30 May 2024
EMA/282777/2024
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/P46/016

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	01 Apr 2024	01 Apr 2024	☐
☐	CHMP Rapporteur Assessment Report	06 May 2024	06 May 2024	☐
☐	CHMP members comments	21 May 2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	23 May 2024	n/a	☐
☒	CHMP adoption of conclusions:	30 May 2024	30 May 2024	☐

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1. Introduction

On 04 March 2024, the MAH submitted the final CSR for CAIN457A2311, a completed paediatric study for Cosentyx (secukinumab; AIN457), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are submitted as part of a post-authorisation (P46) measure.

A critical expert overview, summarising results from the study, has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that submission of the final CSR for Study CAIN457A2311 "A randomized, open-label, multicenter trial to assess the efficacy of subcutaneous secukinumab after twelve weeks of treatment, and to assess the long-term safety, tolerability and efficacy in subjects from 6 to less than 18 years of age with moderate to severe chronic plaque psoriasis" is a stand-alone submission. Of note, efficacy data up to 24 weeks from the study were previously submitted in support of the variation application in which an extension of indication into paediatric plaque psoriasis was granted for secukinumab (procedure EMEA/H/C/003729/II/0057); moreover, results up to 52 weeks were provided within procedure EMEA/H/C/003729/II/0073 and have thereby also been previously assessed. For the reader's convenience, key results from the previous procedures are very briefly summarised herein; for additional details, reference is made to the European Public Assessment Reports for procedures II/0057 and II/0073. A line listing of all the concerned studies is annexed.

According to the MAH, Study A2311 was an interventional study conducted to assess the efficacy of secukinumab based on both psoriasis area and severity index (PASI) 75 and Investigator's global assessment modified 2011 (IGA mod 2011) 0 or 1 response rates at Week 12, compared to placebo (historical control) in children and adolescents aged 6 to <18 years at randomisation with moderate to severe chronic plaque psoriasis who were candidates for systemic therapy. Moreover, this study also assessed the long-term efficacy, safety and tolerability of secukinumab in paediatric patients over a period of up to 4 years. This study was conducted to provide efficacy, safety and PK data to support the extension of the label of secukinumab to include children and adolescents (6 to <18 years) with moderate to severe chronic plaque psoriasis. Study A2311 enrolled 84 paediatric patients and concluded on 12-Sep-2023 (last patient last visit [LPLV]).

The study demonstrated the long-term efficacy and safety of secukinumab in paediatric patients aged 6 years to less than 18 years with moderate to severe chronic plaque psoriasis. Secukinumab continues to demonstrate a favourable benefit-risk profile in paediatric psoriasis patients.

In light of the final results of Study CAIN457A2311, the MAH considers that no changes to the approved EU SmPC are warranted, and none are proposed.

2.2. Information on the pharmaceutical formulation used in the study

Secukinumab was tested at low and high doses and was supplied as 150 mg/1.0 mL and 75 mg/0.5 mL pre-filled syringes (PFS).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- CAIN457A2311: A randomized, open-label, multicenter trial to assess the efficacy of subcutaneous secukinumab after twelve weeks of treatment, and to assess the long-term safety, tolerability and efficacy in subjects from 6 to less than 18 years of age with moderate to severe chronic plaque psoriasis

2.3.2. Clinical study

Description

Study CAIN457A2311 was a randomised, open-label Phase III study with a historical placebo control group, conducted in paediatric patients from 6 years of age with moderate to severe chronic plaque psoriasis.

Methods

Study design

The study was an open-label, parallel group, two-arm, historical controlled multi-centre trial in paediatric patients aged 6 years to less than 18 years at randomisation, with moderate to severe chronic plaque psoriasis.

The study consisted of 3 periods:

- Screening: up to 4 weeks in which eligibility was assessed and patients were tapered off prohibited medication,
- Treatment: randomisation to Week (W) 208 or last dose + 84 days exposure (safety analysis) in which endpoints were assessed and patients were followed for long-term safety and efficacy; and
- Post-treatment follow-up: for 16 weeks, visits at W212, W216 and W224.

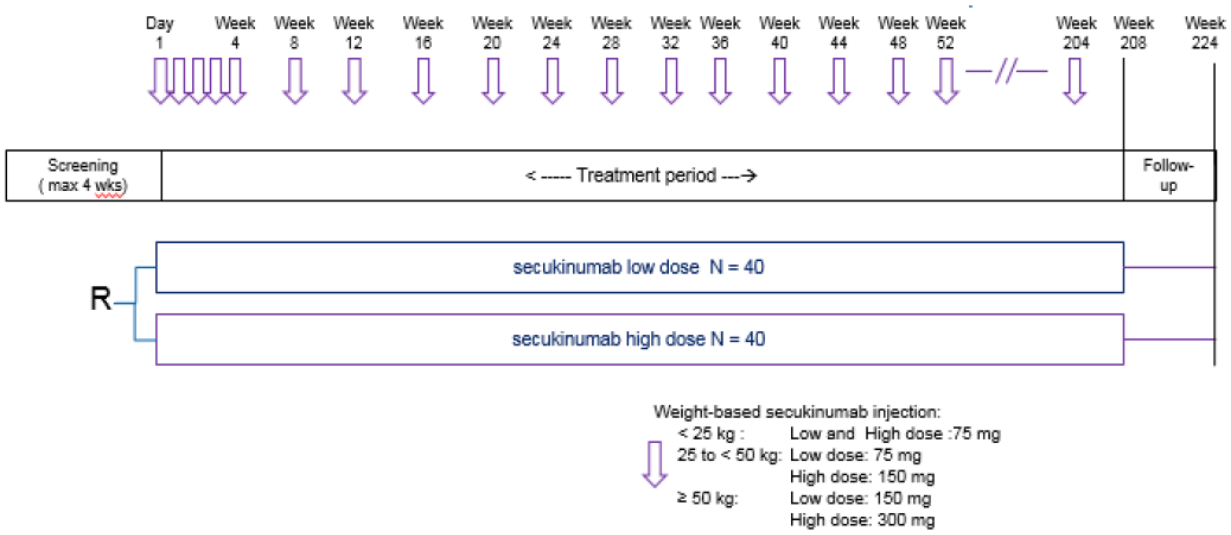
The following definitions are applied in data displays:

- Entire treatment period = randomisation to Week 208 (EOT); for safety analyses, includes follow-up period up to last dose + 84 days for early discontinued patients.
- Entire study period = randomisation to end of study (EOS); includes follow up period (Week 212, 216 and 224)

The study assessed the long-term efficacy, safety and tolerability of the secukinumab low dose and the secukinumab high dose based on weight category (< 25 kg, 25- < 50kg, ≥ 50 kg) over a period of up to 4 years to support the long-term use of secukinumab in paediatric patients.

Patients were randomised using a 1:1 ratio into the secukinumab low dose and secukinumab high dose treatment groups. The design is graphically depicted in Figure 1.

Figure 1. Study design for CAIN457A2311



Source: [Study A2311 Final CSR-Figure 9-1]

Study participants

The main inclusion criteria were:

- Written informed assent and parental permission obtained at screening.
- 6 to less than 18 years of age at the time of randomisation.
- Moderate to Severe plaque psoriasis, defined as a PASI score ≥ 12, and IGA mod 2011 score of ≥ 3, and Body Surface Area (BSA) involvement of ≥ 10%, at randomisation.
- History of plaque psoriasis for at least 3 months before randomisation.
- Patient being regarded by the investigator to be a candidate for systemic therapy because of:
    - Inadequate control of symptoms with topical treatment, and/or
    - Failure to respond to or tolerate previous systemic treatment and/or ultraviolet therapy.

The main exclusion criteria were:

- Forms of psoriasis other than chronic plaque-type (e.g. pustular, erythrodermic and guttate psoriasis), active at randomisation.
- Female patients of childbearing potential (menarchal or becoming menarchal during the study) who do not agree to abstinence or, if sexually active, do not agree to the use of contraception.
- Active ongoing inflammatory diseases other than psoriasis that might confound the evaluation of the benefit of secukinumab therapy.
- Underlying condition (including, but not limited to metabolic, haematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal) which in the opinion of the investigator significantly immunocompromises the patient and/or places the patient at unacceptable risk for receiving an immunomodulatory therapy.
- History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection.

- History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years prior to screening.
- Active systemic infections during the last two weeks prior to randomisation and any infections that reoccur on a regular basis.

Treatments

Patients received secukinumab doses according to the following weight categories:

- ≥50 kg: 150 mg (low dose group) and 300 mg (high dose group)
- 25 to <50 kg: 75 mg (low dose group) and 150 mg (high dose group)
- <25 kg: 75 mg for both dose groups.

Secukinumab was administered subcutaneously at Randomisation, Weeks 1, 2, 3, 4 and thereafter every 4 weeks during the entire treatment period of the study until Week 204. The COVID-19 pandemic required the implementation of Protocol Amendment 01, which allowed drug administration at home in case of travel restrictions.

If a patient moved into a higher or lower weight group at two consecutive visits with weight measurements during the Maintenance or Extension treatment period, then the patient was dosed according to the new (higher or lower) weight group, respectively.

Objective(s)

The **primary objective** of the study was to evaluate the efficacy of secukinumab in paediatric patients aged 6 years to less than 18 years old with moderate to severe chronic plaque psoriasis with respect to PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared to placebo (historical control).

Secondary objectives were:

- To evaluate the efficacy of secukinumab in paediatric patients with moderate to severe chronic plaque psoriasis with respect to PASI 90 at Week 12, compared to placebo (historical control)
- To investigate the clinical safety and tolerability of secukinumab as assessed by growth, weight gain, vital signs, clinical laboratory variables, electrocardiograms (ECGs), and adverse events (AEs) monitoring
- To evaluate the pharmacokinetics (PK) of secukinumab in paediatric patients

Exploratory objectives were:

- To assess efficacy of secukinumab with respect to PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 over time up to End of Treatment
- To assess the efficacy of secukinumab with respect to changes in PASI score and IGA mod 2011 score over time up to End of Treatment
- To investigate the effects of treatment with secukinumab with respect to changes in Children's Dermatology Life Quality Index (CDLQI) over time up to End of Treatment
- To investigate the effects of treatment with secukinumab with respect to CDLQI 0 or 1 score over time, up to End of Treatment
- To assess the occurrence of relapse following secukinumab treatment

- To assess the occurrence of rebound following secukinumab treatment
- To assess impact of treatment with secukinumab on physical development (Tanner stages)
- To investigate the development of immunogenicity against secukinumab

Outcomes/endpoints

Efficacy was assessed with the Investigator's Global Assessment (IGA mod 2011; scale 0 – 4) and the Psoriasis Area and Severity Index (PASI; score 0 – 72). The co-primary efficacy endpoints in the study were PASI 75 response and IGA mod 2011 0/1 response at Week 12.

The impact of psoriasis on various aspects of a patient's health-related quality of life (HRQoL) were assessed by CDLQI (score 0 – 30, with a higher score indicating greater degree of QoL impairment.

Safety assessments consisted of collecting all AEs and SAEs, including injection site reactions, with their severity and relationship to study drug. Safety assessments also included the regular monitoring of haematology, blood chemistry and urinalysis, regular assessments of vital signs, ECG, physical examination, IG assessment, growth development assessment (height and body weight), pubertal development assessment (Tanner stages) and pregnancy assessment.

Rebound was defined as PASI increase to > 125% of baseline PASI, or if new pustular psoriasis, or new erythrodermic psoriasis, or more inflammatory psoriasis occurs within 8 weeks after the last dose of study treatment has been administered. Rebound like event was defined as the above event observed within up to 12 weeks (i.e., ≤ 84 days) from last dose.

Relapse was defined as a > 50% reduction in the maximal PASI improvement achieved during the study after stopping therapy.

Sample size

Approximately 80 paediatric patients aged 6 years to less than 18 years with moderate to severe chronic plaque psoriasis were to be enrolled. The targets were to enrol at least 60 patients with moderate severity, at least 5 patients in the <25 kg weight group, and at least 10 patients in each of the other two weight groups (25 - <50 kg and ≥50 kg).

Randomisation

All eligible patients were randomised via Interactive Response Technology in a 1:1 ratio into either the low dose or the high dose group. Randomisation was stratified by body weight (< 25kg, 25-< 50 kg, ≥ 50kg) and disease severity (either moderate (PASI score 12-<20 and IGA 3 or 4 or PASI score ≥ 20 and IGA 3) or severe (PASI score ≥ 20 and IGA of 4), collected at Randomisation Visit.

Statistical Methods

All data are reported using descriptive statistics. Analyses of the long-term data beyond Week 52 were based on observed cases for all of the efficacy endpoints.

Results

Participant flow

A total of 92 patients were screened, of which 84 patients were randomised into the study. All except three patients (all 3 from the secukinumab high dose group) completed the Week 24 visit (81/84 patients; 96.4% overall). Two patients discontinued treatment due to AEs and one patient discontinued due to lack of efficacy.

At Week 52, all except 6 patients (3 each from the secukinumab low dose and the secukinumab high dose groups) completed the Week 52 visit (78/84 patients; 92.9% overall). In the low dose group, one patient discontinued treatment due to lack of efficacy and 2 patients discontinued treatment due to patient decision. In the high dose group, 2 patients discontinued treatment due to AEs and one patient discontinued due to lack of efficacy.

Entire treatment period

Overall, 67/84 enrolled patients (79.8%) completed treatment, 17 patients (20.2%) discontinued the treatment and the most common reason for discontinuation was lack of efficacy (6 patients, 7.1%) (Table 1). The discontinuations were more frequent in the secukinumab low dose group (11 patients, 26.2%) compared to the secukinumab high dose group (6 patients, 14.3%), and the primary reason for this was lack of efficacy (5 patients, 11.9% in the low dose vs 1 patient, 2.4% in high dose group). Overall, 3 patients (3.6%) were discontinued due to AEs; 1 patient in the low dose group (Crohn's disease) and 2 patients in the high dose group (ALT and AST elevations; haemorrhagic diarrhoea).

Table 1. Patient disposition by treatment – Entire treatment period (Randomised set)

Disposition/Reason	AIN457 Low dose N=42 n (%)	AIN457 High dose N=42 n (%)	Total N=84 n (%)
Randomized	42	42	84
Completed treatment	31 (73.8)	36 (85.7)	67 (79.8)
Discontinued treatment	11 (26.2)	6 (14.3)	17 (20.2)
Primary reason for discontinuing			
Adverse event	1 (2.4)	2 (4.8)	3 (3.6)
Lack of efficacy	5 (11.9)	1 (2.4)	6 (7.1)
Pregnancy	0 (0.0)	2 (4.8)	2 (2.4)
Protocol deviation	1 (2.4)	0 (0.0)	1 (1.2)
Physician decision	1 (2.4)	0 (0.0)	1 (1.2)
Subject decision	2 (4.8)	1 (2.4)	3 (3.6)
Guardian decision	1 (2.4)	0 (0.0)	1 (1.2)

Source: Table 14.1-1.2.1

Entire study period

Overall, 65/84 randomised patients (77.4%) entered the treatment-free follow-up period. Of these, 56 patients (66.7%) completed, and 9 patients (10.7%) discontinued the follow-up. A total of 49 patients (58.3%) completed the study, i.e., completed both the treatment period and the treatment-free follow up period, and 35 patients (41.7%) discontinued the study. The primary reasons for study discontinuation were patient decision (11 patients, 13.1%) and physician decision (8 patients, 9.5%) (Table 2).

Table 2. Patient disposition by treatment – Entire study period (Randomised set)

Disposition/Reason	AIN457 Low dose N=42 n (%)	AIN457 High dose N=42 n (%)	Total N=84 n (%)
Randomized	42	42	84
Entered follow up	33 (78.6)	32 (76.2)	65 (77.4)
Completed follow up	28 (66.7)	28 (66.7)	56 (66.7)
Discontinued follow up	5 (11.9)	4 (9.5)	9 (10.7)
Completed study	25 (59.5)	24 (57.1)	49 (58.3)
Discontinued study	17 (40.5)	18 (42.9)	35 (41.7)
Primary reason for discontinuing study			
Adverse event	1 (2.4)	2 (4.8)	3 (3.6)
Lack of efficacy	5 (11.9)	1 (2.4)	6 (7.1)
Pregnancy	0 (0.0)	2 (4.8)	2 (2.4)
Protocol deviation	1 (2.4)	0 (0.0)	1 (1.2)
Physician decision	3 (7.1)	5 (11.9)	8 (9.5)
Subject decision	5 (11.9)	6 (14.3)	11 (13.1)
Guardian decision	2 (4.8)	2 (4.8)	4 (4.8)

Source: Table 14.1-1.3

Recruitment

First patient first visit took place on 29 August 2018, and last patient last visit took place on 12 September 2023.

Study centres were located as follows: Belgium (2), Czech Republic (2), Estonia (1), Germany (2), Peru (1), Poland (3), Russia (4), Spain (4), and United States (4). Table 3 summarises patient enrolment by country.

Table 3. Patient enrolment summary by country

Country	Total number of subjects enrolled
Belgium	04
Czech Republic	05
Estonia	07
Germany	11
Peru	05
Poland	17
Russia	14
Spain	10
United States	11
Total	84

Demographic and baseline characteristics

Mean age was 12.6 years overall at the time of enrolment and similar between the treatment groups. The majority of patients (51/84 patients; 60.7%) were in the 12 - <18 years age group. More males were enrolled in the low dose (22/42 patients; 52.4%) compared to the high dose (17/42 patients; 40.5%) group. Most of the patients were White (77/84 patients; 91.7%). Mean weight and mean height of the patients were similar in both treatment groups. Sixty-one (71.6%) patients had moderate and 23 (27.4%) severe psoriatic disease at baseline. Fifty-one out of 84 (60.7%) patients were enrolled in the weight category ≥ 50 kg, 25/84 (29.8%) patients were enrolled in the weight category 25 - < 50 kg and 8/84 (9.5%) patients were enrolled in the weight category < 25 kg. The proportion of patients in all weight categories (<25 kg, 25 - < 50 kg, ≥ 50 kg) was comparable between the two treatment groups. The mean BMI of the patients was 21.92 kg/m2 and similar between the two treatment groups. The baseline disease characteristics were generally balanced and comparable between the dose groups.

All patients had received psoriasis therapies prior to study entry. A total of 36/84 patients (42.9%) had previous exposure to systemic psoriasis therapies; the proportion was similar in both the low dose and high dose groups (18/42 patients; 42.9% in each group). The majority of patients (34/36; 94.4% in Any AIN457 dose) with previous exposure to systemic psoriasis therapies had failed on that therapy, the proportion being similar between the low dose and high dose groups (17/18 patients; 94.4% in each group). Overall, 10 patients (11.9%) had previous exposure to biologic psoriasis therapies (4 patients (9.5%) in the low dose group, and 6 patients (14.3%) in the high dose group).

Overall, 97.6% (82/84 subjects) used topicals, and 38.1% (32/84 subjects) used phototherapy,

Number analysed

The number of patients in each analysis set by treatment group is summarised in Table 4. All 84 randomised patients were included in the Full Analysis set (FAS) and Safety set.

Table 4. Analysis sets (all randomised subjects)

Analysis Population	AIN457 Low dose	AIN457 High dose	Total N=92
Screened	--	--	92
Screen failures	--	--	8
Randomized set (RAN)	42	42	84
Full analysis set (FAS)	42	42	84
Safety set (SAF)	42	42	84

Source: Table 14.1-4.1

Efficacy results

For full results relating to the primary and secondary objectives at Week 24 and Week 52, reference is made to the European Public Assessment Reports for procedures II/0057 and II/0073, respectively.

Briefly, the primary objective was met; both secukinumab doses (low and high) were superior to historical placebo with respect to PASI 75 response and IGA mod 2011 0/1 response at Week 12. The estimated posterior probability of a positive treatment effect (i.e. log OR > 0) for the low or high dose compared to historical placebo is 1 (100%) for both PASI 75 response and IGA mod 2011 0/1 response. Similar efficacy was observed in the low dose and high dose at Week 12 for PASI 75 (92.9% in both the low and high dose group) and IGA mod 2011 0/1 (78.6% in the low dose and 83.3% in the high dose group). The secondary efficacy objective was also met; both secukinumab doses (low and

high dose) were superior to historical placebo with respect to PASI 90 response at Week 12. The estimated posterior probability of a positive treatment effect for the low or high dose compared to historical placebo (i.e., log OR >0) is 1 (100%). Response rates were 69.0% in the low dose and 76.2% in the high dose group.

The main efficacy results for the Entire treatment period are summarised in Table 5 and Figure 2 Based on observed cases, effects on IGA mod 2011 0/1 as well as PASI 75, PASI 90, and PASI 100 responses were generally maintained in both dose groups for the duration of the study.

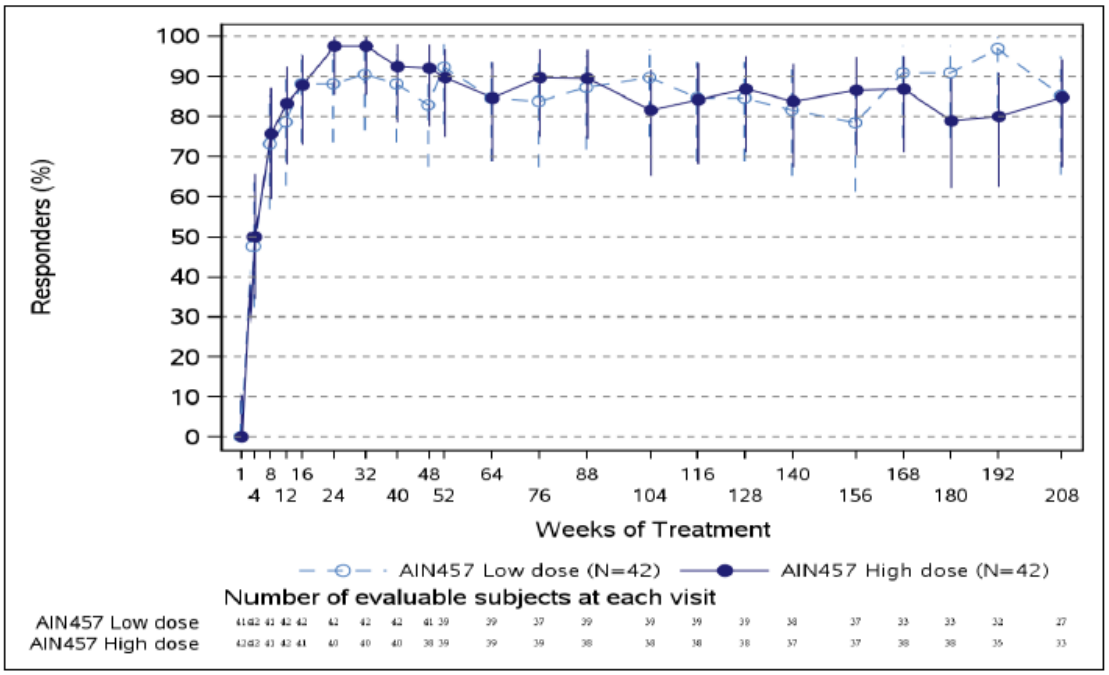
Table 5. Number (%) of subjects with IGA 0 or 1 and PASI 75, PASI 90, PASI 100 response by visit (observed cases) – Entire treatment period (Full Analysis set)

Visit	Criterion	AIN457 Low dose N=42 n/m (%)	AIN457 High dose N=42 n/m (%)
Week 1	IGA 0/1	0/ 41 (0.0)	0/ 42 (0.0)
	PASI 75	0/ 41 (0.0)	0/ 42 (0.0)
	PASI 90	0/ 41 (0.0)	0/ 42 (0.0)
	PASI 100	0/ 41 (0.0)	0/ 42 (0.0)
Week 12	IGA 0/1	33/ 42 (78.6)	35/ 42 (83.3)
	PASI 75	39/ 42 (92.9)	39/ 42 (92.9)
	PASI 90	29/ 42 (69.0)	32/ 42 (76.2)
	PASI 100	25/ 42 (59.5)	23/ 42 (54.8)
Week 24	IGA 0/1	37/ 42 (88.1)	39/ 40 (97.5)
	PASI 75	40/ 42 (95.2)	40/ 41 (97.6)
	PASI 90	37/ 42 (88.1)	37/ 41 (90.2)
	PASI 100	28/ 42 (66.7)	28/ 41 (68.3)
Week 48	IGA 0/1	34/ 41 (82.9)	35/ 38 (92.1)
	PASI 75	37/ 41 (90.2)	37/ 38 (97.4)
	PASI 90	33/ 41 (80.5)	35/ 38 (92.1)
	PASI 100	27/ 41 (65.9)	30/ 38 (78.9)
Week 52	IGA 0/1	36/ 39 (92.3)	35/ 39 (89.7)
	PASI 75	37/ 39 (94.9)	38/ 39 (97.4)
	PASI 90	32/ 39 (82.1)	35/ 39 (89.7)
	PASI 100	22/ 39 (56.4)	29/ 39 (74.4)
Week 104	IGA 0/1	35/ 39 (89.7)	31/ 38 (81.6)
	PASI 75	38/ 39 (97.4)	37/ 38 (97.4)
	PASI 90	31/ 39 (79.5)	35/ 38 (92.1)
	PASI 100	23/ 39 (59.0)	29/ 38 (76.3)
Week 156	IGA 0/1	29/ 37 (78.4)	32/ 37 (86.5)
	PASI 75	32/ 37 (86.5)	36/ 37 (97.3)
	PASI 90	30/ 37 (81.1)	32/ 37 (86.5)
	PASI 100	23/ 37 (62.2)	26/ 37 (70.3)
Week 208(EOT)	IGA 0/1	23/ 27 (85.2)	28/ 33 (84.8)
	PASI 75	26/ 27 (96.3)	29/ 33 (87.9)
	PASI 90	24/ 27 (88.9)	27/ 33 (81.8)
	PASI 100	14/ 27 (51.9)	24/ 33 (72.7)
At any time up to week 208	IGA 0/1	40/ 42 (95.2)	40/ 42 (95.2)
	PASI 75	42/ 42 (100.0)	42/ 42 (100.0)
	PASI 90	40/ 42 (95.2)	41/ 42 (97.6)
	PASI 100	37/ 42 (88.1)	38/ 42 (90.5)

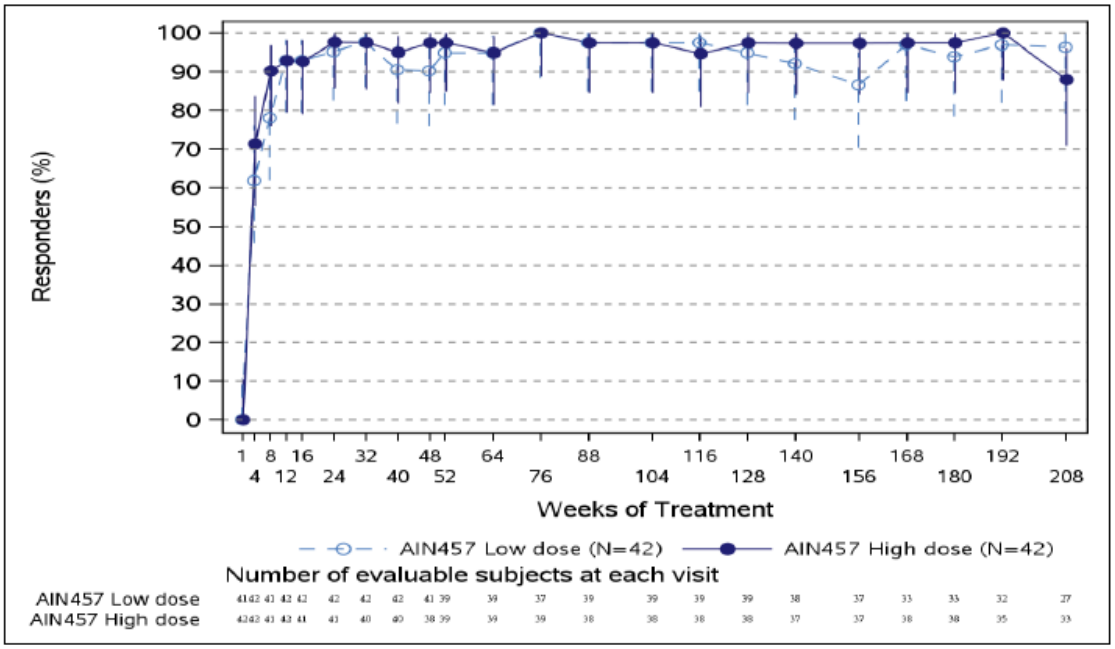
- n = number of subjects with response.
- m = number of subjects evaluable.
Source: Table 14.2-1.1f

Figure 2. IGA mod 2011 0/1, PASI 75, PASI 90 and PASI 100 response over time (estimate + 95% CI) (observed cases) – Entire treatment period (Full analysis set)

Parameter : IGA mod 2011 0/1



Parameter : PASI 75



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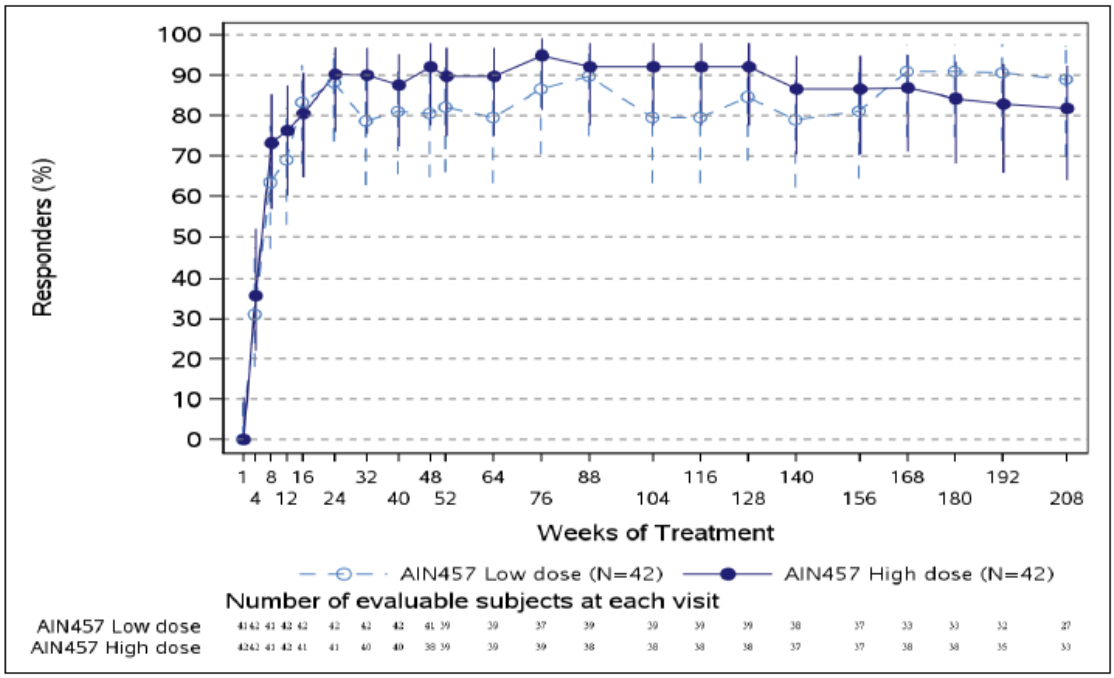

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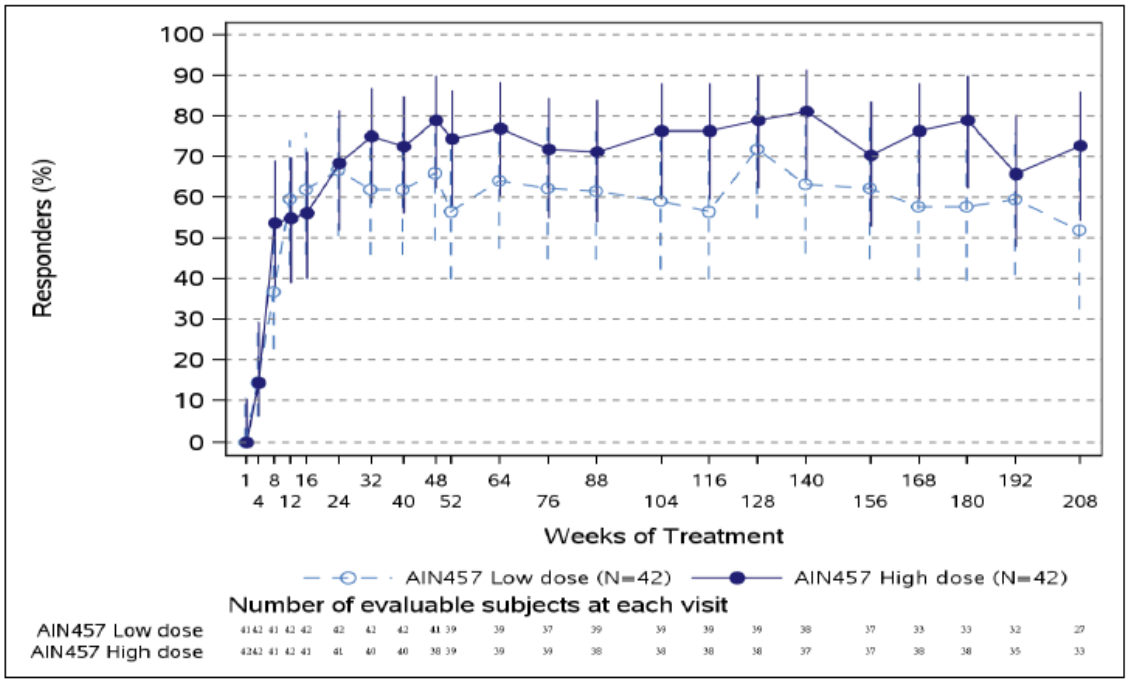


Source:Figure14.2-1.2f

Based on observed values, the mean percentage change of PASI score from baseline to Week 12 was -92.6% (mean absolute score 1.42) in the low dose group and -93.9% (mean absolute score 1.19) in the high dose group. From Weeks 12 to 208, the mean percentage change from baseline was maintained and was similar between the dose groups. At Week 208, the mean percentage change from baseline was -95.7% (mean absolute score 0.76) in the low dose group and -94.5% (mean absolute score 1.07) in the high dose group.

Similarly, based on observed values, the number of subjects in both dose groups shifted continuously from higher to lower IGA mod 2011 score categories (indicating improvement) over time, up to Week 52. From Weeks 52 and up to Week 208, more subjects in the high dose group remained at the lowest IGA score of 0 (clear) compared with the low dose group (Week 52: 30/39 (76.9%) vs 22/39 (56.4%); Week 208: 24/33 (72.7%) vs 14/27 (51.9)). In both dose groups by Week 74, there were no subjects reporting an IGA score of 4 (severe), which was maintained through Week 208 (except for 1 subject in the low dose group at Week 156). At Week 208, there were 2/33 subjects (6.1%) with an IGA score of 3 (moderate) in the high dose group and none in the low dose group.

The proportion of subjects experiencing relapse events after the last treatment administration was higher in the low dose group (8/41, 19.5% vs 4/41. 9.8% in the high dose group). Out of the 8 subjects who experienced relapse in the low dose group, 3 subjects had discontinued the treatment due to lack of efficacy, and thus, this is reflected in their high PASI score values. The remaining 5 subjects had their relapse between 120-157 days after their last dose, when such a decrease in efficacy is not unusual. Similarly, the 4 subjects in the high dose group had their first relapse event 98-140 days after their last dose. Of the 42 evaluable subjects in each dose group, none experienced rebound or rebound-like events up to 8 and 12 weeks, respectively, after the last study treatment.

The proportion of patients achieving CDLQI 0/1 response throughout the Entire treatment period is shown in Table 6.

Table 6. Number (%) of subjects with Child Dermatology Life Quality Index response (CDLQI 0 or 1) by visit (Observed cases) - Entire treatment period (Full Analysis set)

		AIN457 Low dose N=42			AIN457 High dose N=42		
Visit	**Criterion**	**n/m**	**(%)**	**95% CI**	**n/m**	**(%)**	**95% CI**
Baseline	CDLQI 0 or 1 achievement	3/39	(7.7)	(2.0,22.0)	1/40	(2.5)	(0.1,14.7)
Week 4	CDLQI 0 or 1 achievement	11/40	(27.5)	(15.1,44.1)	10/41	(24.4)	(12.9,40.6)
Week 8	CDLQI 0 or 1 achievement	20/42	(47.6)	(32.3,63.4)	20/39	(51.3)	(35.0,67.3)
Week 12	CDLQI 0 or 1 achievement	21/42	(50.0)	(34.4,65.6)	24/40	(60.0)	(43.4,74.7)
Week 24	CDLQI 0 or 1 achievement	28/38	(73.7)	(56.6,86.0)	21/36	(58.3)	(40.9,74.0)
Week 52	CDLQI 0 or 1 achievement	27/36	(75.0)	(57.5,87.3)	24/32	(75.0)	(56.2,87.9)
Week 64	CDLQI 0 or 1 achievement	26/34	(76.5)	(58.4,88.6)	24/31	(77.4)	(58.5,89.7)
Week 76	CDLQI 0 or 1 achievement	23/29	(79.3)	(59.7,91.3)	21/27	(77.8)	(57.3,90.6)
Week 88	CDLQI 0 or 1 achievement	24/28	(85.7)	(66.4,95.3)	21/26	(80.8)	(60.0,92.7)
Week 104	CDLQI 0 or 1 achievement	22/28	(78.6)	(58.5,91.0)	20/26	(76.9)	(55.9,90.2)
Week 116	CDLQI 0 or 1 achievement	17/26	(65.4)	(44.4,82.1)	16/24	(66.7)	(44.7,83.6)
Week 128	CDLQI 0 or 1 achievement	18/25	(72.0)	(50.4,87.1)	17/22	(77.3)	(54.2,91.3)
Week 140	CDLQI 0 or 1 achievement	20/25	(80.0)	(58.7,92.4)	19/22	(86.4)	(64.0,96.4)
Week 156	CDLQI 0 or 1 achievement	17/24	(70.8)	(48.8,86.6)	15/22	(68.2)	(45.1,85.3)
Week 168	CDLQI 0 or 1 achievement	18/22	(81.8)	(59.0,94.0)	16/20	(80.0)	(55.7,93.4)
Week 180	CDLQI 0 or 1 achievement	14/20	(70.0)	(45.7,87.2)	17/20	(85.0)	(61.1,96.0)
Week 192	CDLQI 0 or 1 achievement	14/20	(70.0)	(45.7,87.2)	18/19	(94.7)	(71.9,99.7)
Week 208 (EOT)	CDLQI 0 or 1 achievement	12/16	(75.0)	(47.4,91.7)	15/17	(88.2)	(62.3,97.9)

- n = number of subjects with response, m = number of subjects evaluable.
- Subjects with < 18 years of age at the time of assessment were included in the summary report.
Source: Table 14.2-7.3

Pharmacokinetic and immunogenicity results

Mean serum concentrations in the secukinumab low and high dose groups are presented in Table 7. The mean pre-dose concentrations at nearly all time points showed a dose-proportional increase in exposure to secukinumab from the low dose level to the high dose level. The mean secukinumab trough concentrations in samples drawn at Week 4, and at Week 12 were higher than at Week 24 and Week 52, as expected due to weekly dosing until Week 4. Steady-state PK behaviour was observed at Weeks 24 and 52 with some decline in trough concentrations at later time points until Week 208. According to the MAH, this might be due to an increase in body weight - within the same body weight and dose category - over the four years of treatment.

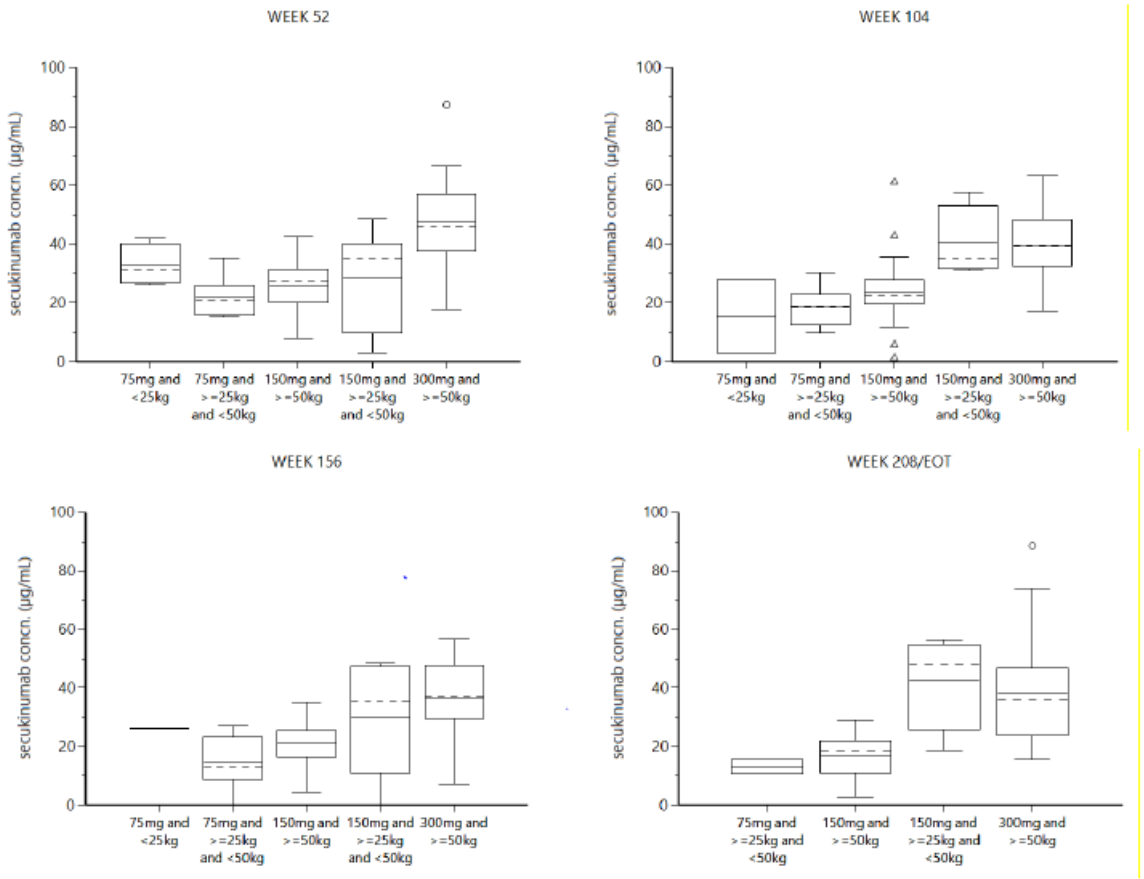
Table 7. Mean (%CV) serum secukinumab concentrations in the secukinumab Low and High dose groups – Entire treatment period (Full analysis set)

	AIN457 Low dose			AIN457 High dose		
Visit	n	Mean (µg/mL)	CV (%) mean	n	Mean (µg/mL)	CV (%) mean
Baseline	42	0	-	42	0	-
Week 4	40	74.2	44.5	40	135	33.7
Week 12	40	34.8	31.2	39	69.6	41.9
Week 16	40	30.9	36.1	38	55.9	44.6
Week 24	42	26.0	41.6	39	46.9	47.3
Week 52	37	25.0	36.0	38	42.7	39.8
Week 104	39	21.9	49.2	33	39.3	30.8
Week 156	34	19.3	45.0	32	35.0	40.3
Week 208	25	16.7	37.4	28	38.8	44.3

CV=coefficient of variation.
Nominal (CRF) visits are used in the analysis
Data from Baseline and up to Week 24 are from the Week 52 PK analysis. Five additional samples were received post Week 52 analysis and data from Week 52 onwards are from the final PK analysis
Source: [AIN457A2311 Week 52 CSR Table 14.2-8.1], and Table 14.2-8.1

Box plots of serum concentrations of secukinumab at the high and low dose level in the different body-weight categories until Week 208 are shown in Figure 3.

Figure 3. Box plots of serum secukinumab concentrations by dose group, visit and body weight category



Source: [AIN457A2311 Week 52 CSR Table 14.2-8.2], and Table 14.2-8.2

Seven subjects presented with positive treatment-emergent (TE) anti-drug-antibodies (ADAs) i.e. negative at baseline and positive after start of secukinumab. A summary of the number of TE-ADA-positive cases and ADA incidence for the entire study is presented in Table 8. TE-ADAs were detected in three occasions in one subject at Weeks 156, 208 during treatment and at Week 224 during treatment-free follow-up in the low dose group. TE-ADA cases were not observed in subjects in the high dose group during treatment period. Overall, six subjects in total in the low and high dose groups were positive only during the treatment-free follow-up period. None of the seven subjects with positive TE-ADAs showed presence of neutralising antibodies, and none presented with AEs possibly related to immunogenicity.

One subject randomised to secukinumab high dose (300 mg) group was positive for ADA (Anti-AIN457 antibodies [titre]: 7.98) at randomisation (Day 1, i.e. not treatment emergent).

Table 8. Overview of subjects with anti-drug antibodies (ADA) - Safety set

Group	Prior biologics	ADA (titer) / N-Ab	AE possibly IG related (Day of onset)	PK
Subjects with treatment emergent ADA (n=7)				
AIN457 Low Dose	None	Week 224 (EOF) (2.50)/ NEGATIVE	No	Irregular, low concentrations at W104, 208
AIN457 Low Dose	None	Week 224 (EOF) (2.50)/ NEGATIVE	No	Normal
AIN457 Low Dose	None	Week 156 (2.50)/ NEGATIVE	No	No steady-state PK behavior
		Week 208 (EOT) (5.00)/ NEGATIVE	No	
		Week 224 (EOF) (5.00)/ NEGATIVE	No	
AIN457 High Dose	None	Week 224 (EOF) (2.50)/ NEGATIVE	No	Normal
AIN457 High Dose	None	Week 224 (EOF) (2.50)/ NEGATIVE	No	Normal
AIN457 High Dose	None	Week 224 (EOF) (2.50)/ NEGATIVE	No	Concentration at W156 3-fold lower than at other time points
AIN457 High Dose	None	Week 224 (EOF) (20.00)/ NEGATIVE	No	Normal

Source: Listing 16.2.8-1.2, Listing 16.2.7-1.1 and Listing 16.2.5-1.1

Safety results

During the treatment period, all 84 (100%) subjects in the secukinumab treatment groups received the study treatment. The median (range) duration of exposure during the treatment period was 1513.0 (348 – 1534) days in the low dose group and 1512.5 (85 – 1627) days in the high dose group. The cumulative exposure across the secukinumab treatment groups was 156.1 patient-years in the low dose group and 157.8 patient-years in the Any AIN457 high dose group (i.e., 313.9 subject-years in total).

Overall, 81.0% (68/84) of subjects had AEs. The incidence of TEAEs was similar in the low dose (33/42 subjects; 78.6%) and high dose (35/42 subjects; 83.3%) groups. Consistent with the Week 24 and Week 52 analyses, the most commonly affected SOCs were Infections and infestations, Gastrointestinal disorders and Skin and subcutaneous tissue disorders (Table 9). The AEs under the SOC of Infections and infestations were mainly driven by COVID-19 and nasopharyngitis, both of which were reported with higher incidences in the low dose group. The incidence of AEs under the SOC of Gastrointestinal disorders was mainly due to abdominal pain and diarrhoea and under the SOC of Skin and subcutaneous tissue disorders was mainly due to acne (Table 10). The AEs under Psychiatric disorders were anxiety and intentional self-injury (reported as SAE) in one subject in the low dose group (1/42 subjects; 2.4%) and anxiety, depression, depressive symptom and panic attack in high dose group (4/42 subjects; 9.5%).

Table 9. Absolute and relative frequencies for treatment-emergent adverse events, by primary system organ class - Entire treatment period (Safety set)

	AIN457 Low dose N=42	AIN457 High dose N=42	Any AIN457 dose N=84
Primary system organ class	**n (%)**	**n (%)**	**n (%)**
-Total	33 (78.6)	35 (83.3)	68 (81.0)
Infections and infestations	27 (64.3)	28 (66.7)	55 (65.5)
Gastrointestinal disorders	9 (21.4)	10 (23.8)	19 (22.6)
Skin and subcutaneous tissue disorders	12 (28.6)	7 (16.7)	19 (22.6)
Blood and lymphatic system disorders	6 (14.3)	5 (11.9)	11 (13.1)
Injury, poisoning and procedural complications	7 (16.7)	4 (9.5)	11 (13.1)
General disorders and administration site conditions	7 (16.7)	3 (7.1)	10 (11.9)
Musculoskeletal and connective tissue disorders	5 (11.9)	4 (9.5)	9 (10.7)
Nervous system disorders	4 (9.5)	5 (11.9)	9 (10.7)
Respiratory, thoracic and mediastinal disorders	5 (11.9)	4 (9.5)	9 (10.7)
Psychiatric disorders	1 (2.4)	4 (9.5)	5 (6.0)
Reproductive system and breast disorders	3 (7.1)	2 (4.8)	5 (6.0)
Cardiac disorders	2 (4.8)	2 (4.8)	4 (4.8)
Immune system disorders	3 (7.1)	1 (2.4)	4 (4.8)
Investigations	1 (2.4)	3 (7.1)	4 (4.8)
Metabolism and nutrition disorders	2 (4.8)	1 (2.4)	3 (3.6)
Ear and labyrinth disorders	2 (4.8)	0 (0.0)	2 (2.4)
Eye disorders	1 (2.4)	1 (2.4)	2 (2.4)
Hepatobiliary disorders	2 (4.8)	0 (0.0)	2 (2.4)
Renal and urinary disorders	2 (4.8)	0 (0.0)	2 (2.4)
Congenital, familial and genetic disorders	0 (0.0)	1 (2.4)	1 (1.2)
Endocrine disorders	0 (0.0)	1 (2.4)	1 (1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	1 (2.4)	1 (1.2)
Vascular disorders	1 (2.4)	0 (0.0)	1 (1.2)

- Primary system organ classes are sorted in descending frequency of AEs in the Any AIN457 column.
- A subject with multiple AEs with the same primary system organ classes is counted only once for that primary system organ classes.
- MedDRA version 26.0 was used for reporting.

Source: Table 14.3.1-1.2

Table 10. Most frequent (greater than or equal to 4.0% in any treatment group) treatment-emergent adverse events, by preferred term - Entire treatment period (Safety set)

Preferred term	AIN457 Low dose N=42 n (%)	AIN457 High dose N=42 n (%)	Any AIN457 dose N=84 n (%)
-Any preferred term	33 (78.6)	35 (83.3)	68 (81.0)
COVID-19	12 (28.6)	9 (21.4)	21 (25.0)
Nasopharyngitis	13 (31.0)	7 (16.7)	20 (23.8)
Acne	7 (16.7)	2 (4.8)	9 (10.7)
Viral upper respiratory tract infection	1 (2.4)	7 (16.7)	8 (9.5)
Pyrexia	6 (14.3)	1 (2.4)	7 (8.3)
Abdominal pain	4 (9.5)	2 (4.8)	6 (7.1)
Tonsillitis	2 (4.8)	4 (9.5)	6 (7.1)
Upper respiratory tract infection	0 (0.0)	6 (14.3)	6 (7.1)
Diarrhoea	2 (4.8)	3 (7.1)	5 (6.0)
Headache	3 (7.1)	2 (4.8)	5 (6.0)
Vomiting	3 (7.1)	2 (4.8)	5 (6.0)
Arthralgia	3 (7.1)	1 (2.4)	4 (4.8)
Cough	2 (4.8)	2 (4.8)	4 (4.8)
Eczema	4 (9.5)	0 (0.0)	4 (4.8)
Influenza	3 (7.1)	1 (2.4)	4 (4.8)
Leukopenia	3 (7.1)	1 (2.4)	4 (4.8)
Neutropenia	3 (7.1)	1 (2.4)	4 (4.8)
Rhinitis	1 (2.4)	3 (7.1)	4 (4.8)
Alanine aminotransferase increased	1 (2.4)	2 (4.8)	3 (3.6)
Aspartate aminotransferase increased	1 (2.4)	2 (4.8)	3 (3.6)
Conjunctivitis	2 (4.8)	1 (2.4)	3 (3.6)
Dysmenorrhea	2 (4.8)	1 (2.4)	3 (3.6)
Ear infection	2 (4.8)	1 (2.4)	3 (3.6)
Folliculitis	2 (4.8)	1 (2.4)	3 (3.6)
Oropharyngeal pain	1 (2.4)	2 (4.8)	3 (3.6)
Pharyngitis	2 (4.8)	1 (2.4)	3 (3.6)
Sinusitis	1 (2.4)	2 (4.8)	3 (3.6)
Abdominal pain upper	0 (0.0)	2 (4.8)	2 (2.4)
Anemia	0 (0.0)	2 (4.8)	2 (2.4)
Atrioventricular block first degree	2 (4.8)	0 (0.0)	2 (2.4)
Back pain	0 (0.0)	2 (4.8)	2 (2.4)
Gastroenteritis	2 (4.8)	0 (0.0)	2 (2.4)
Hordeolum	0 (0.0)	2 (4.8)	2 (2.4)
Otitis media	2 (4.8)	0 (0.0)	2 (2.4)
Pruritus	2 (4.8)	0 (0.0)	2 (2.4)
Varicella	2 (4.8)	0 (0.0)	2 (2.4)

- Preferred terms are sorted in descending frequency of AEs in the Any AIN457 column.
- A subject with multiple AEs with the same preferred term is counted only once for that preferred term.
- MedDRA version 26.0 was used for reporting.
Source: Table 14.3.1-6.1.1

Overall, the majority of AEs were mild (40/84 subjects; 47.6%), with higher incidence rates in secukinumab high dose (23/42 subjects; 54.8%) compared to low dose (17/42 subjects; 40.5%) groups. Moderate AEs were reported in 25/84 subjects (29.8%). The incidence of moderate AEs was higher in the low dose group (15/42 subjects; 35.7%) compared to the high dose group.

Severe AEs were reported in 3/84 subjects (3.6%): one subject from the low dose group and 2 subjects from the high dose group had severe AEs. One subject in the low dose (150 mg) group had a severe AE of intentional self-injury, which was also considered an SAE. One subject in the high dose (150 mg to 300 mg) group was diagnosed with a severe AE of appendicitis, which was also considered an SAE. One subject in the high dose (300 mg) group had a severe non-serious AE of nasopharyngitis on Day 7. The subject was treated with [phytotherapeutic agent], and the event resolved on Day 12. The event was considered to be related to the study drug.

During the study, 21 (25.0%) subjects had AEs of COVID-19. All the events were either mild or moderate in severity. The majority of the subjects did not require any action on the study treatment, none of these AEs led to study treatment discontinuation, and all subjects who reported COVID-19 infections recovered, indicating no evidence of secukinumab playing a role in increasing the risk of COVID-19 infection or its exacerbation. According to the MAH, overall, the COVID-19 pandemic had minimal impact on the safety results.

No deaths were reported during the study. Non-fatal treatment-emergent SAEs during the Entire treatment period were reported in 4 patients (9.5%) in the low dose group and 2 patients (4.8%) in the high dose group (Table 11). All the SAEs by PT were reported as single occurrence (Table 12).

Table 11. Deaths, other serious or clinically significant adverse events or related discontinuations – Entire treatment period (Safety set)

	AIN457 Low dose N=42 n (%)	AIN457 High dose N=42 n (%)	Any AIN457 dose N=84 n (%)
Subjects with any AE(s)	33 (78.6)	35 (83.3)	68 (81.0)
Subjects with serious or other significant events			
Death	0 (0.0)	0 (0.0)	0 (0.0)
Non-fatal SAE(s)	4 (9.5)	2 (4.8)	6 (7.1)
Discontinued study treatment due to any AE(s)	1 (2.4)	2 (4.8)	3 (3.6)

Source: Listing 14.3.2-1, Listing 14.3.2-2, Table 14.3.1-4.1.1 Table 14.3.1-1.2

Table 12. Serious adverse events by preferred term – Entire treatment period (Safety set)

Preferred term	AIN457 Low dose N=42 n (%)	AIN457 High dose N=42 n (%)	Any AIN457 dose N=84 n (%)
Any Preferred term	4 (9.5)	2 (4.8)	6 (7.1)
Appendicitis	0 (0.0)	1 (2.4)	1 (1.2)
COVID-19	1 (2.4)	0 (0.0)	1 (1.2)
Crohn's disease	1 (2.4)	0 (0.0)	1 (1.2)
Infectious mononucleosis	1 (2.4)	0 (0.0)	1 (1.2)
Intentional self-injury	1 (2.4)	0 (0.0)	1 (1.2)
Tibia fracture	1 (2.4)	0 (0.0)	1 (1.2)
Tonsillitis	0 (0.0)	1 (2.4)	1 (1.2)

Preferred terms are sorted in descending frequency of AEs in the Any AIN457 column.
A subject with multiple AEs with the same preferred term is counted only once for that preferred term.
MedDRA version 26.0 was used for reporting.
Source: Table 14.3.1-7.2

The subject for whom the SAE of intentional self-injury was reported was a [12-<18] year old patient with a history of plaque psoriasis of moderate severity; prior therapies for psoriasis included methotrexate, topical therapy, and phototherapy. The subject had a relevant medical history of psychiatric disorder. Active medical conditions included visual field defect, insomnia, anxiety and depressed mood. Anxiety and depressed mood were both treated with psychological behaviour therapy (non-drug therapy). The subject was randomised into the low dose (150 mg) group and received the first dose of study medication on Day 1. On Day 64, the subject felt anxious, insecure, and demonstrated maladaptive behaviour. On Day 231, the subject was sad and experienced insomnia.

On Day 309, the subject received the last dose of study medication On Day 313, the subject attempted deliberate self-harm with linear superficial and mild cuts. The subject was aware that the injury would not have any consequences to [their] well-being. After this event, the subject consulted a psychiatrist who stated that the subject's life has not been endangered at any moment and the subject was not at risk. The event was reported as a severe SAE of intentional self-injury. No treatment was reported. On Day 313, the event of intentional self-injury was considered as resolved and the subject decided to discontinue the treatment and received the last dose of the study drug on Day 309. The event was considered as not related to the study drug. The subject completed the treatment-free follow-up and performed the last study visit on Day 458. Anxiety was ongoing at the time of the last study visit.

Data related to safety topics of interest (including important identified and potential risks in the Risk Management Plan for secukinumab) are summarised in Table 13. The AE categories and search terms were pre-defined in the MAH’s case retrieval strategy system for product-specific safety risks.

Table 13. Absolute and relative frequencies for safety topics of interest (level 1 and level 2) based on all adverse events – Entire treatment period (Safety set)

Risk Category Risk name Level 1 Level 2	Secukinumab low dose N=42 n (%)	Secukinumab high dose N=42 n (%)	Any secukinumab dose N=84 n (%)
Important identified risk			
Hypersensitivity			
Hypersensitivity (SMQ) (narrow)	7 (16.7)	1 (2.4)	8 (9.5)
Angioedema (PT)	1 (2.4)	0 (0.0)	1 (1.2)
Dermatitis contact (PT)	1 (2.4)	1 (2.4)	2 (2.4)
Drug hypersensitivity (PT)	1 (2.4)	0 (0.0)	1 (1.2)
Eczema (PT)	4 (9.5)	0 (0.0)	4 (4.8)
Erythema nodosum (PT)	0 (0.0)	1 (2.4)	1 (1.2)
Hand dermatitis (PT)	1 (2.4)	0 (0.0)	1 (1.2)
Penile dermatitis (PT)	1 (2.4)	0 (0.0)	1 (1.2)
Infections			
Infections and infestations (SOC)	27 (64.3)	29* (69.0)	56 (66.7)
Ancillary infectious topics (HLGT)	1 (2.4)	0 (0.0)	1 (1.2)
Bacterial infectious disorders (HLGT)	3 (7.1)	4 (9.5)	7 (8.3)
Ectoparasitic disorders (HLGT)	1 (2.4)	0 (0.0)	1 (1.2)
Fungal infectious disorders (HLGT)	3 (7.1)	5 (11.9)	8 (9.5)
Helminthic disorders (HLGT)	0 (0.0)	1 (2.4)	1 (1.2)
Infections - pathogen unspecified (HLGT)	22 (52.4)	21 (50.0)	43 (51.2)
Viral infectious disorders (HLGT)	18 (42.9)	16 (38.1)	34 (40.5)
Neutropenia			
Neutropenia (NMQ) (narrow)	4 (9.5)	2 (4.8)	6 (7.1)
Leukopenia (PT)	3 (7.1)	1 (2.4)	4 (4.8)
Neutropenia (PT)	3 (7.1)	1 (2.4)	4 (4.8)
Important potential risk			
Inflammatory Bowel Disease			
Inflammatory bowel disease (NMQ) (narrow)	1 (2.4)	1 (2.4)	2 (2.4)
Crohn's disease (PT)	1 (2.4)	0 (0.0)	1 (1.2)
Diarrhoea haemorrhagic (PT)	0 (0.0)	1 (2.4)	1 (1.2)
Interactions with live vaccines			
Vaccination related complications (HLT)	1 (2.4)	1 (2.4)	2 (2.4)
Immunization reaction (PT)	0 (0.0)	1 (2.4)	1 (1.2)
Vaccination complication (PT)	1 (2.4)	0 (0.0)	1 (1.2)
Suicidal ideation and behavior			
Suicide/self-injury (SMQ)	1 (2.4)	0 (0.0)	1 (1.2)
Intentional self-injury (PT)	1 (2.4)	0 (0.0)	1 (1.2)

Risk levels are not mutually exclusive.
Level 1 is sorted within risk level in descending order of frequency in the Any secukinumab dose column.
Level 2 is sorted as per the alphabetical order.
A patient with multiple occurrences of a level under one treatment is counted only once for the same risk level for that treatment.
MedDRA version 26.0 and NMQs as of 2020-05-02 have been used for reporting.

*It must be noted that the search for infection risk includes all PTs under the Infections and infestations SOC, regardless primary or secondary. As the result, lip wart (PT: oral papilloma) was included in this risks table under infections although its primary SOC is not Infections and infestations.

Source: [Study A2311 Final CSR-Table 12-5]

The majority of newly occurring or worsening laboratory abnormalities in haematology parameters during the study were of CTCAE grade 1 or 2. The most commonly reported haematological abnormalities were CTCAE grade 1 leukocyte count (23/81 subjects; 28.4%, overall), followed by CTCAE grade 2 neutropenia (12/82 subjects; 14.6%). There were no clinically meaningful differences in the newly occurring or worsening haematology abnormalities between the dose groups. Short summaries of the haematology CTCAE grade 3 abnormalities are provided below:

- One subject in the low dose (75 mg - 150 mg) group was reported with CTCAE grade 3 neutropenia (neutrophils: 0.62 10E9/L; normal range: 1.54 to 7.04 10E9/L) on a single occasion on Day 617. The neutrophil counts reached grade 2 (1.44 10E9/L) on Day 625 and returned to normal (2.72 10E9/L) on Day 729.
- One subject in the high dose (150 mg - 300 mg) group was reported with CTCAE grade 3 neutropenia (neutrophils: 0.78 10E9/L; normal range: 1.82 to 7.47 10E9/L) on a single occasion Day 617. The neutrophil counts returned to normal (2.59 10E9/L) on Day 730.
- One subject in the high dose (150 mg) group was reported with CTCAE grade 3 neutropenia (neutrophils: 0.92 10E9/L; normal range: 1.54 to 7.04 10E9/L) on a single occasion on Day 1481, i.e., 24 days after the last treatment received. The neutrophil values returned to normal (1.84 10E9/L) on Day 1571.
- One subject in the high dose (150 mg - 300 mg) group was reported with CTCAE grade 3 lymphopenia (lymphocytes: 0.34 10E9/L normal range: 1.02 to 3.36 10E9/L) on Day 636. The lymphocyte values returned to normal (1.33 10E9/L) on Day 644.

None of the above grade 3 CTCAE haematology laboratory values were reported as AEs, and none of them were temporally associated with infection AEs.

The majority of the chemistry abnormalities reported were grade 1. Grade 1 ALP elevation was the most commonly reported (21/77 subjects; 27.3%) chemistry abnormality, followed by grade 1 ALT elevations (19/76 subjects; 25.0%) and grade 1 AST elevations (16/80 subjects; 20.0%). No subject had abnormalities during the study that met the Hy's law laboratory criteria. Short summaries of the clinical chemistry CTCAE grade 3 events are provided below:

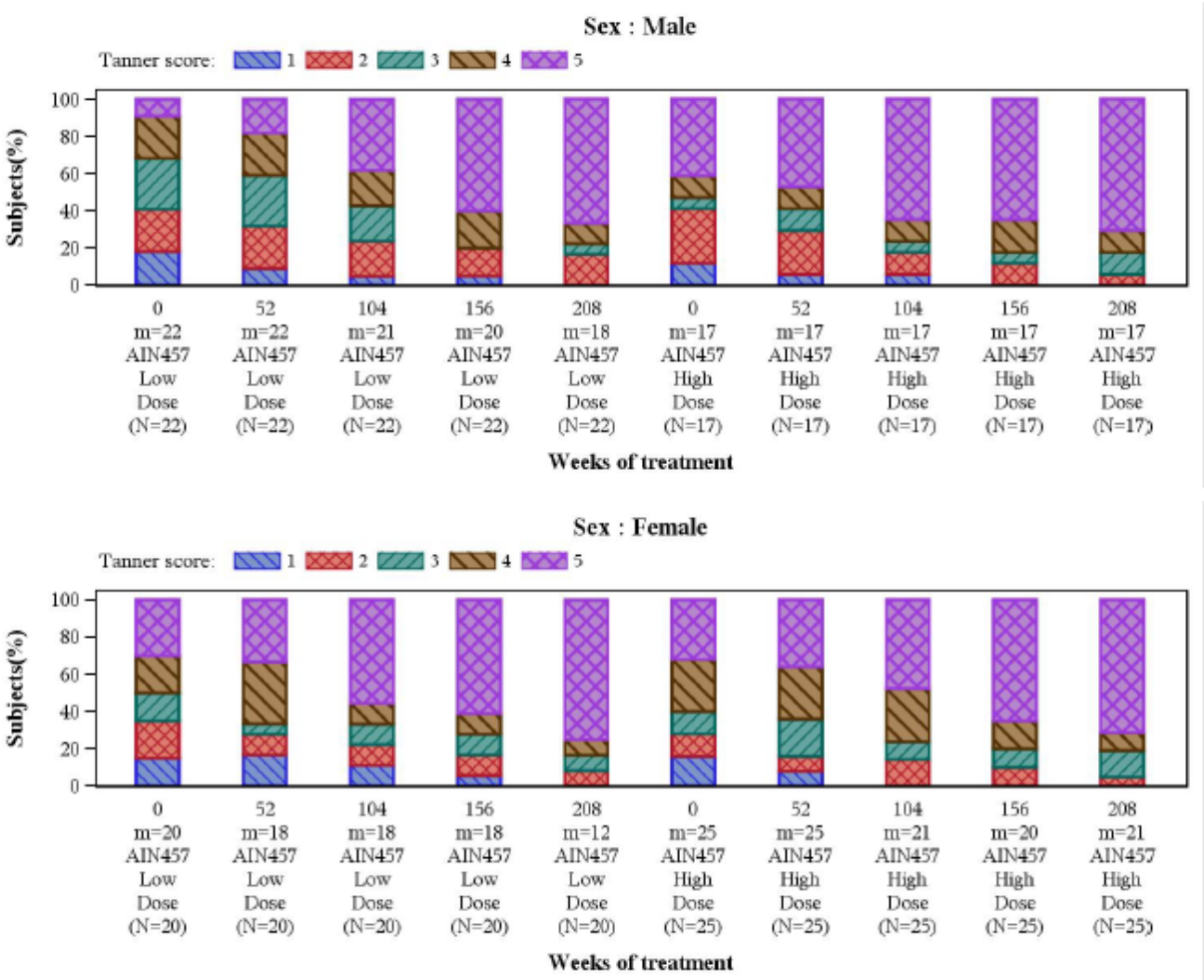
- One subject in the high dose (150 mg - 300 mg) group was reported with a mild AE of ALT elevation on Day 454 (52 U/L, CTCAE grade 1) and a mild AE of AST elevation (51 U/L, CTCAE grade 1) on Day 636. Both events were considered not to be related to study drug, and no concomitant treatment was administered. The ALT level remained at grade 1 until Day 822, when it increased to CTCAE grade 3 (226 U/L) and thereafter fluctuated between grade 2 and 3 until Day 1342, after which it continued to remain grade 3 until end of the follow-up period. The last reported ALT value on Day 1580 was 251 U/L (grade 3). The AST values remained at grade 1 until Day 1475, except for a transient increase to grade 2 on Day 1001. On Day 1475, AST values increased to CTCAE grade 3 (194 U/L), returning to grade 2 (150 U/L) on Day 1531 and remaining at that level on Day 1580. Both the ALT and AST elevations were ongoing at the end of study visit. On Day 1567, the subject was diagnosed with pancreatic steatosis and hepatic steatosis. Both events were non-serious, mild in severity and were considered as non-treatment emergent and not related to study drug.
- One subject in the low dose (75 mg - 150 mg) group presented with CTCAE grade 3 ALT elevation (169 U/L, normal range: 5 to 30 U/L) on Day 458, and the event was reported as a mild AE. The subject also reported mild AEs of AST increased and GGT increased on the same day. The study drug was temporarily interrupted and resumed on Day 533. No concomitant treatment was reported. The ALT values decreased to grade 2 on Day 491 (95 U/L) and

remained at the same grade until Day 1106, when levels further decreased to grade 1 (76 U/L) and remained at the same level until end of treatment. The AEs of ALT increased, AST increased and GGT increased were considered as resolved on Day 897. The events were considered as not related to the study drug.

- One subject in the low dose (150 mg) group was reported with CTCAE grade 3 GGT elevation (112 U/L, normal range: 3 to 22 U/L) on Day 448. The event went down to grade 2 (96 U/L) on Day 532 and remained at the same grade until Day 897, when it decreased to grade 1 (96 U/L) and remained at the same grade until Day 1178 (47 U/L). The GGT levels returned to normal on Day 1261 (40 U/L).

Changes in percentages of patients in Tanner staging scores (measuring pubertal development) over time during the Entire treatment period, by gender and treatment are depicted in Figure 4.

Figure 4. Stacked plot reporting percentage of subjects in each Tanner stage over time, by gender and treatment (Safety set)



- m = number of subjects evaluable.
- Once a subject reaches Tanner score 5 at a specific visit (including baseline), all missing Tanner assessments at subsequent performed visits will be imputed with score 5.
- The higher score between breast development and pubic hair assessments for female and the higher score between genital stage and pubic hair assessments for males are plotted.

Source: Figure 14.3-1.1

Overall, 2 cases of pregnancy were reported during the study. Short narratives are presented below:

- One subject, aged [12-<18] years at screening, from secukinumab high dose group (300 mg) became pregnant during the study. The study drug was discontinued due to pregnancy, with the last dose received on Day 337 (Week 48 dose). The subject had a full-term pregnancy with no pre-natal care and delivered a healthy baby through normal vaginal delivery.
- One subject, aged [12-<18] years at screening, from secukinumab high dose group (300 mg) became pregnant during the study, with the last dose received on Day 1317 (Week 188 dose). Subject gave birth to a healthy baby.

2.3.3. Discussion on clinical aspects

The long-term follow-up for Study CAIN457A2311 has been completed, with results summarised by the MAH in the Full Clinical Study Report provided as a P46 submission.

Overall, the results seem consistent with those reported in earlier submissions. Although long-term results have only been provided on an observed case basis, efficacy appeared to be well maintained in patients continuing on secukinumab for the full duration of the study, and no concerning trends are identified. Similar to results in the other study with secukinumab in paediatric psoriasis (CAIN457A2310), the added benefit of the high dose appeared quite limited, and the current dosing recommendations in the SmPC are thus supported.

The safety profile observed on long-term follow-up appeared consistent with previous experience. Infections were the most commonly reported adverse events but seemed to be well manageable; the COVID-19 pandemic was ongoing at the time of the study but appears to have had minimal impact on study conduct, and no new risks became evident. One event of intentional self-injury is noted among the SAEs. Repeated Tanner staging showed subjects consistently moving toward higher scores through the study.

No unexpected trends were observed on long-term pharmacokinetic characteristics based on trough concentrations from a sparse sampling schedule. Consistent with earlier experience, the immunogenic potential of secukinumab appeared to remain low also during long-term use.

3. CHMP overall conclusion and recommendation

The reported final long-term results from Study CAIN457A2311 in paediatric patients with chronic plaque psoriasis confirm and corroborate findings from earlier (Week 24 and Week 52) analyses of the study, and no concerning trends regarding efficacy or safety are identified based on observed case analyses. The MAH is proposing no changes to the current SmPC, and this proposal is endorsed.

☒ Fulfilled:

No regulatory action required.

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

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 randomized, double-blind, placebo- and active controlled multicenter trial to demonstrate efficacy of subcutaneous secukinumab compared to placebo and etanercept (in a single-blinded arm) after twelve weeks of treatment, and to assess the safety, tolerability, and long-term efficacy in subjects from 6 to less than 18 years of age with severe chronic plaque psoriasis	CAIN457A2310	30-Mar-2023	15-Sept-2023
A randomized, open-label, multicenter trial to assess the efficacy of subcutaneous secukinumab after twelve weeks of treatment, and to assess the long-term safety, tolerability and efficacy in subjects from 6 to less than 18 years of age with moderate to severe chronic plaque psoriasis	CAIN457A2311	Planned for September 2023	Planned for March 2024