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# 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/P46/009

## Note

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

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# 1. Introduction

On 10 January 2020, the MAH submitted a clinical study report for a completed non-interventional clinical study (study number CAIN457AJP02) for Cosentyx. In principle, the completed study was not a paediatric study, but since a single adolescent (17-year-old) patient had been enrolled into the study, the clinical study report was submitted in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

A clinical expert overview has also been provided. It briefly summarises the study results in the overall population as well as results from the single adolescent patient.

# 2. Scientific discussion

## *2.1. Information on the development program*

Secukinumab (Cosentyx) is a high-affinity recombinant, fully human monoclonal anti-human Interleukin-17A (IL-17A) antibody of the IgG1 (immunoglobulin G1)/κ-class that binds to IL-17A and neutralises the bioactivity of this cytokine. IL-17A is the central lymphokine of a defined subset of inflammatory T cells (Th17). It is mainly produced by memory CD4+ and CD8+ T lymphocytes and is recognized as an important pro-inflammatory cytokine in immune-mediated inflammatory diseases. Cosentyx is approved in more than 90 countries worldwide for the treatment of plaque psoriasis, psoriatic arthritis and ankylosing spondylitis.

Study CAIN457AJP02 was an open-label, multicentre, uncontrolled, single-arm, prospective observational study to collect data on the long-term safety and efficacy of Cosentyx in clinical use in Japanese patients with psoriasis vulgaris or psoriatic arthritis. This study recruited one single paediatric patient aged 17 years. A line listing of any other potentially concerned studies is not annexed.

According to the MAH, the results of this trial do not reveal any new concern about the safety and efficacy of Cosentyx in Japanese patients with psoriasis vulgaris and psoriatic arthritis and demonstrates its safety and efficacy in clinical use. Furthermore, the MAH stated that data from the single 17-year-old patient do not warrant an update of the currently approved product labelling.

## *2.2. Information on the pharmaceutical formulation used in the study*

This non-interventional study was conducted after Cosentyx was released on the Japanese market. The following commercial presentations are listed in the study report as having been used:

(1) Cosentyx 150 mg Syringe for Subcutaneous Injection

(2) Cosentyx 150 mg for Subcutaneous Injection

(3) Cosentyx 150 mg Pen for Subcutaneous Injection

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted a final report for:

- Study CAIN457AJP02, titled "*Specified use-results survey to evaluate the long-term safety and efficacy of Cosentyx Subcutaneous Injection in psoriasis vulgaris patients and psoriatic arthritis patients, including retrospective observation.*"

### 2.3.2. Clinical study

Study CAIN457AJP02 "*Specified use-results survey to evaluate the long-term safety and efficacy of Cosentyx Subcutaneous Injection in psoriasis vulgaris patients and psoriatic arthritis patients, including retrospective observation.*"

#### Description

This non-interventional survey was developed and carried out by the MAH to collect safety and efficacy data for Cosentyx, including retrospective data, from the patient population that received Cosentyx soon after its market release in Japan and before a similar, authority-mandated survey was subsequently initiated.

#### Methods

***Objective(s)***

The stated objective of the survey was to collect long-term safety and efficacy data of Cosentyx Subcutaneous Injection in clinical use in psoriasis vulgaris or psoriatic arthritis patients.

***Study design***

The study was an open-label, multicentre, uncontrolled, single-arm, observational study involving psoriasis vulgaris or psoriatic arthritis patients who received Cosentyx for the first time after its approval in Japan and in accordance with the Japanese labelling. The duration of observation for each patient was 52 weeks from the start of treatment with Cosentyx.

This non-interventional survey had no binding treatment strategy, diagnosis/treatment steps or visit schedule. The patients were treated with Cosentyx in accordance with the approved labelling. Routine medical practice was followed for the visit frequency and the type of testing, and only such data were collected as part of this survey.

***Study population /Sample size***

Psoriasis vulgaris or psoriatic arthritis patients who were confirmed to meet all of the following inclusion criteria and none of the exclusion criteria were registered in this survey:

Inclusion criteria:

- Patients who provided written consent to cooperate with this survey before registration
- Patients who met either of the following:
    - Patients who were not adequately responding to ultraviolet phototherapy and other conventional systemic therapies (excluding biological products) and had eruption covering 10% of the body surface area or more

- Patients with refractory eruption or joint symptoms

Exclusion criteria:

- Patients previously treated with a product containing the same active substance as Cosentyx (as an investigational drug or in a post-marketing clinical study)
- Patients who will be treated with a product containing the same active substance as Cosentyx (in a post-marketing clinical study)

A total of 300 patients was planned to be included in the safety analysis population. The planned maximum number of sites was 150.

***Treatments***

Cosentyx was to be used in accordance with its authorised posology in Japan. There were no comparative treatments.

***Outcomes/endpoints***

Efficacy and safety in clinical use were evaluated with conventionally used assessment tools.

Efficacy for skin symptoms: Novartis Investigator's Global Assessment, 2011 modification (IGA mod 2011); Psoriasis Area and Severity Index (PASI); Eruption-covered Body Surface Area (BSA); Dermatology Life Quality Index (DLQI); Investigator's global impression of change of skin symptoms.

Efficacy for joint symptoms: Health Assessment Questionnaire - Disability Index [HAQ-DI; Japanese version of HAQ (J-HAQ)]; 28-joint Disease Activity Score (DAS28-CRP); Physician's global assessment of disease activity; Patient's global assessment of psoriatic arthritis pain; Assessment of dactylitis in fingers and toes; Presence/absence of swollen/tender distal interphalangeal joints of fingers and toes; Presence/absence of tenderness in entheses (Achilles tendons, humerus lateral epicondyles, medial condyles of femur, and plantar aponeuroses); Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); Investigator's global impression of change of joint symptoms.

Safety: Adverse event queries; Laboratory assessments. A group of adverse events, comprising events that are of special interest in relation to the use of secukinumab, was separately pre-defined as "priority survey items". This group of events comprised serious infections, tuberculosis, neutropenia, fungus infections, hypersensitivity reactions, malignant tumours, inflammatory bowel disease, and cardiovascular/cerebrovascular events.

***Statistical Methods***

The data has been summarised with descriptive statistics on safety and efficacy.

***CHMP comment***

*The study reported within the current submission was a non-interventional survey developed and carried out by the MAH to collect safety and efficacy data for Cosentyx, including retrospective data, from the patient population that received Cosentyx soon after its market release in Japan. The study design and execution in themselves seem typical for a non-interventional survey, with no unusual features.*

*For purposes of assessment from the perspective of Article 46, the overall relevance of the study is very limited, as it primarily enrolled an adult population in accordance with the authorised use.*

## Results

### *Recruitment/ Numbers analysed*

The survey period for this study started on 4 November 2015. The registration period ended on 30 September 2016, and the data collection period ended upon database lock on 19 July 2019.

In total, 312 patients were registered for this survey at 100 sites in Japan. Six patients were excluded from the safety analysis population due to administrative reasons, and 306 patients were thus included in the safety analysis population. Patients with no assessment of global impression of change of skin symptoms or who were not evaluable at all time points were excluded from the efficacy analysis population. Consequently, out of the 306 patients included in the safety analysis population, a total of 250 patients were included in the efficacy analysis population.

No patients under the age of 15 years (Japanese definition of paediatric patients) were enrolled, but one 17-year-old patient was enrolled and was thus considered as a paediatric patient as per the EU definition.

In terms of patient disposition, 242/306 (79%) patients in the safety analysis population completed the 52-week observation period. In total, 57 patients did not formally discontinue but were recorded as not completing the 52-week observation period, as either a second survey form was not collected, their duration of observation was less than 52 weeks, or their second survey form data was excluded from analysis. Seven patients discontinued the study, with 6 patients failing to return mid-course and 1 patient withdrawing consent.

### *Baseline data*

In the overall population, 27% of patients were female, and mean (SD) age at the start of treatment with Cosentyx was 55.9 (13.9) years. Overall, 68% of patients used Cosentyx for psoriasis vulgaris and 32% for psoriatic arthritis; in both groups, over 80% of patients had a disease duration exceeding 5 years. Previous use of biological products for psoriasis was reported for 174 (57%) patients overall; the most frequently used prior biological products included adalimumab (101 patients), infliximab (92 patients), and ustekinumab (87 patients) (patients who had received more than one biological product are counted separately for each product). Most of these patients had discontinued prior biologics due to lack of efficacy.

The distribution of IGA scores and PASI scores at baseline is shown in Table 1.

**Table 1 Distribution of IGA and PASI scores at baseline (safety analysis population)**

| | | | |
|---|---|---|---|
| IGA score - n (%) | 0 = clear | 9 | ( 2.94) |
| | 1 = almost clear | 15 | ( 4.90) |
| | 2 = mild | 41 | ( 13.40) |
| | 3 = moderate | 80 | ( 26.14) |
| | 4 = severe | 39 | ( 12.75) |
| | Unknown/not recorded | 122 | ( 39.87) |
| PASI score | ≤20 | 169 | ( 55.23) |
| | >20 | 56 | ( 18.30) |
| | Unknown/not recorded | 81 | ( 26.47) |

The single paediatric patient was a 17-year-old patient with psoriatic arthritis who had a total disease duration of ≥ 1 year - < 5 years, no other medical history, a BMI of 19.9, and a history of a prior biological treatment.

***Efficacy results***

Skin symptoms

In the overall population, the PASI 75 response rate was 55% at Week 4. After 12 weeks of treatment with Cosentyx, PASI 75, PASI 90 and PASI 100 response rates were 79%, 62% and 42%, respectively. At Week 24, the corresponding response rates were 79%, 60% and 41%.

Among patients with a baseline IGA score of 2 or higher, an IGA score of 0 or 1 was reported for 54% of patients at Week 4, for 78% of patients at Week 12, and for 81% of patients at Week 24.

In the Investigator's global impression of change of skin symptoms, a complete or partial response was reported for 90% of patients at Week 4, and for 95% of patients at Week 12 and Week 24.

PASI response rates over time were also separately analysed according to the patients' prior use of biological products. The results of this analysis are displayed in Table 2.

**Table 2 PASI response rates by use/non-use of prior biological products**

| Time of assessment | Response criterion | Previous biological products prior to the start of Cosentyx | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | No | | | | Yes | | | |
| | | No. of patients | Responder | | | No. of patients | Responder | | |
| | | | No. of patients | (%) | 95% CI | | No. of patients | (%) | 95% CI |
| Week 4 | PASI 75 | 64 | 43 | ( 67.19) | (54.31, 78.41) | 79 | 35 | ( 44.30) | (33.12, 55.92) |
| | PASI 90 | 64 | 30 | ( 46.88) | (34.28, 59.77) | 79 | 23 | ( 29.11) | (19.43, 40.42) |
| | PASI 100 | 64 | 16 | ( 25.00) | (15.02, 37.40) | 79 | 11 | ( 13.92) | (7.16, 23.55) |
| Week 12 | PASI 75 | 62 | 52 | ( 83.87) | (72.33, 91.98) | 84 | 63 | ( 75.00) | (64.36, 83.81) |
| | PASI 90 | 62 | 44 | ( 70.97) | (58.05, 81.80) | 84 | 46 | ( 54.76) | (43.52, 65.66) |
| | PASI 100 | 62 | 29 | ( 46.77) | (33.98, 59.88) | 84 | 32 | ( 38.10) | (27.71, 49.34) |
| Week 24 | PASI 75 | 62 | 57 | ( 91.94) | (82.17, 97.33) | 83 | 58 | ( 69.88) | (58.82, 79.47) |
| | PASI 90 | 62 | 46 | ( 74.19) | (61.50, 84.47) | 83 | 41 | ( 49.40) | (38.24, 60.60) |
| | PASI 100 | 62 | 33 | ( 53.23) | (40.12, 66.02) | 83 | 27 | ( 32.53) | (22.65, 43.70) |

A factorial analysis of response rates based on various baseline characteristics (such as age, sex, weight, disease duration, medical history) identified no particular trends.

Joint symptoms

This analysis was performed for patients with joint symptom evaluation results among the 80 patients (32.00%) in the efficacy analysis population (250 patients) who were diagnosed with psoriatic arthritis at the start of Cosentyx. For many endpoints, data was only available or a small proportion of patients, e.g. 12 patients for HAQ-DI, 19 patients for DAS28-CRP, and 21 patients for physician assessment of disease activity. Overall, decreasing trends were observed across the endpoints assessed. At the last available assessment, a complete response was reported in 27/61 (44%) patients, and a partial response in 24/61 (39%) patients in the Investigator's global impression of change of joint symptoms.

Paediatric patient

For the single paediatric patient, no data was available on the global impression of change for either skin or joint symptoms. It can be noted however that "decreased therapeutic response" was reported as a non-serious adverse reaction for this patient.

***Safety results***

Overall population

In the overall study population, mean (SD) duration of observation was 355 (38) days, and mean duration of treatment with Cosentyx was 316 (81) days. Over 90% of patients were treated for ≥ 24 weeks and over 70% for ≥ 48 weeks. The starting dose of Cosentyx was 150 mg in 2.6% and 300 mg in 97.4% of patients, and the most frequent dose of Cosentyx was 150 mg in 3.3% and 300 mg in 96.7% of patients.

Adverse events were observed in 41.2% (126 patients) of the 306 patients in the safety analysis population. MedDRA System Organ Classes with most reports included Infections and infestations (18.3%, 56 patients), Skin and subcutaneous tissue disorders (13.1%, 40 patients), General disorders and administration site conditions (6.9%, 21 patients), Investigations (6.9%, 21 patients), Gastrointestinal disorders (4.6%, 14 patients), Musculoskeletal and connective tissue disorders (4.3%, 13 patients), and Respiratory, thoracic and mediastinal disorders (3.6%, 11 patients). The most common individual adverse events, reported by over 3% of patients, were nasopharyngitis (4.9%; 15 patients) and psoriasis (4.6%; 14 patients).

Adverse reactions were noted in 24.2% (74 patients) of the 306 patients in the safety analysis population. The most common adverse reactions, reported by 1% of patients or more, were oral candidiasis (2.9%, 9 patients), psoriasis (2.3%, 7 patients), nasopharyngitis (1.6%, 5 patients) and generalised pruritus (1.31%, 4 patients).

Adverse reactions were reported in 49 of the 174 patients (28.2%) who had received biological products prior to the start of Cosentyx, compared to 25 of the 131 patients (19.1%) who had not received prior biological products.

No deaths were reported in the study. Non-fatal serious adverse events were observed in 7.19% (22 patients) of the 306 patients in the safety analysis population. Herpes zoster and a decreased therapeutic response were each reported in two patients, with the other SAEs occurring in single patients. Of these SAEs, the ones suspected to be drug related were asthma, influenza like illness, Crohn's disease, pulmonary tuberculosis, latent tuberculosis, anaphylactic reaction, supraventricular tachycardia, diarrhoea, facial paralysis, malaise, cell marker increased, therapeutic response decreased, concomitant disease progression, nasopharyngitis, myocardial infarction and psoriasis in 1 patient each. The outcomes of these events were "recovered" or "recovering", except for limb injury, which did not recover.

In the safety analysis population (306 patients), adverse events led to treatment discontinuation in 6.54% (20 patients). The adverse event that led to treatment discontinuation most frequently was psoriasis (4 patients), and all the cases were non-serious and not causally related to Cosentyx. The adverse events that led to treatment discontinuation in 2 or more patients were drug ineffective (3 patients), interstitial lung disease, psoriatic arthropathy and therapeutic product effect incomplete (2 patients), of which drug ineffective and interstitial lung disease in 2 patients and therapeutic product effect incomplete in 1 patient were assessed to be related to Cosentyx. Adverse events leading to treatment discontinuation were more commonly reported among patients with previous use of biological products (15/174 (8.6%) patients vs. 5/131 (3.8%) patients); most common events among

this subgroup of patients were psoriasis (4 patients), drug ineffective (3 patients), and therapeutic product effect incomplete (2 patients).

Adverse events belonging to priority survey items were reported in 48 patients (15.7%) overall. The most common events were oral candidiasis (9 patients), rash (5 patients), eczema (4 patients), and tinea pedis (3 patients). Temporal characteristics of these events are depicted in Table 3.

**Table 3 Temporal characteristics of adverse reactions related to priority survey items (time to initial occurrence, time to resolution) (safety analysis population)**

| Priority survey items | No. of patients (%) | 95% CI of incidences | Days to occurrence*1 (day) | | | | | | Days to "recovered" or "recovering"*2 (day) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No. of patients | Mean | SD | Median | Min | Max | No. of patients (%) *3 | Mean | SD | Median | Min | Max |
| Serious infections | 5 ( 1.63) | (0.53, 3.77) | 5 | 229.0 | 111.68 | 276.0 | 85 | 335 | 5 (100.00) | 121.4 | 148.67 | 30.0 | 6 | 341 |
| Fungal infections | 18 ( 5.88) | (3.52, 9.14) | 15 | 183.1 | 103.10 | 204.0 | 8 | 344 | 13 ( 72.22) | 94.0 | 154.09 | 43.0 | 28 | 595 |
| Tuberculosis | 2 ( 0.65) | (0.08, 2.34) | 2 | 324.0 | 15.56 | 324.0 | 313 | 335 | 2 (100.00) | 276.0 | 91.92 | 276.0 | 211 | 341 |
| Neutropenia | 2 ( 0.65) | (0.08, 2.34) | 2 | 103.0 | 94.75 | 103.0 | 36 | 170 | 2 (100.00) | 144.5 | 143.54 | 144.5 | 43 | 246 |
| Hypersensitivity reactions | 9 ( 2.94) | (1.35, 5.51) | 8 | 135.9 | 98.60 | 198.0 | 8 | 222 | 6 ( 66.67) | 50.0 | 60.11 | 19.5 | 3 | 141 |
| Malignant tumors | 1 ( 0.33) | (0.01, 1.81) | 1 | 334.0 | - | 334.0 | 334 | 334 | 0 ( - ) | - | - | - | - | - |
| Inflammatory bowel disease | 1 ( 0.33) | (0.01, 1.81) | 1 | 187.0 | - | 187.0 | 187 | 187 | 1 (100.00) | 49.0 | - | 49.0 | 49 | 49 |
| Cardiovascular/cerebrovascular events | 2 ( 0.65) | (0.08, 2.34) | 2 | 218.0 | 130.11 | 218.0 | 126 | 310 | 2 (100.00) | 47.0 | 32.53 | 47.0 | 24 | 70 |

*1 Included are the patients for whom the number of days from the start day of Cosentyx to the day of the first occurrence can be calculated.

*2 Numbers of days to recovered or recovering for the initial-onset events

*3 Numbers and proportions of patients with the outcome of recovered or recovering for the initial-onset event, denominator for the proportions: number of patients with each item. Included are the patients for whom the number of days to outcome (recovered or recovering) can be calculated.

A factorial analysis of adverse event data based on various baseline characteristics (such as age, sex, weight, disease duration, medical history) identified no particular trends.

Paediatric patient

For the paediatric patient, non-serious adverse reactions of a staphylococcal ear infection, decreased therapeutic response and arthralgia were reported. The corresponding outcomes were "recovered", "not recovered" and "recovering".

***CHMP comment***

*The efficacy and safety data reported in the survey are in line with previous results from controlled clinical studies with secukinumab, and there are no new findings or observations of concern. The safety findings are appropriately addressed in existing Product Information for secukinumab.*

*In terms of paediatric use, the reported survey assessed adult patients, and no conclusions relevant to Article 46 can be made based on a single treated adolescent patient.*

*Overall, the results of the study do not change the benefit-risk profile of secukinumab.*

## 2.3.3. Discussion on clinical aspects

The study reported within the current submission was a non-interventional survey developed and carried out by the MAH to collect safety and efficacy data for Cosentyx, including retrospective data, from the patient population that received Cosentyx soon after its market release in Japan. The study design and execution in themselves seem typical for a non-interventional survey. For purposes of assessment from the perspective of Article 46, the overall relevance of the study is very limited, as it primarily enrolled an adult population in accordance with the authorised use.

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# 3. CHMP's overall conclusion and recommendation

☒ Fulfilled

No regulatory action required.

# 4. Additional clarification requested

None.