14 December 2023
EMA/581967/2023
Committee for Medicinal Products for Human Use (CHMP)

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

Cosentyx

International non-proprietary name: Secukinumab

Procedure No. EMEA/H/C/003729/P46/015

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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	16 Oct 2023	16 Oct 2023	☐
☐	CHMP Rapporteur Assessment Report	20 Nov 2023	17 Nov 2023	☐
☐	CHMP members comments	04 Dec 2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Dec 2023	n/a	☐
☒	CHMP adoption of conclusions:	14 Dec 2023	14 Dec 2023	☐

Table of contents

1. Introduction

On 15 September 2023, the MAH submitted the final CSR for CAIN457A2310, 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 programme

The MAH stated that submission of the final CSR for Study CAIN457A2310 "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" is a stand-alone submission. Of note, 52-week results 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) and have thereby been previously assessed. These results are only very briefly summarised herein; for additional details, reference is made to the European Public Assessment Report for procedure II/0057. A line listing of all the concerned studies is annexed.

According to the MAH, Study CAIN457A2310 was an interventional study conducted to demonstrate the superior efficacy of secukinumab versus placebo in children and adolescents aged 6 to <18 years with severe chronic plaque psoriasis with respect to both Psoriasis Area and Severity Index (PASI) 75 and Investigator's Global Assessment modified 2011 (IGA mod 2011) 0 or 1 response (co-primary endpoints) at Week 12. This study also assessed the efficacy and safety of secukinumab compared to etanercept (up to Week 52) and the long-term efficacy, safety and tolerability of secukinumab in this paediatric age group over the study duration (up to Week 252). Study CAIN457A2310 enrolled 162 paediatric patients and concluded on 30-Mar-2023 (last patient last visit [LPLV]).

This study demonstrated the long-term efficacy and safety of secukinumab in paediatric patients aged 6 to <18 years with 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 CAIN457A2310, 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).

Secukinumab placebo was supplied in a PFS in a form to match secukinumab syringes.

Etanercept (active comparator) was provided centrally or as available in local markets.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- CAIN457A2310: 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.

2.3.2. Clinical study

Description

Study CAIN457A2310 was a randomised, double-blind placebo- and single-blind active -controlled Phase III study conducted in paediatric patients from 6 years of age with severe chronic plaque psoriasis.

Methods

Study design

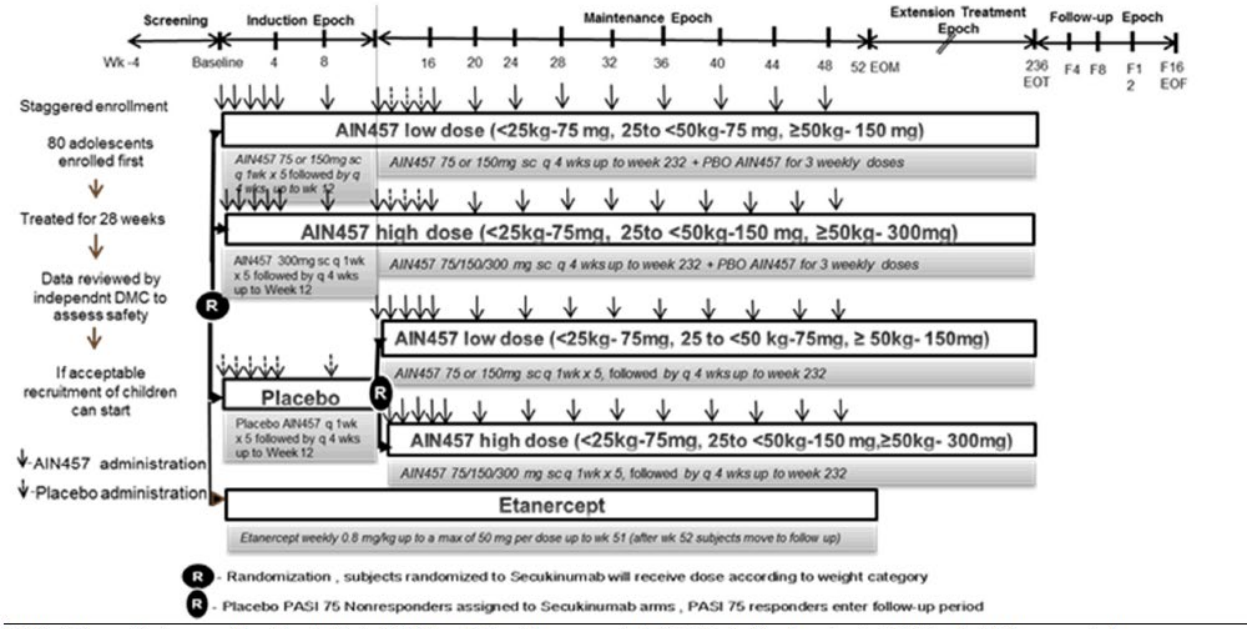
This study was a multicentre, randomised, parallel-group, double-blind placebo-controlled (patients and all site staff were blinded) and single-blind active-controlled (etanercept in single-blinded group, i.e., only the efficacy assessor was blinded) study in paediatric patients aged 6 to < 18 years with severe chronic plaque psoriasis.

The study consisted of 5 periods: screening (up to 4 weeks), induction (12 weeks), maintenance (40 weeks), extension treatment (open-label of 184 weeks) and post-treatment Follow-up (16 weeks).

Patients were randomised using a 1:1:1:1 ratio into one of the treatment groups: secukinumab low dose, secukinumab high dose, etanercept or placebo.

The design is graphically depicted in Figure 1

Figure 1 Study design for CAIN457A2310



DMC= Data monitoring committee; Epoch=Period; EOM=end-of-maintenance period; EOT=End-of-treatment period; EOF=end-of-follow-up period

Study participants

The main inclusion criteria were:

- Patients 6 to <18 years of age at the time of randomisation
    - Patients 12 to < 18 years were enrolled from the beginning of trial
    - Patients 6 to < 12 years were enrolled after positive external Data Monitoring Committee (DMC) recommendation following review of data from the first 80 adolescents treated for 28 weeks
- Severe plaque psoriasis, defined as a PASI score ≥ 20, and IGA mod 2011 score of 4, and body surface area (BSA) involvement of ≥ 10%, at randomisation
- History of plaque psoriasis for at least 3 months
- Patient being regarded by the investigator to be a candidate for systemic therapy because of:
    - inadequate control of symptoms with topical treatment, or
    - failure to respond to or tolerate previous systemic treatment and/or ultraviolet (UV) therapy

The main exclusion criteria were:

- Forms of psoriasis other than chronic plaque-type active at randomisation
- Female patients of childbearing potential (menarchal or become menarchal during the study) who did not agree to abstinence or, if sexually active, did not agree to the use of contraception
- Active ongoing inflammatory diseases other than psoriasis that could 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 could significantly immunocompromise the patient and/or place the patient at unacceptable risk for receiving an immunomodulatory therapy

- Ongoing infections as evidenced by chest X-ray, CT scan or MRI, obtained within 12 weeks prior to randomisation
- 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

Treatments

Patients randomised to secukinumab received 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.

In order to maintain the treatment blind, all subjects in the secukinumab and placebo arms received 2 s.c. injections at each dose, except for subjects in the <25kg weight category who received only 1 injection of either 75 mg secukinumab or matching placebo.

If a subject randomised into a secukinumab or placebo to secukinumab treatment arm moved into a higher or lower weight group at two consecutive visits with weight measurements during the maintenance (from Week 12 onwards as assessed at monthly visits, i.e. Week 13, 14, 15 was not taken into account) or during extension treatment period (as assessed at scheduled site visits), the subject was to receive dosing according to the new (higher or lower) weight group, respectively.

Secukinumab low dose group:

- Induction period: secukinumab 75 mg / 150 mg s.c. Q1W x 5 then Q4W up to Week 12
- Maintenance period: secukinumab 75 mg / 150 mg s.c. Q4W up to Week 48 and placebo secukinumab at Weeks 13, 14 and 15.
- Extension treatment period: secukinumab 75 mg / 150 mg s.c. at Week 52 and then Q4W up to Week 232.

Secukinumab high dose group:

- Induction period: secukinumab 75 mg / 150 mg / 300 mg s.c. Q1W x 5 then Q4W up to Week 12
- Maintenance period: secukinumab 75 mg / 150 mg / 300 mg s.c. Q4W up to Week 48 and placebo secukinumab at Weeks 13, 14 and 15.
- Extension treatment period: secukinumab 75 mg / 150 mg / 300 mg s.c. at Week 52 and then Q4W up to Week 232.

Placebo group:

- Induction period: Placebo secukinumab Q1W x 5 then Q4W up to Week 12

- Maintenance period: PASI 75 non-responders received Secukinumab low dose OR Secukinumab high dose Q1W x 5, then Q4W up to Week 232. PASI 75 responders entered the Follow-up period.

Etanercept group:

- Induction and Maintenance period: s.c. etanercept 0.8 mg/kg (up to a maximum dose of 50 mg) once per week, up to Week 51. After Week 52, patients entered the Follow-up period.

If a subject moved into a higher or lower weight group at two consecutive visits with weight measurements during the maintenance (from Week 12 onwards as assessed at monthly visits, i.e. Week 13, 14, 15 was not taken into account) or during extension treatment period (as assessed at scheduled site visits), the subject was to receive dosing according to the new (higher or lower) weight group, respectively.

Objective(s)

The **primary objective** of the study was to demonstrate the superiority of secukinumab (low and high dose) in paediatric patients with severe chronic plaque psoriasis with respect to both PASI 75 and IGA mod 2011 0/1 response (co-primary endpoints) at Week 12, compared to placebo. The primary objective was assessed and reported in the Week 24 primary efficacy analyses (PEA) study report, dated 20-Sep-2019.

Secondary objectives were:

- To demonstrate superiority of secukinumab (low and high dose) in patients with severe chronic plaque psoriasis with respect to PASI 90 response at Week 12, compared to placebo.
- To assess efficacy of secukinumab in patients with severe chronic plaque psoriasis with respect to PASI 50 and PASI 100 at Week 12, compared to placebo.
- To assess efficacy of secukinumab in patients with severe chronic plaque psoriasis with respect to PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0/1 at Week 16 and over time up to Week 52.
- To assess the efficacy of secukinumab with respect to changes in PASI score and IGA mod 2011 score at Week 12, compared to placebo, and over time up to Week 52.
- To investigate the effects of treatment with secukinumab with respect to changes in Children's Quality of Life Index (CDLQI) at Week 12, compared to placebo, and over time up to Week 52.
- To investigate the effects of treatment of secukinumab with respect to CDLQI 0 or 1 achievement at Week 12, compared to placebo, and over time up to Week 52.
- To evaluate the effects of treatment of secukinumab on disability at Week 12 and over time up to Week 52 by use of the Childhood Health Assessment Questionnaire (CHAQ©), for patients with history of psoriatic arthritis.
- To investigate the clinical safety and tolerability of secukinumab as assessed by growth, weight gain, tolerability of subcutaneous (s.c.) injections, vital signs, clinical laboratory variables, electrocardiogram (ECGs), and AEs monitoring, compared to placebo.

The results of secondary objective analyses supported by the data available at the Week 24 cutoff date (07-Mar-2019) including the Week 12 efficacy assessments were reported in the Week 24 PEA study report, dated 20-Sep-2019. Cumulative efficacy data up to Week 52, as well as cumulative safety and

tolerability data up to the last visit prior to the Week 52 analysis cut-off (18-Sep-2019) were reported in the Week 52 analysis study report, dated 16-Mar-2020.

Exploratory objectives were:

- To describe the efficacy of secukinumab compared to etanercept with respect to PASI 75, PASI 90, PASI 100 and IGA mod 2011.
- To assess the efficacy of secukinumab with respect to onset of effect of secukinumab, compared to placebo and etanercept.
- To describe the safety of secukinumab compared to etanercept.
- To assess the occurrence of relapse following secukinumab and etanercept therapy (during follow-up period).
- To assess the occurrence of rebound following secukinumab and etanercept therapy (during follow-up period).
- To assess impact of treatment with secukinumab on physical development in children and adolescents from ages 6 – 18 years, by use of the Tanner stages scale over time (Parts I and II).
- To assess PK parameters.
- To investigate the development of immunogenicity (IG) against secukinumab.
- To perform exploratory PG assessments to examine whether individual genetic variation in genes relating to drug metabolism, psoriasis, and the drug target pathway confer differential response to secukinumab.
- To assess the long-term efficacy of secukinumab on severe chronic plaque-type psoriasis with respect to PASI 50/75/90/100 and IGA 0 or 1 response, after Week 52.
- To assess the long-term efficacy of secukinumab on severe chronic plaque-type psoriasis with respect to PASI score and IGA mod 2011 score after Week 52.
- To investigate the clinical safety and tolerability of secukinumab as assessed by growth, weight gain, tolerability of s.c. injections, vital signs, clinical laboratory variables, ECGs, and AEs monitoring after Week 52.
- To investigate the effects of treatment with secukinumab with respect to changes in CDLQI after Week 52.
- To investigate the effects of treatment of secukinumab with respect to CDLQI 0 or 1 achievement after Week 52.

The exploratory objectives up to Week 12 were assessed for secukinumab compared to etanercept and reported in the Week 24 PEA study report. Data for exploratory objectives up to the Week 52 analysis cut-off (18-Sep-2019) were summarised in the Week 52 analysis study report, dated 16-Mar-2020. In this report, the data of secukinumab in comparison with etanercept were reported.

The final study report that has now been submitted presents data for the Extension and Entire treatment and/or Study period predominantly for Any AIN457 low dose, Any AIN457 high dose and Any AIN457 dose, unless otherwise specified.

Outcomes/endpoints

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

Health-related quality of life was assessed with the Children's Quality of Life Index (CDLQI). The impact of psoriatic arthritis, on those patients who reported a history of psoriatic arthritis, was assessed by their parent/custodian via the use of Childhood Health Assessment Questionnaire (CHAQ).

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.

Sample size

It was planned to enrol approximately 160 paediatric patients from 6 to less than 18 years of age, with 2 subgroups: 6 to less than 12 years of age, and 12 to less than 18 years of age. Stratification was planned for age (< 12 years, ≥ 12 years) and weight (< 25 kg, 25 - < 50 kg and ≥ 50 kg). It was targeted to have at least 30 patients in the < 12 years subgroup. Enrolment of children aged 6 to less than 12 years proceeded after efficacy and safety data for approximately 80 (approximately 40 treated with secukinumab) enrolled adolescents (aged 12 to less than 18 years) treated for 28 weeks had been reviewed and deemed satisfactory by the DMC.

Randomisation and blinding (masking)

At Randomisation (Visit 2), all eligible patients were randomised via Interactive Response Technology (IRT) at a 1:1:1:1 ratio to one of the treatment arms (secukinumab high dose; secukinumab low dose; placebo; etanercept). Randomisation was stratified by age and body weight collected at randomisation visit. The age strata were age < 12" or "age ≥ 12". The weight strata were body weight < 25 kg", "25 kg ≤ body weight < 50 kg" or "body weight ≥ 50 kg". It was targeted to have at least approximately 30% of the subjects in each weight stratum. Within each weight stratum, subjects were assigned to the high dose or the low dose treatment group for secukinumab or placebo.

The secukinumab and the placebo arms were double blind (patient, investigator and assessor) until the data base lock for Week 52 analysis. However, for placebo PASI 75 responders unblinding occurred at Week 12, since these subjects could not continue into the Maintenance period but needed to enter the post treatment follow-up period.

The etanercept arm was single (assessor) blind until the moment subjects completed the Week 52 visit and entered the follow-up period. Site staff (with the exception of the efficacy assessor), subject and sponsor were not blinded to the etanercept arm for the entire treatment duration with etanercept.

Statistical Methods

Data for the Extension period and Entire treatment period are summarised with descriptive statistics and are based on observed cases.

Results

Participant flow

Induction period: A total of 162 patients were randomised to the 4 treatment groups in the Induction period: secukinumab low dose (n=40), secukinumab high dose (n=40), placebo (n=41) and etanercept (n=41), and a total of 156 patients (96.3%) completed the Induction period.

Maintenance period: A total of 151/156 (~97%) patients entered the Maintenance period. From the placebo group, PASI 75 responders at Week 12 (n=5) did not proceed into the Maintenance period but entered the Follow-up period, while PASI 75 non-responders from the placebo group were assigned to secukinumab low dose (n=16) or secukinumab high dose (n=18) starting at Week 12. The majority of these patients (placebo - secukinumab low dose: n=15 [93.8%] and placebo - secukinumab high dose: n=16 [88.9%]) completed the Maintenance period. From the etanercept group, 40/41 patients entered the Maintenance period, of which 34 (82.9%) patients completed it.

Extension period: Of the 114 patients who received secukinumab at initial randomisation visit or switched from placebo to secukinumab at Week 12, 106 patients (93.0%) entered the Extension period (n=53 each in the Any secukinumab low and high dose groups). There were more patients discontinuing during the Extension period in the Any secukinumab low dose group (n=14 [25.0%]) compared to the Any secukinumab high dose group (n=10 [17.2%]). The most common reason for discontinuation was lack of efficacy; this was more frequent in the Any secukinumab low dose group (n=6 [10.7%]) than in the Any secukinumab high dose group (n=3 [5.2%]). Two patients in each of the Any secukinumab low and Any secukinumab high dose groups (3.6% and 3.4% respectively) discontinued the extension period due to an AE. Patient disposition for the Extension period is summarised in Table 1.

Table 1 Patient disposition by treatment - Extension period (Randomised set)

Disposition/ Reason	Any AIN457 Low dose N=56 n (%)	Any AIN457 High dose N=58 n (%)	Any AIN457 dose N=114 n (%)
Entered extension period	53 (94.6)	53 (91.4)	106 (93.0)
Completed	39 (69.6)	43 (74.1)	82 (71.9)
Discontinued	14 (25.0)	10 (17.2)	24 (21.1)
Primary reason for discontinuation			
Adverse event	2 (3.6)	2 (3.4)	4 (3.5)
Lack of efficacy	6 (10.7)	3 (5.2)	9 (7.9)
Pregnancy	2 (3.6)	0 (0.0)	2 (1.8)
Technical problems	1 (1.8)	0 (0.0)	1 (0.9)
Lost to follow-up	0 (0.0)	2 (3.4)	2 (1.8)
Subject/guardian decision	3 (5.4)	3 (5.2)	6 (5.3)

Follow-up period: 80/114 randomised patients (70.2%) entered the Follow-up period (n=40 each in the Any secukinumab high and low dose groups); 63 patients (55.3%) completed the Follow-up period. The most common reason for not completing the study period was the early termination of the study by the sponsor (n=9 [7.9%]). Patient disposition for the Follow-up period is summarised in Table 2.

Table 2 Patient disposition by treatment - Follow up period (Randomised set)

Disposition/ Reason	Any AIN457 Low dose N=56 n (%)	Any AIN457 High dose N=58 n (%)	Any AIN457 dose N=114 n (%)
Entered follow-up period	40 (71.4)	40 (69.0)	80 (70.2)
Completed	28 (50.0)	35 (60.3)	63 (55.3)
Discontinued	12 (21.4)	5 (8.6)	17 (14.9)
Primary reason for discontinuation			
Adverse event	1 (1.8)	0 (0.0)	1 (0.9)
Lack of efficacy	1 (1.8)	0 (0.0)	1 (0.9)
New therapy for study indication	1 (1.8)	0 (0.0)	1 (0.9)
Study terminated by sponsor	5 (8.9)	4 (6.9)	9 (7.9)
Lost to follow-up	1 (1.8)	0 (0.0)	1 (0.9)
Physician decision	1 (1.8)	0 (0.0)	1 (0.9)
Subject/guardian decision	2 (3.6)	1 (1.7)	3 (2.6)

Recruitment

First patient first visit took place on 29 September 2015. The sponsor decided on early termination of the study on 11 January 2023, and last patient last visit took place on 30 March 2023. According to the MAH, the decision on early termination was based on technical grounds, as the EDC system used in the study would no longer have been supported as of mid-2023. The decision was therefore made to terminate the study after all planned treatment visits had been taken place. There were no safety findings that contributed to this decision, and the early termination decision did not impact on any important study outcomes.

Study centres were located as follows: Belgium (3), Colombia (2), Egypt (2), Estonia (1), France (3), Germany (7), Guatemala (3), Hungary (3), Israel (3), Italy (2), Japan (1), Latvia (2), Poland (3), Romania (1) Russia (5), Spain (3), Switzerland (1), United Kingdom (1) United states (1). Table 3 summarises patient enrolment by country.

Table 3 Patient enrolment summary by country

Country	Total number of subjects enrolled
Belgium	07
Colombia	09
Egypt	11
Estonia	11
France	03
Germany	25
Guatemala	10
Hungary	08
Israel	10
Italy	02
Japan	05
Latvia	04
Poland	28
Romania	04
Russian Federation	13
Spain	08
Switzerland	01
United Kingdom	01
United States	02
Total	162

Baseline data

For the Entire treatment period, the demographic and background characteristics of the treatment groups (Any AIN457 low dose and Any AIN457 high dose) were generally similar. The mean age of the patients was 13.5 years and similar in the treatment groups. More than three quarters (78.1%) of the patients were in the ≥ 12 years age group. The patients were predominantly Caucasian (85.1%). More females were enrolled compared to males (58.8% vs. 41.2%). The mean weight of the patients was similar in the treatment groups, and the majority of patients (52.6%) weighed ≥ 50 kg (< 25 kg: 7.0% and 25 - < 50 kg: 40.4%). The proportion of patients in all weight categories (< 25 kg, 25 - < 50 kg, ≥ 50 kg) was generally comparable across the two treatment groups. The demographic characteristics were generally well balanced between the Any AIN457 low dose group and the Any AIN457 high dose group, except that the proportion of males was higher in the Any AIN457 high dose group than in the Any AIN457 low dose group (Table 4).

Table 4 Demographics and background characteristics – Entire treatment period groups (Randomised set)

Characteristic	Any AIN457 Low dose N=56	Any AIN457 High dose N=58	Any AIN457 dose N=114
Age group (years)- n (%)			
< 12	13 (23.2)	12 (20.7)	25 (21.9)
>= 12	43 (76.8)	46 (79.3)	89 (78.1)
Age (years)			
n	56	58	114
Mean	13.6	13.5	13.5
SD	3.00	3.24	3.11
Median	14.0	14.5	14.0
Min - Max	7 - 17	6 - 17	6 - 17
Sex – n (%)			
Male	20 (35.7)	27 (46.6)	47 (41.2)
Female	36 (64.3)	31 (53.4)	67 (58.8)
Race – n (%)			
Caucasian	47 (83.9)	50 (86.2)	97 (85.1)
Black	1 (1.8)	1 (1.7)	2 (1.8)
Asian	2 (3.6)	2 (3.4)	4 (3.5)
Native American	5 (8.9)	4 (6.9)	9 (7.9)
Other	1 (1.8)	1 (1.7)	2 (1.8)
Ethnicity – n (%)			
Hispanic/Latino	6 (10.7)	6 (10.3)	12 (10.5)
East Asian	2 (3.6)	1 (1.7)	3 (2.6)
Southeast Asian	0 (0.0)	1 (1.7)	1 (0.9)
West Asian	2 (3.6)	0 (0.0)	2 (1.8)
Russian	7 (12.5)	4 (6.9)	11 (9.6)
Mixed Ethnicity	1 (1.8)	0 (0.0)	1 (0.9)
Unknown	4 (7.1)	3 (5.2)	7 (6.1)
Other	31 (55.4)	37 (63.8)	68 (59.6)
Not Reported	3 (5.4)	6 (10.3)	9 (7.9)
Weight (kg)			

Table 4 continued, Demographics and background characteristics – Entire treatment period groups (Randomised set)

Characteristic	Any AIN457 Low dose N=56	Any AIN457 High dose N=58	Any AIN457 dose N=114
n	56	58	114
Mean	52.33	55.93	54.16
SD	16.188	22.602	19.711
Median	50.10	51.65	50.75
Min - Max	21.0 - 88.9	17.6 - 116.0	17.6 - 116.0
Weight strata (kg) - n (%)			
<25	4 (7.1)	4 (6.9)	8 (7.0)
25 - <50	24 (42.9)	22 (37.9)	46 (40.4)
>= 50	28 (50.0)	32 (55.2)	60 (52.6)
Height (cm)			
n	56	58	114
Mean	158.11	156.15	157.11
SD	15.547	18.265	16.938
Median	160.00	159.00	160.00
Min - Max	121.0 - 185.0	115.0 - 194.0	115.0 - 194.0
BMI (kg/m^2)			
n	56	58	114
Mean	20.41	22.09	21.27
SD	3.819	5.758	4.954
Median	19.50	21.30	20.35
Min - Max	14.1 - 30.7	11.1 - 42.5	11.1 - 42.5
Child Bearing status - n (%)			
Able to bear children	23 (63.9)	23 (74.2)	46 (68.7)
Premenarche	13 (36.1)	8 (25.8)	21 (31.3)

- Age is collected at screening.
- Weight and height are taken from screening vital signs evaluations.
- BMI=body mass index is calculated based on raw data measurements.
- Percentages for "Child Bearing status" are calculated based on female population.

For the Entire treatment period groups, the baseline disease characteristics were generally balanced and comparable between the Any AIN457 low dose group and the Any AIN457 high dose group and were consistent with the population of patients with severe chronic plaque psoriasis (Table 5). The mean total BSA affected by plaque-type psoriasis for overall patients was 38.65%. The mean Baseline PASI score was 27.7, with most patients having a PASI score of > 20. One patient in the secukinumab high dose group had a Baseline PASI score ≤ 20 (documented as a protocol deviation) but was not excluded from any analyses. All patients had an IGA mod 2011 score of 4 (severe disease) except for one patient in the secukinumab high dose group who had a Baseline IGA mod 2011 score of 3; this was documented as a protocol deviation but the patient was not excluded from any analyses. The majority (90.4%) of patients did not have psoriatic arthritis at baseline.

Table 5 Disease history and baseline disease characteristics – Entire treatment period groups (Randomised set)

Background Characteristics	Any AIN457 Low dose N=56	Any AIN457 High dose N=58	Any AIN457 dose N=114
Baseline PASI score			
n	56	58	114
Mean	28.2	27.2	27.7
SD	7.37	7.83	7.59
Median	26.0	25.5	25.8
Min - Max	20 - 48	17 - 59	17 - 59
Baseline PASI, n (%)			
<= 20	0 (0.0)	1 (1.7)	1 (0.9)
> 20	56 (100.0)	57 (98.3)	113 (99.1)
Baseline total BSA			
n	56	58	114
Mean	38.75	38.56	38.65
SD	15.94	16.52	16.17
Median	36.35	35.25	36.00
Min - Max	12.00 - 72.50	16.00 - 94.00	12.00 - 94.00
Baseline IGA mod 2011 score, n (%)			
3 = Moderate disease	0 (0.0)	1 (1.7)	1 (0.9)
4 = Severe disease	56 (100.0)	57 (98.3)	113 (99.1)
Diagnosis of plaque-type psoriasis - n (%)			
Yes	56 (100.0)	58 (100.0)	114 (100.0)
Time since first diagnosis of plaque-type psoriasis (years)			
n	56	58	114
Mean	4.93	5.89	5.42
SD	4.36	5.02	4.71
Median	3.78	4.09	3.91
Min - Max	0.3 – 17.0	0.4 - 17.5	0.28 - 17.5
Psoriasis History - n (%)			
Generalized pustural psoriasis	1 (1.8)	2 (3.4)	3 (2.6)
Erythrodermic psoriasis	0 (0.0)	1 (1.7)	1 (0.9)
Diagnosis of psoriatic arthritis - n (%)			
Yes	6 (10.7)	5 (8.6)	11 (9.6)
No	50 (89.3)	53 (91.4)	103 (90.4)
Time since first diagnosis of psoriatic arthritis (years)			
n	6	5	11
Mean	3.96	2.41	3.25
SD	3.58	2.49	3.09

Table 5 continued, Disease history and baseline disease characteristics – Entire treatment period groups (Randomised set)

Background Characteristics	Any AIN457 Low dose N=56	Any AIN457 High dose N=58	Any AIN457 dose N=114
Median	2.80	0.79	2.09
Min - Max	0.14 - 9.7	0.45 - 5.90	0.14 - 9.65
Previous psoriasis therapies- n (%)			
Yes	56 (100.0)	58 (100.0)	114 (100.0)

All patients had received psoriasis therapies prior to study entry. Approximately half of the patients (65 [57.0%] patients) had previous exposure to systemic psoriasis therapies; the proportion was similar in the Any AIN457 low dose group (33 [58.9%] patients) compared to the Any AIN457 high dose group (32 [55.2%] patients). The majority (57 [87.7%] patients overall) of the patients with previous exposure to systemic psoriasis therapies had failed on this therapy. The proportion of patients previously exposed to biologic psoriasis therapies was very low overall and was reported only in the Any AIN457 low dose group (3 [5.4%] patients).

Number analysed

The number of patients in each analysis set by treatment group for the Extension and Entire treatment periods are summarised in Table 6 and Table 7, respectively. All randomised patients were included in the FAS and Safety set. During the Extension period, 53 patients in each of the Any AIN457 low dose and Any AIN457 high dose groups were part of the analysis sets. For the Entire treatment period, 56 patients in Any AIN457 low dose and 58 patients in Any AIN457 high dose groups were part of the analysis sets.

Table 6 Analysis sets by treatment period (all patients enrolled) – Extension period

Analysis Set	AIN457 Low dose	AIN457 High dose	Placebo-AIN457 Low dose	Placebo-AIN457 High dose	Any AIN457 Low dose	Any AIN457 High dose	Any AIN457 dose
Randomized set	38	37	15	16	53	53	106
Full analysis set	38	37	15	16	53	53	106
Safety set	38	37	15	16	53	53	106

Table 7 Analysis sets by treatment period (All patients enrolled) – Entire treatment period

Analysis set	AIN457 Low dose	AIN457 High dose	Placebo-AIN457 Low dose	Placebo-AIN457 High dose	Placebo	Etanercept	Any AIN457 Low dose	Any AIN457 High dose	Any AIN457 dose
Randomized set	40	40	16	18	7	41	56	58	114
Full analysis set	40	40	16	18	7	41	56	58	114
Safety set	40	40	16	18	7	41	56	58	114

Efficacy results

For full results relating to the primary and secondary objectives at Week 12 and Week 52, reference is made to the European Public Assessment Report for procedure II/0057. Briefly, the primary objectives were met; both secukinumab doses (low and high) were superior to placebo with respect to PASI 75

response and IGA mod 2011 0/1 response at Week 12. The odds ratio estimates in favour of both secukinumab doses were statistically significant (p<0.0001). The key secondary objective was also met; both secukinumab doses (low and high dose) were superior to placebo with respect to PASI 90 response at Week 12 (71.1% and 69.3% vs. 2.5%). The odds ratio estimates in favour of both secukinumab doses were statistically significant (p<0.0001).

The main efficacy results for the Entire treatment period are summarised in Table 8 and Figure 3. Based on observed cases, effects on IGA mod 2011 0/1 as well as PASI 50, PASI 75, PASI 90, and PASI 100 responses were generally maintained in both the Any AIN457 low dose and Any AIN457 high dose groups for the duration of the study. For PASI 100, response rates were consistently higher in the Any AIN457 high dose group compared to the Any AIN457 low dose group, whereas for the other variables, no clear dose dependent increase in effect was seen.

Table 8 Number (%) of subjects with IGA 0 or 1 and PASI 50, PASI 75, PASI 90, PASI 100 response by visit (observed cases) – Entire treatment period (Full Analysis set)

		Any AIN457 Low dose N=56			Any AIN457 High dose N=58		
Visit	Criterion	n/m	(%)	95% CI	n/m	(%)	95% CI
Week 1	IGA 0/1	0/ 38	(0.0)	(0.0, 11.4)	0/ 37	(0.0)	(0.0, 11.7)
	PASI 50	5/ 38	(13.2)	(4.9, 28.9)	4/ 37	(10.8)	(3.5, 26.4)
	PASI 75	0/ 38	(0.0)	(0.0, 11.4)	1/ 37	(2.7)	(0.1, 15.8)
	PASI 90	0/ 38	(0.0)	(0.0, 11.4)	0/ 37	(0.0)	(0.0, 11.7)
	PASI 100	0/ 38	(0.0)	(0.0, 11.4)	0/ 37	(0.0)	(0.0, 11.7)
Week 12	IGA 0/1	24/ 45	(53.3)	(38.0, 68.1)	23/ 53	(43.4)	(30.1, 57.6)
	PASI 50	29/ 45	(64.4)	(48.7, 77.7)	35/ 53	(66.0)	(51.6, 78.1)
	PASI 75	28/ 45	(62.2)	(46.5, 75.8)	31/ 53	(58.5)	(44.2, 71.6)
	PASI 90	26/ 45	(57.8)	(42.2, 72.0)	26/ 53	(49.1)	(35.3, 63.0)
	PASI 100	11/ 45	(24.4)	(13.4, 39.9)	11/ 53	(20.8)	(11.3, 34.5)
Week 24	IGA 0/1	49/ 55	(89.1)	(77.1, 95.5)	44/ 54	(81.5)	(68.1, 90.3)
	PASI 50	53/ 55	(96.4)	(86.4, 99.4)	53/ 54	(98.1)	(88.8, 99.9)
	PASI 75	52/ 55	(94.5)	(83.9, 98.6)	49/ 54	(90.7)	(78.9, 96.5)
	PASI 90	46/ 55	(83.6)	(70.7, 91.8)	43/ 54	(79.6)	(66.1, 88.9)
	PASI 100	29/ 55	(52.7)	(38.9, 66.1)	23/ 54	(42.6)	(29.5, 56.7)
Week 36	IGA 0/1	46/ 54	(85.2)	(72.3, 92.9)	43/ 54	(79.6)	(66.1, 88.9)
	PASI 50	53/ 54	(98.1)	(88.8, 99.9)	53/ 54	(98.1)	(88.8, 99.9)
	PASI 75	51/ 54	(94.4)	(83.7, 98.6)	51/ 54	(94.4)	(83.7, 98.6)
	PASI 90	44/ 54	(81.5)	(68.1, 90.3)	43/ 54	(79.6)	(66.1, 88.9)
	PASI 100	27/ 54	(50.0)	(36.3, 63.7)	27/ 54	(50.0)	(36.3, 63.7)
Week 52	IGA 0/1	43/ 54	(79.6)	(66.1, 88.9)	43/ 55	(78.2)	(64.6, 87.8)
	PASI 50	54/ 54	(100.0)	(91.7, 100.0)	54/ 55	(98.2)	(89.0, 99.9)
	PASI 75	49/ 54	(90.7)	(78.9, 96.5)	52/ 55	(94.5)	(83.9, 98.6)
	PASI 90	43/ 54	(79.6)	(66.1, 88.9)	46/ 55	(83.6)	(70.7, 91.8)
	PASI 100	26/ 54	(48.1)	(34.5, 62.0)	29/ 55	(52.7)	(38.9, 66.1)

Table 8 continued, Number (%) of subjects with IGA 0 or 1 and PASI 50, PASI 75, PASI 90, PASI 100 response by visit (observed cases) – Entire treatment period (Full Analysis set)

		Any AIN457 Low dose N=56			Any AIN457 High dose N=58		
Visit	Criterion	n/m	(%)	95% CI	n/m	(%)	95% CI
Week 104	IGA 0/1	37/ 51	(72.5)	(58.0, 83.7)	38/ 49	(77.6)	(63.0, 87.8)
	PASI 50	48/ 51	(94.1)	(82.8, 98.5)	49/ 49	(100.0)	(90.9, 100.0)
	PASI 75	46/ 51	(90.2)	(77.8, 96.3)	46/ 49	(93.9)	(82.1, 98.4)
	PASI 90	37/ 51	(72.5)	(58.0, 83.7)	44/ 49	(89.8)	(77.0, 96.2)
	PASI 100	20/ 51	(39.2)	(26.2, 53.9)	27/ 49	(55.1)	(40.3, 69.1)
Week 156	IGA 0/1	30/ 45	(66.7)	(50.9, 79.6)	35/ 47	(74.5)	(59.4, 85.6)
	PASI 50	43/ 45	(95.6)	(83.6, 99.2)	45/ 47	(95.7)	(84.3, 99.3)
	PASI 75	42/ 45	(93.3)	(80.7, 98.3)	43/ 47	(91.5)	(78.7, 97.2)
	PASI 90	37/ 45	(82.2)	(67.4, 91.5)	40/ 47	(85.1)	(71.1, 93.3)
	PASI 100	18/ 45	(40.0)	(26.1, 55.6)	27/ 47	(57.4)	(42.3, 71.4)
Week 208	IGA 0/1	30/ 38	(78.9)	(62.2, 89.9)	31/ 43	(72.1)	(56.1, 84.2)
	PASI 50	37/ 38	(97.4)	(84.6, 99.9)	42/ 43	(97.7)	(86.2, 99.9)
	PASI 75	37/ 38	(97.4)	(84.6, 99.9)	40/ 43	(93.0)	(79.9, 98.2)
	PASI 90	32/ 38	(84.2)	(68.1, 93.4)	37/ 43	(86.0)	(71.4, 94.2)
	PASI 100	19/ 38	(50.0)	(33.7, 66.3)	25/ 43	(58.1)	(42.2, 72.6)
Week 236	IGA 0/1	25/ 36	(69.4)	(51.7, 83.1)	31/ 39	(79.5)	(63.1, 90.1)
	PASI 50	36/ 36	(100.0)	(88.0, 100.0)	39/ 39	(100.0)	(88.8, 100.0)
	PASI 75	35/ 36	(97.2)	(83.8, 99.9)	38/ 39	(97.4)	(84.9, 99.9)
	PASI 90	28/ 36	(77.8)	(60.4, 89.3)	33/ 39	(84.6)	(68.8, 93.6)
	PASI 100	18/ 36	(50.0)	(33.2, 66.8)	27/ 39	(69.2)	(52.3, 82.5)
At any time up to Week 236	IGA 0/1	54/ 55	(98.2)	(89.0, 99.9)	52/ 57	(91.2)	(80.0, 96.7)
	PASI 50	55/ 55	(100.0)	(91.9, 100.0)	56/ 57	(98.2)	(89.4, 99.9)
	PASI 75	55/ 55	(100.0)	(91.9, 100.0)	55/ 57	(96.5)	(86.8, 99.4)
	PASI 90	54/ 55	(98.2)	(89.0, 99.9)	53/ 57	(93.0)	(82.2, 97.7)
	PASI 100	48/ 55	(87.3)	(74.9, 94.3)	47/ 57	(82.5)	(69.6, 90.8)

- n = number of subjects with response, m=number of subjects evaluable.
- 95% CI are calculated using the Newcombe method.

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

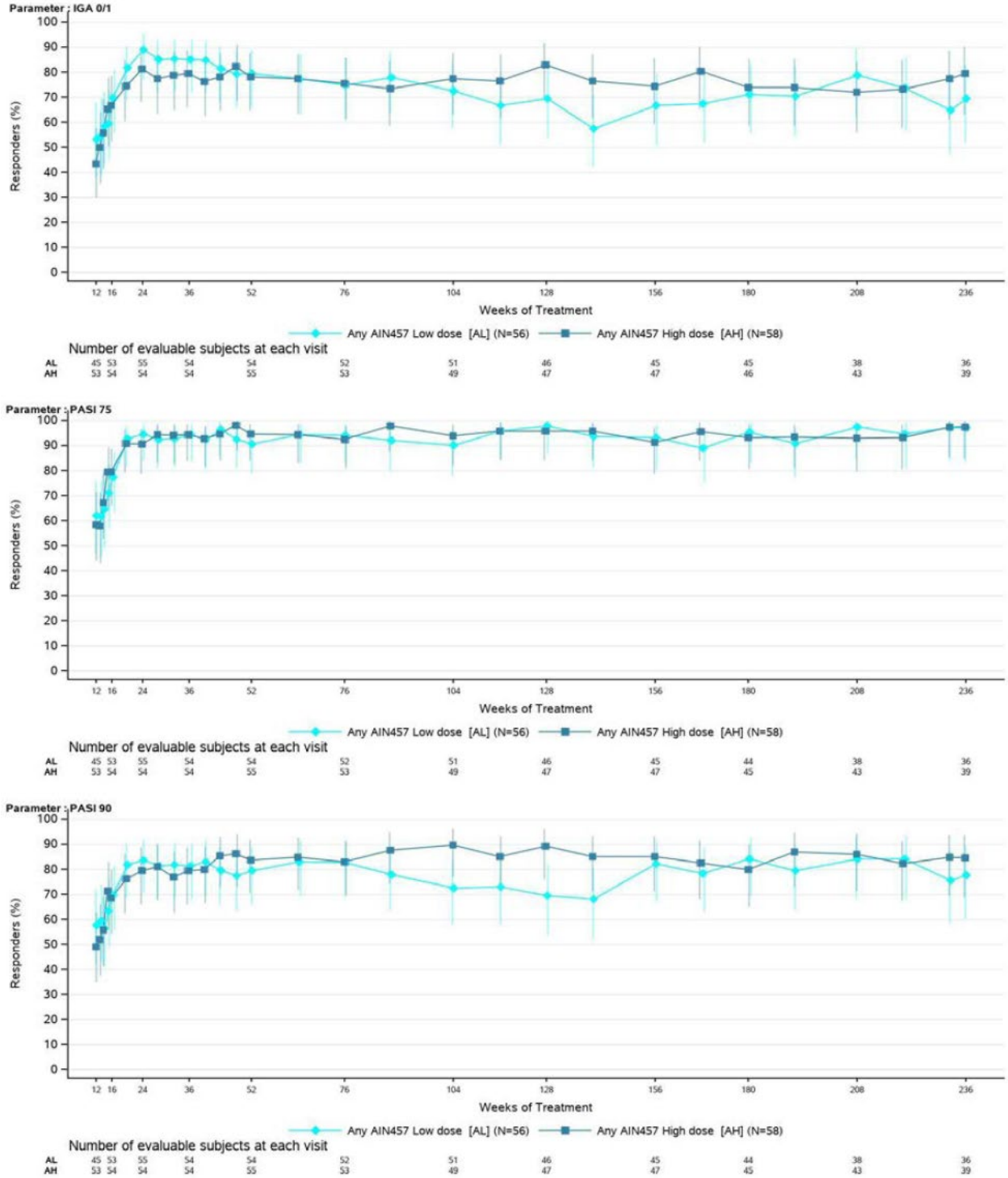
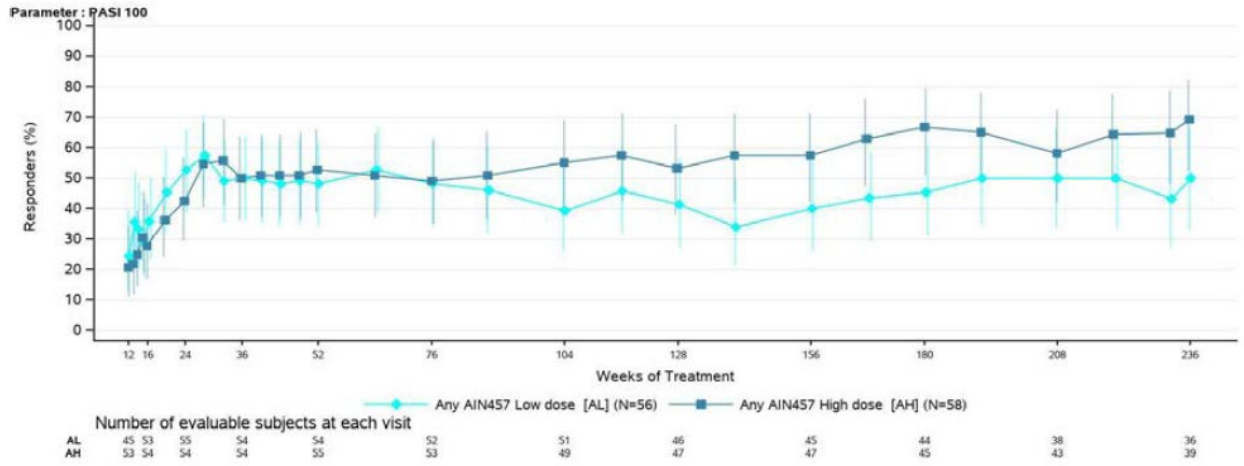


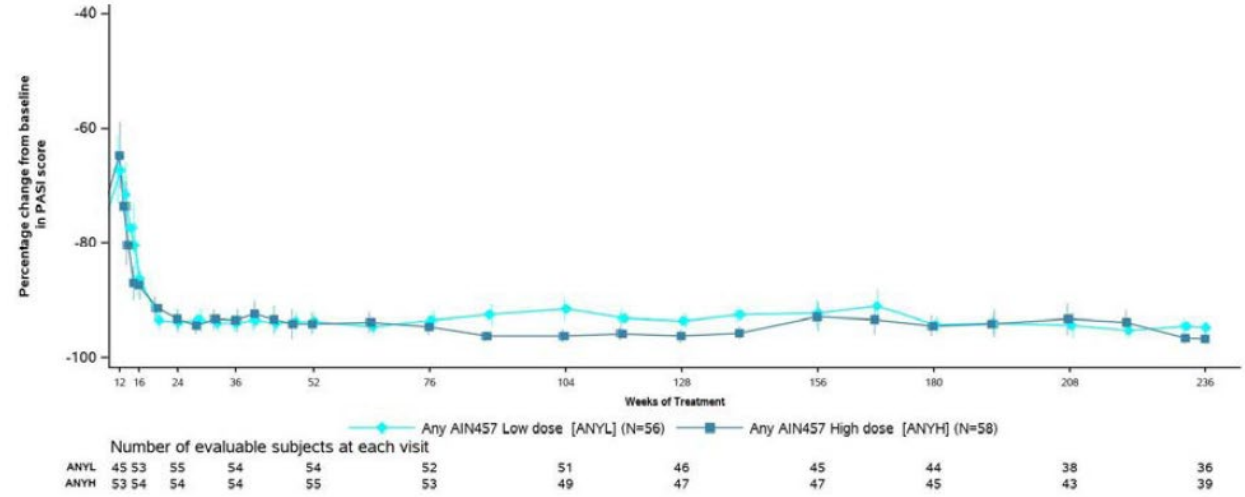
Figure 2 continued Time course of IGA mod 2011 0/1, PASI 75, PASI 90 and PASI 100 responders over time (estimate + 95% CI) (observed cases) – Entire treatment period (Full analysis set)



- N = number of subjects in the treatment arm.
- 95% CI are calculated using the Newcombe method.

During the Entire treatment period, the mean PASI scores in both secukinumab dose groups (Any AIN457 low dose group and Any AIN457 high dose group) continued to decrease (improve) up to Week 52, with similar reductions in both groups (Figure 3). At Week 52, the mean PASI scores decreased from baseline by 94% in both groups, reaching 1.86 in the Any AIN457 low dose group and 1.72 in the Any AIN457 high dose group. The mean PASI score decrease was maintained through the Extension period. At Week 236, the mean PASI score for the Any AIN457 low dose group showed a decrease of 95% from baseline (reaching 1.35 compared to 1.86 at Week 52) and for the Any AIN457 high dose group a decrease of 97% from baseline (reaching 1.22 compared to 1.72 at Week 52).

Figure 3 Time course of percentage change from baseline in PASI score (mean +/- SE) (observed cases) – Entire treatment period (Full analysis set)



- N = number of patients in the treatment arm.

At Week 52, the IGA mod 2011 0/1 (clear to almost clear) response rates were similar between the Any AIN457 low dose group (79.6%) and Any AIN457 high dose group (78.1%). At Week 104, the IGA mod 2011 0/1 response rate was 72.5% in the Any AIN457 low dose group and 77.5% in the Any AIN457 high dose group, i.e. higher in the Any AIN457 high dose group. In contrast, at Week 208, the IGA mod 2011 0/1 response rate was 79.0% in the Any AIN457 low dose group and 72.1% in the Any AIN457 high dose group, i.e. higher in the Any AIN457 low dose group.

Relapses, defined as a situation when the achieved maximal PASI improvement from baseline is reduced by >50%, appeared to occur at a higher frequency in the low dose / Any low dose group (Table 9). However, for this analysis, an evaluable subject was defined as a subject who discontinued/completed treatment and had at least one post baseline PASI assessment before stopping treatment and one PASI assessment after last dose date, implying that later relapses might be captured with lower sensitivity.

Table 9 Number (%) of subjects experiencing relapse events after last study treatment administration Full Analysis set

	AIN457 Low dose N=40			AIN457 High dose N=40		
Parameter	n/m	(%)	95% CI	n/m	(%)	95% CI
Relapse up to Week 4	2/ 37	(5.4)	(0.9, 19.5)	0/ 37	(0.0)	(0.0, 11.7)
Relapse up to Week 8	5/ 37	(13.5)	(5.1, 29.6)	0/ 37	(0.0)	(0.0, 11.7)
Relapse up to Week 12	7/ 37	(18.9)	(8.6, 35.7)	1/ 37	(2.7)	(0.1, 15.8)
Relapse up to Week 16	8/ 37	(21.6)	(10.4, 38.7)	1/ 37	(2.7)	(0.1, 15.8)
Relapse up to Week 20	9/ 37	(24.3)	(12.4, 41.6)	1/ 37	(2.7)	(0.1, 15.8)
Relapse after last study treatment	9/ 37	(24.3)	(12.4, 41.6)	1/ 37	(2.7)	(0.1, 15.8)

	Any AIN457 Low dose N=56			Any AIN457 High dose N=58		
Parameter	n/m	(%)	95% CI	n/m	(%)	95% CI
Relapse up to Week 4	2/ 53	(3.8)	(0.7, 14.1)	0/ 54	(0.0)	(0.0, 8.3)
Relapse up to Week 8	5/ 53	(9.4)	(3.5, 21.4)	0/ 54	(0.0)	(0.0, 8.3)
Relapse up to Week 12	7/ 53	(13.2)	(5.9, 26.0)	1/ 54	(1.9)	(0.1, 11.2)
Relapse up to Week 16	10/ 53	(18.9)	(9.9, 32.4)	2/ 54	(3.7)	(0.6, 13.8)
Relapse up to Week 20	11/ 53	(20.8)	(11.3, 34.5)	2/ 54	(3.7)	(0.6, 13.8)
Relapse after last study treatment	11/ 53	(20.8)	(11.3, 34.5)	2/ 54	(3.7)	(0.6, 13.8)

- n=number of subjects meet criteria, m=number of subjects evaluable.
- Subjects evaluable is defined as subjects who discontinued/completed treatment and had at least one post baseline PASI assessment before stopping treatment AND one PASI assessment after last dose date.
- 95% CI are calculated using the Newcombe method.

Consistent with the Maintenance period results, both secukinumab dose groups had a high proportion of patients achieving CDLQI 0/1 response throughout the Extension period (Table 10).

Table 10 Number (%) of subjects with Child Dermatology Life Quality Index response (CDLQI 0 or 1) by visit (Observed cases) - Entire treatment period (Full Analysis set)

	Any AIN457 Low dose N=56			Any AIN457 High dose N=58		
Visit	n/m	(%)	95% CI	n/m	(%)	95% CI
Week 12	16/ 44	(36.4)	(22.8, 52.3)	19/ 52	(36.5)	(24.0, 51.1)
Week 24	27/ 48	(56.3)	(41.3, 70.2)	25/ 47	(53.2)	(38.2, 67.6)
Week 36	30/ 46	(65.2)	(49.7, 78.2)	26/ 42	(61.9)	(45.7, 76.0)
Week 52	28/ 45	(62.2)	(46.5, 75.8)	31/ 44	(70.5)	(54.6, 82.8)
Week 64	28/ 44	(63.6)	(47.7, 77.2)	22/ 40	(55.0)	(38.7, 70.4)
Week 76	26/ 38	(68.4)	(51.2, 82.0)	23/ 36	(63.9)	(46.2, 78.7)
Week 88	23/ 29	(79.3)	(59.7, 91.3)	23/ 34	(67.6)	(49.4, 82.0)
Week 104	21/ 31	(67.7)	(48.5, 82.7)	21/ 34	(61.8)	(43.6, 77.3)
Week 116	20/ 30	(66.7)	(47.1, 82.1)	22/ 32	(68.8)	(49.9, 83.3)
Week 128	19/ 27	(70.4)	(49.7, 85.5)	17/ 26	(65.4)	(44.4, 82.1)
Week 140	20/ 27	(74.1)	(53.4, 88.1)	17/ 26	(65.4)	(44.4, 82.1)
Week 156	17/ 26	(65.4)	(44.4, 82.1)	16/ 26	(61.5)	(40.7, 79.1)
Week 168	16/ 25	(64.0)	(42.6, 81.3)	14/ 23	(60.9)	(38.8, 79.5)
Week 180	18/ 23	(78.3)	(55.8, 91.7)	14/ 23	(60.9)	(38.8, 79.5)
Week 192	16/ 23	(69.6)	(47.0, 85.9)	13/ 20	(65.0)	(40.9, 83.7)
Week 208	14/ 20	(70.0)	(45.7, 87.2)	15/ 19	(78.9)	(53.9, 93.0)
Week 220	14/ 18	(77.8)	(51.9, 92.6)	10/ 16	(62.5)	(35.9, 83.7)
Week 232	13/ 16	(81.3)	(53.7, 95.0)	12/ 15	(80.0)	(51.4, 94.7)
Week 236	13/ 16	(81.3)	(53.7, 95.0)	8/ 12	(66.7)	(35.4, 88.7)

- n=number of subjects with response, m=number of subjects evaluable.
- 95% CI are calculated using the Newcombe method.

Pharmacokinetic and immunogenicity results

Mean serum concentrations in the secukinumab low and high dose groups from Week 52 onward are presented in Table 11. The mean pre-dose concentrations at all time points showed a dose-proportional increase in exposure to secukinumab from the low dose level to the high dose level.

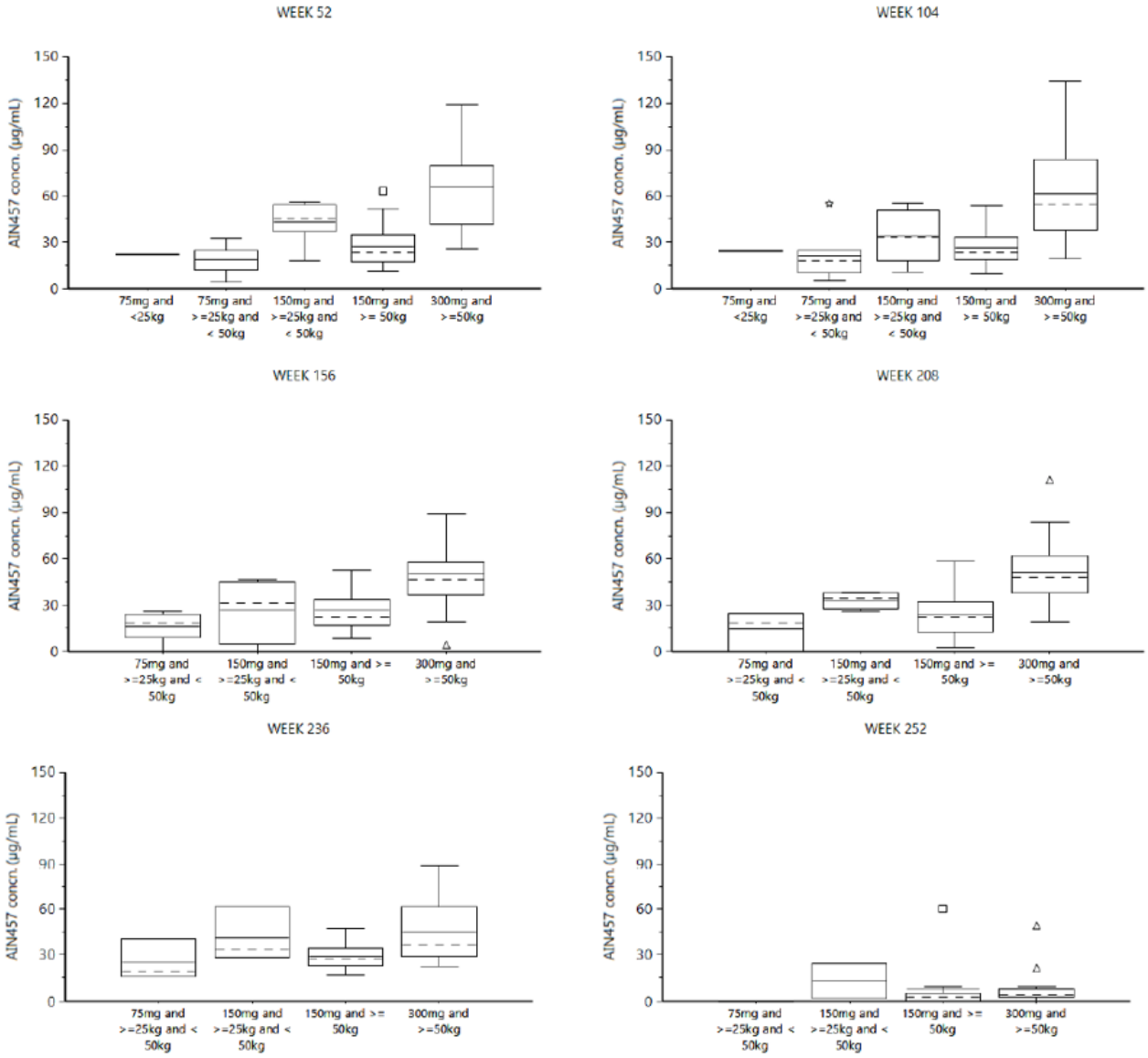
Table 11 Mean (%CV) serum secukinumab concentrations in the secukinumab Low and High dose groups – Entire treatment period (Full analysis set)

	AIN457 Low dose			AIN457 High dose			Placebo–AIN457 Low dose			Placebo – AIN457 High dose		
Week	n	Mean (µg/mL)	CV (%)	n	Mean (µg/mL)	CV (%)	n	Mean (µg/mL)	CV (%)	n	Mean (µg/mL)	CV (%)
52	37	23.7	50.8	34	60.0	45.0	14	22.7	40.6	14	34.4	40.8
104	29	25.2	51.4	30	55.6	54.2	13	21.6	29.4	13	31.7	45.8
156	26	24.1	54.0	34	46.0	48.9	14	25.4	29.9	11	40.3	35.8
208	21	22.5	59.4	31	49.1	40.6	12	23.5	31.5	12	36.4	45.6
236	22	28.6	31.5	28	44.2	43.1	14	24.5	31.6	12	33.8	42.2
252	12	7.14	237.5	21	8.38	133.1	8	4.88	158.3	11	3.24	153.1

* In two placebo patients who switched to secukinumab treatment at Week 12, pre-dose concentration of 10.1 µg/mL and 41.7 µg/mL were observed, respectively. As highlighted in Week 24 PEA study report, a sample mix up cannot be excluded for these cases.

Box plots of serum concentrations of secukinumab at the high and low dose level in the different body-weight categories until Week 252 are shown in Figure 4. Patients who changed dose, as per protocol, following weight group change after Week 12, were included into their new weight/dose group. With a 2-fold increase in the dose in the same body weight category (i.e., 150 mg instead of 75 mg for body weight between 25 and 50 kg and 300 mg, instead of 150 mg for body weights ≥ 50 kg), a dose proportional increase in serum exposure was observed. Further, at most time-points within the Any AIN457 low and the Any AIN457 high dose groups, similar exposure was observed for body weights of 25 to < 50 kg compared with body weights of ≥ 50kg.

Figure 4 Box plots of serum secukinumab concentrations by dose group, visit and body weight category



Solid horizontal line, mean concentration, dashed horizontal line, median concentration. The ends of the "box" are the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5 interquartile range (IQR) of the lower quartile, and the highest value still within 1.5 IQR of the upper quartile, where IQR is the interquartile range (the difference between the third and first quartiles, the middle 50%). Patient's data are summarized according to the actual weight and the dose received. Patients who were affected by IRT dosing error at Week 13 or Week 14 or Week 15 are not included in the summary statistics.

Five patients had treatment-emergent anti-drug antibodies, with titres ranging from 2.5 to 10; in four cases, these were only detected during washout after the last dose, and one of them at Week 236 and during washout at Week 252. No neutralising antibodies were detected in any patient, and no AEs possibly related to immunogenicity were observed. Normal PK, defined as trough concentrations during treatment showing steady-state behaviour and being in the range of concentrations from ADA-negative patients, was observed in four of the ADA positive patients; in one patient (a [6-17]-year old), steady state behaviour was not seen at Weeks 104 and 156, with trough concentrations being variable and lower than the range of concentrations among ADA-negative patients (i.e., 21.5 ug/mL at Week 52, 5.2 ug/mL at Week 104 and 12.5 ug/mL at Week 156).

Safety results

During the Entire treatment period, all 114 (100%) patients in the secukinumab treatment groups received the study treatment. The median (range) duration of exposure during the Entire treatment period was 1576.5 (9 - 1674) days in the Any AIN457 low dose group and 1651.0 (15 - 1680) days in the Any AIN457 high dose group. The cumulative exposure across the secukinumab treatment groups was 215.9 patient-years in the Any AIN457 low dose group and 220.1 patient-years in the Any AIN457 high dose group (i.e., 435.95 patient-years in the Any AIN457 dose group).

Overall, 49 (87.5%) patients from the Any AIN457 low dose group and 53 (91.4%) patients from the Any AIN457 high dose group had treatment-emergent AEs (Table 12). Consistent with the Week 24 and Week 52 analyses, the Infections and infestations SOC was the most commonly affected SOC across the Entire treatment period. The incidence of AEs in this SOC was similar in the Any AIN457 high dose group (75.9%) and the Any AIN457 low dose group (76.8%). Nasopharyngitis and cough were reported more frequently in the Any AIN457 high dose group, while tonsilitis was more frequently reported in the Any AIN457 low dose group (Table 13).

Table 12 Absolute and relative frequencies for treatment-emergent adverse events, by primary system organ class - Entire treatment period (Safety set)

Primary system organ class	Any AIN457 Low dose N=56 n (%)	Any AIN457 High dose N=58 n (%)	Any AIN457 dose N=114 n (%)
Any primary system organ class	49 (87.5)	53 (91.4)	102 (89.5)
Infections and infestations	43 (76.8)	44 (75.9)	87 (76.3)
Gastrointestinal disorders	20 (35.7)	24 (41.4)	44 (38.6)
Skin and subcutaneous tissue disorders	22 (39.3)	21 (36.2)	43 (37.7)
Respiratory, thoracic and mediastinal disorders	12 (21.4)	20 (34.5)	32 (28.1)
General disorders and administration site conditions	13 (23.2)	18 (31.0)	31 (27.2)
Nervous system disorders	14 (25.0)	13 (22.4)	27 (23.7)
Injury, poisoning and procedural complications	11 (19.6)	14 (24.1)	25 (21.9)
Investigations	14 (25.0)	11 (19.0)	25 (21.9)
Musculoskeletal and connective tissue disorders	9 (16.1)	10 (17.2)	19 (16.7)
Reproductive system and breast disorders	6 (10.7)	8 (13.8)	14 (12.3)
Blood and lymphatic system disorders	7 (12.5)	3 (5.2)	10 (8.8)
Renal and urinary disorders	5 (8.9)	5 (8.6)	10 (8.8)
Eye disorders	2 (3.6)	6 (10.3)	8 (7.0)
Psychiatric disorders	5 (8.9)	1 (1.7)	6 (5.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (3.6)	3 (5.2)	5 (4.4)
Vascular disorders	2 (3.6)	3 (5.2)	5 (4.4)
Immune system disorders	1 (1.8)	3 (5.2)	4 (3.5)
Metabolism and nutrition disorders	1 (1.8)	3 (5.2)	4 (3.5)
Cardiac disorders	3 (5.4)	0 (0.0)	3 (2.6)
Ear and labyrinth disorders	2 (3.6)	1 (1.7)	3 (2.6)
Hepatobiliary disorders	1 (1.8)	0 (0.0)	1 (0.9)
Social circumstances	1 (1.8)	0 (0.0)	1 (0.9)

- Primary system organ classes are sorted in decreasing order of frequency in Any AIN457 dose column.
- A subject with multiple AEs within a primary system organ class is counted only once in the Any AIN457 dose.
- MedDRA version 26.0 was used for reporting.

Table 13 Most frequent (>=5.0%, in any treatment group) treatment-emergent adverse events, by preferred term - Entire treatment period (Safety set)

Preferred term	Any AIN457 Low dose N=56 n (%)	Any AIN457 High dose N=58 n (%)	Any AIN457 dose N=114 n (%)
Any preferred term	49 (87.5)	53 (91.4)	102 (89.5)
Nasopharyngitis	17 (30.4)	25 (43.1)	42 (36.8)
Headache	11 (19.6)	11 (19.0)	22 (19.3)
Tonsillitis	11 (19.6)	7 (12.1)	18 (15.8)
Pharyngitis	9 (16.1)	8 (13.8)	17 (14.9)
Diarrhoea	7 (12.5)	7 (12.1)	14 (12.3)
Acne	8 (14.3)	5 (8.6)	13 (11.4)
Cough	4 (7.1)	9 (15.5)	13 (11.4)
Rhinitis	5 (8.9)	7 (12.1)	12 (10.5)
Glomerular filtration rate decreased	7 (12.5)	4 (6.9)	11 (9.6)
Abdominal pain	4 (7.1)	6 (10.3)	10 (8.8)
Oropharyngeal pain	4 (7.1)	6 (10.3)	10 (8.8)
Pyrexia	4 (7.1)	6 (10.3)	10 (8.8)
Upper respiratory tract infection	7 (12.5)	3 (5.2)	10 (8.8)
Abdominal pain upper	4 (7.1)	5 (8.6)	9 (7.9)
Arthralgia	4 (7.1)	5 (8.6)	9 (7.9)
Bronchitis	3 (5.4)	6 (10.3)	9 (7.9)
COVID-19	4 (7.1)	5 (8.6)	9 (7.9)
Eczema	3 (5.4)	5 (8.6)	8 (7.0)
Gastroenteritis	5 (8.9)	3 (5.2)	8 (7.0)
Pruritus	3 (5.4)	5 (8.6)	8 (7.0)
Psoriasis	7 (12.5)	1 (1.7)	8 (7.0)
Conjunctivitis	2 (3.6)	5 (8.6)	7 (6.1)
Folliculitis	3 (5.4)	4 (6.9)	7 (6.1)
Respiratory tract infection	3 (5.4)	4 (6.9)	7 (6.1)
Urinary tract infection	5 (8.9)	2 (3.4)	7 (6.1)
Viral upper respiratory tract infection	3 (5.4)	4 (6.9)	7 (6.1)
Aspartate aminotransferase increased	2 (3.6)	4 (6.9)	6 (5.3)
Fatigue	3 (5.4)	3 (5.2)	6 (5.3)
Gastrointestinal infection	2 (3.6)	4 (6.9)	6 (5.3)
Seborrhoeic dermatitis	2 (3.6)	4 (6.9)	6 (5.3)
Sinusitis	4 (7.1)	2 (3.4)	6 (5.3)
Vomiting	1 (1.8)	5 (8.6)	6 (5.3)
Dysmenorrhoea	1 (1.8)	4 (6.9)	5 (4.4)
Oral herpes	3 (5.4)	2 (3.4)	5 (4.4)
Pharyngotonsillitis	4 (7.1)	1 (1.7)	5 (4.4)
Toothache	1 (1.8)	4 (6.9)	5 (4.4)
Asthenia	1 (1.8)	3 (5.2)	4 (3.5)
Contusion	1 (1.8)	3 (5.2)	4 (3.5)
Dental caries	1 (1.8)	3 (5.2)	4 (3.5)
Gastroenteritis viral	3 (5.4)	1 (1.7)	4 (3.5)
Influenza	4 (7.1)	0 (0.0)	4 (3.5)
Intertrigo	3 (5.4)	1 (1.7)	4 (3.5)
Nasal congestion	3 (5.4)	1 (1.7)	4 (3.5)
Neutropenia	3 (5.4)	1 (1.7)	4 (3.5)
Paronychia	1 (1.8)	3 (5.2)	4 (3.5)
Eosinophilia	3 (5.4)	0 (0.0)	3 (2.6)

Table 13, cont'd Most frequent (>=5.0%, in any treatment group) treatment-emergent adverse events, by preferred term - Entire treatment period (Safety set)

Preferred term	Any AIN457 Low dose N=56 n (%)	Any AIN457 High dose N=58 n (%)	Any AIN457 dose N=114 n (%)
Epistaxis	0 (0.0)	3 (5.2)	3 (2.6)
Impetigo	0 (0.0)	3 (5.2)	3 (2.6)
Menstruation irregular	0 (0.0)	3 (5.2)	3 (2.6)

- Preferred terms are sorted in descending order of frequency in the Any AIN457 dose column.
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- MedDRA version 26.0 was used for reporting.

The majority of the AEs were of mild to moderate severity with comparable incidence across the Any AIN457 low dose group and the Any AIN457 high dose group (Mild: 30.4% vs. 29.3%; Moderate: 48.2% vs. 46.6%, respectively). The incidence of severe AEs reported in the Any AIN457 low dose group was lower compared to the AIN457 high dose group (8.9% vs. 15.5%, respectively).

In the Any AIN457 low dose group the following severe events were reported (n = 1 each; 1.8%): dental caries, pharyngitis, bronchitis, gastrointestinal infection, cellulitis, multiple injuries, psoriatic arthropathy, nasal obstruction, and nasal septum deviation. In the Any AIN457 high dose group the following severe events were reported (n = 1 each; 1.7%): lymphadenopathy, photoelectric conjunctivitis, abdominal hernia, Crohn's disease, therapy non-responder, gingivitis, pneumonia, enterocolitis bacterial, infectious pleural effusion, lung abscess, tinea pedis, toxic shock syndrome, increased aspartate aminotransferase (AST), thrombophlebitis, venous thrombosis limb.

No deaths were reported during the entire study duration. Non-fatal SAEs occurred with similar frequency across both treatment groups (12.5% and 13.8% for Any AIN457 low dose and Any AIN457 high dose, respectively). The AEs leading to treatment discontinuation for the Entire treatment period were also comparable in both treatment groups (Table 14).

Table 14 Deaths, other serious adverse events and adverse event -related discontinuations – Entire treatment period (Safety set)

	Any AIN457 Low dose N=56 n (%)	Any AIN457 High dose N=58 n (%)	Any AIN457 dose N=114 n (%)
Subjects with AE(s)	49 (87.5)	53 (91.4)	102 (89.5)
Subjects with serious or other significant events			
Death	0 (0.0)	0 (0.0)	0 (0.0)
Non-fatal SAE(s)	7 (12.5)	8 (13.8)	15 (13.2)
Discontinued study treatment due to any AE(s)	4 (7.1)	3 (5.2)	7 (6.1)

The frequencies of SAEs together with exposure-adjusted incidence rates are displayed in Table 15.

Table 15 Exposure adjusted incidence rates for treatment-emergent serious adverse events, by preferred term - Entire treatment period (Safety set)

Preferred term	Any AIN457 Low dose N=56 n/EX (IR)	Any AIN457 High dose N=58 n/EX (IR)	Any AIN457 dose N=114 n/EX (IR)
Any preferred term	7/2.07 (3.4)	8/2.04 (3.9)	15/4.11 (3.7)
Abdominal hernia	0/2.16 (0.0)	1/2.17 (0.5)	1/4.33 (0.2)
Alanine aminotransferase increased	1/2.15 (0.5)	0/2.20 (0.0)	1/4.35 (0.2)
Arthritis reactive	1/2.16 (0.5)	0/2.20 (0.0)	1/4.36 (0.2)
Bronchitis	1/2.15 (0.5)	0/2.20 (0.0)	1/4.35 (0.2)
Cellulitis	1/2.13 (0.5)	0/2.20 (0.0)	1/4.33 (0.2)
Clavicle fracture	0/2.16 (0.0)	1/2.16 (0.5)	1/4.32 (0.2)
Concussion	0/2.16 (0.0)	1/2.20 (0.5)	1/4.35 (0.2)
Contusion	0/2.16 (0.0)	1/2.20 (0.5)	1/4.35 (0.2)
Enterocolitis bacterial	0/2.16 (0.0)	1/2.16 (0.5)	1/4.32 (0.2)
Infectious pleural effusion	0/2.16 (0.0)	1/2.16 (0.5)	1/4.32 (0.2)
Lactose intolerance	0/2.16 (0.0)	1/2.18 (0.5)	1/4.34 (0.2)
Lung abscess	0/2.16 (0.0)	1/2.16 (0.5)	1/4.32 (0.2)
Lymphadenopathy	0/2.16 (0.0)	1/2.19 (0.5)	1/4.35 (0.2)
Major depression	1/2.16 (0.5)	0/2.20 (0.0)	1/4.36 (0.2)
Non-cardiac chest pain	0/2.16 (0.0)	1/2.20 (0.5)	1/4.35 (0.2)
Pneumonia	0/2.16 (0.0)	1/2.16 (0.5)	1/4.32 (0.2)
Psoriatic arthropathy	1/2.16 (0.5)	0/2.20 (0.0)	1/4.36 (0.2)
Suicidal ideation	1/2.16 (0.5)	0/2.20 (0.0)	1/4.36 (0.2)
Testicular torsion	1/2.12 (0.5)	0/2.20 (0.0)	1/4.32 (0.2)
Thrombophlebitis	0/2.16 (0.0)	1/2.16 (0.5)	1/4.32 (0.2)
Toxic shock syndrome	0/2.16 (0.0)	1/2.20 (0.5)	1/4.36 (0.2)
Venous thrombosis limb	0/2.16 (0.0)	1/2.16 (0.5)	1/4.32 (0.2)

- Preferred terms are sorted decreasing order of IR in Any AIN457 dose column.
- A subject with multiple serious AE under one treatment is counted only once for that treatment.
- EX=exposure in 100 subject years. IR=incidence rate per 100 subject years.
- For subjects with event, exposure time is censored at time of first event.
- MedDRA version 26.0 was used for reporting.

Major depression and suicidal ideation were reported in a [6-17]-year old in the low dose group. Depression of moderate intensity was reported on Day 185, and on Day 239, the patient was suspected with mental disorder and behaviour disorder (both moderate).The patient was hospitalised. She was treated and study medication was permanently discontinued due to the events. The patient had a follow up consultation 62 days after the last dose of study medication, and it was noted that signs and symptoms of depression had decreased; 138 days after the last dose of study medication, mental disorder, behaviour disorder, suicidal ideation, and major depression were reported as resolved. The Investigator reported that the underlying psoriasis affected the social life of the patient. The Investigator suspected a relationship between mental disorder, behaviour disorder, suicidal ideation, major depression, and the study medication.

Data related to safety topics of interest (including important identified and potential risks in the Risk Management Plan for secukinumab) are summarised in Table 16.

Table 16 Absolute and relative frequencies for important identified and potential risks (level 1 and level 2) based on all adverse events – Entire treatment period (Safety set)

Risk category Risk name Level 1 Level 2	Any AIN457 Low dose N=56 n (%)	Any AIN457 High dose N=58 n (%)	Any AIN457 dose N=114 n (%)
Important identified risks			
Hypersensitivity			
Hypersensitivity (SMQ) (narrow)	6 (10.7)	13 (22.4)	19 (16.7)
Infections			
Infections and infestations (SOC)	43 (76.8)	44 (75.9)	87 (76.3)
Neutropenia			
Neutropenia (NMQ) (narrow)	3 (5.4)	1 (1.7)	4 (3.5)
Important potential risks			
Hepatitis B reactivation			
Hepatitis viral infections (HLT)	0 (0.0)	0 (0.0)	0 (0.0)
Inflammatory Bowel Disease_PS			
Inflammatory bowel disease (NMQ) (narrow)	0 (0.0)	1 (1.7)	1 (0.9)
Interactions with live vaccines			
Vaccination related complications (HLT)	0 (0.0)	1 (1.7)	1 (0.9)
Major adverse cardiovascular events (MACE)			
MACE (Myocardial infarction, Stroke, Cardiovascular death) (NMQ)	0 (0.0)	0 (0.0)	0 (0.0)
Malignant or unspecified tumours			
Malignant or unspecified tumours (SMQ)	0 (0.0)	0 (0.0)	0 (0.0)
Suicidal ideation and behavior			
Suicide/self-injury (SMQ)	1 (1.8)	0 (0.0)	1 (0.9)

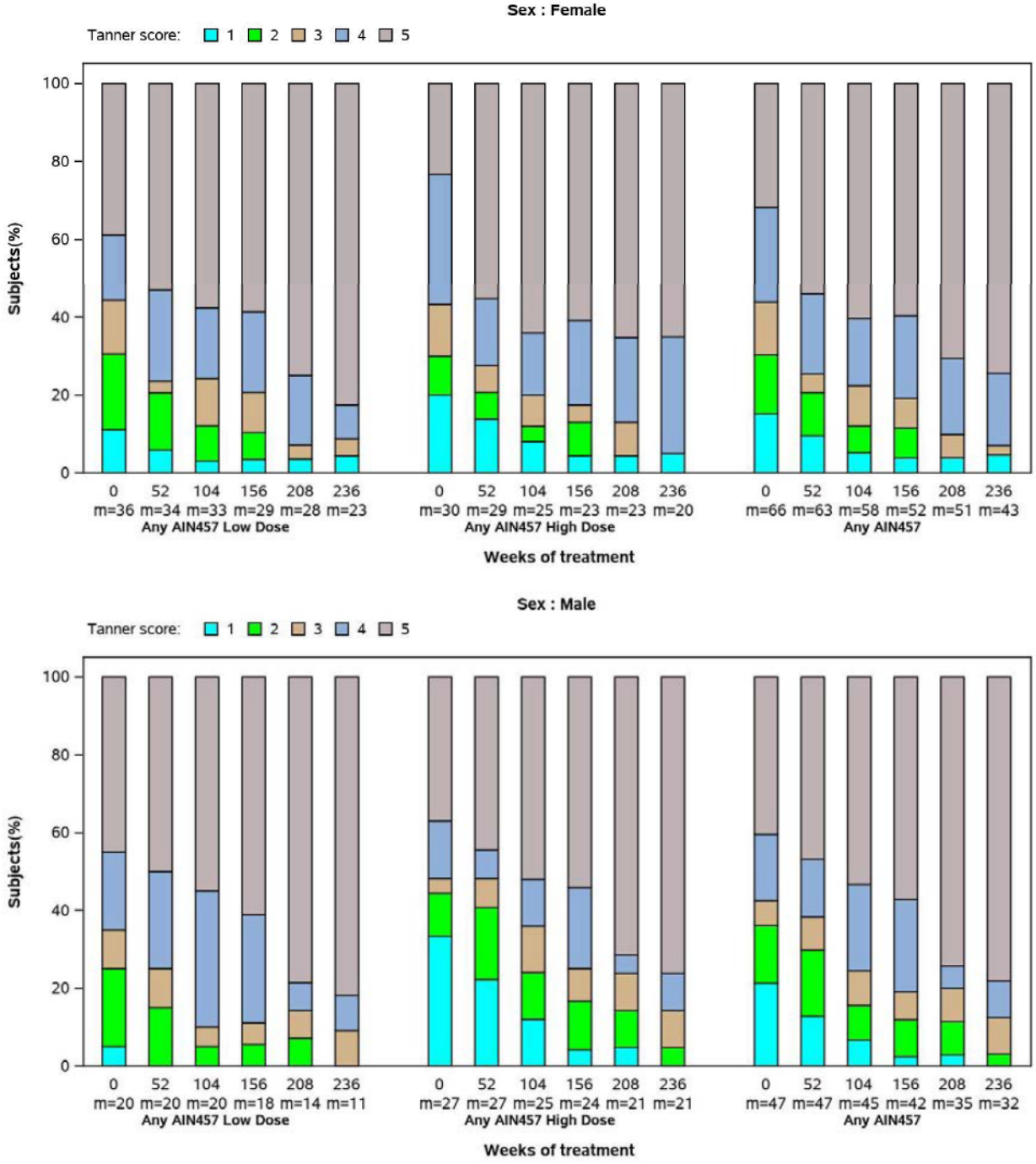
- Risk category, risk name are sorted alphabetically, and Level 1 is sorted within risk name in descending order of frequency in the Any AIN457 dose column.
- A subject with multiple occurrences of a level under one treatment is counted only once for the same risk for that treatment.
- MedDRA version 26.0 and NMQs as of 12-Jan-2021 have been used for reporting.

Newly occurring or worsening laboratory abnormalities in haematology parameters were CTCAE grade 1 or 2, except for one patient in the Any AIN457 low dose group with grade 3 decrease in the absolute neutrophil count and 2 patients in the Any AIN457 high dose group with grade 3 decrease in the absolute lymphocyte count. The most commonly reported haematology abnormalities were grade 1 decrease in leukocytes (30.3% for Any AIN457 dose), grade 1 decrease in haemoglobin (27.1% for Any AIN457 dose) and grade 1 decrease in neutrophils (21.1% for Any AIN457 dose).

For clinical chemistry, laboratory abnormalities were CTCAE grade 1 or 2, except for one patient in the Any AIN457 low dose group with grade 3 increase in bilirubin and 1 patient in the Any AIN457 high dose group with grade 3 increase in aspartate aminotransferase. The most commonly reported chemistry abnormalities were grade 1 increase in alanine aminotransferase (28.2% for Any AIN457 dose), grade 1 increase in aspartate aminotransferase (20.4% for Any AIN457 dose) and grade 1 increase in creatinine (15.6% for Any AIN457 dose).

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 5.

Figure 5 Changes in percentages of subjects in Tanner staging scores over time, by gender and treatment - Entire treatment period (Safety set)



- m=Number of patients evaluable.
- The tanner staging scores based on the higher score between breast development and public hair assessments for female and the higher sore between genital stage and pubic hair assessments for males are plotted.
- Once a subject reached tanner stage 5 at specific visit, subsequent evaluable missing visits were imputed as tanner stage 5.

2.3.3. Discussion on clinical aspects

The long-term follow-up for Study CAIN457A2310 has been completed, with results summarised by the MAH in the Full Clinical Study Report provided as a P46 submission.

The effects observed at earlier time points of the study seem to be well maintained in patients continuing on secukinumab for the full duration of the study, and no concerning trends are identified either on variables related to disease activity or health-related quality of life. This conclusion has to be made with the caveat that that long-term results have only been provided on an observed case basis, and lack of efficacy was reported as the most common reason for discontinuing the study. Nevertheless, a very reasonable proportion of patients completed the Extension phase in both treatment groups.

Similar to results seen in the earlier analyses, the added benefit of the high dose appeared quite limited. As such, the current dosing recommendations in the SmPC seem to be supported also by the long-term analyses.

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. One event of major depression and suicidal ideation is noted among the SAEs. Suicidal ideation and behaviour is identified as an important potential risk for secukinumab and is monitored as part of Periodic Safety Updates. For this single event, no further conclusions can be made. No adverse effect on sexual maturation is discernible on repeated Tanner staging.

No unexpected trends were observed on long-term pharmacokinetic characteristics based on through concentrations from a sparse sampling schedule. The immunogenic potential of secukinumab appeared to be low also on long-term use.

3. CHMP overall conclusion and recommendation

The reported final long-term results from Study CAIN457A2310 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 are identified based on observed case analyses. It can be agreed with the MAH that the reported results warrant no changes to the current SmPC.

☒ 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