22 July 2021
EMA/471835/2021
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Cosentyx

secukinumab

Procedure no: EMEA/H/C/003729/P46/012

Note

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

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1. Introduction

The MAH has submitted the final report of study CAIN457F2304, a completed paediatric study for Cosentyx (Marketing Authorization EMEA/H/C/003729) in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are submitted as part of the post-authorisation measure (PAM).

No critical expert overview has been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study CAIN457F2304 is part of a clinical development program.

2.2. Information on the pharmaceutical formulation used in the study

Secukinumab for SC injection was supplied as 150 mg in a 1 mL pre-filled syringes (PFS) and as 75 mg in 0.5 mL PFS. Secukinumab placebo for SC injection was supplied as 1 mL and 0.5 mL PFS, matching the appearance of secukinumab syringes. Secukinumab and secukinumab placebo were supplied by Novartis Global Clinical Supplies.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the final report for secukinumab (AIN457) study CAIN457F2304 (EUDRACT no. 2016-003761-26).

Title of study: 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.

2.3.2. Clinical study

Description

Study CAIN457F2304 is a Phase III, placebo-controlled, event-driven, randomized withdrawal design study conducted to demonstrate the clinical efficacy of secukinumab compared with placebo in paediatric patients with active JIA (ERA or JPsA categories). This study recruited patients aged 2 to <18 years.

Phase of development (phase of this clinical study): Phase III

Indication sought:

Juvenile Idiopathic Arthritis (JIA)

1. Enthesitis-Related Arthritis (ERA)

Cosentyx is indicated for the treatment of active enthesitis-related arthritis in patients 2 years and older.

2. Juvenile Psoriatic Arthritis (JPsA)

Cosentyx is indicated for the treatment of active juvenile psoriatic arthritis in patients 2 years and older.

Methods

Objective(s)

Objectives	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure
Primary objective	
To demonstrate that the time to flare in treatment period 2 (TP2) is longer with secukinumab for combined enthesitis-related arthritis (ERA) and JPsA (Juvenile Psoriatic Arthritis) groups than with placebo	Time to disease flare (active vs. control) Timeframe: TP2
Secondary objectives	
1. To evaluate the effect of secukinumab treatment for all subjects and each juvenile idiopathic arthritis (JIA) category in treatment period 1 (TP1) up to Week 12 (end of TP1) with respect to: • JIA American College of Rheumatology (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
2. 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
3. To evaluate pharmacokinetics (PK) of secukinumab and confirm the predicted dose in TP1	Secukinumab serum concentrations and derived PK parameters Timeframe: TP1
4. To evaluate the safety/tolerability and immunogenicity of secukinumab	Adverse events (AEs), laboratory values, vital signs, Anti-Drug Antibodies (ADA) Timeframe: Entire study

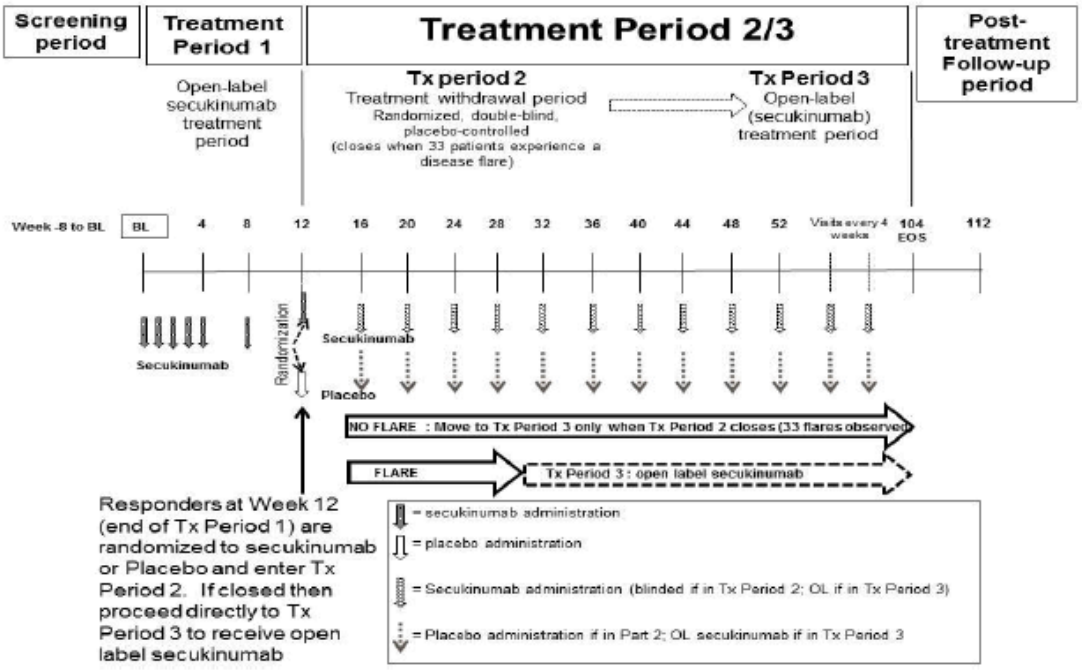
The study was completed as planned.

Study design

This was a double-blind, placebo-controlled, event-driven randomized withdrawal study to investigate the JIA categories of JPsA and ERA. The study was divided into 3 parts (plus a post-treatment follow-up period) consisting of open-label, single-arm active treatment in treatment

period 1 (TP1) and treatment period 3 (TP3), and a randomised, double-blind, placebo controlled, event-driven withdrawal design in TP2. The study design is outlined in Figure 2.3.2.1.

Figure 2.3.2.1 Study design for study CAIN457F2304



Study population /Sample size

It was planned that approximately 80 subjects were to be enrolled in TP1 (to reach the minimum required sample size of 60 subjects in TP2) and that every effort was to be made in order to randomize at least 20 subjects from each JIA category to TP2. A total of 97 subjects were screened, of which 86 subjects (88.7%) completed and 11 subjects (11.3%) discontinued the screening phase. A total of 86 subjects from 32 sites entered into TP1 and 75 subjects were randomized in 1:1 ratio to secukinumab (37 subjects) or placebo (38 subjects) in TP2.

Treatments

Secukinumab for SC injection was supplied as 150 mg in a 1 mL pre-filled syringes (PFS) and as 75 mg in 0.5 mL PFS. Secukinumab placebo for SC injection was supplied as 1 mL and 0.5 mL PFS, matching secukinumab syringes. Secukinumab and secukinumab placebo were supplied by Novartis Global Clinical Supplies.

All subjects fulfilling all entry criteria were assigned to AIN457/secukinumab 75 or 150 mg, based on body weight (< 50 kg or ≥ 50 kg) and continued to receive an appropriate secukinumab dose at each visit based on their weight at that visit. At the Week 12 visit, all responders were eligible to enter TP2 where they were randomized via IRT to one of the two treatment arms, active as secukinumab 75 or 150 mg, or matching placebo based on their weight at that visit.

Outcomes/endpoints

Efficacy: The primary and secondary efficacy outcome measures used in this study are standard measures used across JIA trials.

- JIA ACR 30, 50, 70, 90 and 100 response criteria

- Physician's Global Assessment of disease activity (Visual Analogue Scale [VAS])
- Parent's/subject's Global Assessment of subject's overall well-being (VAS included within Childhood Health Assessment Questionnaire [CHAQ])
- CHAQ
- Active joint count
- Joint count with limited range of motion
- C-reactive Protein (local)
- Inactive disease status
- JADAS score
- Total dactylitis count
- Total enthesitis count

All efficacy assessments were performed prior to administration of study treatment at that visit.

Pharmacokinetics: PK samples were obtained for all subjects and secukinumab concentrations were assessed in serum. An enzyme-linked immunosorbent assay (ELISA) method was used for bioanalytical analysis of secukinumab in serum, with lower limit of quantifications (LLOQs) of 80 and 500 ng/mL in the two bioanalytical CRO's involved in this study.

Safety: Safety assessments consisted of collecting all AEs and serious adverse event (SAEs), including injection site reactions, with their severity and relationship to the study drug, abnormal findings in ECGs, physical examination (including height and body weight), vital signs, and laboratory assessments (haematology, clinical chemistry, lipid panel and urinalysis), pregnancy and assessment of fertility, tolerability of secukinumab and anti-secukinumab antibody development (immunogenicity).

Statistical Methods

The primary analysis was based on the full analysis set 2 (FAS2) for TP2. The FAS 2 consist of all randomized subjects who received at least one dose of study drug in TP2. Following the intent-to-treat principle, subjects were analysed according to the treatment they were assigned to at randomization 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 another factor methotrexate (MTX) use at baseline (yes or 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 stratification factor as explanatory variables. Kaplan-Meier estimates of the probability to experience a flare event were calculated from the beginning of TP2 along with 95% confidence intervals using Greenwood's formula. The cumulative probability to stay flare free (1-the probability of experiencing a flare) was plotted against time. Specifically, the survival analysis of time to flare in TP2 included randomized treatment, number of subjects, number of events, Kaplan-Meier estimate of median time to flare in days, hazard ratio (95% Confidence interval) and p-value for the Stratified log-rank test. In addition, a figure of Kaplan-Meier estimates of the probability to stay flare free by treatment groups in TP2 was plotted against days.

The analysis of secondary variables was descriptive only for FAS. Summary statistics were presented. Baseline, post-baseline and absolute change was presented for all summary statistics.

The analysis of safety data by treatment were provided for each Treatment Period separately and all periods combined, as appropriate. The analysis of safety data was conducted on the Safety Set, which included subjects who received any study treatment. Safety analyses was performed on treatment received or actual treatment. Safety variables were tabulated by descriptive statistics. No formal statistical testing was planned.

The following PK parameters was determined: Cmin, ss. All completed subjects with quantifiable PK measurements of secukinumab was included in the PK data analysis. Serum concentrations was expressed in mass per volume units. PK concentrations were summarized by Treatment Period, visit and treatment group. In addition to mean, SD, CV, median and quartiles, the geometric mean and geometric CV and n(log) were presented.

Results

Number of subjects (planned and analysed)

It was planned that approximately 80 subjects were to be enrolled in TP1 (to reach the minimum required sample size of 60 subjects in TP2) and that every effort was to be made in order to randomize at least 20 subjects from each JIA category to TP2.

A total of 97 subjects were screened, of which 86 subjects (88.7%) completed and 11 subjects (11.3%) discontinued the screening phase. A total of 86 subjects from 32 sites entered into TP1 and subjects were randomized in 1:1 ratio to secukinumab (37 subjects) or placebo (38 subjects) in TP2.

Baseline data

The mean age of subjects enrolled in the study was 13.1 years (range 2 to 17 years). The majority of subjects were male (66.3%), 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. In subjects enrolled, 52 subjects had ERA (60.5%) and 34 subjects had JPsA (39.5%) at baseline.

The mean age of subjects randomized in TP2 was 12.8 years. Overall, the demographic and baseline characteristics of subjects randomized in TP2 were generally similar between the treatment groups and by each JIA category, ERA and JPsA, with the exception of the male to female ratio for subjects with ERA (ERA: total 44 subjects, male 81.8%; JPsA: total 31 subjects, male 48.4%). The baseline disease characteristics of subjects by each JIA category in TP2 were comparable between the treatment groups and were generally in line with the overall population in TP1. Subjects who entered TP2 and were randomized included those with active ERA (44 subjects, 58.7%) or JPsA (31 subjects, 41.3%). Values for mean JADAS-27 score, JADAS-71 score, total enthesitis count, and total dactylitis count were similar across treatment groups in TP2. Over 65% of the subjects used MTX prior to randomization, with similar distribution among treatment groups and JIA categories.

Efficacy results

The primary endpoint was met. The results for the primary analysis as well as secondary efficacy analyses are presented below:

Objectives	Endpoint Title, and Reporting Time Frame for analysis	Results
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**	Primary endpoint was met. Statistically significant prolongation in time to disease flare with secukinumab compared to the placebo for combined ERA and JPsA categories. The risk of flare was reduced by 72% for subjects on secukinumab compared with subjects on placebo in TP2. Hazard ratio of flare events, HR = 0.28, 95% CI: 0.13 to 0.63, p<0.001.
Secondary objectives		
1. 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**	**JIA ACR 30:** 90.4% (75/83), **JIA ACR 50:** 86.7% (72/83) **JIA ACR 70:** 69.9% (58/83) **JIA ACR 90:** 39.8% (33/83) **JIA ACR 100:** 25.3% (21/83) **Inactive disease status** 36.1% subjects (30/83) **By each JIA category:** There was a similarly rapid improvement in ERA and JPsA in all JIA ACR response categories starting as early as Weeks 1 and 2 and continuing to Week 12, in line with the overall population.
		JIA ACR core components: the mean percent improvement in: 3. physician global assessment of disease activity: 77.4% (n=83) 4. parent/subject global assessment of overall well-being: 53.1% (n=81) 5. functional ability (CHAQ): 53.8% (n=74) 6. number of joints with active arthritis: 79.3% (n=83) 7. number of joints with limited range of motion: 72.5% (n=78) 8. median percent improvement in CRP standardized value: 13.6% (n=82) **By each JIA category:** 9. physician global assessment of disease activity - ERA: 74.4%; JPsA: 82.3% 10. parent/subject global assessment of overall well-being - ERA: 45.3%; JPsA: 65.0% 11. functional ability (CHAQ) - ERA: 51.6%; JPsA: 57.6%

		• number of joints with active arthritis - ERA: 77.3%; JPsA: 82.7% • number of joints with limited range of motion - ERA: 70.1%; JPsA: 76.5% • median percent improvement in CRP standardized value - ERA: 50.0%; JPsA: 0.6% The JPsA median change from baseline is lower when compared to ERA. This can be attributed to the lower baseline values for the JPsA (median CRP value at baseline for ERA: 6.98; for JPsA: 4.99)
		JADAS-27 score • JADAS-27 improvement started at Week 1 with marked further improvement by Week 4 and then stabilization until Week 12 (at Week 12 mean (SD) change from the baseline: -10.487 [7.2262]) • A similar rapid decrease in JADAS-27 in each of the JIA category was observed (at Week 12, mean (SD) change from the baseline, ERA: -9.598 [7.4788]; JPsA: -11.904 [6.6735]) **JADAS-71 score** • JADAS 71 improvement started at Week 1 with marked further improvement by Week 4 and then stabilization until Week 12 (at Week 12 mean (SD) change from the baseline: --13.403 [9.7300] • A similar rapid decrease in JADAS-71 in each of the JIA category was observed (at Week 12, mean (SD) change from the baseline, ERA: -11.794 [7.6803]; JPsA: -15.967 [12.0101]
		Total enthesitis count • mean (SD) total enthesitis count at baseline: 2.6 (2.51) for all subjects, 2.7 (2.16) for ERA and 2.3 (2.99) for JPsA • the improvement in mean (SD) total enthesitis count at Week 12: -1.8 (2.31) for all subjects, - 2.2 (1.87) for ERA and -1.2 (2.83) for JPsA.
		Total dactylitis count • mean (SD) total dactylitis count at baseline: 1.0 (2.15) for all subjects, 0.4 (1.44) for ERA and 1.8 (2.69) for JPsA • the improvement in mean (SD) total dactylitis count at Week 12: -0.8 (1.83) for all subjects, -0.2 (0.79) for ERA and -1.5 (2.53) for JPsA. The less pronounced improvement from baseline in subjects with ERA was possibly due to less dactylitis at baseline.
2. 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**	In TP2 also, improvement was observed from baseline at all the JIA ACR response levels for secukinumab. and placebo: • JIA ACR 30: 89.2% vs. 64.9%, • JIA ACR 50: 78.4% vs. 62.2%, • JIA ACR 70: 67.6% vs. 43.2%, • JIA ACR 90: 51.4% vs. 40.5%, • JIA ACR 100: 43.2% vs. 37.8% • and for inactive disease status (secukinumab 47.2% vs. placebo 37.8) The difference observed for proportion of subjects who achieved the response in the secukinumab treatment group notably higher compared to placebo for JIA ACR 30 (p=0.014) and JIA ACR 70 category responses (p=0.042). Note: p-values are from the Cochran-Mantel-Haenszel test, adjusted for analysis factors JIA category (ERA or JPsA) and MTX use at baseline, without adjustment for multiplicity. By each JIA category: This trend for JIA ACR response levels and for inactive disease status each of the JIA categories of ERA and JPsA.

Pharmacokinetic results

Trough secukinumab serum concentrations at Weeks 2, 4, 8, 12, 24, 52, 76 and 104 weeks with the three latter time points being at steady-state, were similar in the two weight categories of <50 kg and ≥50 kg.

Safety results

The safety profile of secukinumab in this study was consistent with the known safety profile for secukinumab and there were no new or unexpected signals.

The overall mean (±SD) duration of exposure to the study treatment was 601.0 ± 232.67 days, with a total patient-time of 141.5 PY. Treatment comparisons between secukinumab and placebo in TP2 groups have not been made, as the exposure times for these groups were different over the entire treatment period.

- There were no deaths reported during the entire treatment period of the study.
- Overall, 11 out of 86 subjects (12.8%) had incidence of treatment-emergent SAEs during the entire treatment period, with Infections and infestations reported as most commonly affected SOC for SAEs (7/86 subjects, 8.1%). All SAEs by PT were single events with no trend over time observed in the types of SAEs.
- The overall exposure-adjusted incidence rate (EAIR, per 100 PY) of treatment-emergent SAEs by any primary SOC in the entire treatment period was 8.2/100 PY in all subjects. The most commonly reported SAEs were in the SOC Infections and infestations and Gastrointestinal disorders (5.1/100 PY and 1.4/100 PY, respectively).
- Overall, 79 out of 86 subjects (91.9%) had incidence of treatment-emergent AEs in the entire treatment period, with Infections and infestations (68/86 subjects, 79.1%), Gastrointestinal disorders (45/86 subjects, 52.3%) and Musculoskeletal and connective tissue disorders (32/86 subjects, 37.2%) reported as most commonly affected SOC for AEs. The most commonly reported AEs (in ≥15% subjects) by PT in the entire treatment group were nasopharyngitis (27/86 subjects, 31.4%), diarrhoea (17/86 subjects, 19.8%), nausea (19/86 subjects, 22.1%), upper respiratory tract infection (19/86 subjects, 22.1%) and cough (13/86 subjects, 15.1%).
- The overall EAIR (per 100 PY) of treatment-emergent AEs by any primary SOC in the entire treatment period was 290.7/100 PY in all subjects. The most commonly reported SOCs with AEs were Infections and infestations, Gastrointestinal disorders and Musculoskeletal and connective tissue disorders (134.2/100PY, 50.4/100 PY, and 31.0/100 PY respectively). Mostly mild (40/86 subjects, 46.5%) and moderate (37/86 subjects, 43.0%) treatment emergent AEs were reported in both treatment groups during the entire treatment period. Severe events were reported in 2 subjects (2/86 subjects, 2.3%). The severe AEs reported were joint effusion in 1 subject and aphthous ulcer in another subject in TP1.
- For the entire treatment period, 8 out of 86 subjects (9.3%) had AEs causing study drug discontinuation. All discontinuations due to AEs were reported by no more than 1-2 subjects in either treatment group. Other than the AEs leading to study drug discontinuation of severe joint effusion for which the subject recovered, the remaining SAEs were of mild or moderate severity.
- For the entire treatment period, 7 out of 86 subjects (8.1%) had AEs leading to temporary dose interruption. In TP2, 1 subject each had AEs diarrhoea and transaminases increased in the secukinumab treatment group only leading to temporary dose interruption.

- Of the important identified risks reported for the entire treatment period, the SOC infections and infestations (68/86 subjects, 79.1%) represented the most frequently reported risk among all risks from the RMP. The most frequently reported compound and class-related risk for the entire treatment period was skin structure infections (21/86 subjects, 24.4%). Inflammatory bowel disease (NMQ, narrow search) for the important potential risk of Crohn's disease revealed 1 SAE with mild severity in the secukinumab treatment group in TP2. No cases of MACE, mycobacterial infections, hepatitis B reactivation, and malignancy were reported.
- Analysis of laboratory parameters, vital signs, urinalysis, and ECGs during the entire treatment period showed no new safety signals. Most of the abnormalities reported in haematology and clinical chemistry were of CTCAE Grade 1 or 2. Grade 3 abnormalities in haematology parameter of absolute neutrophils (<1.0-0.5 x10e9/L) were observed in 2 subjects (2/85 subjects, 2.4%) in secukinumab treatment group over the entire treatment period. These abnormalities occurred during TP2. Grade 3 abnormalities in clinical chemistry parameter of serum aspartate aminotransferase (>5.0-20.0×ULN) were observed in 1 subject (1/86 subjects, 1.2%) in secukinumab treatment group over the entire treatment period. This Grade 3 abnormality was observed during TP3. Grade 3 abnormalities in clinical chemistry parameter of serum alanine aminotransferase (>5.0-20.0×ULN) were observed in 2 subjects (2/86 subjects, 2.3%) in the secukinumab treatment group over the entire treatment group. These Grade 3 abnormalities were observed during TP2. One of these subjects was receiving MTX at the time of Grade 3 abnormality.
- The overall incidence of liver enzyme abnormalities for the entire treatment period was low. No subject was reported with Hy's Law laboratory criteria during the entire treatment period.
- No treatment emergent anti-drug antibodies (ADA) were detected in any sample of subjects within the secukinumab treatment groups. One subject was ADA-positive at Baseline only and negative during treatment.

Conclusions by the Applicant

- Secukinumab demonstrated a significantly longer time to flare in TP2, thus had significantly superior efficacy over placebo in the treatment of subjects with JIA (combined ERA and JPsA groups) at a dose of 150 mg for subjects ≥50 kg and 75 mg for subjects <50 kg, given at Week 0, 1, 2, 3, 4 and every 4 weeks thereafter. Trends of prolongation in time to disease flare was observed in both categories of JIA subjects studied (ERA and JPsA) treated with secukinumab compared to placebo in TP2.
- There was a rapid improvement in all subjects in almost all JIA ACR response categories which continued through Week 12 in TP1. This trend was observed in each of the JIA categories, ERA and JPsA.
- Exposure of secukinumab in serum was similar in the two weight categories of <50 kg and ≥50 kg, which justifies the dosing rationale for subjects with body weights <50 kg.
- The safety profile of secukinumab in this study of paediatric population with Juvenile Idiopathic arthritis subtypes of psoriatic and enthesitis-related arthritis showed no new or unexpected safety signals and was consistent with the overall safety profile of secukinumab based on the existing extensive safety data across multiple indications, including psoriasis, PsA, and axial SpA (both non-radiographic axial SpA and AS).

2.3.3. Discussion on clinical aspects (by the CHMP)

In accordance with Article 46 of Regulation (EC) No 1901/2006, as amended, the Applicant has submitted the final report of study CAIN457F2304. The study CAIN457F2304 is a Phase III, placebo-controlled, event-driven, randomized withdrawal design study conducted to demonstrate the clinical efficacy of secukinumab compared with placebo in paediatric patients with active JIA (ERA or JPsA categories). As this study recruited patients aged 2 to <18 years, the study results are submitted under Article 46 of the EU paediatric regulation.

No detailed assessment of these data are performed in connection with this submission, as a type II variation application is planned to be submitted in June, 2021, (for a procedure start date on July 17th 2021) for the JIA categories of ERA and JPsA. Labeling will be submitted at that time. The submission will include, among other submission related documents, a summary of clinical efficacy, a summary of clinical safety, and a clinical overview. The results of study CAIN457F2304 will be used to support a label update. Full assessment of the study will thus be performed within the upcoming type II variation application.

For purposes of compliance with Article 46 of Regulation (EC) No 1901/2006, as amended, this P46 is considered fulfilled.

3. CHMP's overall conclusion and recommendation

☒ Fulfilled:

No further action required for this P46; however, the MAH has submitted a type II variation with the same study results in parallel to the P46; the CHMP will assess the data in further details in the context of this type II variation application before any conclusion on product information amendments can be made.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Cosentyx Active substance: secukinumab

Study title	Study number	Date of completion	Date of submission of final study report
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	CAIN457F2304	09/11/2020	10/05/2021