23 February 2023
EMA/34114/2023
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/P46/014

Note

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

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1. Introduction

On 05 December 2022, the MAH submitted a clinical study report for a non-interventional clinical study (study number CAIN457A1401) for Cosentyx. In principle, the completed study was not a paediatric study, but since 9 adolescent patients (between 15 and 17 years old) had been enrolled into the study, the clinical study report was submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided. It briefly summarises the study results in the overall population as well as for the adolescent patients.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study CAIN457A1401, titled "Special drug-use investigation for Cosentyx subcutaneous injection (psoriasis vulgaris and psoriatic arthritis)" was a post-marketing surveillance study conducted after the request of the Japanese regulatory authorities, at approval of the psoriasis vulgaris and psoriatic arthritis indications, to collect safety and efficacy data of Cosentyx subcutaneous injection in clinical use. This study included 9 adolescent patients (between 15 and 17 years old).

The results of the study were submitted to the CHMP as a stand-alone submission. 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, demonstrating the safety and efficacy in clinical use. Data from the paediatric patients do not warrant an update of the currently approved product labelling.

2.2. Information on the pharmaceutical formulation used in the study

The study was a post-marketing surveillance study. The following 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 Clinical Study Report for:

- Study CAIN457A1401, titled "Special drug-use investigation for Cosentyx subcutaneous injection (psoriasis vulgaris and psoriatic arthritis)"

2.3.2. Clinical study

Study CAIN457A1401, titled "Special drug-use investigation for Cosentyx subcutaneous injection (psoriasis vulgaris and psoriatic arthritis)"

Description

The study was a post-marketing surveillance conducted as requested by the Japanese regulatory authorities at approval to collect safety and efficacy data of Cosentyx subcutaneous injection (hereafter called Cosentyx) in clinical use in the approved indications.

Methods

The study was an open-label, multicentre, uncontrolled, single-arm, prospective observational surveillance to evaluate the safety and efficacy of Cosentyx in clinical use in Japanese patients with psoriasis vulgaris or psoriatic arthritis. The study was to be conducted at up to around 300 Japanese dermatology departments and other sites that have dermatologists familiar with the diagnosis and treatment of psoriasis vulgaris and psoriatic arthritis and at which Cosentyx had been adopted or to which Cosentyx had been delivered.

The observation period was 52 weeks from the start of treatment with Cosentyx. The follow-up period was 2 years from the end of the observation period (156 weeks from the start of treatment with Cosentyx).

Study participants

Male and female patients with either psoriasis vulgaris or psoriatic arthritis who were not adequately responding to conventional therapies, and who are receiving Cosentyx for the first time since its marketing were registered in this surveillance. Patients had to meet all of the following inclusion criteria and none of the exclusion criteria:

Inclusion criteria

1. Patients who provide written consent to cooperate with this surveillance before registration
2. Patients who meet either of the following
    a. Patients not adequately responding to ultraviolet light therapy and other conventional systemic therapies (other than biological drugs) and whose eruption covers 10% of the body surface area or more
    b. Patients with refractory eruption or joint symptoms

Exclusion criteria

1. Patients previously treated with secukinumab or a product containing the same active ingredient as Cosentyx (either as an investigational drug or in a post-marketing clinical study)
2. Patients who were to be treated with a product containing the same active ingredient as Cosentyx (in a post-marketing clinical study)

Treatments

Being a non-interventional surveillance, there was no binding treatment strategy, and patients were treated in accordance with approved labelling.

As per the Japanese package insert of July 2022, the approved adult dosage of secukinumab (genetical recombination) for subcutaneous use is 300 mg per administration for the initial dosing, at week 1, week 2, week 3, and week 4, and thereafter at 4-week intervals. Secukinumab may also be administered at a dose of 150 mg per administration depending on the body weight.

The usual paediatric (≥ 6 years) dosage of secukinumab (genetical recombination) for subcutaneous use is 75 mg per administration in patients weighing < 50 kg and 150 mg per administration in patients weighing ≥ 50 kg for the initial dosing, at week 1, week 2, week 3, and 4 weeks later, and thereafter at 4-week intervals. In patients weighing ≥ 50 kg, secukinumab may be administered at 300 mg depending on the condition.

Objective

The stated objective of the surveillance was to evaluate the long-term safety and efficacy of Cosentyx in clinical use in psoriasis vulgaris and psoriatic arthritis patients.

Outcomes/endpoints

Primary Endpoint

- Incidence of adverse events during the 52-week observation period in patients treated with Cosentyx

Secondary endpoints

- Number of patients with incidences of serious infections and malignant tumours during a total of 156 weeks of the observation period and the follow-up period.
- Investigator's Global Assessment (IGA modified 2011)
- Psoriasis Area Severity Index (PASI) (eruption-covered body surface area [BSA] only if PASI is not done)
- Dermatology Life Quality Index (DLQI)
- For patients with psoriatic arthritis only:
    - Health Assessment Questionnaire – Disability Index (HAQ-DI)
    - Disease Activity Score 28 (DAS28-CRP)
    - Physician's global assessment of disease activity
    - Patient's global assessment of PsA pain
    - Assessment of dactylitis in fingers and toes
    - Assessment of the presence or absence of tenderness in entheses
    - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
    - Global impression of change of joint symptoms

There were no binding treatment steps or visit schedule. Routine medical practice was followed for the visit frequency and tests to be performed, and only these data were collected as part of the surveillance.

The following adverse event categories were separately defined as priority investigation items for purposes of the surveillance: serious infections, tuberculosis, neutropenia, fungal infections, hypersensitivity reactions, malignant tumours, inflammatory bowel disease, and cardiovascular/cerebrovascular events.

Sample size

The target sample size of the safety analysis population in this surveillance was set at 900 patients and the target number of patients to be registered was set at 950 patients, expecting some patients would be excluded from safety analysis.

Randomisation and blinding (masking)

Not applicable.

Statistical Methods

The safety analysis period was the same as the observation period (52 weeks from the start date of treatment with Cosentyx) and all adverse events that occurred during this period are included in the summary. The total observation period was defined as the observation period + the follow-up period (156 weeks in total), and serious infections and malignant tumours that occurred during this period are included in the summary.

Presentation of data is based on descriptive statistics.

Results

Recruitment and numbers analysed

The first patient was registered and FPFV occurred on 03 December 2015. The end date of registration period (LPFV) was on 31 August 2018, and the end date of the surveillance period (LPLV) was on 27 August 2021.

The surveillance results are based on data obtained from the start date of this surveillance (04 November 2015) and its end date (06 June 2022). A total of 1002 patients were enrolled at 221 sites, and the surveillance form data were locked for 997 patients at 218 sites. Of these patients, 976 were included in the safety analysis set (including all 9 paediatric patients recruited within the surveillance study) after excluding 21 ineligible patients (none of them paediatric patients). A total of 729 patients were included in the efficacy analysis set (including 7 paediatric patients recruited within the surveillance study), after excluding 247 patients in the safety analysis set who were not evaluable for efficacy. Of the 9 paediatric patients included in the study, 2 were dropouts and were excluded from the efficacy analysis set.

Baseline data

In the safety analysis population (n = 976), 69.77% (681 patients) were male and 30.23% (295 patients) were female. Mean (SD) age at the start of treatment with Cosentyx was 54.1 (14.90) years. Patients aged ≥ 15 years and < 65 years accounted for 72.54% (708 patients) and the elderly aged ≥

65 years accounted for 27.46% (268 patients). Nine patients were 15 to 17 years of age and therefore considered paediatric patients as per the EU definition.

The reasons for Cosentyx use were psoriasis vulgaris in 71.62% (699 patients) and psoriatic arthritis in 28.38% (277 patients). The most common total disease duration category of psoriasis vulgaris and psoriatic arthritis was ≥ 10 years to < 20 years in 33.61% (328 patients), followed by ≥ 5 years to < 10 years in 18.03% (176 patients), ≥ 20 years to < 30 years in 15.37% (150 patients) and ≥ 1 year to < 5 years in 13.83% (135 patients). The most common disease duration of psoriatic arthritis (in 277 psoriatic arthritis) was ≥ 1 year to < 5 years in 9.63% (94 patients), followed by < 1 year in 5.74% (56 patients) and ≥ 5 years to < 10 years in 4.61% (45 patients).

The mean (SD) weight was 68.96 (16.110) kg with most patients weighing > 60.0 kg (51.74%, 505 patients). The mean (SD) BMI was 25.02 (4.832) kg/m2; specifically ≥ 18.5 kg/m2 to < 25.0 kg/m2 in 35.76% (349 patients), followed by ≥ 25.0 kg/m2 to < 35.0 kg/m2 in 28.38% (277 patients), < 18.5 kg/m2 in 4.00% (39 patients), and ≥ 35.0 kg/m2 in 2.15% (21 patients).

Current medical conditions were present in 56.35% (550 patients), and the most frequently reported current medical conditions were cardiovascular/cerebrovascular events in 18.85% (184 patients), hepatic impairment in 13.01% (127 patients), renal impairment in 7.79% (76 patients), hypersensitivity reactions in 4.51% (44 patients), and fungal infections in 3.79% (37 patients).

Most patients (90.98%, 888 patients) had a history of prior use of psoriasis medication. Biological products were used for the treatment of psoriasis and other indications in 42.52% (415 patients) and for the treatment of psoriasis in 42.32% (413 patients). Drugs other than biological products were used in 76.95% (751 patients). The most common drugs other than biological products were steroids for external use in 48.36% (472 patients), followed by cyclosporine in 5.12% (50 patients).

A total of 203 patients (20.80%) received phototherapy for psoriasis vulgaris and psoriatic arthritis before the start of treatment with Cosentyx; of these, narrow band UVB was the most common type (16.09%, 157 patients).

The most common IGA score at the start of treatment with Cosentyx was "3 (moderate)" in 28.79% (281 patients), followed by "2 (mild)" in 16.60% (162 patients) and "4 (severe)" in 11.99% (117 patients) (except for unknown/not recorded). PASI score at the start of treatment with Cosentyx was ≤ 20 for 54.51% (532 patients) and > 20 for 14.65% (143 patients).

Paediatric patients

The nine enrolled paediatric patients were aged as follows: 15 years (3 patients), 16 years (4 patients), and 17 years (2 patients). Four of these patients had psoriasis vulgaris and 5 patients had psoriatic arthritis. One patient had an unspecified medical history condition.

Duration of psoriasis was as follows: < 1 year (3 patients), ≥ 1 year < 5 years (3 patients), ≥ 5 years < 10 years (2 patients), ≥ 10 years < 20 years (1 patient). BMI ranged from 18.4 kg/m2 to 34.0 kg/m2, and 2 patients had first degree relatives with psoriasis. A concurrent condition of hypersensitivity reactions was reported for 5 patients, and cardiovascular/cerebrovascular events and hepatic disease were reported in 1 patient each. None had a history of cigarette smoking or alcohol use.

Previously, 8 paediatric patients had received psoriasis drugs other than biological products, 4 had received biological products, and 4 had received other drugs.

Efficacy results

Changes over time in IGA score were evaluated among patients with an IGA score of ≥ 2 at the start of treatment with Cosentyx who provided results at the start of treatment and at the last evaluation

among the efficacy analysis population (n = 729); 551 patients met those criteria and were included in the evaluation.

The respective IGA scores at the start of treatment and the proportions of patients falling into these categories were: 2 (mild) in 28.86% (159 patients), 3 (moderate) in 50.27% (277 patients), and 4 (severe) in 20.87% (115 patients). The proportion of patients with an IGA score improvement after the start of treatment increased over time from the start of treatment to reach 44.41% (163/367 patients) at Week 4, 71.38% (217/304 patients) at Week 16, and 77.36% (270/349 patients) at Week 24. Thereafter, the proportion was stable and reached 76.24% (154/202 patients) at Week 52.

The changes over time in PASI score were evaluated for patients with PASI scores at both the start of treatment with Cosentyx and the last evaluation among the efficacy analysis population. A total of 588 patients were evaluated for mean PASI score over time, and 564 patients were evaluated for mean percent changes from baseline in PASI score.

The mean (SD) PASI score decreased over time from Week 2 of treatment: 12.94 (10.708) at the start of treatment, 4.20 (5.500) at Week 4, and 1.73 (3.632) at Week 16. The mean PASI score was stable from Week 12 to Week 52, and the result at Week 52 was 1.44 (3.143).

The mean (SD) percent changes in PASI score from baseline were −44.024% (1.8916) at Week 2 of treatment, −80.593% (2.2263) at Week 16, and −85.118% (1.8501) at Week 52. There were decreases with time until Week 12, and the PASI score was stable thereafter.

The PASI 75 response rate increased over time from Week 2 of treatment to Week 12 of treatment and was stable thereafter up to Week 52. The PASI 90 and PASI 100 response rates increased over time from Week 2 of treatment to Week 24 and were stable thereafter up to Week 52.

At Week 16 of treatment, the PASI 75 response rate was 73.83% (237/321 patients), the PASI 90 response rate was 55.14% (177/321 patients), and the PASI 100 response rate was 37.69% (121/321 patients). At Week 52 of treatment, the PASI 75 response rate was 78.30% (184/235 patients), the PASI 90 response rate was 64.26% (151/235 patients), and the PASI 100 response rate was 46.81% (110/235 patients).

DLQI total score evaluation was performed for 426 patients with DLQI total scores available at the start of treatment with Cosentyx and the last evaluation among the efficacy analysis population (n = 729).

The mean (SD) DLQI total score decreased over time until Week 16 from the start of treatment and was stable up to Week 52 of treatment. The DLQI total scores were 7.4 (6.13) at the start of treatment, 3.7 (4.57) at Week 4, 2.1 (3.56) at Week 16, and 1.8 (2.54) at Week 52.

The proportions of patients with a DLQI total score of 0 or 1 at the respective evaluation time points were 14.79% (63/426 patients) at the start of treatment, 40.25% (130/323 patients) at Week 4, 66.67% (162/243 patients) at Week 16, and 63.56% (75/118 patients) at Week 52.

Joint symptom evaluations were performed among the subset of patients within the efficacy analysis population who had a diagnosis of psoriatic arthritis. HAQ-DI analysis was performed for 107 patients with HAQ-DI scores available at the start of treatment and at the last evaluation. The mean (SD) HAQ-DI score decreased over time: 0.68 (0.798) at the start of treatment, 0.42 (0.572) at Week 16, and 0.39 (0.658) at Week 52. The mean (SD) changes in HAQ-DI score from the start of treatment were −0.20 (0.527) at Week 12, −0.17 (0.511) at Week 16, and −0.31 (0.595) at Week 52. Thus, the mean HAQ-DI score started improving (decreasing) after the start of treatment and was stable from Week 12 of treatment to Week 52.

DAS28-CRP analysis was performed for 111 patients with DAS28-CRP scores available at the start of treatment with Cosentyx and the last evaluation. The mean (SD) DAS28-CRP score decreased over time: 3.65 (1.422) at the start of treatment, 2.62 (1.323) at Week 16, and 2.52 (1.279) at Week 52. The mean (SD) changes in DAS28-CRP score from the start of treatment were −1.08 (1.370) at Week 12, −1.33 (1.297) at Week 16, and −1.20 (1.526) at Week 52. The mean DAS28-CRP score started improving after the start of treatment and was stable from Week 12 of treatment to Week 52.

Mean changes on other secondary efficacy endpoints among the subset of evaluable patients with psoriatic arthritis consistently indicated improvement upon treatment with Cosentyx.

Paediatric patients

For the 7 paediatric patients evaluable for efficacy, results were provided for IGA assessments. For the psoriatic arthritis patients, IGA was used to evaluate the skin manifestations of psoriatic disease.

Of the 4 paediatric patients with psoriasis vulgaris, 1 patient was a dropout and was excluded from the efficacy analysis of IGA. The IGA efficacy evaluation results for the other 3 patients were as follows: Clear (2 patients); Mild (1 patient).

Of the 5 paediatric patients with psoriatic arthritis, 1 patient was a dropout and was excluded from the IGA efficacy analysis. The IGA efficacy evaluation results for the other 4 patients were as follows: Clear (1 patient); Almost clear (3 patients).

Safety results

In the safety analysis population (n = 976), the mean (SD) observation duration was 346.8 (61.81) days, and 90.88% (887 patients) of the population had an observation duration longer than 48 weeks. The mean (SD) Cosentyx administration duration was 288.1 (106.51) days, and the median (min-max) was 344.0 (1-365) days. Treatment duration was > 4 weeks for 95.70% (934 patients), > 16 weeks for 87.09% (850 patients), and > 48 weeks for 61.78% (603 patients).

The initial dose per administration was 300 mg in 97.44% (951 patients), and the most commonly used dose per administration was 300 mg in 96.21% (939 patients). The mean (SD) total number of administrations was 13.6 (3.87). During the observation period, 72.03% (703 patients) performed self-administration at least once. Dose adjustments were reported in 4.51% (44 patients) during the observation period. Among these patients, dose reductions were reported in 3.69% (36 patients). The most frequently reported reasons for dose reductions were adequate efficacy and "other reasons" in 1.43% (14 patients) each, and occurrence of AE in 0.82% (8 patients). Dose increases were reported in 1.84% (18 patients). The most frequently reported reasons for dose increases were lack of efficacy in 1.23% (12 patients) and "other reasons" in 0.51% (5 patients). Both dose increases and decreases were reported in 1.02% (10 patients).

The mean (SD) total observation duration in the safety analysis population, including the follow-up period, was 939.4 (306.69) days. Most of the patients completed the 52-week observation period and entered the follow-up period, completing (52 weeks), with > 52 weeks in 90.57% (884 patients), > 104 weeks in 83.20% (812 patients), > 156 weeks in 76.23% (744 patients).

In the safety analysis population, 9.53% (93 patients) discontinued during the 52-week observation period. The reported reasons were "failure to return before completion (including hospital change)" in 6.66% (65 patients), "withdrawal of consent by the patient" in 1.84% (18 patients), "death" in 0.82% (8 patients), and "others" and "unknown" in 0.10% (1 patient) each.

Adverse events (AEs) were reported in 353 patients (36.17%) during the 52-week observation period. The most frequently reported AEs (≥ 1.00%) were nasopharyngitis in 30 patients (3.07%), psoriatic

arthropathy in 29 patients (2.97%), psoriasis in 26 patients (2.66%), oral candidiasis in 20 patients (2.05%), tinea pedis in 19 patients (1.95%), pruritus in 16 patients (1.64%), cellulitis in 14 patients (1.43%); and upper respiratory tract inflammation and diarrhoea in 10 patients (1.02%) each. During the first 12 weeks of Cosentyx treatment, AEs were reported in 144 patients (14.75%). The most frequently reported AEs (≥ 1.00%) were oral candidiasis in 1.23% (12 patients) and nasopharyngitis in 1.02% (10 patients). The incidences of adverse events by presence/absence of a history of biological product use were 40.44% (167/413 patients) in the patients with a history of use and 33.27% (186/559 patients) in the patients without a history of use.

AEs that led to treatment discontinuation were reported in 79 patients (8.09%), including 1 paediatric patient. The most frequently reported events leading to discontinuation were psoriasis (verbatim: worsening of underlying disease etc.) in 13 patients (1.33%), psoriatic arthropathy (verbatim: worsening of underlying disease etc.) in 10 patients (1.02%), and drug ineffective in 5 patients (0.51%). Events reported as severe were psoriasis in 3 patients, and psoriatic arthropathy and drug ineffective in 1 patient each. All other events were mild or moderate in severity (and severity unknown in 1 patient each with psoriatic arthropathy and drug ineffective). All the events were assessed to be non-serious, and the outcomes were all resolved or resolving, except for psoriasis in 1 patient whose outcome was not resolved.

Other AEs that led to treatment discontinuation (≥ 2 patients) were interstitial lung disease, diarrhoea, erythema, rash, toxic skin eruption, and therapeutic response decreased in 3 patients (0.31%) each; and blepharitis, pruritus, urticaria, arthritis, malaise and platelet count decreased in 2 patients (0.20%) each. Of these, AEs reported as severe were erythema, thrombocytopenia, and pruritus in 1 patient each; all other events were mild or moderate in severity (and severity unknown in 1 patient each with blepharitis and erythema). The events whose outcomes were neither resolved nor resolving were rash (not resolved), toxic skin eruption (death), and platelet count decreased (unknown) in 1 patient each. These events included serious events (toxic skin eruption and platelet count decreased in 1 patient each).

Serious adverse events (SAEs) were reported in 57 patients (5.84%). The most frequently reported SAEs (≥ 2 patients) were cellulitis in 4 patients (0.41%); herpes zoster, pneumonia, myocardial infarction, and interstitial lung disease in 3 patients (0.31%) each; and septic shock, hyperkalaemia, and cerebral infarction in 2 patients (0.20%) each. Among these events, a fatal outcome was reported in 3 patients, with infection involved in all cases:

- Pneumonia in 2 patients
- Septic shock, hyperkalaemia, and cerebral infarction in 1 patient each (cerebral infarction and pneumonia in the same patient)

Among these events, recovery with sequelae was reported as the outcome for herpes zoster and cerebral infarction in 1 patient each, with outcome for the other events being reported as resolved or resolving.

In the total observation period of 156 weeks, there were 11 deaths in total. The fatal events suspected by the investigators to be related to Cosentyx were death (cause unknown) and toxic skin eruption in 1 patient each. Case details were as follows:

- Death (cause unknown): This patient, a 69 year-old male, had no reported medical history and no previous treatment with biological products; renal disease was reported as a current medical condition. The patient developed platelet count decreased (serious) about 2 months before death (date of occurrence unknown), back pain (nonserious) at 225 days from the start of treatment, and eosinophil count increased (nonserious) at 288 days from the start of

treatment. The outcomes were all unknown. The action taken for platelet count decreased was Cosentyx treatment discontinuation, and the patient died 314 days from the start of Cosentyx treatment (34 days after the most recent administration) Reported PT was "death". The causal relationships to Cosentyx were related except for back pain.

- Toxic skin eruption: This patient, a 76 year-old male, had no reported medical history, previous treatment with biological products (not specified), and current medical conditions (not specified). Toxic skin eruption (serious) occurred 5 days after the first Cosentyx administration. The causal relationship to Cosentyx was related, and the action taken was Cosentyx treatment discontinuation. Pneumonia (serious) occurred 330 days after the start of treatment with Cosentyx. The patient died 43 days after the occurrence of pneumonia. The pneumonia was assessed as not related to Cosentyx, and the current medical conditions were the non-Cosentyx factors.

Among the fatal events, the following events were not suspected to be related to Cosentyx: cardiac failure acute, pulmonary oedema, myelodysplastic syndrome, anaemia, and pleural effusion in 1 patient each (same patient); device related infection, septic shock, and renal impairment in 1 patient each (same patient); cerebral infarction, dermatitis exfoliative generalised, haemoglobin decreased, pneumonia, and renal failure in 1 patient each (same patient); frontotemporal dementia, pneumonia bacterial, nasopharyngeal cancer, head injury, pneumonia, and hyperkalaemia in 1 patient each.

Adverse reactions (AEs assessed by the investigators as causally related to Cosentyx) were reported in 184 patients (18.85%). The most frequently reported adverse reactions (≥ 1.00%) were oral candidiasis in 19 patients (1.95%), psoriatic arthropathy (verbatim: worsening of underlying disease etc.) in 13 patients (1.33%), pruritus in 12 patients (1.23%), and psoriasis (verbatim: worsening of underlying disease etc.) in 11 patients (1.13%).

Serious adverse reactions (SAEs assessed by the investigators as causally related to Cosentyx) were reported in 24 patients (2.46%). These reported serious adverse reactions included cellulitis in 3 patients (0.31%); herpes zoster and interstitial lung disease in 2 patients (0.20%) each; and erysipelas, pyelonephritis, septic shock, urinary tract infection, candida infection, malignant ascites, ovarian cancer, malignant neoplasm of unknown primary site, pleomorphic adenoma, depression, cerebral infarction, amaurosis fugax, organising pneumonia, colitis ulcerative, diarrhoea, gastroenteritis eosinophilic, inflammatory bowel disease, erythema, toxic skin eruption, rheumatoid arthritis, death, malaise, pyrexia, eosinophil count increased, platelet count decreased, and KL-6 increased in 1 patient (0.10%) each. The outcomes were all resolved or resolving, except for 5 patients whose outcomes were resolved with sequelae (herpes zoster and cerebral infarction in 1 patient each), fatal (toxic skin eruption and death in 1 patient each), and unknown (platelet count decreased and KL-6 increased in 1 patient each). Case summaries for the fatal events are provided above; cases with outcome "recovered with sequelae" or "unknown" are summarised below:

- Cerebral infarction: This patient was a 70-year-old male with a history of previous biological product use and current medical conditions of cerebrovascular/cardiovascular events and hepatic disease. Cerebral infarction occurred at 86th day from the start of treatment with Cosentyx (2 days from the most recent administration day). The number of administrations up to the occurrence was 7 times and Cosentyx administration was continued after the occurrence. Cerebral infarction recurred at 170th day from the start of treatment with Cosentyx (2 days from the most recent administration day). The number of administrations up to the recurrence was 10 times and Cosentyx administration was continued after the recurrence. This event was moderate in severity, the outcomes after actions (concomitant drugs etc. changed, hospitalisation/prolongation of existing hospitalisation) were both sequelae

and current medical conditions (diabetes mellitus and hypertension) were the non-Cosentyx factors.

- Herpes zoster: This patient was an 82-year-old male with a medical history but without a history of previous biological product use who had current medical conditions of cerebrovascular/cardiovascular events and hepatic disease. Herpes zoster occurred at 177th day from the start of treatment with Cosentyx (5 days from the most recent administration day). The number of administrations up to the occurrence was 10 times and Cosentyx administration was continued after the occurrence. This event was moderate in severity, the outcome after an action (hospitalisation/prolongation of existing hospitalisation) was sequelae and a current medical condition (diabetes mellitus) was the non-Cosentyx factor.
- KL-6 increased: This patient was a 75-year-old female without a medical history and with a history of previous biological product use who had current medical conditions of cerebrovascular/cardiovascular events. KL-6 increased occurred at 116th day from the start of treatment with Cosentyx (31 days from the most recent administration day). The number of administrations up to the occurrence was 7 times and Cosentyx administration was discontinued after the occurrence. This event was severe in severity, the outcome after an action (hospitalisation/prolongation of existing hospitalisation) was unknown.

As regards the evaluation of priority investigation items, AEs of "serious infections" were reported in 17 adult patients (1.74%) during the 52-week observation period. Of these, the most frequently reported AEs (in ≥ 2 patients) were cellulitis in 4 patients (0.41%), herpes zoster and pneumonia in 3 patients (0.31%) each, and septic shock in 2 patients (0.20%).

Adverse reactions of "serious infections" were reported in 9 patients (0.92%). Of these, adverse reactions reported in 2 or more patients were cellulitis in 3 patients (0.31%) and herpes zoster in 2 patients (0.20%). The median (min-max) number of days from the start of treatment with Cosentyx to the occurrence of adverse reactions (first occurrence) was 81.0 (1-308) days. Events reported as severe were herpes zoster and septic shock in 1 patient each; all other events were moderate in severity. The outcomes in the 9 patients were all resolved or resolving except for herpes zoster (recovered with sequelae). The median (min-max) number of days to resolved or resolving was 21.0 (1-113) days.

During > 52 weeks-≤ 104 weeks in the follow-up period, adverse events of "serious infections" occurred in 8 patients, including appendicitis in 2 patients; and pneumonia, herpes zoster, urinary tract infections, nasopharyngitis, peritonitis and pneumonia bacterial in 1 patient each. During > 104 weeks in the follow-up period, adverse events of "serious infections" occurred in 3 patients, including pneumonia, diverticulitis and sepsis in 1 patient each. According to the MAH, the AEs of "serious infections" that occurred during the follow-up period (> 52 weeks and ≤ 104 weeks) were similar to the events that occurred within the observation period, with no tendency towards increased occurrence of AEs of "serious infections" with longer-term treatment with Cosentyx.

Adverse events of "neutropenia" were reported in 6 patients (0.61%). The adverse events were white blood cell count decreased in 4 patients (0.41%) and neutrophil count decreased in 3 patients (0.31%).

No increased risk of opportunistic infections was observed. No tuberculosis was reported (regardless of causality). Adverse events of "fungal infections" were reported in 54 patients (5.53%). Common adverse events (≥ 2 patients) were oral candidiasis in 20 patients (2.05%), tinea pedis in 19 patients (1.95%), body tinea in 5 patients (0.51%), and oesophageal candidiasis, skin candida and candida infection in 2 patients (0.20%). Viral infections were reported in 3 patients, 2 with unspecified "viral infection" and 1 with an AE of "gastroenteritis viral".

Adverse events of "hypersensitivity reactions" were reported in 43 patients (4.41%). Common adverse events (≥ 2 patients) were mainly cutaneous events: rash in 9 patients (0.92%), urticaria in 8 patients (0.82%), eczema in 7 patients (0.72%), dermatitis contact in 5 patients (0.51%), rhinitis allergic in 4 patients (0.41%), toxic skin eruption in 3 patients (0.31%), and dermatitis exfoliative generalised in 2 patients (0.20%).

During the 52-week observation period, malignancy was reported in 7 adult patients (0.72%). No specific AE of malignancy occurred in ≥ 2 patients, and the reported AEs were bladder cancer, gastric cancer, malignant neoplasm of renal pelvis, ovarian cancer, squamous cell carcinoma, nasopharyngeal cancer, malignant neoplasm of unknown primary site, and pleomorphic adenoma in 1 patient (0.10%) each.

The reported malignancies were assessed by the investigators as related to Cosentyx in 3 of the 7 patients. The specific tumours were ovarian cancer, malignant neoplasm of unknown primary site, and pleomorphic adenoma. The median (min-max) number of days from the start of treatment with Cosentyx to the occurrence of adverse reactions (first occurrence) was 260.0 (133-305) days. The outcomes after actions (temporary Cosentyx interruption, Cosentyx treatment discontinuation, hospitalisation/prolongation of existing hospitalisation) were resolving. The median (min-max) number of days to resolving was 268.0 (114-524) days.

During > 52 weeks-≤ 104 weeks in the follow-up period, adverse events of "malignant tumours" occurred in 8 patients, including colon cancer and oesophageal carcinoma in 2 patients, and bladder cancer, gastric cancer, squamous cell carcinoma of lung, lung neoplasm malignant, pancreatic carcinoma and squamous cell carcinoma of skin in 1 patient each. During > 104 weeks in the follow-up period, adverse events of "malignant tumours" occurred in 5 patients, including bladder cancer, gastric cancer, squamous cell carcinoma of lung, lung neoplasm malignant and extramammary Paget's disease in 1 patient each. The adverse events suspected to be related to Cosentyx and thus regarded as adverse reactions were bladder cancer, pancreatic carcinoma, and lung neoplasm malignant in 1 patient each.

An adverse reaction of "inflammatory bowel disease" was reported in 2 patients (0.20%). The observed adverse reactions were colitis ulcerative and inflammatory bowel disease (PT) in 1 patient (0.10%) each. Both were assessed as serious, moderate in severity and the outcomes for both were "resolved".

The incidence of adverse events of "cardiovascular/cerebrovascular events" was 2.15% (21 patients). Common adverse events (≥ 2 patients) were hypertension in 0.51% (5 patients), myocardial infarction in 0.31% (3 patients), cerebral infarction and oedema peripheral in 0.20% (2 patients) each. The incidence of adverse reactions of "cardiovascular/cerebrovascular events" was 0.51% (5 patients). No adverse reaction occurred in 2 patients or more and the adverse reactions were cerebral infarction, amaurosis fugax, death, loss of consciousness and peripheral swelling in 0.10% (1 patient) each. The severity was severe in 1 patient (death), moderate in 1 patient (cerebral infarction), and mild in all other events. The outcomes in the 5 patients were all resolved except for fatal (adverse reaction term: death) and sequelae [2 cases of cerebral infarction (same patient)].

A factorial analysis of adverse reaction data based on various baseline characteristics (such as age, sex, body weight, disease duration, medical history, prior use of biologicals) identified no particular trends apart from a slightly higher rate of adverse reactions among patients with a history of cardiovascular/cerebrovascular events as opposed to patients without a history (odds ratio: 1.85, 95%CI: 1.24, 2.73).

Paediatric patients

For the 52-week observation period, all 9 paediatric patients had an observation period of > 52 weeks (365 days). Duration of drug treatment was > 4 weeks for all 9 patients (100%), > 16 weeks for 8 patients (88.89%), > 24 weeks for 7 patients (77.78%), > 40 weeks for 5 patients (55.56%), > 48 weeks for 4 patients (44.44%), and > 52 weeks for 1 patient (11.11%).

Mean (SD) duration of Cosentyx treatment was 250.4 (109.99) days (from minimum of 93 days to maximum of 365 days), with a total exposure of 6.2 patient-years. Initial drug dose was 300 mg for 8 patients and 150 mg for 1 patient. The most commonly administered dose was 300 mg once every 4 weeks. The mean (SD) total number of drug doses was 12.9 (4.65). Regarding dose adjustments, 1 patient each (11.11%) had a dose increase and a dose reduction. Five patients used self-administration, and 4 patients did not use self-administration.

Overall, 30 AEs were reported in 4 of the 9 total paediatric patients. The different AEs (preferred terms) occurred in only 1 paediatric patient each, except the following: allergic rhinitis in 4 patients; and autonomic imbalance, upper respiratory tract inflammation, psoriatic arthropathy, and pain in 2 patients each.

No SAEs occurred in the paediatric patients. One paediatric patient discontinued treatment due to an AE of "drug ineffective" 1 day after receiving their eighth dose of Cosentyx.

Two paediatric patients experienced mild nonserious AEs during the follow-up period, specifically conjunctivitis allergic, irritable bowel syndrome, and rhinitis allergic in 1 patient and Behcet's syndrome in 1 patient. None of these AEs were considered related to Cosentyx.

2.3.3. Discussion on clinical aspects

The study reported within the current submission was a non-interventional surveillance study developed and carried out by the MAH to collect safety and efficacy data from the patient population that received Cosentyx after its approval in Japan. The study design and execution seem typical for a non-interventional surveillance study. For purposes of assessment from the perspective of Article 46, the overall relevance of the study is quite limited, as it primarily enrolled an adult population in accordance with the authorised use. No patients under the age of 15 years (Japanese definition of paediatric patients) were enrolled, but nine patients from 15 to 17 years of age were enrolled and were thus considered paediatric patients as per the EU definition.

The study was an uncontrolled non-interventional survey, and quite limited conclusions can therefore be drawn from the results. However, the reported results are consistent with previous results from controlled clinical studies with secukinumab in the corresponding indications, and there are no new findings or observations of concern. The safety findings are also appropriately addressed in existing EU Product Information for secukinumab, and no updates are warranted. In terms of paediatric use, the reported survey primarily assessed adult patients, and no conclusions relevant to Article 46 can be made based on a handful of treated adolescent patients. Overall, the results of the study do not change the benefit-risk profile of secukinumab.

The MAH has concluded that the surveillance results do not show any new safety concerns with long-term treatment with Cosentyx (observation up to 156 weeks after start of Cosentyx treatment) in Japanese patients with psoriasis vulgaris and psoriatic arthritis. The reported AEs were consistent with the overall safety profile for secukinumab, and no new safety signal was identified in paediatric patients. No additional safety measures are considered necessary. In addition, this study confirmed the long-term efficacy and safety of Cosentyx in Japanese patients with psoriasis vulgaris and psoriatic

arthritis. Nine paediatric patients < 18 years old were included in Study CAIN457A1401. Data from these paediatric patients do not warrant an update of the currently approved product labelling.

The MAH's conclusions are generally agreed with. Due to the nature of the study, it cannot be agreed that confirmatory evidence of long-term efficacy or safety would have been provided, but it is agreed that the results are generally consistent with previously reported pivotal trials, and that no regulatory action is considered necessary.

3. CHMP overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.