took placebo in TP2 and secukinumab in other TPs (N=38). Similarly, the IR for SAEs with secukinumab in the entire study was 8.2 (4.1 to 14.6), whereas it was 10.4 (4.2 to 21.4) with patients who received secukinumab throughout the study and 5.9 (1.6 to 15.2) in all patients who took placebo in TP2 and secukinumab in other TPs. The IR (95% CI) per 100 PY of follow-up for the *Medical Dictionary for Regulatory Activities* (MedDRA) System Organ Class ‘Infections and infestations’ was numerically higher with secukinumab than placebo (134.2 [104.2 to 170.1] vs. 112.5 [75.9 to 160.7]). The same was true for ‘Respiratory, thoracic, and mediastinal disorders’ (IR [95% CI] secukinumab versus placebo: 23.1 [14.9 to 34.0] vs. 15.4 [7.1 to 29.3]).

Figure S1. Study design



*Patients only randomised if they achieve ACR 30. If ACR30 is not achieved, patient is discontinued from the study. †Closes when 33 patients experience a disease flare. ‡Treatment period 2 is a withdrawal-period

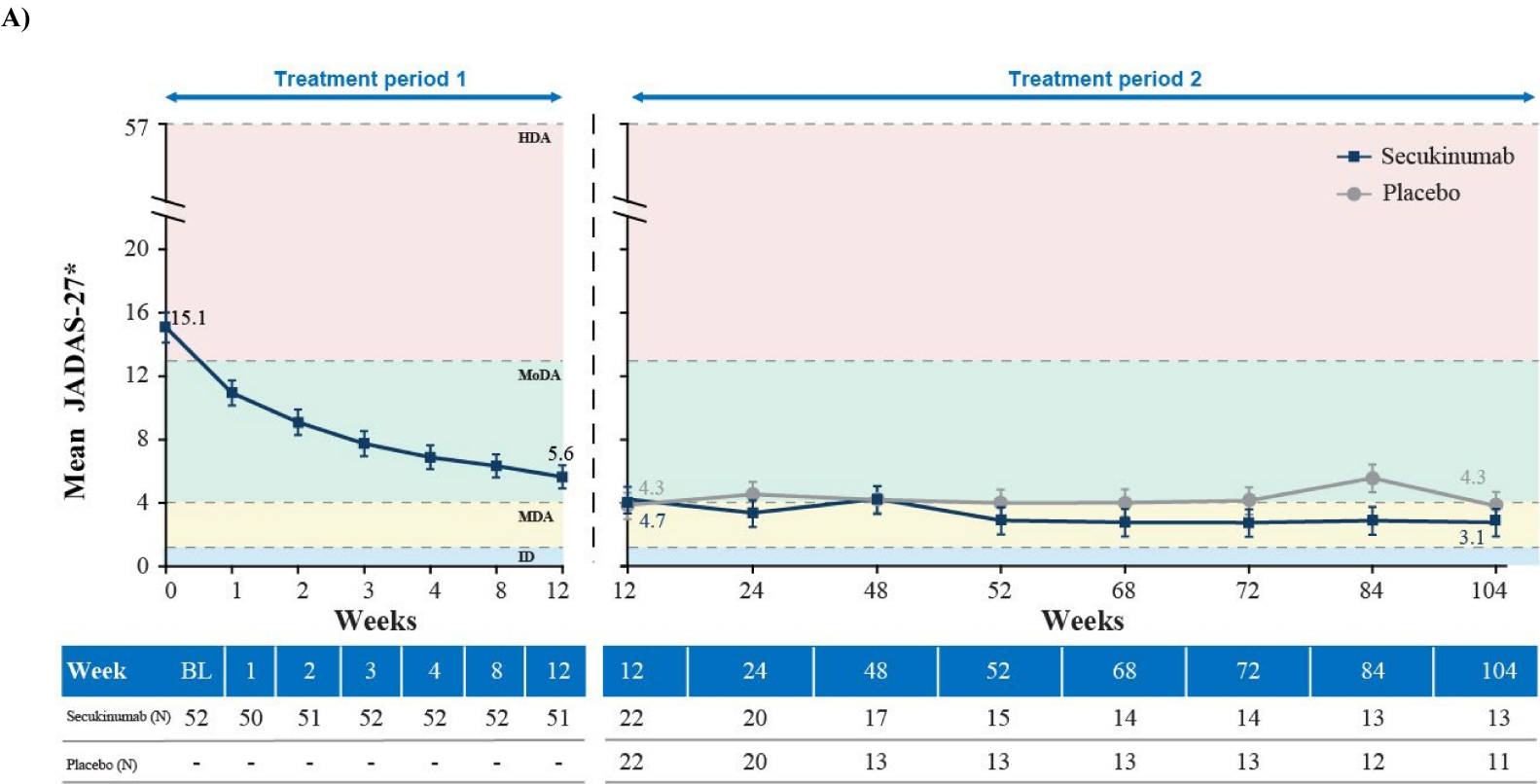
BL, baseline; cs- or b-DMARD, conventional synthetic or biological disease-modifying antirheumatic drug; ERA, enthesitis-related arthritis; ILAR, International League Against Rheumatism; JPsA, juvenile psoriatic arthritis; NSAID, non-steroidal anti-inflammatory drug; R, randomised; s.c. subcutaneous; TP, treatment period

Figure S2. Patient disposition

*Includes patients who completed the given period and discontinued prematurely from the study treatment on the same date; # Patients in the placebo group in TP2 switched to open-label secukinumab in TP3.

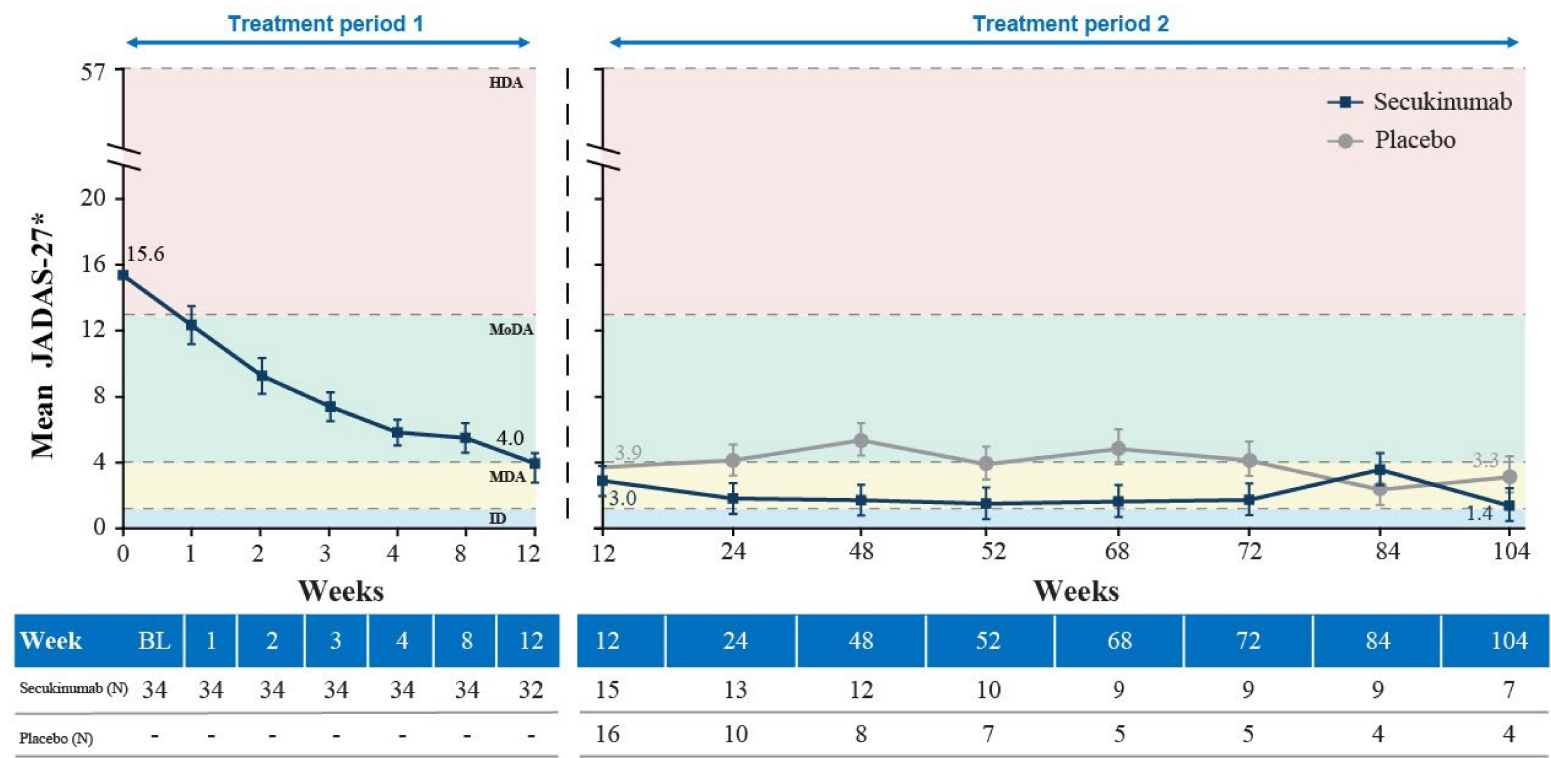
SEC, secukinumab; TP, treatment period

Figure S3. Improvement in mean JADAS-27 in (A) ERA and (B) JPsA subcategories in TP1 and TP2



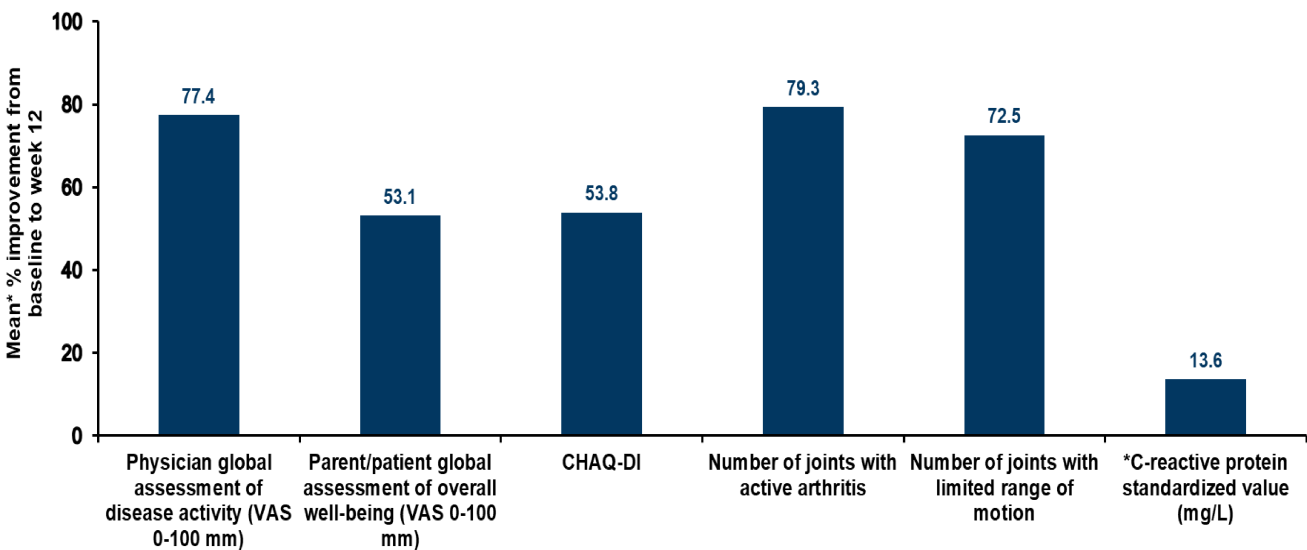
Full analysis set. MMRM analysis.
*Least square mean values. JADAS-27 ranges from 0 to 57 (higher scores indicate more disease activity).
ERA, enthesitis-related arthritis; HDA, high disease activity; ID, inactive disease; JADAS-27, Juvenile Arthritis Disease Activity Score in 27 joints; MDA, minimal disease activity; MMRM, mixed-effect model repeated measure; MoDA, moderate disease activity; N, total number of patients in the treatment group; TP, treatment period

B)



Full analysis set. MMRM analysis.
*Least square mean values. JADAS-27 ranges from 0 to 57 (higher scores indicate more disease activity).
HDA, high disease activity; ID, inactive disease; JADAS-27, Juvenile Arthritis Disease Activity Score in 27 joints; JPsA, juvenile psoriatic arthritis; MDA, minimal disease activity; MMRM, mixed-effect model repeated measure; MoDA, moderate disease activity; N, total number of patients in the treatment group; TP, treatment period

Figure S4. Improvement of JIA ACR core set variables from baseline to the end of TP1

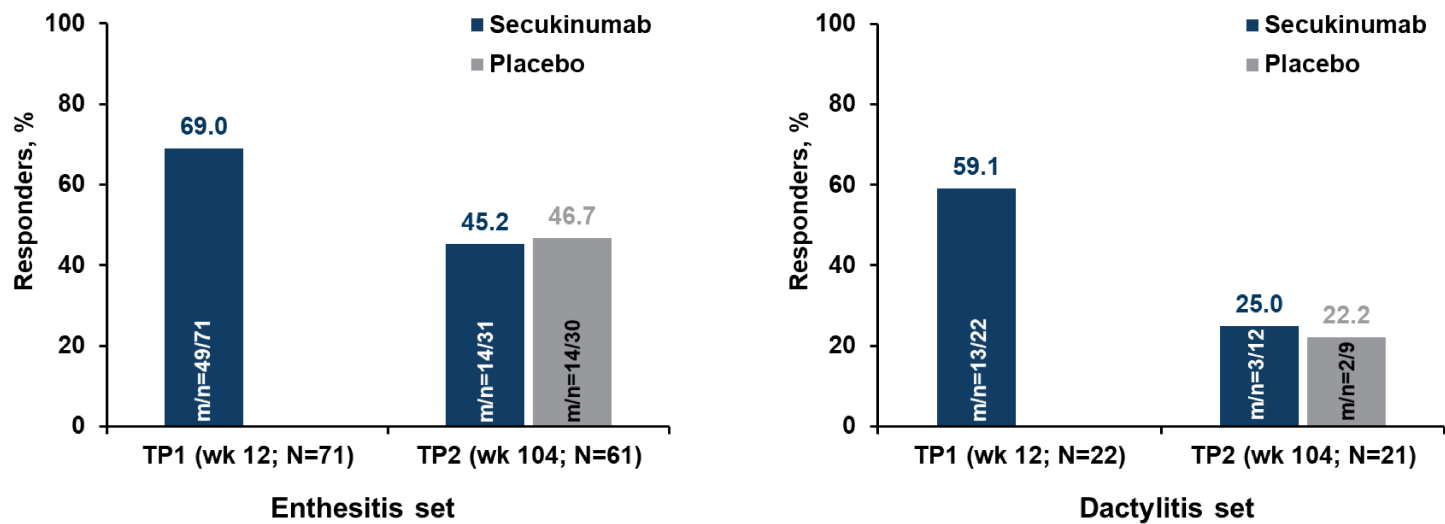


*C-reactive protein is shown as median percent improvement from baseline, due to outliers of C-reactive protein values.

Baseline is defined as the last observation on the day of or before the first dose of study drug. Only patients with a non-zero value at baseline and a value at week 12 are included.

ACR, American College of Rheumatology; CHAQ-DI, Childhood Health Assessment Questionnaire-Disability Index; JIA, juvenile idiopathic arthritis; VAS, visual analog scale

Figure S5. Resolution of enthesitis and dactylitis in the overall JIA population



NRI analysis. FAS consisted of all patients who received at least one dose of study drug.

Enthesitis/dactylitis set included all FAS patients who had enthesitis/dactylitis at baseline.

FAS, full analysis set; JIA, juvenile idiopathic arthritis; m, number of patients with a response; N, total number of patients with enthesitis/dactylitis; NRI, non-responder imputation; n, number of patients with enthesitis/dactylitis in each group; TP, treatment period; wk, week

Table S1. Baseline demographics and clinical characteristics of all JIA patients randomised into TP2 and each JIA category

Characteristic	ERA (N=44)		JPsA (N=31)		JIA (N=75)	
	SEC (N=22)	PBO (N=22)	SEC (N=15)	PBO (N=16)	SEC (N=37)	PBO (N=38)
Age (years), mean (SD)	14.0 (2.5)	13.0 (2.9)	13.1 (3.1)	10.6 (3.7)	13.6 (2.7)	12.0 (3.5)
Male, n (%)	18 (81.8)	18 (81.8)	6 (40.0)	9 (56.3)	24 (64.9)	27 (71.1)
Race, n (%)						
White	22 (100)	21 (95.5)	14 (93.3)	14 (87.5)	36 (97.3)	35 (92.1)
Other*	0	1 (4.5)	1 (6.7)	2 (12.5)	1 (2.7)	3 (7.9)
Ethnicity, n (%)						
Hispanic or Latino	0	1 (4.5)	3 (20.0)	0	3 (8.1)	1 (2.6)
Caucasian	17 (77.3)	20 (90.9)	8 (53.3)	15 (93.8)	25 (67.6)	35 (92.1)
Unknown [#]	5 (22.7)	1 (4.5)	4 (26.7)	1 (6.3)	9 (24.3)	2 (5.3)
JADAS-27 score, mean (SD)	15.9 (8.1)	14.8 (5.7)	14.3 (8.2)	16.7 (8.3)	15.2 (8.0)	15.6 (6.9)
Physician global assessment of disease activity (VAS 0–100 mm), mean (SD)	47.3 (22.6)	43.5 (15.6)	40.9 (21.2)	50.3 (24.4)	44.7 (21.9)	46.4 (19.8)
Parent/patient global assessment of overall well-	53.2 (29.7)	49.7 (27.9)	37.1 (29.5)	54.6 (28.6)	46.7 (30.3)	51.8 (27.9)

being (VAS 0–100 mm), mean (SD)						
Childhood Health Assessment Questionnaire–Disability Index, mean (SD)	0.8 (0.6)	0.8 (0.5)	0.5 (0.5)	1.0 (0.8)	0.7 (0.6)	0.9 (0.6)
Number of joints with active arthritis, mean (SD)	6.9 (4.7)	5.6 (3.2)	10.4 (9.5)	10.8 (12.5)	8.3 (7.4)	7.8 (8.7)
Number of joints with limited range of motion, mean (SD)	5.5 (3.5)	4.7 (2.4)	6.1 (3.2)	7.8 (8.5)	5.8 (3.3)	6.0 (5.9)
C-reactive protein standardized value (mg/L), mean (SD)	28.9 (41.2)	26.1 (42.1)	8.1 (9.6)	12.7 (17.8)	20.5 (33.6)	20.5 (34.3)
Total enthesitis count, mean (SD)	3.1 (2.6); n=22	2.2 (1.8); n=22	2.1 (3.2); n=15	2.9 (3.0); n=15	2.7 (2.9); n=37	2.5 (2.3); n=37
Total dactylitis count, mean (SD)	0.6 (1.7); n=22	0.3 (1.3); n=21	2.0 (2.6); n=15	2.0 (2.9); n=16	1.2 (2.2); n=37	1.0 (2.3); n=37
MTX use, n (%) Yes	15 (68.2)	14 (63.6)	11 (73.3)	11 (68.8)	26 (70.3)	25 (65.8)
*Asian and other races; #ethnicity not reported or unknown ERA, enthesitis-related arthritis; JADAS, Juvenile Arthritis Disease Activity Score; JIA, juvenile idiopathic arthritis; JPsA, juvenile psoriatic arthritis; MTX, methotrexate; N, total number of patients in the treatment group; PBO, placebo; SEC, secukinumab; TP, treatment period; VAS, visual analogue scale						

Table S2. Efficacy of secukinumab in ERA and JPsA subcategories at the end of TP1 and TP2

Efficacy Outcomes, %	TP1 (week 12)	TP2	
	SEC	SEC	PBO
ERA (TP1: N=52; TP2: SEC N=22; PBO N=22)			
JIA ACR30	84.6	90.9	68.2
JIA ACR50	78.8	81.8	68.2
JIA ACR70	65.4	68.2	54.5
JIA ACR90	32.7	45.5	50.0
JIA ACR100	26.9	36.4	45.5
Inactive disease[#]	38.5	50.0	50.0
Resolution of enthesitis*	72.3	72.7	77.3
Resolution of dactylitis*	50.0	86.4	95.5
JPsA (TP1: N=34; TP2: SEC N=15; PBO N=16)			
JIA ACR30	91.2	86.7	62.5
JIA ACR50	91.2	73.3	56.3
JIA ACR70	70.6	66.7	31.3
JIA ACR90	47.1	60.0	25.0
JIA ACR100	20.6	53.3	25.0
Inactive disease[#]	29.4	46.7	18.8
Resolution of enthesitis*	62.5	66.7	50.0
Resolution of dactylitis*	62.5	93.3	62.5
NRI analysis. [#] Inactive disease: Definition adapted from JIA ACR criteria of Wallace et al., 2011. ⁷			

*TP1, Enthesitis set (ERA: SEC, N=47; JPsA: SEC, N=24); Dactylitis set (ERA: SEC, N=6; JPsA: N=16).

ACR, American College of Rheumatology; ERA, enthesitis-related arthritis; JIA, juvenile idiopathic arthritis; JPsA, juvenile psoriatic arthritis; N, total number of patients in the treatment group; NRI, non-responder imputation; PBO, placebo; SEC, secukinumab; TP, treatment period

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