EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cosentyx

International non-proprietary name: secukinumab

Procedure No. EMEA/H/C/003729/II/0057

Note

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

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List of abbreviations

ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Events of Special Interest
AIN457	Secukinumab ("phonebook code")
ALP	Alkaline Phosphatase
ALT	Alanine amino Transferase
AR	Assessment Report
AS	Ankylosing Spondylitis
AST	Aspartate amino Transferase
CDLQI	Children's Dermatology Life Quality Index
CHAQ	Childhood Health Assessment Questionnaire
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
e.g.	for example (*exempli gratia*)
EAIR	Exposure Adjusted Incidence Rate
EC	European Commission
ECG	Electrocardiogram
eGFR	estimated Glomerular Filtration Rate
ELISA	Enzyme Linked Immunosorbent Assay
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
HIV	Human Immunodeficiency Virus
i.e.	that is (*id est*)
IGA	Investigator´s Global Assessment
IGA mod 2011	Novartis Investigators´s Global Assessment modified 2011
IgG1	Immunoglobulin G1
IL-17A	Interleukin 17A
IRT	Interactive Response Technology
IWRS	Interactive Web Response System
KBE	Key Binding Element
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
MACE	Major Adverse Cardiovascular Events
MAH	Marketing Authorisation Holder
MAP	Meta-Analytic-Predictive
MAR	Missing At Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation

MRI	Magnetic Resonance Imaging
NMQ	Novartis customised MedDRA Query
NPDE	Normalised Prediction Distribution Error
Nr-Ax-Spa	Non-radiographic Axial Spondylarthritis
OR	Odds Ratio
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamics
PDCO	Paediatric Committee
PI	Product Information
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
PK/PD	Pharmacokinetic/Pharmacodynamic
PL	Package Leaflet
PRO	Patient Reported Outcome
PsA	Psoriatic Arthritis
Pso	Plaque psoriasis
PSUR	Periodic Safety Update Report
PT	Preferred Term
PY	Patient Year
QFT	QuantiFERON TB-Gold test
RMP	Risk Management Plan
RSI	Request for Supplementary Information
s.c.	Subcutanous(ly)
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TBL	Total Bilirubin
TCS	Topical Corticosteroid
TEAE	Treament Emergent Adverse Event
Th17	T Helper 17 cells
ULN	Upper Limit of Normal
UV	Ultraviolet
WBC	White Blood Cell

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 12 November 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy for Cosentyx;
as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated. Section 6.6 of the SmPC for the solution for injection is also updated.
The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. The RMP version 6.0 has also been submitted. Furthermore, the Annex II is brought in line with the latest QRD template version 11.0.

The variation requested amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0352/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0352/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Tuomo Lapveteläinen Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	12 November 2019
Start of procedure:	30 November 2019
CHMP Rapporteur Assessment Report	21 January 2020
PRAC Rapporteur Assessment Report	27 January 2020
PRAC members comments	5 February 2020
Updated PRAC Rapporteur Assessment Report	6 February 2020
PRAC Outcome	13 February 2020
CHMP members comments	17 February 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 February 2020
Request for supplementary information (RSI)	27 February 2020
CHMP Rapporteur Assessment Report	28 Apr 2020
PRAC Rapporteur Assessment Report	29 Apr 2020
PRAC members comments	06 May 2020
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	14 May 2020
CHMP members comments	18 May 2020
Updated CHMP Rapporteur Assessment Report	20 May 2020
2nd Request for supplementary information	28 May 2020
CHMP Rapporteur Assessment Report	10 June 2020
CHMP members comments	15 June 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 June 2020
Opinion	25 June 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Psoriasis is a multifactorial skin disorder, caused by the combined action of multiple disease genes, and is also triggered by environmental factors. T-cells are clearly involved, as psoriasis responds to treatment with calcineurin inhibitors, which inhibit T-cell activity (*e.g.*, cyclosporine, tacrolimus). Successful psoriasis therapy correlates with inhibition of IL-17 signalling and is seen, *e.g.*, after IL-17A blockade with secukinumab, and it can therefore be concluded that IL-17A contributes to the disease process.

Psoriasis is one of the most common human skin diseases affecting 2 to 3% of the general population. Plaque psoriasis affects 80% to 90% of all psoriasis patients of all age groups and is also the most common variant of the disease in paediatric patients. Most children manifest with plaque psoriasis in patterns similar to adult patients, and it is accepted that paediatric and adult psoriasis represent manifestations of the same disease process, as opposed to being distinct disease entities.

Disease prevalence in children varies depending on study population and age, with 1% as a commonly quoted figure. Worldwide, the incidence of paediatric psoriasis is increasing, affecting up to 2% of children in some populations. In Europe, psoriasis is reported to affect 0.5-1% of children, and chronic plaque psoriasis is also common among adolescents.

According to the MAH, the prevalence of psoriasis in children under 6 years is very low (with the highest prevalence published of 0.3%), and the proportion of children with a severe condition in need of a systemic treatment is 4%, giving a final prevalence of the condition to be about 1 per 10,000 in this age group.

The indication initially proposed by the MAH was as follows:

Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy.

The following weight-tiered posology was initially proposed:

The recommended dose is based on body weight (Table 1) and administered by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Each 75 mg dose is given as 1 subcutaneous injection of 75 mg. Each 150 mg dose is given as 1 subcutaneous injection of 150 mg. Each 300 mg dose is given as 2 subcutaneous injections of 150 mg.

Table 1. Recommended dose for paediatric plaque psoriasis

Body weight at time of dosing	*Recommended Dose*
<25 kg	*75 mg*
25 to <50 kg	*75 mg (*may be increased to 150 mg)*
≥50 kg	*150 mg (*may be increased to 300 mg)*

**Some patients may derive additional benefit from the higher dose.*

Management

Topical treatments are the mainstay of therapeutic approaches in paediatric psoriasis, and a significant proportion of patients can be adequately treated with topical therapies such as emollients, vitamin D analogues, corticosteroids or calcineurin inhibitors. Various forms of phototherapy are also successfully used in many patients. Available systemic treatments include methotrexate, cyclosporine and retinoids. It should however be recognised that many of these products have no formal authorisation for use in paediatric psoriasis and can be associated with significant safety concerns. In this respect, and apart from the better studied biological agents, paediatric psoriasis patients can still be considered a significantly underserved patient population.

Three biological agents are currently authorised in the EU for the treatment of plaque psoriasis in the paediatric population: etanercept (authorised in 2009), adalimumab (authorised in 2015), and ustekinumab (authorised in 2015). Etanercept is currently authorised for severe disease from 6 years of age; adalimumab is authorised for severe disease from 4 years of age, and ustekinumab is authorised for moderate to severe disease from 6 years of age. All three products are authorised as second-line therapies, for use in patients who are inadequately controlled by or are intolerant to other systemic therapies or phototherapies (the exact wording varies slightly by individual product).

On 28 May 2020, the CHMP adopted a positive opinion for the following new indication for Taltz (ixekizumab) another medicinal product targeting IL-17: "Paediatric plaque psoriasis: Taltz is indicated for the treatment of moderate to severe plaque psoriasis in children from the age of 6 years and with a body weight of at least 25 kg and adolescents who are candidates for systemic therapy."

2.1.2. About the product

Cosentyx (secukinumab) is a fully human monoclonal anti-human interleukin-17A (IL-17A) antibody of the Immunoglobulin G1 (IgG1)/κ-class. It binds to IL-17A and neutralises the activity of this cytokine. Cosentyx was initially approved in the EU on 15 January 2015 for the treatment of plaque psoriasis (Pso) in adult patients (procedure EMEA/H/C/003729). Indications for psoriatic arthritis (PsA) and ankylosing spondylitis (AS) were approved on 19 November 2015, and an extension of indication application for non-radiographic axial spondyloarthritis (Nr-Ax-Spa) was approved on 28 April 2020 (procedure EMEA/H/C/003729/II/0053/G). Cosentyx is currently approved in over 90 countries worldwide.

The currently approved adult psoriasis indication and posology read as follows:

Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Each 300 mg dose is given as two subcutaneous injections of 150 mg.

2.1.3. The development programme

The main studies within the submission are:

- Study A2310, an ongoing randomised, double-blind, placebo- and etanercept -controlled study in paediatric patients 6-17 years of age with severe plaque psoriasis. An interim study report,

containing efficacy data until Week 52 as well as summaries of safety data over various periods of time in study, including a summary of all safety data until data cut-off, has been provided.

- Study A2311, an ongoing randomised, open-label study with a historical placebo control in paediatric patients 6-17 years of age with moderate to severe plaque psoriasis. An interim study report, containing efficacy data until Week 24 and a summary of all safety data until last data cut-off has been provided.

The above studies were conducted in line with the agreed PIP (studies 3 and 4 of the PIP). Study 5 of the PIP is not yet completed and is not referenced in the application.

An extensive extrapolation/modelling/simulation package was also submitted to support the full indication and posology being applied for.

Severe psoriasis criteria were agreed with PDCO during the psoriasis PIP discussions and subsequently moderate psoriasis criteria were defined. These severity definitions are used in both ongoing paediatric studies for psoriasis and in the adult data comparison. The disease severity classification is outlined in Table 1.

Table 1 ***Definition of psoriasis severity by IGA mod 2011 and PASI score***

IGA	PASI score	Psoriasis severity
3	12-< 20	Moderate
3	≥ 20	Moderate
4	12-< 20	Moderate
4	≥ 20	Severe

- IGA = Investigator's global assessment
- PASI = Psoriasis area and severity index

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

The two non-clinical studies included in the PIP were assessed in connection with the adult psoriasis indication as part of the initial marketing authorisation:

- Study 1: Fertility and early embryonic development (FEED) study in mice using a surrogate antibody.
- Study 2: Peri- and postnatal study in mice using a surrogate antibody.

2.2.1. Ecotoxicity/environmental risk assessment

As a monoclonal antibody, secukinumab is exempt from testing in accordance with the current CHMP guideline (CHMP/SWP/4447/00) on environmental risk assessment.

2.2.2. Discussion on non-clinical aspects

Previously conducted non-clinical studies submitted in support of the marketing authorisation of secukinumab are considered adequate and sufficient to support the extension of indication to children and adolescents from the age of 6 years of age for the treatment of moderate to severe plaque psoriasis.

The reproductive and developmental toxicity studies in mice and in cynomolgus monkeys indicate that reproduction or growth and development of the offspring after exposure during gestation period are unaffected by inhibition of IL-17A. In mice, there were no adverse effects on the reproductive function, fertility and early embryonic development. Also, in the mouse pre- and post-natal developmental toxicity study, there were no BZN035-related effects on F0 generation, nor were there any effects on survival, growth, development, behaviour or reproductive performance on the F1 offspring. However, pharmacology-related changes were observed in lymphocyte populations in the thymus, spleen and blood on the F1 generation. No effects were observed in the F2 generation. In cynomolgus monkeys, maternal toxicity, embryo-foetal toxicity or teratogenicity were not observed. Collectively, the preclinical data reveal no hazard to reproduction, growth or development, and indicate no difference in safety profile in adult and juvenile animals.

2.2.3. Conclusion on the non-clinical aspects

No concerns have been raised based on preclinical data. Section 5.3 of the SmPC has been updated to indicate that the preclinical safety data support use in both adults and children which was acceptable to CHMP.

2.3. Clinical aspects

2.3.1. Introduction

This submission includes data from two ongoing studies: 1) a clinical study report from an ongoing randomised, placebo- and etanercept-controlled Phase 3 study (A2310) assessing the efficacy, safety and tolerability of two dosages of secukinumab, administered subcutaneously according to a weight-tiered regimen, in paediatric patients with severe plaque psoriasis, and 2) a clinical study report of Week 24 data from an ongoing randomised, open-label trial (A2311) assessing the efficacy, safety and tolerability of two dosages of secukinumab in paediatric patients with moderate to severe chronic plaque psoriasis. In addition, data from an extrapolation/modelling/simulation approach, using data from the secukinumab development program in adult psoriasis along with PK, efficacy and safety data from study A2310 is provided to support the full indication being applied for.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies:

Table 2 ***Overview of key studies and sources of data***

Source of data	Details
Phase III controlled study in the target indication	Study A2310: a randomised, double-blind, placebo- and etanercept controlled study conducted in severe paediatric patients
Supportive study in the target indication	Study A2311: a randomised, open-label study with a historical control group, conducted in moderate to severe paediatric patients

Source of data	Details
Dose selection studies	Phase II/III studies in adults and modeling and simulation. These studies are not presented here. No specific dose selection studies were carried out in paediatric population
Supportive studies	Studies A2302, A2303, A2308, A2309 (adult pool): four randomised, double-blind, placebo-controlled studies (and etanercept-controlled for Study A2303) conducted in adult patients previously used to demonstrate the efficacy and safety of secukinumab in the adult moderate to severe psoriasis indication
Long-term efficacy data	Paediatric Study A2310 is ongoing and efficacy analyses up to Week 52 visit are presented. Paediatric Study A2311 is ongoing and efficacy analyses up to Week 24 visit are presented.
Long-term safety data	Paediatric Study A2310 is ongoing and safety analyses up to the cut-off date of 18-Sep-2019 are presented. Paediatric Study A2311 is ongoing and safety analyses up to the cut-off date of 14-Nov-2019 are presented.
Studies used for combined efficacy and safety analysis	No pooling of paediatric studies. Four pivotal studies in adult population were pooled and used as a supportive data source (comparison with paediatric data). (see supportive studies)

2.3.2. Pharmacokinetics

Pharmacokinetic samples were taken in studies A2310 and A2311. In study A2311 pharmacokinetic parameters Cmax, AUC84-112d and Tmax were evaluated. Furthermore, the sparse samples from study 2310 were included into a previously developed population pharmacokinetic model which was based on adult data of secukinumab PK; for this, see Section 2.3.4 on pharmacokinetic/pharmacodynamics (PK/PD) modelling.

In study A2310, blood samples for PK assessments were collected before dose administration at baseline, and immediately before dosing at Weeks 4, 12, 24 and 52. An ELISA method was used for bioanalytical analysis of secukinumab in serum, with a lower limit of quantification (LLOQ) of 500 ng/mL. At randomisation (before treatment with secukinumab), none of the patients had quantifiable concentrations.

The mean pre-dose concentrations at Weeks 4, 12, 24 and 52 showed a dose-proportional increase in exposure to secukinumab from the low dose level, to the high dose level. Due to more frequent dosing, mean exposure to secukinumab in samples drawn at Week 4 and 12 in the 'not affected group' was higher than at steady-state at Week 24 and Week 52 in both secukinumab low and high dose groups. At Week 52, the secukinumab concentrations were still higher in the 'IRT dose affected group' than in the not affected patients, especially in the high dose group (see Table 3).

Table 3 ***Mean (%CV) secukinumab serum concentrations in the secukinumab Low and High dose groups (Full analysis set) (study A2310)***

	AIN457 Low dose			AIN457 High dose			Placebo – AIN457 Low dose			Placebo – AIN457 High dose		
Visit	n	Mean (µg/mL)	CV (%)	n	Mean (µg/mL)	CV (%)	n	Mean (µg/mL)	CV (%)	n	Mean (µg/mL)	CV (%)
Baseline	39	0	-	38	0	-	-	-	-		-	-
Week 4	35	66.7	34.4	33	139	26.8	-	-	-		-	-
Week 12	35	33.0	46.1	35	70.4	46.2	16	2.6*	400.0	18	0.561*	424.3
Week 24	22	22.4	35.8	17	44.7	62.0	13	34.1	38.7	16	53.6	37.0
Week 52	22	21.4	42.0	15	44.1	39.9	14	22.7	40.6	15	33.4	42.3

* In two placebo patients (A2310-1281-004 and A2310-1614-001) 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 CSR a sample mix up cannot be excluded for these cases.

Patients who were affected by IRT dosing error at Week 13 or Week 14 or Week 15 are not included at Week 24 and Week 52 timepoint.

	Not affected by IRT error						Affected by IRT error					
	AIN457 Low dose			AIN457 High dose			AIN457 Low dose			AIN457 High dose		
Visit	n	Mean (µg/mL)	CV (%)	n	Mean (µg/mL)	CV (%)	n	Mean (µg/mL)	CV (%)	n	Mean (µg/mL)	CV (%)
Baseline	24	0	-	18	0	-	15	0	-	20	0	-
Week 4	20	61.7	33.1	14	132	30.6	15	73.3	34.3	19	144	24.2
Week 12	19	30.1	34.5	15	64.4	63.9	16	36.4	52.9	20	74.9	32.7
Week 24	22	22.4	35.8	17	44.7	62.0	16	47.6	67.5	20	86.0	26.6
Week 52	22	21.4	42.0	15	44.1	39.9	15	27.0	56.2	20	72.6	35.9

CV=coefficient of variation

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 at most of the time points. Further, at most time points within the low and high dose groups, similar exposure was observed with the 2-fold dose reduction for body weights between 25 kg and 50 kg compared with exposure for patients with body weights ≥ 50 kg, (see Table 4).

Table 4 ***Summary statistics for serum secukinumab concentrations by visit, body weight category and dose group (Full analysis set)***

Week	Stats	AIN457 75 mg <25kg	AIN457 75 mg 25 - <50kg	AIN457 150 mg 25 - <50 kg	AIN457 150 mg ≥50 kg	AIN457 300 mg ≥50 kg
4	n	4	14	7	4	5
	Mean (µg/mL)	105	52.0	127	77.2	147
	%CV	16.1	20.7	39.8	24.2	20.2
12	n	5	13	6	4	6
	Mean (µg/mL)	31.6	27.4	52.4	32.6	96.4
	%CV	33.4	36.4	67.3	30.6	34.5
24	n	2	14	10	7	6
	Mean (µg/mL)	29.4	20.4	30.6	24.7	71.8
	%CV	25.3	36.5	53.6	32.5	34.3
52	n	1	14	5	8	9
	Mean (µg/mL)	22.2	18.7	41.9	26.1	47.7
	%CV	-	43.7	36.8	34.0	38.9
Week	**Stats**	**Placebo-AIN457 75 mg <25kg**	**Placebo-AIN457 75 mg 25 - <50kg**	**Placebo-AIN457 150 mg 25 - <50 kg**	**Placebo-AIN457 150 mg ≥50 kg**	**Placebo-AIN457 300 mg ≥50 kg***
12	n	2	8	7	7	10
	Mean (µg/mL)	0.00	5.21*	0.00	0.00	1.01
	%CV	-	282.8	-	-	316.2
24	n	1	6	4	7	11
	Mean (µg/mL)	69.0	24.9	46.6	42.1	54.8
	%CV	-	44.1	26.9	22.4	40.8
52	n	1	6	5	7	9
	Mean (µg/mL)	40.7	19.0	26.8	27.2	36.2
	%CV	-	34.7	42.8	35.3	42.8

CV=coefficient of variation.

* In two placebo patients (A2310-1281-004 and A2310-1614-001) 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 CSR a sample mix up cannot be excluded for these cases.

Patient A2310-1200-014 in the placebo- low dose arm and 25-50 kg category stayed on 75 mg even after a weight increase to >50 kg from Week 40 and thereafter with a weight of 54 kg at Week 52. This patient is not summarized in this table and is reported separately in Table 14.2-6.2.1.

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.

Source: Table 14.2-6.2.1

In the on-going study A2311 blood samples for PK analysis were obtained prior to dosing from all patients on Day 1 and at Weeks 4, 12, and 16. Further, PK samples were drawn at Weeks 13, 14 and 15. The

mean trough concentrations to secukinumab in samples drawn at Week 4, and at Week 12, were higher than at Week 16, as expected due to weekly dosing until Week 4. The rise in concentrations from Week 12 to Week 13 and the decline from Week 13 to Week 16 represent the typical PK profile during the 4 weeks dosing interval after s.c. administration, both at the Low and High dose level (see Table 5).

Table 5 ***Mean (%CV) secukinumab serum concentrations in the secukinumab low and high dose groups (full analysis set) – Data up until Week 16***

	AIN457 low dose			AIN457 high dose		
Visit	n	Mean (µg/mL)	CV (%)	n	Mean (µg/mL)	CV (%)
Baseline	42	0	-	42	0	-
Week 4	36	74.6	46.9	37	138	32.4
Week 12	41	34.6	31.4	36	69.5	43.4
Week 13	36	47.0	38.1	29	93.9	34.1
Week 14	39	40.9	38.4	32	83.3	32.8
Week 15	38	34.1	36.5	27	69.0	41.7
Week 16	37	30.3	37.4	31	55.1	45.9

CV=coefficient of variation.

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 at all time points. Further, at all time points, similar exposure was observed with the 2-fold dose reduction for body weights between 25 and 50 kg compared with exposure for patients with body weights ≥50 kg. Serum exposure in patients with body weight <25 kg who received 75 mg doses was in the range of what was observed at the higher dose levels in the higher body weight categories (see Table 6).

Table 6 ***Summary statistics for serum secukinumab concentrations by visit, body weight category and dose group – Data up to Week 16 (Full analysis set)***

Week	Statistics	AIN457 75 mg <25kg	AIN457 75 mg 25 - <50kg	AIN457 150 mg 25 - <50 kg	AIN457 150 mg ≥50 kg	AIN457 300 mg ≥50 kg
4	n	7	12	9	21	24
	Mean	111	65.1	116	75.3	150
	%CV	57.4	21.4	31.9	44.7	27.8
12	n	8	12	11	25	21
	Mean	41.9	30.4	54.9	36.6	81.1
	%CV	62.7	17.3	45.1	30.9	34.2
13	n	7	11	7	21	19
	Mean	58.5	40.0	81.3	51.4	101
	%CV	44.0	21.1	40.6	38.3	32.4
14	n	7	12	7	23	22
	Mean	51.6	35.3	62.6	43.5	92.5
	%CV	41.4	17.3	42.8	39.7	26.6
15	n	5	13	6	22	19
	Mean	36.4	28.4	56.3	38.0	75.6
	%CV	44.7	20.9	50.9	35.3	37.5
16	n	7	12	7	22	20
	mean	36.7	26.5	47.9	31.7	61.2
	%CV	43.4	21.2	42.7	42.3	42.8

CV=coefficient of variation.

Subject's data are summarized according to the randomized weight and the dose received up until week 16 visit.

A dose proportional increase was observed in mean Cmax and mean AUC84-112d from the low dose level, *i.e.*, 75 mg for 25 to < 50 kg, 150 mg for ≥50 kg to the high dose level, i.e. 150 mg for 25 to <50 kg and 300 mg for ≥50 kg (see Table 7).

Table 7 ***Summary of mean pharmacokinetic parameters Cmax, Tmax and AUC84-112d of secukinumab by weight and dose group***

	75 mg, <25 kg	75 mg, 25-<50kg	150 mg 25-<50kg	150 mg ≥50kg	300 mg ≥50kg
Cmax (µg/mL) (CV%, n)	56.5 (36.6%, 5)	40.7 (21.2%, 10)	85.7 (44.8%, 5)	53.7 (38.5, 18)	115 (30.0%, 10)
Tmax (days) (CV%, n)	95.9 (90.9-113, 5)	90.9 (90.0-98.0, 10)	91.0 (90.9-97.9, 5)	91.1 (90.8-112, 18)	91.0 (90.2-101, 10)
AUC84-112d (µg.day/mL) (CV%, n)	1210 (44.2%, 5)	930 (16.9%, 10)	1860 (45.4%, 5)	1220 (37.9, 18)	2610 (32.7, 10)

Source: Table 14.2-10.1.1

Median Tmax and range is given, (%CV, n in brackets) Patient's data are summarized according to the randomized weight and the dose received. Only patients with complete data at Weeks 12, 13, 14, 15 and 16 (i.e. no missing data) are included and PK parameters are derived on these data.

Additional plasma concentration data of secukinumab (AIN457) obtained in different patient groups at time points 4, 12 24 and 52 weeks were requested by the CHMP. The concentrations at 12 and 24 weeks are presented in Tables 8 and 9.

Table 8 ***Summary statistics for serum AIN457 concentration (mcg/mL) by visit, body weight and dose group in paediatric population (A2310 and A2311)***

Visit	Statistic	AIN457 75 mg and <25 kg	AIN457 75 mg and 25-<50 kg	AIN457 150 mg and 25-<50 kg	AIN457 150 mg and >=50 kg	AIN457 300 mg and >=50 kg
Week 12	n	13	24	22	45	45
	Mean	37.9	29.0	56.2	36.2	81.6
	SD	21.6	8.19	25.9	14.3	27.2
	CV(%) mean	57.0	28.2	46.1	39.5	33.3
	Min	7.78	14.7	13.7	16.6	24.1
	Q1	24.5	23.7	35.7	25.0	62.5
	Median	39.5	28.5	52.9	34.6	82.0
	Q3	44.3	36.0	74.6	44.7	102
	Max	91.8	48.6	114	81.0	129
	n(log)	13	24	22	45	45
	Geo-mean	31.8	27.8	49.8	33.6	76.5
	CV(%) geo-mean	75.0	30.2	57.9	39.9	40.0
Week 24	n	8	24	18	36	33
	Mean	32.6	19.8	33.1	27.3	56.2
	SD	10.8	6.96	16.5	10.1	23.5
	CV(%) mean	33.3	35.2	50.0	37.0	41.8
	Min	10.2	5.44	11.6	8.78	3.77
	Q1	28.2	15.3	19.8	19.4	40.4
	Median	35.0	19.5	30.5	26.5	57.0
	Q3	40.5	24.8	45.6	35.7	72.0
	Max	43.0	30.5	66.1	46.6	114
	n(log)	8	24	18	36	33
	Geo-mean	30.2	18.4	29.1	25.3	49.2
	CV(%) geo-mean	50.2	44.7	58.0	42.9	69.3

- In A2310 study, patient who are affected by IRT dosing error at week 13 or week 14 or week 15 are not included in the report at week 24, but are included at week 52.

Table 9 ***Summary statistics for serum AIN457 concentration (mcg/mL) by visit, body weight and dose group in paediatric population (A2310 and A2311)***

Visit	Statistic	Placebo - AIN457 75 mg and <25 kg	Placebo - AIN457 75 mg and 25-<50 kg	Placebo - AIN457 150 mg and 25-<50 kg	Placebo - AIN457 150 mg and >=50 kg	Placebo - AIN457 300 mg and >=50 kg
Week 12	n	2	8	7	7	10
	Mean	0.00	5.21	0.00	0.00	1.01
	SD	0.00	14.7	0.00	0.00	3.19
	CV(%) mean		282.8			316.2
	Min	0.00	0.00	0.00	0.00	0.00
	Q1	0.00	0.00	0.00	0.00	0.00
	Median	0.00	0.00	0.00	0.00	0.00
	Q3	0.00	0.00	0.00	0.00	0.00
	Max	0.00	41.7	0.00	0.00	10.1
	n(log)	0	1	0	0	1
	Geo-mean		41.7			10.1
	CV(%) geo-mean					
Week 24	n	1	6	4	7	11
	Mean	69.0	24.9	46.6	42.1	54.8
	SD		11.0	12.5	9.43	22.4
	CV(%) mean		44.1	26.9	22.4	40.8
	Min	69.0	11.1	35.1	26.2	22.4
	Q1	69.0	16.8	36.5	31.9	36.7
	Median	69.0	25.5	44.7	46.4	54.3
	Q3	69.0	35.2	56.8	48.5	66.3
	Max	69.0	35.2	62.0	51.8	103
	n(log)	1	6	4	7	11
	Geo-mean	69.0	22.6	45.4	41.0	50.6
	CV(%) geo-mean		52.5	27.1	25.6	44.6

- In A2310 study, patient who are affected by IRT dosing error at week 13 or week 14 or week 15 are not included in the report at week 24, but are included at week 52.

2.3.3. Pharmacodynamics

The objectives of the population PK modelling exercise were to confirm that the secukinumab paediatric doses used in studies A2310 and A2311 achieve similar exposure levels to those observed in adult patients, and to support that paediatric exposure comparable to that in adults produces comparable efficacy. The pooled analysis uses data from 10 phase I-III studies in adult patients with moderate to

severe plaque psoriasis and from the paediatric study A2310 data until week 24. A subset of dataset, originally used in the model building, was used for the population PK model fitting. The PK comparison was made with data from Phase 3 studies using the same dosing regimen. The exposure-psoriasis area and severity index (PASI) response analysis was based on the phase III studies using the same dosing regimen (study A2304 excluded because of the lack of placebo control in the study).

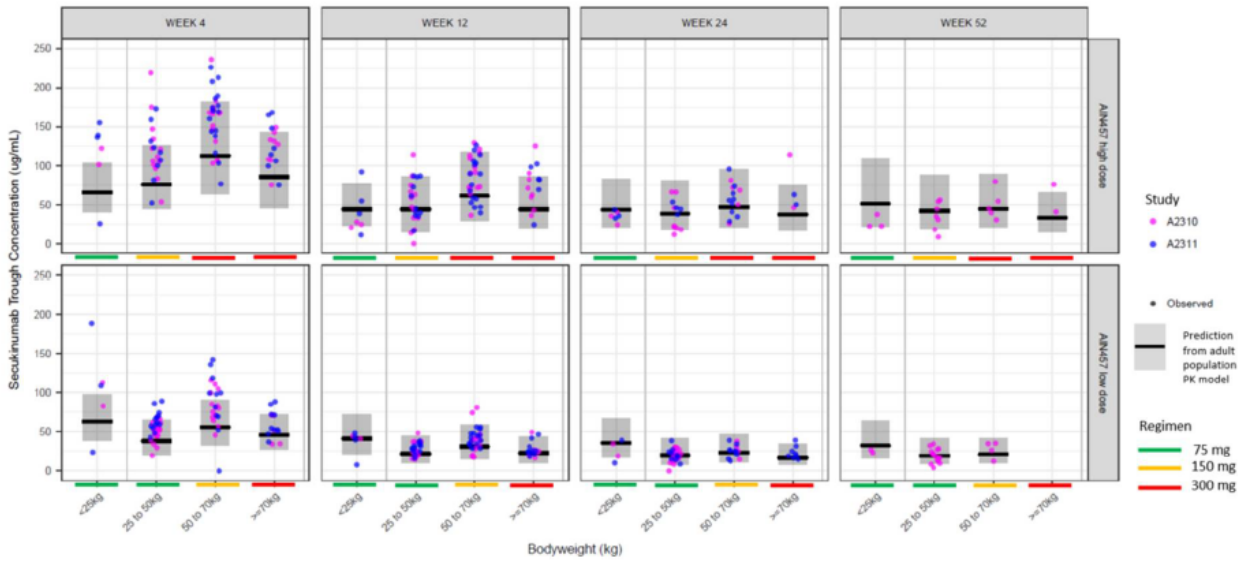
Some of the PK analyses excluded the concentration after 12 Weeks for 36 subjects (16 subjects in Low dose group and 20 subjects in High dose group) from Study A2310 who erroneously received active medication at Weeks 13, 14, 15. For the descriptive exposure-response analysis, the following data from A2310 were excluded:

- Data after 12 Weeks for 36 subjects who erroneously received active medication at Weeks 13, 14, 15.
- Data from two patients who had at least one missing dose over the 24 weeks of treatment (2 subjects in the High dose group).

For the model-based exposure-response analysis, no data from A2310 were excluded.

2.3.3.1. Population PK model

The appropriateness of the paediatric dose selection based on secukinumab exposure was first assessed graphically. Paediatric Exposure at week 4, 12, 24 and 52 in paediatric patients (studies A2310 and A2311) stratified by weight group were graphically compared to the predicted exposure from the population PK model developed on adults, the results of which are shown in the figure below.



Dots: Observed pediatric trough concentrations in Studies A2310 and A2311.
Horizontal line: Median of simulations. Shaded region: 90% PI of simulations. These simulations are based on the established population PK model developed on adult data. The horizontal color line indicate the scheduled dose (75, 150, or 300 mg) determined by the weight and the dosing regimen.
The Weeks 24 and 52 panels do not include the patients who received erroneously additional doses at Weeks 13, 14, and 15 in Study A2310.

Figure 1 Predicted versus observed paediatric secukinumab trough concentrations for Weeks 4, 12 , 24 and 52

To further quantify the paediatric effect on secukinumab exposure, the entire pooled dataset (including A2310 data until week 24) was used to fit alternative models including model with fixed allometric exponents and paediatric effect on bioavailability. The models in question were linear two-compartment

mammillary models with first-order absorption and elimination. The models are listed in Table 10 and the parameter estimates of the most relevant models are detailed in Table 11.

Table 10 ***List of population PK models***

Data set	Model	Description
Original PK data pool updated with pediatric study A2310	Model 0 = Original Population PK model	Post-hoc Estimation (MAXEVAL=0)
	Model 1	Fit using same structural model as Model 0
	Model 2	Fit using same structural model as Model 0 + fixed standard allometric exponent*
	Model 3	Fit using same structural model as Model 0 + population-specific BAV
	Model 4	Fit using same structural model as Model 0 + study-specific BAV

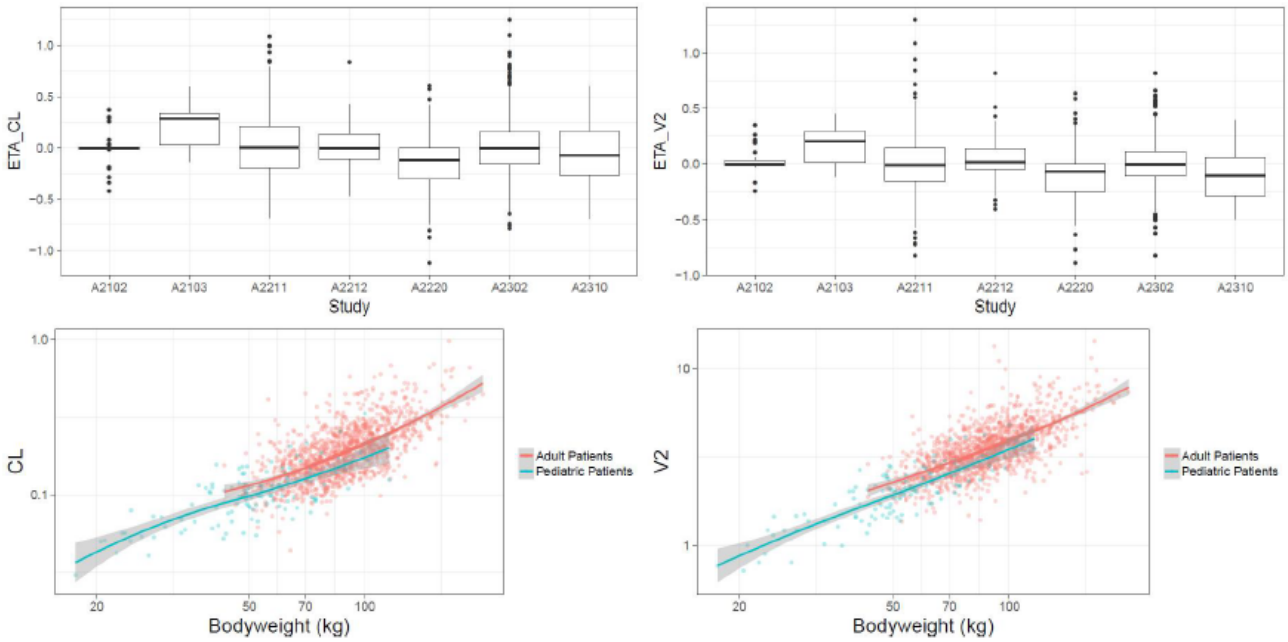
*Standard allometric exponent values: 0.75 for CL and Q, and 1 for V2 and V3.

Table 11 ***Parameter values of the previous and updated PK models***

		Model 0: Original Model (fixed adult parameters)		**Model 1 (= Model 0 with re-estimated parameters)**		**Model 2 (= Model 0 with allometric coefficients fixed to standard values)**		**Model 3 (Model 0 + pediatric effect on BAV),**	
Name	**Parameter**	**Value**	**RSE (%)**	**Value**	**RSE (%)**	**Value**	**RSE (%)**	**Value**	**RSE (%)**
Objective Function Value	OFV	181653*	-	181613	-	181764	-	181577	-
CL [L/d]	TH1	0.19	2	0.19	2	0.19	2	0.19	2
V2 [L]	TH2	3.61	3	3.58	3	3.57	3	3.61	3
Q [L/d]	TH3	0.39	5	0.39	5	0.37	4	0.39	5
V3 [L]	TH4	2.87	2	2.86	2	2.87	2	2.87	2
KA [1/d]	TH7	0.18	4	0.18	4	0.18	3	0.18	4
TVF1** ***	TH8	0.99	6	0.99	6	0.97	6	A: 0.99 P Diff: 1.12	A: 6 P: 30
WT on CL	TH10	1.00	3	1.03	3	0.75 FIX	-	0.94	3
WT on V2	TH11	0.81	9	0.88	8	1.00 FIX	-	0.82	9
WT on Q	TH12	0.68	25	1.12	17	0.75 FIX	-	0.97	19
WT on V3	TH13	0.56	10	0.77	9	1.00 FIX	-	0.68	11
IIV CL	OM1:1	0.32	2	0.32	2	0.33	2	0.32	2
IIV V2	OM2:2	0.30	5	0.30	5	0.31	4	0.29	5
IIV CL-V2	OM2:1	0.70	4	0.69	4	0.64	4	0.68	4
IIV V3	OM3:3	0.18	9	0.19	9	0.22	7	0.19	9
IIV CL-V3	OM3:1	0.14	34	0.12	39	0.02	229	0.10	47
IIV V2-V3	OM3:2	0.72	7	0.74	6	0.73	6	0.73	7
IIV KA	OM7:7	0.35	7	0.35	6	0.33	7	0.35	7
Proportional error	SI1:1	0.17	0.4	0.18	0.4	0.17	0.4	0.18	0.4
Additive Error (ng/ml)	SI2:2	371	0.2	369	0.2	371	0.2	370	0.2

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CL = clearance, V2 = volume of central compartment, Q = inter-compartmental exchange flow rate, V3 = volume of peripheral compartment, KA= absorption rate constant, TVF1=bioavailability, IIV = inter-individual variability, WT = bodyweight.

The different bioavailability for the paediatric population was hypothesized due to a seemingly systematic difference in apparent clearance and volume of distribution in children versus adults (Figure below).



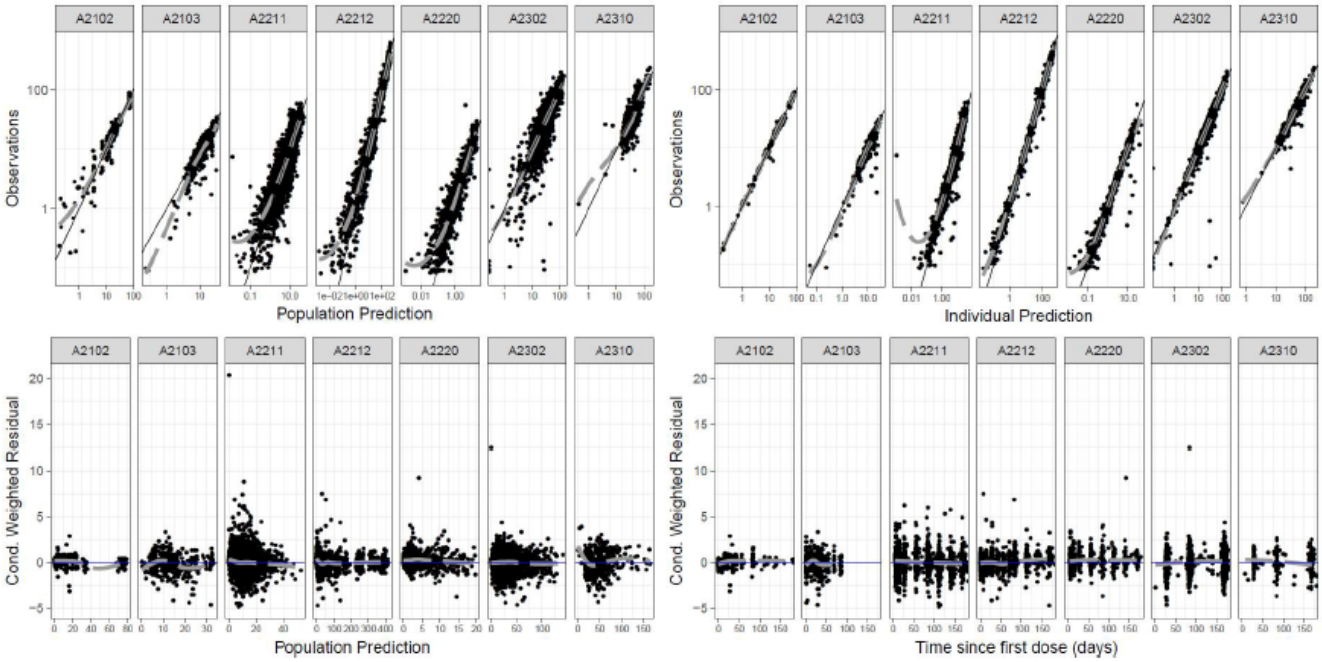
Top: The lower and upper ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers extend to the 1.5 time the interquartile range (IQR) beyond the box or the more extreme values whichever is closer to the box. Dots represent the outliers.

Bottom: Lines are local regression (loess in R) with 95% CI. Dots are individual parameters estimates.

Figure 2 Distribution of individual CL and V2 random component by study. Individual CL and V2 versus body weight – Model 1

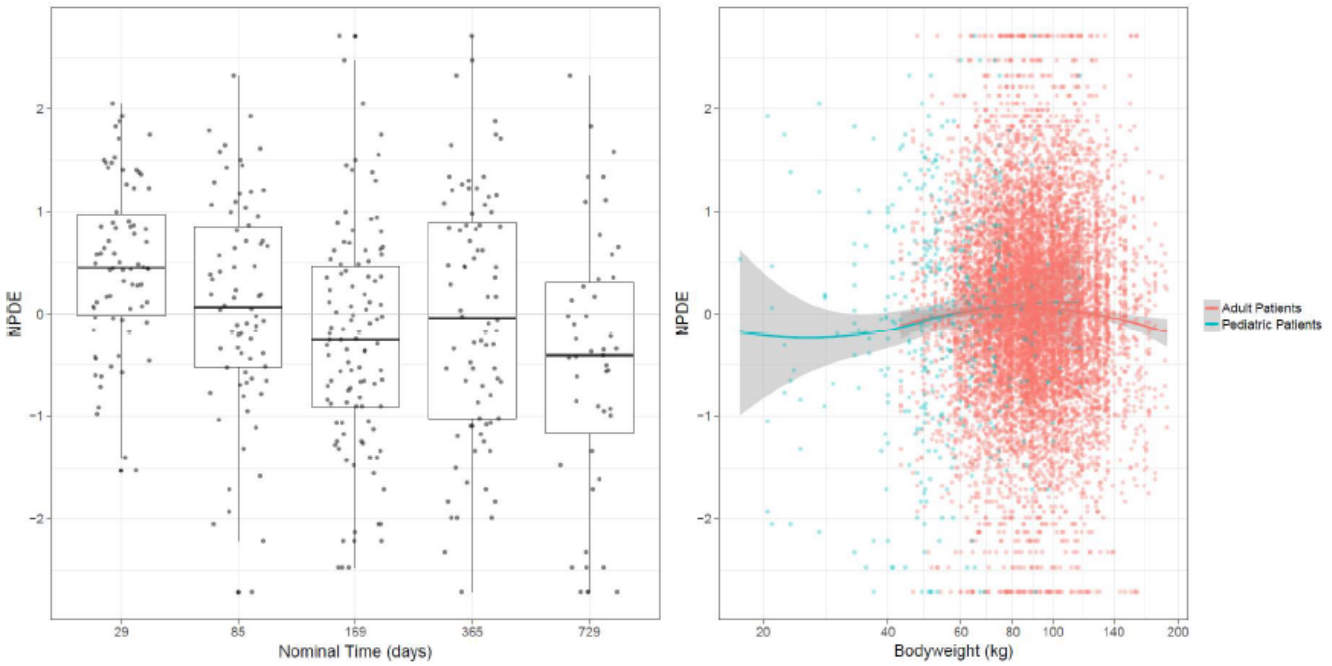
The CHMP was of the opinion that the rationale for testing a different bioavailability for the paediatric population in Model 3 is clear and acceptable.

Model 3 was considered to adequately describe the exposure data, as summarized by the diagnostics in the Figures below.



Note: Prediction and observation are given in µg/mL The dashed line through the points in each plot is a local regression (loess in R).

Figure 3 Goodness-of-fit diagnostics per study - Model 3



Left: The lower and upper ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers extend to the 1.5 time the interquartile range (IQR) beyond the box or the more extreme values whichever is closer to the box. Dots represent the outliers.

Right: Lines are local regression (loess in R) with 95% CI. Dots are individual parameters estimates.

Sources:

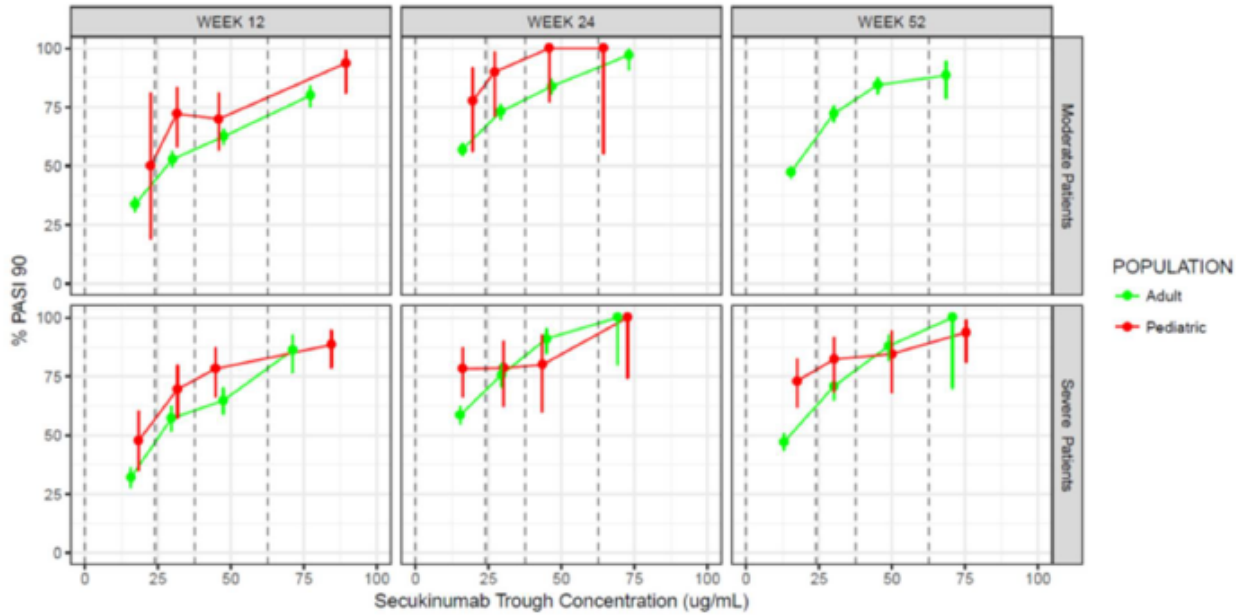
Figure 4 Normalised Prediction Didstribution Error (NPDE) versus time in paediatric patients and versus weight in paediatric and adult patients – Model 3

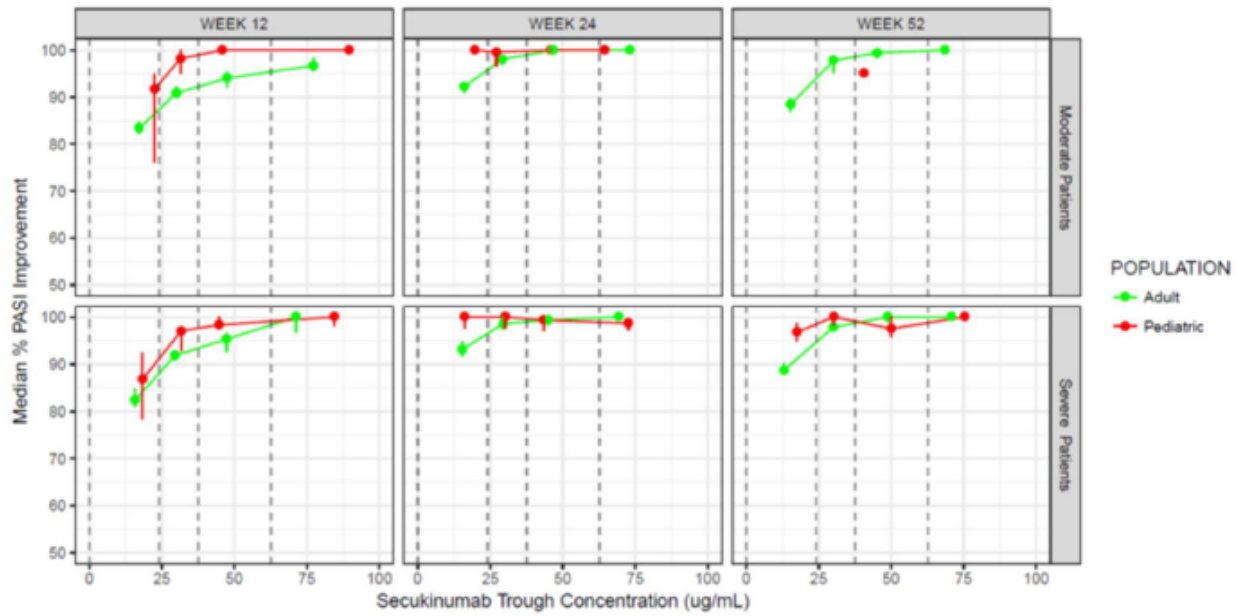
2.3.3.2. Exposure-response model

For the exposure-response model, graphical exploration for exposure- efficacy responses (%PASI improvement, PASI75 and PASI90) were performed. The confidence intervals for the probability of PASI response was obtained by means of exact method (Clopper, 1934). The confidence intervals for the median % PASI improvement from baseline was obtained by bootstrapping (simulate outcomes for 1000 copies of the original dataset and summarize % PASI Improvement across simulated datasets for each concentration bin).

Data from studies A2310 and A2311 were used for the graphical exploration.

Figure below depicts the paediatric and adult concentration-efficacy response relationships. Specifically, the median response (%PASI improvement from baseline), and the %PASI90 response rate are summarized by patient population and paediatric secukinumab concentration quartile bin at week 12.





Dots and vertical bars represent (top plot) the percentage of PASI 90 responders and the associated 66% confidence interval, obtained by exact method or (bottom plot) the median % PASI improvement from baseline and the associated 66% confidence interval, obtained by bootstrapping methods, by secukinumab concentration bin, population (adult or pediatric), disease baseline severity, and week from pediatric studies A2310 and A2311 and from adult studies A2302, A2303, A2308, and A2309. They are plotted versus the median concentration in the bin. The vertical dashed lines represent the pediatric quartile bins cut points (0.01, 24, 37.6, and 62.6 and 236 ug/mL). The Week 24 panel does not include the patients who received erroneously additional doses at Weeks 13, 14 and 15 in study A2310. There was one patient in Study A2310 with moderate severity; this patient was not included in the plot.

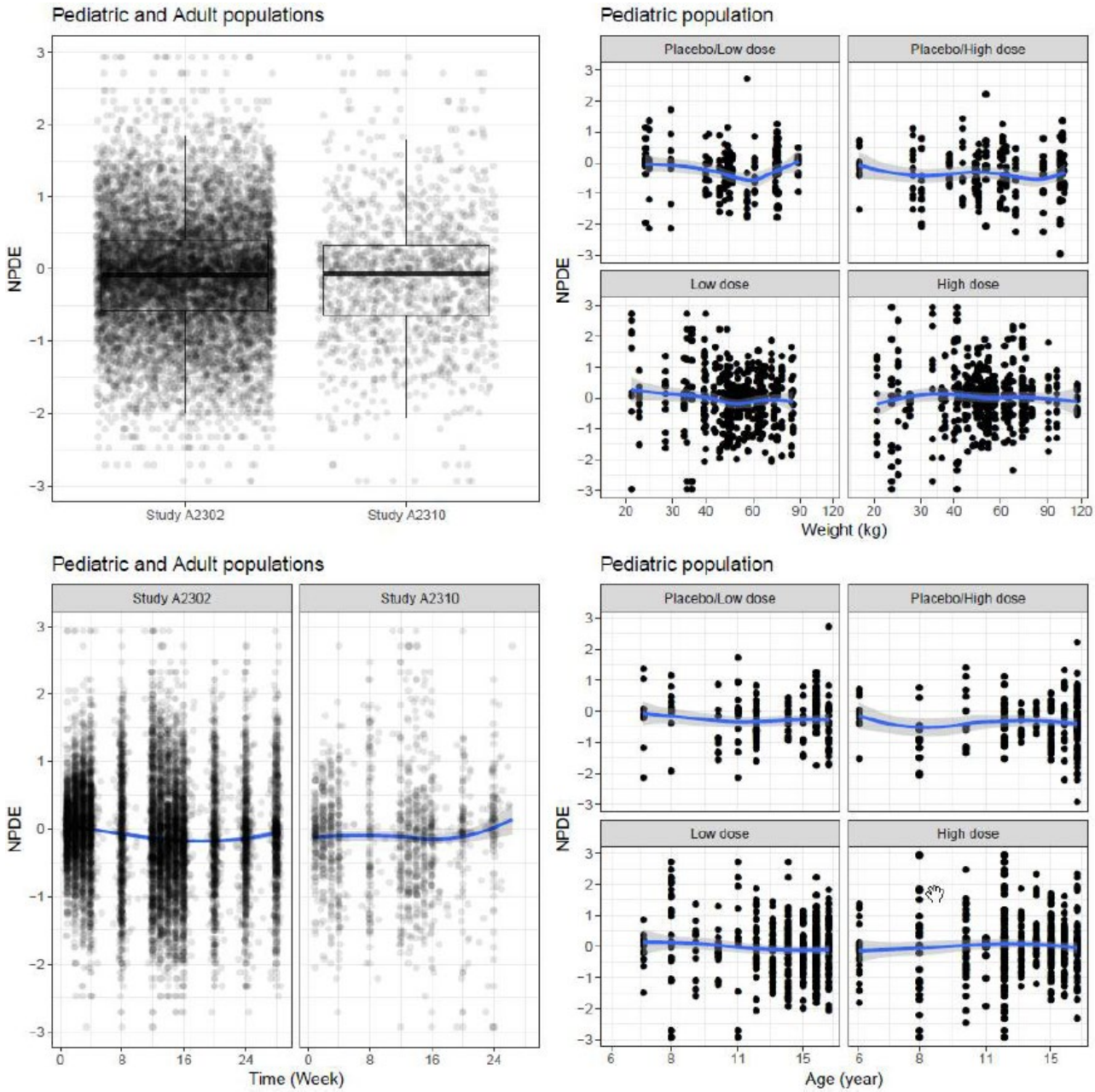
Figure 5 Median PASI improvement from baseline at Weeks 12 and 24 versus binned trough secukinumab concentration, by population and severity

The paediatric concentration-response relationships are generally similar to the adult relationships. Overall, these results support the extrapolation from the adult to the paediatric population, at least at higher secukinumab concentrations.

The consistency of the relationship between secukinumab concentration and PASI score of the patients from paediatric Study A2310 across the weight and age ranges was assessed by means of the exposure-PASI model used for the original adult submission.

A preliminary step was to check that the adult exposure-PASI model described adequately the relationship between secukinumab concentration and PASI score in paediatric patients. The adequateness was confirmed by Figure below in which:

- the NPDEs from Study A2310 have similar distribution, overall and versus time, to the adult study A2302 NPDEs (used for comparison purpose), and
- the NPDEs from Study A2310 versus weight and age by treatment group are reasonably distributed around zero.



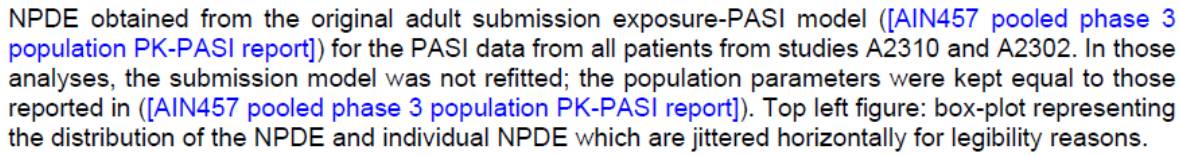
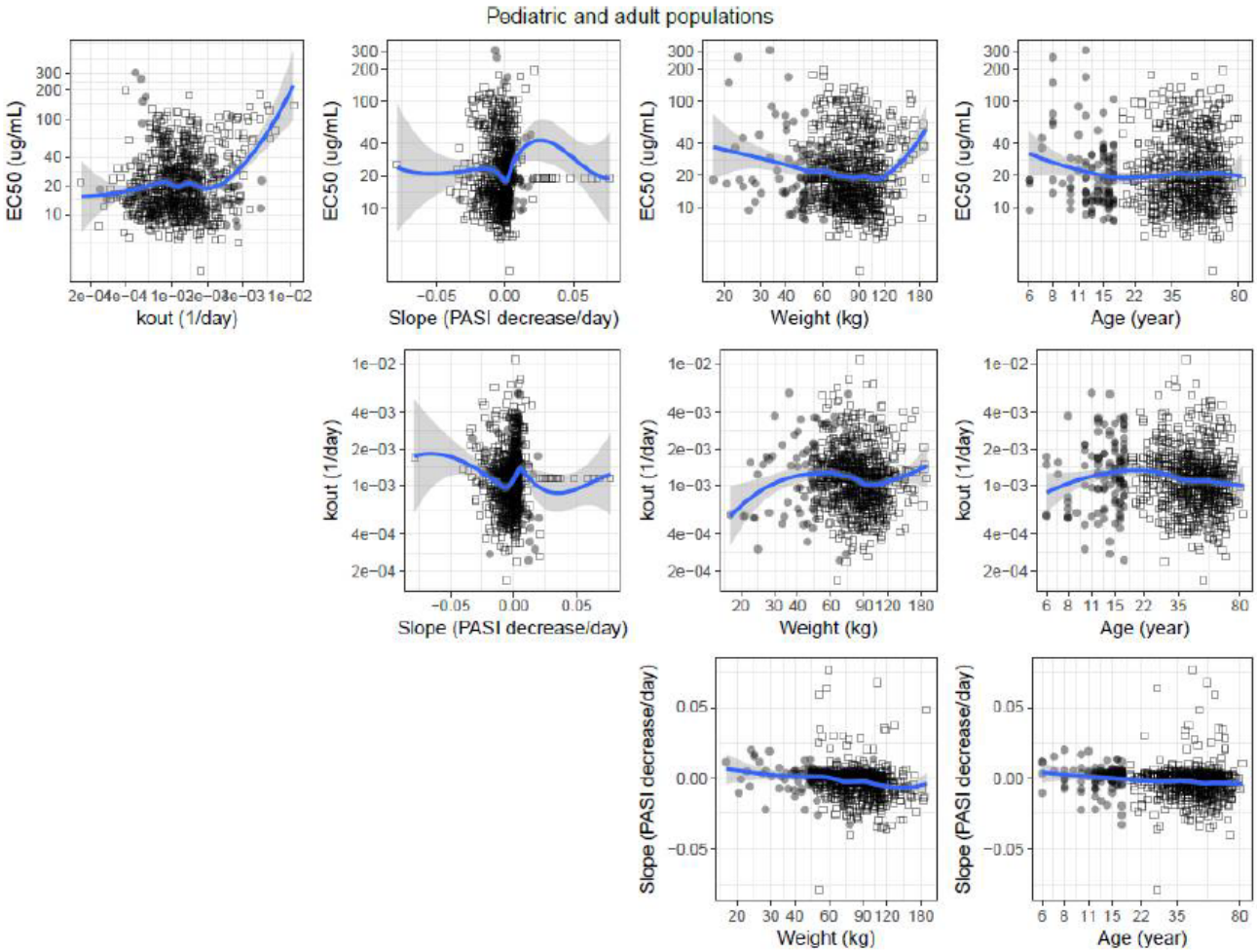


Figure 6 Diagnostic of the adequateness of the adult PK-PASI model to describe A2310 (paediatric) data

The consistency of the PK-PASI relationship across weights and ages was assessed by using the adult model to estimate three individual (i.e., subject-specific) PD parameters informing (1) how much drug concentration is necessary to provide half of the maximum PASI decrease (*EC50*), (2) how fast the secukinumab concentration effect on the PASI is washed out (*kout*), and (3) the PASI slope over time in absence of secukinumab concentration (*Slope*). This was done for each paediatric patient from Study A2310 as well as, for comparison purpose, for each adult patient from Study A2302.

There was no meaningful relationship between the PD parameters of the paediatric patients and weight or age (Figure below, 3rd and 4th columns). The apparent higher *EC50* for lighter (paediatric) patients is mostly due to four paediatric patients with very high *EC50* of >150 ug/mL that do not fit the exposure-PASI model well. When those patients are excluded from the analyses, the apparent relationship between weight and *EC50* disappears (Figure not reported).



Individual PD parameters obtained from the original adult submission exposure-PASI model ([AIN457 pooled phase 3 population PK-PASI report]) for patients from pediatric study A2310 (plain circles) and adult study A2302 (open squares) treated with secukinumab. In those analyses, the submission model was not refitted: the population parameters were kept equal to those reported in ([AIN457 pooled phase 3 population PK-PASI report]). The smoother is fitted on the pool of the two studies.

Figure 7 Relationship between individual PD parameters and patients' weight and age – Pool of all paediatric patients (A2310) and adult patients (A2302)

2.3.3.3. Extrapolation of efficacy from severe to moderate disease state in children

It is understood that the disease pathology and progression are similar in the adult and the paediatric population. The response to therapy was expected to be similar. Thus, an extrapolation of adult efficacy data to paediatric data was considered appropriate.

Summary statistics for key efficacy parameters from the paediatric population and from the adult pool population are presented side-by-side, to facilitate comparison and to allow a comparative assessment of efficacy of secukinumab for the intended use in the paediatric population. The statistical analysis includes efficacy data up to Week 24 visit of study A2310.

The efficacy responses at Week 12 for the paediatric Study A2310 and for the pool of adult studies (studies A2302, A2303, A2308, and A2309) are presented side-by-side in Table below.

The efficacy response (PASI75, Investigator's Global Assessment (IGA)0/1 and PASI90) of Study A2310 were comparable for the Low and High doses of secukinumab. When compared with the historical data from the secukinumab adult studies, the paediatric efficacy response rates for the Low dose arm were

similar (for PASI75) or numerically higher (for IGA0/1 and PASI90) to the adult efficacy response rates in the 150 mg group and were similar to adult 300 mg group.

Table 12 ***Side-by-side comparison of paediatric and adult efficacy responses at Week 12 - Pure non-responder imputation - full analysis set (FAS)***

	Pediatric (Study A2310)	Adult pool (studies A2302, A2303, A2308 and A2309)	
	Severe psoriasis	Moderate psoriasis	Severe psoriasis
Response	n/m (%)	n/m (%)	n/m (%)
	AIN457 Low dose (pediatric) / 150 mg (adult)		
	N=40	N=499	N=193
PASI 75	28/40 (70.0)	349/496 (70.4)	127/193 (65.8)
IGA 0/1	24/40 (60.0)	270/497 (54.3)	85/193 (44.0)
PASI 90	26/40 (65.0)	203/496 (40.9)	80/193 (41.5)
	Pediatric (Study A2310)	Adult pool (studies A2302, A2303, A2308 and A2309)	
	Severe psoriasis	Moderate psoriasis	Severe psoriasis
Response	n/m (%)	n/m (%)	n/m (%)
	AIN457 High dose (pediatric) / 300 mg (adult)		
	N=40	N=493	N=197
PASI 75	30/40 (75.0)	389/490 (79.4)	155/195 (79.5)
IGA 0/1	23/40 (57.5)	331/490 (67.6)	114/195 (58.5)
PASI 90	26/40 (65.0)	280/490 (57.1)	107/195 (54.9)
	Placebo		
	N=41	N=490	N=201
PASI 75	6/41 (14.6)	22/489 (4.5)	7/200 (3.5)
IGA 0/1	2/41 (4.9)	12/489 (2.5)	3/200 (1.5)
PASI 90	1/41 (2.4)	4/489 (0.8)	4/200 (2.0)
	Etanercept		
	N=41	N=226	N=100
PASI 75	25/41 (61.0)	93/224 (41.5)	49/99 (49.5)
IGA 0/1	14/41 (34.1)	62/224 (27.7)	26/99 (26.3)
PASI 90	12/41 (29.3)	42/224 (18.8)	25/99 (25.3)

n = number of patients with response, m = number of patients evaluable.

The analysis approach to demonstrate consistent efficacy between the paediatric population and the adult population with severe plaque psoriasis disease and to predict the efficacy for the paediatric population with moderate psoriasis consisted of 4 steps (Figure below):

1. Efficacy in severe psoriasis paediatric patients: Inferential statistical analysis using Study A2310 data to demonstrate superiority of secukinumab over placebo with respect to PASI75, IGA0/1 and PASI90 and responses at Week 12 in paediatric patients with severe psoriasis
2. Extrapolation from severe adult to severe paediatric population: This step consists of predictions from the severe adult summary pool (consisting of secukinumab Phase III adult studies A2302, A2303, A2308 and A2309) followed by validation with severe paediatric data (from Study A2310)

to demonstrate the consistency of efficacy between adult and paediatric populations with respect to PASI75, IGA0/1 and PASI90 responses at Week 12 (qualification model)

3. Characterization of efficacy and disease severity in adults: Efficacy meta-analysis to characterize difference in efficacy response between moderate and severe patients in adult pool, with respect to PASI75, IGA0/1, and PASI90 at Week 12
4. Efficacy prediction for moderate psoriasis paediatric population: Predictive analysis to provide evidence of a positive treatment effect for secukinumab versus placebo with respect to PASI75, IGA0/1 and PASI90 and responses at Week 12 in paediatric patients with moderate psoriasis. This step provided the adjusted efficacy estimates through paediatric and adult data to provide a predicted treatment effect for a moderate psoriasis paediatric population (extrapolation model).

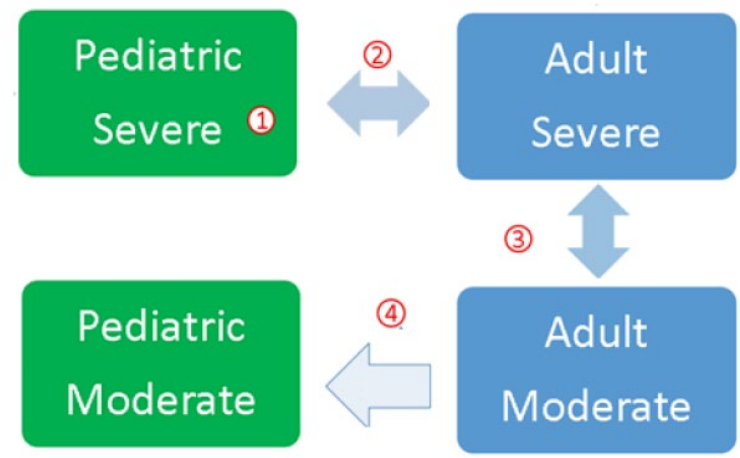


Figure 8 The 4 steps for the planned statistical analysis

Inferential statistical efficacy analysis in severe psoriasis paediatric patients (Study A2310, Step 1)

The inferential statistical analysis using Study A2310 data was to demonstrate superiority of secukinumab over placebo with respect to PASI75, IGA 0/1 and PASI90 responses at Week 12 in severe psoriasis paediatric patients.

Bayesian meta-analytic prediction-validation approach for the severe psoriasis paediatric population (qualification model, Step 2)

The approach to perform extrapolation and validation, as outlined in the EMA Concept Paper on Extrapolation (EMA/189724/2018), is as follows:

Prediction step: A Bayesian meta-analysis using the summary adult efficacy pool in the severe population was performed. From this analysis, posterior predictive distributions were derived to predict outcomes of study designs matching the ones in the available paediatric Study A2310, in terms of treatment effect.

As the overall sample size is relatively large for each adult study, no sensitivity of the results is expected due to the uninformative priors on the regression coefficients. However, the choice of the prior for the between-study heterogeneity parameter can have an influence on the derived predictive distribution. The between-study heterogeneity parameter is a variance parameter which would require a large number of different adult studies in order to be dominated by the data. As only 4 adult studies are available, the prior distribution for the heterogeneity parameter is not expected to be dominated by the data. A prior

on the between-study heterogeneity parameter with smaller (larger) heterogeneity may lead to a narrower (wider) predictive distribution for Study A2310 data. The moderate heterogeneity was considered an adequate choice to reflect the degree of heterogeneity in the adult trials.

The above model was fitted separately for each treatment arm, using MCMC in Stan version 2.17.1. MCMC non-convergence Rhat diagnostic (Gelman and Rubin 1992) was monitored for all model parameters. Any parameter, with a Rhat value greater than 1.1 (suggesting sampling problems) was presented for each analysis. In addition, the number of divergent transitions during the sampling phase of the used hamiltonian monte-carlo (HMC) algorithm implemented in Stan was reported, which was expected to be zero (Upadhyay *et al*, 2015).

Validation step: Assuming similarity between the adult and the paediatric population with respect to the efficacy endpoints, the observed outcome of the paediatric severe population study should be in the range of the predictive distribution derived from the meta-analysis in adult. If so, this was taken as evidence "*to confirm the predicted degree of similarity … in clinical response (efficacy, …)*", according to the EMA Concept Paper on Extrapolation (EMA/189724/2018).

Of note, this approach did not make any model assumption on the paediatric data; it therefore provided a complementary view to assess the extent to which the paediatric data were in line with the prediction derived from the pool of data in adults.

The observed log shifted odds ratios for High and Low doses of secukinumab in the paediatric population with severe psoriasis (Study A2310) were all contained within the 95% credible intervals of their respective predictive distribution calculated with the qualification model, see Table below. This indicates that the response to treatment with Low or High dose of secukinumab would be similar (within the credible interval) in severe psoriasis in the adult and paediatric populations.

Table 13 ***Predictive efficacy at Week 12 in paediatric population with severe psoriasis - Pure non-responder imputation (FAS)***

	AIN457 Low dose	AIN457 High dose
PASI 75		
Predicted log shifted -OR (95% CrI)	3.47 (2.02, 5.49)	4.04 (2.45, 6.23)
Observed log shifted - OR*	2.52	2.83
IGA 0/1		
Predicted log shifted - OR (95% CrI)	3.00 (1.52, 4.71)	3.50 (2.01, 5.29)
Observed log shifted - OR*	3.16	3.18
PASI 90		
Predicted log shifted -OR (95% CrI)	2.79 (1.29, 4.62)	3.27 (1.53, 5.17)
Observed log shifted - OR*	3.90	3.93

*. Observed in Study A2301; N=40 patients in each dose arm.
OR = odds ratio, 95% CrI = 95% credible interval. Comparisons are against placebo. Two patients with moderate psoriasis in the pediatric population (Study A2310) were not included in the analysis.

The CHMP noted that the Step 2 results are displayed in Table above. All the key results are within the 95% credible interval.

Efficacy meta logistic regression analysis testing Baseline severity (Step 3)

A meta-analysis model, based on pooled patient-level data was fitted to assess the extent of difference or similarity in efficacy responses between severe and moderate adult patients.

The logistic regression model was fitted separately for each endpoint. The fixed effects model included treatment arm, study, Baseline severity, Baseline bodyweight and Baseline severity by treatment interaction as fixed explanatory variables.

The treatment by severity interaction was of primary interest, *i.e.*, whether treatment effect (secukinumab 150 mg/300 mg dose vs. placebo) differs according to initial disease severity (moderate or severe). The odds ratio for each treatment comparison for moderate and severe Baseline disease severity groups were computed and presented along with the p value. For results, see Table below.

The treatment effect (secukinumab 150/300 mg dose vs. placebo) did not differ by Baseline disease severity (moderate or severe). In addition, the disease severity comparison in each treatment arm suggests no differences between moderate psoriasis and severe psoriasis with respect to PASI75 and PASI90 responses at both secukinumab doses and placebo as well as IGA 0/1 in the placebo arm. Higher response rates in moderate psoriasis adults were observed at both secukinumab doses for IGA 0/1 compared to severe psoriasis adults (54.3% in moderate adults vs. 44% in severe adults in the secukinumab 150 mg arm with p-value = 0.0155; 67.6% in moderate psoriasis adults vs. 58.5% in severe psoriasis adults in the secukinumab 300 mg arm with p-value = 0.0315). Although this step was not a formal part of the Bayesian approach, it characterized the difference between moderate and severe psoriasis in adults.

Table 14 ***Efficacy meta-analysis at Week 12 in adults comparing disease severity - Pure non-responder imputation (FAS)***

	Disease severity comparison				Disease severity by treatment interaction
Criterion	**Moderate n/m (%)**	**Severe n/m (%)**	**odds ratio estimate (95%CI)**	**p-value**	**p-value**
PASI 75					**0.6820**
AIN457 150 mg	349/496 (70.4)	127/193 (65.8)	1.23 (0.86, 1.77)	0.2501	
AIN457 300 mg	389/490 (79.4)	155/195 (79.5)	0.97 (0.64, 1.47)	0.8959	
Placebo	22/489 (4.5)	7/200 (3.5)	1.22 (0.51, 2.90)	0.6573	
IGA 0/1					**0.9855**
AIN457 150 mg	270/497 (54.3)	85/193 (44.0)	1.52 (1.08, 2.13)	0.0155	
AIN457 300 mg	331/490 (67.6)	114/195 (58.5)	1.46 (1.03, 2.06)	0.0315	
Placebo	12/489 (2.5)	3/200 (1.5)	1.56 (0.44, 5.61)	0.4923	
PASI 90					**0.3567**
AIN457 150 mg	203/496 (40.9)	80/193 (41.5)	0.97 (0.69, 1.36)	0.8512	
AIN457 300 mg	280/490 (57.1)	107/195 (54.9)	1.09 (0.77, 1.53)	0.6262	
Placebo	4/489 (0.8)	4/200 (2.0)	0.38 (0.09, 1.53)	0.1733	

n = number of patients with response, m = number of patients evaluable.

Predicted treatment effect for moderate psoriasis paediatric population (extrapolation model, Step 4)

An extrapolation model using all available adult data (*i.e.*, including data on moderate and severe psoriasis) was analyzed jointly with the severe psoriasis paediatric data from Study A2310. The model was analogous to the qualification model described above but also included, in addition, terms for Baseline severity (moderate vs. severe), population indicator (paediatric vs. adult), treatment by

severity and treatment by population interaction term. This model allowed estimation of the treatment effect in the severe psoriasis paediatric population in independence of the adult data whilst, at the same time, estimating the difference in the treatment effect of severe psoriasis versus moderate psoriasis patients in the adult population. It was assumed that the difference in the treatment effect between severe and moderate adult population is the same as the corresponding difference in the paediatric population. Under this assumption, the severity difference in the treatment effect obtained for the adults was applied to the paediatric severe treatment effect estimated for Study A2310 to provide a predicted treatment effect for a moderate psoriasis paediatric population. Analysis was performed separately on IGA0/1, PASI75 and PASI90 responses at Week 12. The median value of the mean log odds ratio as well as the 95% predictive credible interval for moderate psoriasis paediatric population were reported for secukinumab High and Low dose. The probability of a positive treatment effect (over placebo) was provided for secukinumab High and Low dose arms.

Higher predicted log-Odd Ratios (ORs) were calculated with this model for the hypothetical paediatric population with moderate psoriasis, when compared to those predicted for the paediatric population with severe psoriasis, see Table below. The results showed that the probability of a positive treatment effect over placebo is almost certain, being close to 100%.

Table 15 ***Predicted efficacy at Week 12 in paediatric population with moderate psoriasis - Pure non-responder imputation (FAS)***

Criterion	AIN457 Low dose	AIN457 High dose
PASI 75		
Predicted log-OR (95% CrI)	3.41 (2.29, 4.59)	3.59 (2.42, 4.79)
Probability of (log-OR > 0)*	100%	100%
IGA 0/1		
Predicted log-OR (95% CrI)	4.08 (2.78, 5.40)	4.14 (2.87, 5.48)
Probability of (log-OR > 0)*	100%	100%
PASI 90		
Predicted log-OR (95% CrI)	4.82 (3.46, 6.30)	5.09 (3.73, 6.55)
Probability of (log-OR > 0)*	100%	100%

OR = odds ratio, 95% CrI = 95% credible interval. Comparisons are against placebo.
*. Posterior probability of a positive treatment effect for AIN457 High or Low dose compared to placebo.

Subsequently, upon request for supplementary information, the MAH provided interim efficacy data in moderately psoriatic children from the open-label study A2311, as an external validation of the extrapolation model. These data are displayed in Table below. Upon request for supplementary information, the MAH provided an analysis of type I error rate of the proposed extrapolation model (Figure below). The figure displays the probability of wrongly concluding that severe adult and severe paediatric population are similar (labelled as "error rate" on the y-axis) as a function of a response rate (x-axis) which is assumed to be identical for placebo and secukinumab treatment groups; the similarity implies that the extrapolation concept holds, such that the superiority of secukinumab over placebo in the severe adult population is also true for the severe paediatric population; in other words, the figure shows the probability of wrongly concluding treatment effect through the extrapolation concept if there is no treatment effect at all.

Table 16 ***Predicted response rates for PASI 75, PASI 90 and IGA 0 or 1 at Week 12 in pediatric population with moderate disease (Pure non-responder imputation) (Full analysis set)***

Criterion	AIN457 Low dose N=30	AIN457 High dose N=31
IGA 0/1		
Observed response rate*	83.3	83.9
Predicted response rate (95% CrI)	70.02 (53.95, 82.73)	66.94 (50.27, 80.05)
PASI 75		
Observed response rate*	93.3	93.5
Predicted response rate (95% CrI)	76.62 (61.09, 87.50)	78.17 (62.22, 89.09)
PASI 90		
Observed response rate*	70.0	80.6
Predicted response rate (95% CrI)	63.68 (47.38, 78.00)	66.77 (50.55, 80.89)

* Observed in Study A2311, 95% CrI = 95% credible interval

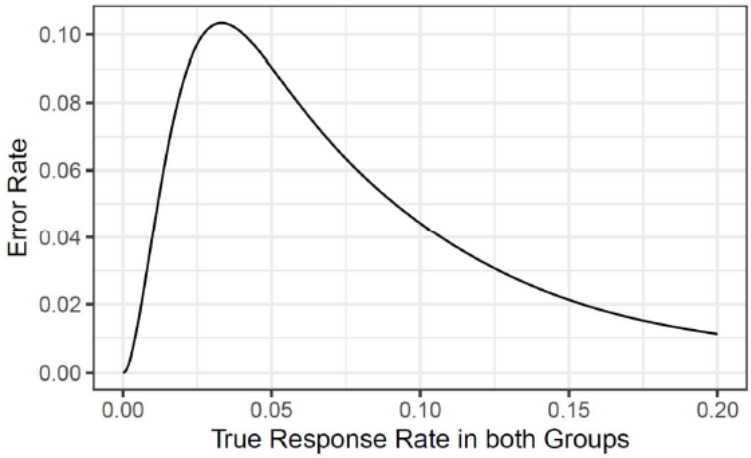


Figure 9 ***Error rates***

2.3.4. Discussion on clinical pharmacology

2.3.4.1. Pharmacokinetics

The MAH has presented secukinumab trough concentrations up to week 52 for low-dose and high-dose groups and at different weight categories for study A2310. In addition, trough data from an on-going study A2311 has been presented and PK parameters between week 12 and week 24 have been calculated. The data indicates that secukinumab concentrations increase with the dose within the same weight groups. The exposure after secukinumab 75 mg dose in children <25 kg is within the range seen in paediatrics in other weight categories. Cmax and AUC84-112d are slightly higher in paediatric patients treated with 150 mg (group: 25-<50 kg) and 300 mg (group: ≥50 kg) than in paediatrics <25 kg treated with 75 mg. Mean secukinumab concentrations after the recommended doses at week 24 are included in the Section 5.2 of the SmPC for the different weight groups which is acceptable to CHMP.

The bioanalytical methods with ELISA are similar between adult and pediatric patients except for quantitation limit. LLOQ of 500 ng/ml was used in the study A2310 with pediatric patients and LLOQ of 80 ng/ml has been used in studies with adult patients. The bioanalytical method used in study A2311

has not been specified. The bioanalytics with pediatric patients were performed at SGS (France) instead of WuXi AppTec (Shanghai, China) where the analysis have been performed previously with samples from adults. Cross validation between the assay from WuXi AppTec and SGS have been performed. The CHMP considered that analytical methods are acceptable and they are adequately described.

2.3.4.2. Population PK model

To describe the raw PK data, the MAH has presented secukinumab trough concentrations at Weeks 4, 12, 24 and 52 for low-dose and high-dose groups, and separately for patients who first received placebo and then were followed by low or high dose.

The MAH submitted additional data from study A2310 and interim data from ongoing study A2311 in their response to CHMP request for supplementary information. These additional data were included in Figure 1 outlining the agreement between paediatric concentration observations and original population PK model predictions. However, the population PK model fittings were performed with a subset of A2310 data until week 24, that were available at the time of original type II variation submission. To investigate the appropriateness of the paediatric dose selection, the MAH has compared the observed paediatric trough concentrations to drug concentrations simulated from the adult population PK model, the results of which are shown in Figure 1. The observed concentrations at Week 4 tend to be systematically higher than the concentrations predicted based on the population pharmacokinetic model built upon adult data. At weeks 12 and 24 this trend diminishes.

The MAH has included the paediatric study A2310 data until week 24 into the adult population PK dataset and fitted new population PK models to the combined dataset. The models are described in Table 10, and the results are displayed in Table 11. Model 1 was a re-estimation of the existing model based on the new dataset including data from study A2310. Model 2 includes allometric scaling exponents of 1 for volume of distribution and 0.75 for clearance, as recommended by the "Modelling and simulation: questions and answers" ("Should fixed or estimated values for allometric scaling exponents be used in paediatric pharmacokinetic models? November 2018" - https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation-questions-answers), which in this case resulted in statistically worse model performance. Model 3 features a different bioavailability for the paediatric population versus the adult population, and model 4 (not included in Table 11) implements a study-specific bioavailability. Model 3 seems to have been chosen as the model to go forward with, and Model 4 was considered an additional investigation.

The rationale for testing a different bioavailability for the paediatric population in Model 3 is clear and acceptable to the CHMP.

Within the diagnostic plots of Model 3, a remaining trend can be seen in the residuals (NPDE in this case) versus nominal time; the residuals are higher at week 4 than during the rest of the treatment. This trend is similar to the trend observed in Figure 1, where the observed trough concentrations at Week 4 were higher than those simulated from the original population PK model based on adult data. However, the observed trend in residuals is unlikely to have major clinical relevance; hence, the issue was not pursued by the CHMP.

2.3.4.3. Exposure-response model

The MAH has performed a graphical analysis of raw exposure-response data from study A2310 up to week 52, and interim data from study A2311 (Figure 5). Displayed are exposure-response data of adults and children with moderate and severe disease states.

Given the raw data analysis, the exposure-response relationship in adults appears similar in moderate *versus* severe disease states. The EMA reflection paper on extrapolation (EMA/189724/2018 section 5.1.3) states that a difference in clinical outcomes between source and target populations could limit extrapolation. Some dissimilarities in exposure-response relationship can be observed between adults and children; however, these differences are considered minor to the CHMP and they point towards children being more responsive to secukinumab.

In order to further investigate exposure-response in children, the MAH has included the paediatric efficacy data from study A2310 up to week 24 into the original adult PK/PD model that was used to support the registration of secukinumab. No new models were fitted to the updated dataset; instead, the original PK/PD model was used to calculate residuals for both the adults and the children, and a graphical assessment of the residuals concluded that the model is performing similarly for both the adults and the children. Then, the model was used to derive individual PK/PD parameter estimates for the children. A graphical assessment of trends in the individual PK/PD parameters of both adults and children was undertaken to examine potential differences in exposure-response in adults versus children (Figure 7).

A trend towards higher EC_{50} values and lower *kout* values at decreasing bodyweights seems to be present. However, overall, the CHMP accepted that the exposure-response profile is similar enough between adults and children to support the extrapolation of efficacy to severely and moderately psoriatic children.

2.3.4.4. Extrapolation of efficacy from severe to moderate disease state in children

To facilitate the comparative assessment of efficacy in adults and children, the MAH has summarized the adult and paediatric (study A2310) efficacy week 12 response data into a single table (Table 12). From the table, it seems as if a dose-response relationship exists for adults, but does not exist for children: No apparent difference in efficacy in children between low and high doses, which is in contrast with the higher adult efficacy at the high 300 mg adult dose when compared to the low 150 mg adult dose. However, an exposure-response relationship in children is seen in Figure 5 which is based on more data.

Data from study A2310 up to week 24 were used in the extrapolation exercise. The MAH has outlined a four-step process for extrapolation of efficacy from adults to children.

- Step 1 aims to establish the efficacy of secukinumab in severely psoriatic children; this step consists of efficacy summaries on the basis of interim data.
- Step 2 aims to establish the similarity of efficacy in severely psoriatic adults versus severely psoriatic children. In this step, a Bayesian model is fitted based on the adult efficacy data, and the model aims to predict the paediatric efficacy data; paediatric data are only used for "external validation" of the model.
- Step 3 aims to establish similarity of secukinumab efficacy in adults with moderate versus severe psoriasis.
- Step 4 extrapolates the efficacy of secukinumab to children with moderate psoriasis on the basis of the prior steps.

Step 2, the model in was fitted separately for each treatment arm, and therefore no parameters for dose strength were estimated. The software used for Bayesian modelling in Steps 2 and 4, Stan, is a relatively new software; not considered industry standard, but acceptable nonetheless to the CHMP.

The Step 2 results are displayed in Table 13. All the key results are within the 95% credible interval.

Step 3 consisted of running a non-Bayesian meta-analysis model, with treatment arm, study, Baseline severity, Baseline bodyweight and Baseline severity by treatment interaction as fixed explanatory variables. The main objective of this step was to establish that there is no interaction between disease severity and treatment; in other words, the aim was to demonstrate that secukinumab efficacy is similar in moderately versus severely psoriatic adults. The results of this step are summarized in Table 14.

Contrary to the MAH's claim, there appears to be an interaction between disease severity and treatment effect for the IGA 0/1 endpoint. Patients with moderate disease state seem to attain the endpoint more readily than patients with severe disease state. However, this was a problem to the CHMP as the extrapolation framework includes a formal assumption that the treatment effect is similar in patients with moderate and severe disease states. The data indicate that the treatment effect may be larger in patients with moderate disease state. Therefore, in this respect, the paediatric predictions from the extrapolation exercise may be considered conservative, and the true treatment effect in children with moderate disease state may be larger than that predicted by the model. The issue of differing treatment effects by disease severity was therefore not pursued by the CHMP because it results in conservative predictions, and not optimistic predictions.

Step 4 involved fitting a Bayesian model to the efficacy data of severely psoriatic children, and moderately and severely psoriatic adults. This model was used to predict secukinumab efficacy in moderately psoriatic children. The model included fixed-effects terms for response rates (control and treatment effect), Baseline severity (moderate vs. severe), population indicator (paediatric vs. adult), treatment by severity and treatment by population interaction term. The variance components of the model were between-study heterogeneity of response rates (control and treatment effect), and for correlations of the study-specific effects. The extrapolation predictions are displayed in Table 15. The model predicts with a positive treatment effect with near certainty.

When interpreting the results, it is useful to remember that the "Probability of log-OR > 0" denotes the probability of the study drug having a positive effect compared to placebo, however a positive effect alone may not be clinically meaningful. Also, a second placebo dose would have a "probability of log-OR > 0" of 50%.

The MAH was requested to provide interim data of the open-label Study A2311 of secukinumab efficacy in moderately psoriatic children, and to present these interim data in the context of external validation for the extrapolation model. The MAH complied and the external validation results are presented in Table 15 from which it becomes apparent that the response rates observed so far are at least as high as the predicted response rates, thus supporting the extrapolation. The MAH was also requested to calculate the probability of erroneously concluding a positive treatment effect for secukinumab when in truth there is no treatment effect. The MAH complied and based on the information supplied in Figure 9, a very small risk of a false positive conclusion in favour of secukinumab treatment effect in moderately psoriatic children is foreseen. This is found acceptable to the CHMP.

2.3.5. Conclusions on clinical pharmacology

Secukimab PK has been studied with population pharmacokinetic methodology. Sparse sampling data from the paediatric efficacy study A2310 have been included into the population pharmacokinetic dataset used in the original submission, the population pharmacokinetic model has been refined based

on the new data, and the appropriateness of the paediatric doses has been evaluated. The modelling steps have been appropriately conducted. The observed concentration data from studies A2310 and A2311 agree with the original population PK model predictions which were used to determine paediatric dose strengths.

The MAH has conducted a statistical extrapolation of efficacy from moderately psoriatic adults to moderately psoriatic children. The rationale is that if secukinumab efficacy is similar for severely psoriatic adults and children, and the efficacy for moderately psoriatic adults is known, then efficacy for moderately psoriatic children can be predicted. The overall strategy is considered rationale by the CHMP, and the extrapolation model has been validated with interim efficacy data of moderately psoriatic children in study A2311. The extrapolation of secukinumab efficacy for moderately psoriatic children is considered acceptable by the CHMP and is adequately described in Section 5.1 of the SmPC.

2.4. Clinical efficacy

2.4.1. Dose response study

No specific studies for dose selection were conducted for secukinumab in paediatric psoriasis patients. The dose selection in paediatric patients was based on the completed Phase III program in adults as well as modelling and simulation based on the results from adult Phase II/III studies.

2.4.2. Main studies

2.4.2.1. CAIN457A2310

"A randomised, double-blind, placebo- and active controlled multicentre 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".

Methods

Study A2310 is an ongoing randomised, double-blind, placebo- and etanercept -controlled study, consisting of a screening period of up to 4 weeks, a placebo- and active-controlled 12 week induction period, an active-controlled 40 week maintenance period, a non-controlled 184 week extension period, and a 16 week post-treatment follow-up period. An outline of the study design is displayed in Figure below.

During the **induction period** (defined as randomisation through Week 12 prior to dose), the study was both active and placebo-controlled, and the primary endpoint (Week 12) was assessed at its completion. At the start of the induction period, eligible patients were randomised in a 1:1:1:1 ratio into one of four treatment groups (etanercept, secukinumab Low dose group, secukinumab High dose group, or placebo group). Moreover, at the Randomisation visit, patients randomised into the placebo group were pre-assigned to either the Low- or High-dose group of secukinumab for the maintenance period in case they did not achieve a PASI 75 response as assessed at Week 12.

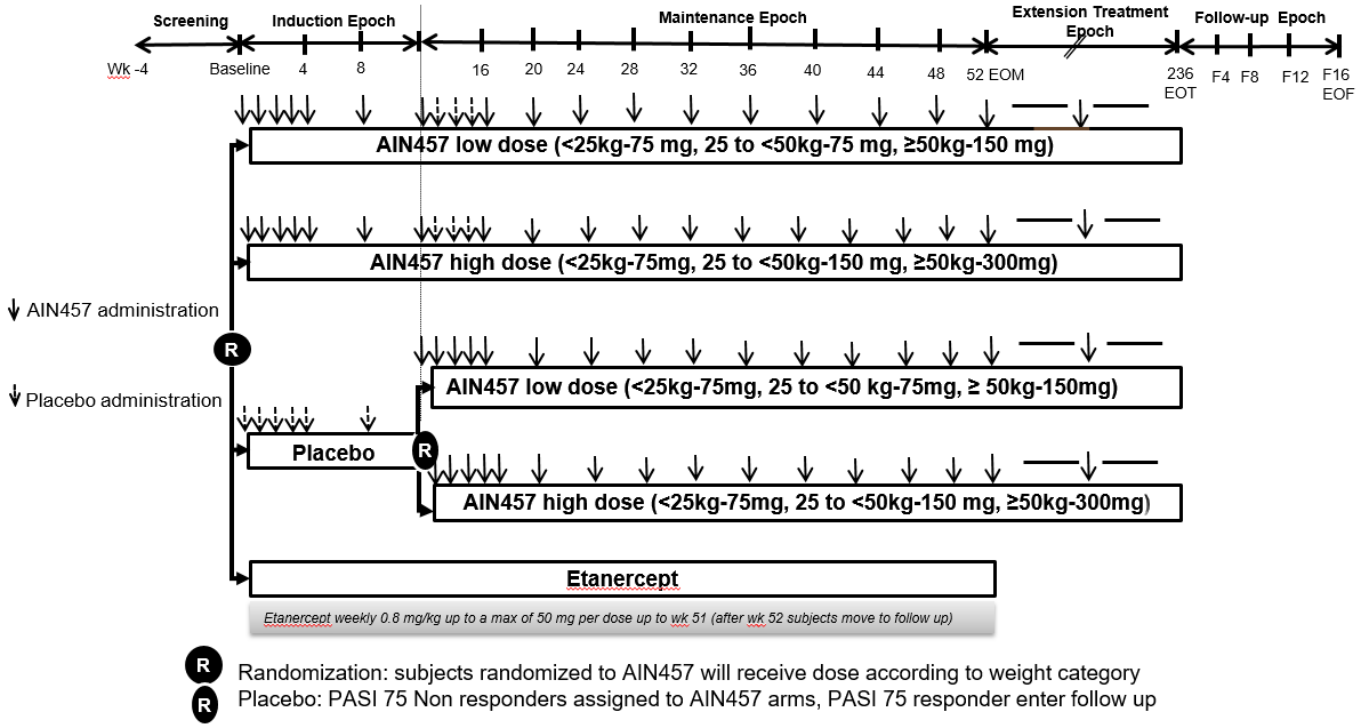


Figure 10 Outline of study design for study A2310

During the **maintenance period** (defined as Week 12 (from dosing) through Week 52), the study was active-controlled and the objectives focused on the maintenance of the response observed at Week 12. Patients who received secukinumab or etanercept during induction continued with the same treatment in maintenance. Patients who were on placebo during induction and were PASI 75 non-responders at Week 12 were switched to either secukinumab Low dose or secukinumab High dose treatment group according to their pre-assignment at baseline; PASI 75 responders on placebo discontinued study treatment at Week 12 and entered the treatment-free follow-up period for 8 weeks or until systemic therapy was started. At the end of the maintenance period, patients on secukinumab entered the extension treatment period whereas patients on etanercept entered the post-treatment follow-up period and thereafter completed the study. At the time of the current assessment, all patients have completed the maintenanceperiod (or withdrawn).

During the **extension treatment period** (defined as Week 52 (from dosing) until Week 236), all patients are treated with secukinumab and the purpose is the collection of long-term safety and efficacy data. At the end of the maintenance period, all patients on secukinumab enter the extension treatment period and continue to receive the same dose of secukinumab. Patients who participate in the maintenance period but prematurely discontinue the study as well as patients receiving etanercept are not eligible to enter the extension treatment period.

During the **post-treatment period**, patients are monitored for an additional 16 weeks after end of treatment.

Recruitment into the study was started in 2015. The study initially enrolled adolescent patients aged 12 to less than 18 years. Enrolment of children aged 6 to less than 12 years began after a favourable recommendation by an independent external Data Monitoring Committee (DMC) who reviewed data of approximately 80 (approximately 40 treated with secukinumab) adolescents (aged 12 to less than 18 years) treated for 28 weeks. The first patient less than 12 years old was randomised in March 2018.

To support the initial submission for this extension of indication, an analysis of data was performed after all patients completed their Week 24 visit; data cut-off was on 07 March 2019. This analysis was

presented in the Week 24 clinical study report (CSR) provided in the initial submission and included primary endpoint data at Week 12 and efficacy data up to Week 24 visit. The results from the Week 24 cut-off date provided 24-week safety data for all paediatric patients as well as long term safety data of varying duration (up to 3 years) in patients enrolled earlier in the study.

Another full analysis of the study was performed when all patients had completed the Week 52 visit, and data was reported in the Week 52 CSR provided for assessment in response to the CHMP's Request for Supplemental Information. Data cut-off for the Week 52 CSR was 18 September 2019.

Study participants

Inclusion criteria

1. Written informed assent and parental permission (age as per local law) obtained at screening before any assessment is performed. If patients reached age of consent (age as per local law) during the study, they needed to also sign the corresponding study Informed Consent(s).
2. Must be 6 to less than 18 years of age at the time of randomisation
    a. Patients 12 to less than 18 years enrolled from beginning of trial
    b. Patients 6 to less than 12 years enrolled after positive DMC recommendation following review of data from the first 80 adolescents
3. Severe plaque psoriasis, defined as a PASI score ≥ 20, and IGA mod 2011 score of 4, and BSA involvement of ≥10%, at randomisation
4. History of plaque psoriasis for at least 3 months
5. Patient being regarded by the investigator to be a candidate for systemic therapy because of:
   (1) inadequate control of symptoms with topical treatment, or
   (2) failure to respond to or tolerate previous systemic treatment and/or UV therapy

Exclusion criteria

1. Forms of psoriasis other than chronic plaque-type (*e.g.*, pustular, erythrodermic and guttate psoriasis), active at randomisation
2. Drug-induced psoriasis (*i.e.*, new onset or current exacerbation from beta-blockers, calcium channel blockers or lithium)
3. Ongoing use of certain prohibited treatments (including biological agents, other systemic immunomodulators, phototherapies, *etc.*) as specified in the protocol. Washout periods were specified and had to be adhered to
4. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or the IL-17 receptor, or to etanercept
5. Use of any other investigational treatment within 4 weeks before randomisation, or within a period of 5 half-lives of the investigational treatment, whichever was longer
6. History of severe hypersensitivity reaction or anaphylaxis to any biological agents (human monoclonal antibody or soluble receptor)
7. Pregnant or nursing (lactating) females

8. Female patients (<18 years of age) of childbearing potential (menarchal or becoming menarchal during the study) who did not agree to abstinence or, if sexually active, did not agree to the use of contraception, with acceptable methods specified in the protocol
9. Female patients (who became ≥ 18 years of age during the study) of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they were using effective methods of contraception during dosing of study treatment and for a defined minimum period after stopping study treatment. Minimum periods and effective contraception methods were specified in the protocol
10. Active ongoing inflammatory diseases other than psoriasis that might confound the evaluation of the benefit of secukinumab and/or etanercept therapy
11. Underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal) which in the opinion of the investigator significantly immunocompromised the patient and/or placed the patient at unacceptable risk for receiving an immunomodulatory therapy
12. Investigator discretion was used for patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders
13. Patients with a estimated glomerular filtration rate (eGFR), estimated by the Schwartz equation, of < 60 mL/min/1.73 m^2 at screening. Assessment could be repeated once, two or more days later, and if eGFR value ≥ 60, patient could be included at the discretion of the investigator
14. Patients with total white blood cell (WBC) count <2,500/µL, or platelets <100,000/µL or neutrophils <1,500/µL or hemoglobin <8.5 g/dL at screening
15. Ongoing infections and in particular tuberculosis. If warranted for a patient and based on the investigator's judgment, an X-ray or magnetic resonance imaging (MRI) at pre specified sites could be performed as part of the screening procedure
16. Active systemic infections during the last two weeks (exception: common cold) prior to randomisation and any infections that reoccurred on a regular basis
17. Investigator/qualified site staff discretion was used regarding patients who had traveled or resided in areas of endemic mycoses, such as histoplasmosis, coccidioidomycosis or blastomycosis and for patients with underlying conditions that could predispose them to infection, such as advanced or poorly controlled diabetes
18. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive QuantiFERON TB-Gold test (QFT) at screening. Patients with a positive QFT test could participate in the study if further work up (according to local practice/guidelines) established conclusively that the patient had no evidence of active tuberculosis. If presence of latent tuberculosis was established, then treatment must have been initiated and maintained according to local country guidelines prior to randomisation
19. Known infection with HIV, hepatitis B or hepatitis C at screening
20. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years prior to screening
21. Plans for administration of live vaccines during the study period or within 6 weeks prior to randomisation

22. Any medical or psychiatric condition which, in the Investigator's opinion, could preclude the participant from adhering to the protocol or completing the study per protocol
23. Hypersensitivity or allergy to any of the ingredients of study treatments, including etanercept
24. History or evidence of ongoing alcohol or drug abuse, within the last 24 weeks before randomisation
25. Patients not willing to limit UV light exposure (*e.g.*, sunbathing and/or the use of tanning devices) during the course of the study
26. Unwillingness to undergo repeated venipuncture or subcutaneous injections

Treatments

The following study treatments were used:

Investigational drug

- Secukinumab prefilled syringes, available as 150 mg in 1.0 mL and as 75 mg in 0.5 mL.

Reference therapies

- Secukinumab placebo: secukinumab placebo available as 1 mL and 0.5 mL prefilled syringes, in a form to match secukinumab prefilled syringes.
- Etanercept active comparator (not a biosimilar).

Treatment arms

Patients were randomised using a 1:1:1:1 ratio into one of the treatment arms: secukinumab Low dose, secukinumab High dose, etanercept or placebo. Patients randomised to secukinumab treatment arms (High dose and Low dose) received a dose based on the weight category (< 25 kg, 25 to < 50 kg, ≥ 50 kg). In order to maintain the treatment blind, all patients in secukinumab or placebo arms received 2 s.c. injections at each dose, except for patients < 25 kg weight category who received only 1 injection of either 75 mg secukinumab or matching placebo. The dosing regimens were as follows:

- Secukinumab Low dose group: According to the weight category, s.c. secukinumab 75 mg (in < 25 kg and 25 to < 50 kg) or 150 mg (≥ 50 kg) injections at Randomisation, Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and placebo at Weeks 13, 14 and 15 during the blinded phase of the study; thereafter at Week 52 and every 4 weeks during the Extension period until Week 232.
- Secukinumab High dose group: According to the weight category , s.c. secukinumab 75 mg (in < 25 kg), 150 mg (25 to < 50 kg), 300 mg (≥ 50 kg) injections at Randomisation, Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and placebo at Weeks 13, 14 and 15 during the blinded phase of the study; thereafter at Week 52 and every 4 weeks during the Extension period until Week 232.
- Etanercept (active comparator) group: s.c. etanercept 0.8 mg/kg (up to a maximum dose of 50 mg) once per week, for 51 weeks. Subjects in this arm were unblinded, but the efficacy assessor was blinded as regards treatment assignment.
- Placebo group: Placebo (one/two s.c. injections per dose) once per week for four weeks (at Randomisation, Weeks 1, 2 and 3), followed by dosing every four weeks (Weeks 4 and 8). At Week 12, subjects in the placebo group based on their PASI 75 response status at Week 12 proceeded as follows:

- PASI 75 responders on placebo discontinued study treatment at Week 12 and entered the treatment-free follow-up period for 8 weeks or until systemic therapy was started.
- PASI 75 non-responders on placebo received High dose or Low dose secukinumab, according to their pre-assignment at the Randomisation visit, and received their treatment according to the weight category based on the weight measured at Week 12 visit (<25 kg, 25- <50 kg, ≥50 kg), on Weeks 12, 13, 14, 15, and then every four weeks starting at Week 16 until Week 48 during the Maintenance period; thereafter at Week 52 and every 4 weeks during the Extension period until week 232.

Concomitant treatments

Other therapies for psoriasis had to be discontinued prior to randomisation, and wash-out periods for different classes were defined in the study protocol. Use of a topical corticosteroid of mild or moderate activity was allowed for the face, scalp, hands, feet and genitoanal area during the screening period. After the screening period, the use of concomitant medication for psoriasis in all body regions was restricted to bland emollients and other non-medicated interventions. The definition of "bland" excluded all topical medications that contain pharmacologically active ingredients such as (but not limited to) lactic acid, salicylic acid, urea, α-hydroxy acids or fruit acids. Topical corticosteroids and other topical treatments were only allowed from the Week 12 visit onward and only if they were used for an indication other than psoriasis and not on the area affected with psoriasis. The use of any other systemic therapies or phototherapies for psoriasis was prohibited throughout the study.

Objectives

The protocol-defined primary objective of the study was to demonstrate the superiority of secukinumab (Low and High dose) in paediatric subjects with severe chronic plaque psoriasis with respect to both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared to placebo.

The secondary objectives were:

- To demonstrate superiority of secukinumab (Low and High dose) in subjects with severe chronic plaque psoriasis with respect to PASI 90 response at Week 12, compared to placebo.
- To assess efficacy of secukinumab in subjects with severe chronic plaques psoriasis with respect to PASI 50 and PASI 100 at Week 12, compared to placebo.
- To assess efficacy of secukinumab in subjects with severe chronic plaque psoriasis with respect to PASI 50, PASI 75, PASI 90 , PASI 100 and IGA mod 2011 0 or 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 the Children's Dermatology Life Quality 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 subjects with history of psoriatic arthritis.

- 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, electrocardiograms (ECGs), and adverse events monitoring, compared to placebo.

The 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 epoch).
- To assess the occurrence of rebound following secukinumab and etanercept therapy (during follow-up epoch).
- 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 pharmacokinetic parameters.
- To investigate the development of immunogenicity 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 adverse events 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.

Outcomes/endpoints

- The co-primary efficacy endpoints were PASI 75 response and IGA mod 2011 0 or 1 response at Week 12.
- The key secondary endpoint was PASI 90 response at Week 12.
- Secondary efficacy endpoints included:
    - PASI 50/100 response at Week 12,

- PASI 50/75/90/100 and IGA mod 2011 0 or 1 response over time,
- time to PASI 75/90 response (up to Week 12), and
- PASI score and IGA mod 2011 score over time.

- Patient reported outcomes (PRO) included CDLQI and CHAQ assessments (in patients with history of psoriatic arthritis).

Sample size

It was planned to enroll 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 (< 25kg, 25 -≤ 50kg and > 50kg). It was targeted to have at least 30 patients in the < 12 years subgroup at a minimum. 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 a data monitoring committee (DMC).

Since two secukinumab dose regimens were tested versus placebo with respect to the co-primary endpoints (PAS 75 response and IGA mod 2011 0 or 1 response at Week 12), the type-I-error was split to 1.25% one-sided for each comparison. With 40 patients per group and assuming a response rate of 10% for PASI 75 response and IGA mod 2011 0 or 1 response in the placebo group, the power to show a response rate of 65% for PASI 75 response and 45% for IGA mod 2011 0 or 1 response in the secukinumab groups based on Fisher's exact test was approximately 99% for PASI 75 response and approximately 88% for IGA mod 2011 0 or 1 response.

For the secondary endpoint of PASI 90 response at week 12, assuming a response rate of 8% in the placebo group, the power to show a significant difference between a secukinumab dose and placebo, assuming a response rate of 39% in the secukinumab groups based on Fisher's exact test was approximately 82% for PASI 90 response. The assumed response rates for secukinumab were based on the confirmatory efficacy in severe patients in the adult phase III program. At Week 12, PASI 75 response rates of 11% and PASI 90 response rates of 7% have been reported in the placebo group in an earlier study with etanercept in children and adolescents aged 4-17 years.

Randomisation

At Randomisation (Visit 2), all eligible patients were randomised via Interactive Response Technology (IRT) to one of the treatment arms. The qualified site personnel contacted the IRT after confirming that the patient fulfilled all the inclusion/exclusion criteria. The patient number, the weight of the patient and the age was entered. Stratification was planned for age (< 12 years, ≥ 12 years) and weight (< 25 kg, 25-< 50 kg and ≥ 50 kg). The IRT assigned a randomisation number to the patient. For the patients who received secukinumab or secukinumab placebo, this number was used to link the patient to a treatment arm and specified a unique medication number for the package or packages of investigational treatment to be dispensed to the patient. Each patient received one or two packages per dispensing visit, depending on the treatment group and treatment period. For those patients who were randomised to etanercept, medication was provided centrally (by a CRO) or purchased from the local market. The randomisation number was not communicated to the caller or other site members.

In this study, an Interactive Response Technology (IRT) error led to additional dosing of patients. The dosing errors happened after the primary endpoint (Week 12) assessment. Specifically, 36 patients who

were assigned to the Low dose (16 patients) and High dose (20 patients) secukinumab groups were dispensed active medication at Week 13, 14, 15 visits.

At these visits, the patients who were randomised to active treatment groups were expected to receive placebo medication as to maintain the blind. Five patients in the secukinumab High dose group (25-<50 kg/150 mg dose) were dispensed in error secukinumab 150 mg at these visits; 16 patients in the secukinumab Low dose group (≥50 kg/150 mg dose) were dispensed in error secukinumab 300 mg at these visits; and 15 patients in the secukinumab High dose group (≥50 kg/300 mg dose) were dispensed in error secukinumab 300 mg at these visits.

The incident was communicated to Investigators and Health Authorities, was presented to internal Novartis boards and a corrective action plan was put in place by the IRT vendor. The unblinded DMC Board also reviewed data from the affected patients and expressed no safety concerns. The dosing error was taken into account in additional efficacy, safety and pharmacokinetic reports and its impact on the results was to be assessed and documented appropriately.

Blinding (masking)

The secukinumab and the placebo arms are 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 patients could not continue into the Maintenance period but entered the post treatment follow-up period.

The etanercept arm is single (assessor) blind until the moment the patient completes the Week 52 visit and enters the follow-up period. Site staff (with the exception of the efficacy assessor), patient and sponsor are not blinded to the Etanercept arm for the entire treatment duration with Etanercept.

After the interim database lock for analysis at Week 24, designated sponsor team members were unblinded to perform the analyses and develop this clinical study report (CSR), whereas patient, investigator staff and persons performing the assessment continued to remain blinded until the database lock at Week 52. The unblinded Novartis members were not allowed to participate further in the conduct of the study nor to communicate any confidential treatment data to blinded Novartis personnel including study monitors. Thus blinded Novartis team continuing with study conduct beyond Week 24, study monitors, Investigators and patients continued to remain blinded until after Week 52 database lock.

Any interim data analyses for the DMC or any other interim analyses which could be requested by health authorities during the blinded portion of the study were performed without unblinding of Novartis personnel. Unblinded data was only made available to independent Novartis/CRO individuals involved in the preparation of the interim analyses and who were not directly involved in the study conduct.

Statistical methods

Analysis sets

Randomised, Full Analysis, and Safety Analysis Sets were defined. The randomised set was defined as all patients who were randomised. Unless otherwise specified, mis-randomised patients, where IRT contacts were made prematurely and double-blind treatment was not administrated were excluded from the randomised set. The Full Analysis Set (FAS) comprised all patients from the randomised set to whom study treatment had been assigned. Following the intent-to-treat principle, patients were analysed according to the treatment assigned at randomisation. If the actual stratum was different to the assigned stratum in IRT, the actual stratum was used in analyses. The safety set included all patients who took

at least one dose of study treatment during the treatment period. Patients were analysed according to treatment received.

The co-primary efficacy endpoints were PASI 75 response at Week 12 and IGA mod 2011 0 or 1 response at Week 12. The analysis of the co-primary and key secondary variables was based on the FAS. The objective was to demonstrate superiority of Low or High dose of secukinumab with respect to PASI 75 response or IGA mod 2011 0 or 1 response at Week 12.

Both co-primary endpoints was to be evaluated using an exact logistic regression model with treatment group, baseline body weight stratum, age stratum and baseline PASI score as explanatory variables. If convergence was not reached, the covariates could be removed from the model one by one until convergence was reached, by starting with continuous covariates (*i.e.*, baseline PASI) and followed by removing categorical covariates (*i.e.*, age stratum, body weight stratum).

Odds ratios were computed for comparisons of secukinumab dose regimens versus placebo utilizing the logistic regression model fitted. Confidence intervals for risk difference were derived based on the exact method. In case of rates of 0% or 100% in one of the treatment groups, for analyses with multiple imputation, confidence intervals for risk difference and p-values from the t-test for the risk difference comparing to 0 were provided; for analyses with non-responder imputation, Fisher's exact test was to be performed and confidence intervals for risk difference were provided.

Missing data

Response variables based on PASI score and IGA mod 2011 categories up to week 24 were imputed with multiple imputation (MI) as primary imputation method for the missing values and pure-non-responder imputation as a sensitivity method. Other response variables (*e.g.*, CDLQI and CHAQ score) were imputed with last observation carried forward (LOCF). MI was a simulation based approach where missing values were replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets were analysed using standard methods. Within this analysis, the PASI score or IGA mod 2011 categories were imputed and response variables were derived based on the imputed scores. In the multiple imputation analysis, the response status was imputed based on the individual treatment arm information. The imputations were done separately for each treatment group.

Supportive analyses were to be performed as follows:

- Co-primary endpoints and key secondary endpoint were to be evaluated using the logistic regression model (as described in primary analysis method) with pure non-responder imputations instead of multiple imputations for missing values.
- Primary analysis was also to be evaluated on the subset of adolescents.

The secondary variable in testing strategy was the PASI 90 response at Week 12 (for superiority comparison of secukinumab doses versus placebo). The secondary efficacy variable PASI 90 at Week 12 in the same way as the primary variables. It was analysed using the FAS unless otherwise specified.

Additional data driven analysis

Upon performing the pure non-responder imputation it was noticed that many Week 12 efficacy assessments were noted as missing and thus patients were accounted as non-responders for the analysis at Week 12. Therefore, an additional sensitivity analysis with extended Week 12 analysis visit window using non-responder imputation and multiple imputation was performed (Week 12 visit window Day 72 - 102 instead of Day 72 - 88).

Subgroups of interests

The co-primary endpoints and important secondary endpoints and selected safety endpoints were to be evaluated using the following subgroups:

- Randomisation weight strata (< 25 kg, 25-< 50 kg, ≥ 50 kg)
- Randomisation age strata (< 12 years or ≥ 12 years)
- Previous systemic therapy (Yes, No)

Multiple testing

The graphical approach for sequentially rejective testing procedure is used to illustrate the testing strategy in Figure below.

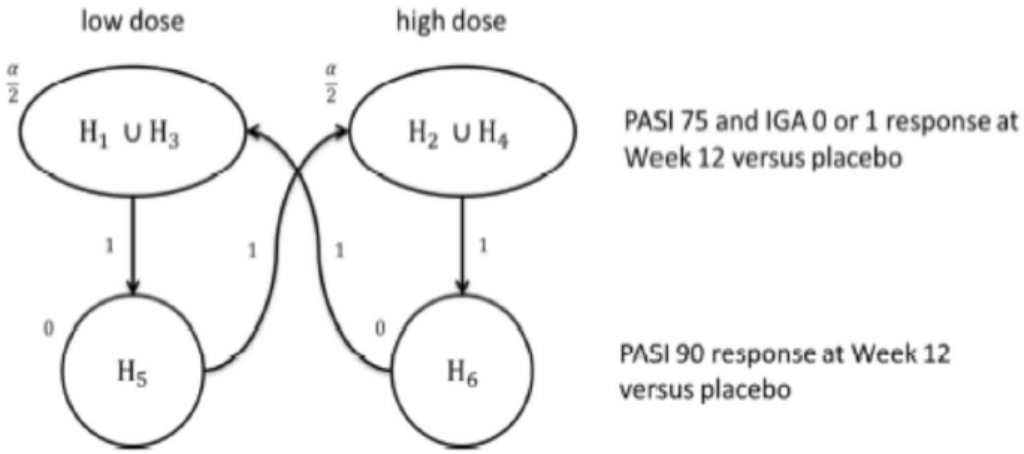


Figure 11 Testing strategy

One-sided p-values were derived. The family-wise error was set to α =2.5% (one sided). The hypotheses were mapped into two sets (H1, H3 and H5) or (H2, H4 and H6) such that hypotheses within a set correspond to the same secukinumab dose regimen. In essence, the type-I-error probability was to be equally split for both sets of hypotheses and within each set the hypothesis were tested sequentially as follows:

Within each pair, of hypotheses (H1 or H3) and (H2 or H4), each hypothesis was to be tested at α/2 (one-sided). Only if both hypotheses of a pair were rejected, the testing sequence was continued.

In the next step of the sequence, the null hypotheses corresponding to the PASI 90 comparison of secukinumab versus placebo was to be tested. H5 and H6 were tested at α/2 (one-sided).

If all hypotheses within a set referring to a secukinumab dose regimen had been rejected, i.e., either (H1, H3 and H5) or (H2, H4 and H6), the corresponding type I error probability could be passed on to the other set of hypotheses, and if needed, hypotheses could be retested at a higher significance level.

Results

Participant flow

A total of 187 patients were screened, of which 162 completed the screening phase and were randomised to the four treatment groups in a 1:1:1:1 ratio. The majority of patients (96.3% overall) completed the

Induction period; 1 to 2 patients in each treatment group discontinued during the Induction period. The reasons for discontinuations were AE (2 patients: toxic shock syndrome in the secukinumab High dose group and pustular psoriasis in the placebo group), subject/guardian decision (2 patients), lack of efficacy (1 patient) and protocol deviation (1 patient). Patient disposition in the Induction period is displayed in Table below.

Table 17 ***Patient disposition by treatment - Induction period (Randomised set)***

Disposition /Reason	AIN457 Low dose N=40 n (%)	AIN457 High dose N=40 n (%)	Placebo N=41 n (%)	Etanercept N=41 n (%)	Total N=162 n (%)
Randomized	40	40	41	41	162
Completed	39 (97.5)	38 (95.0)	39 (95.1)	40 (97.6)	156 (96.3)
Discontinued	1 (2.5)	2 (5.0)	2 (4.9)	1 (2.4)	6 (3.7)
Primary reason for discontinuation					
Adverse event	0 (0.0)	1 (2.5)	1 (2.4)	0 (0.0)	2 (1.2)
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (0.6)
Protocol deviation	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.6)
Subject/guardian decision	1 (2.5)	1 (2.5)	0 (0.0)	0 (0.0)	2 (1.2)

Patient disposition in the Maintenance period is displayed in Table below. Of the 156 patients who completed the Induction period, 151 (~97%) entered the Maintenance period, as 5 placebo PASI 75 responders at Week 12 did not proceed into the Maintenance period as expected per protocol. One placebo patient continued into Maintenance, as the site erroneously entered PASI non-responder in the IRT system; the patient was allowed to proceed in Maintenance and was treated actively until and including Week 16. When the site corrected the entry to PASI responder at Week 16, the system did not allow the patient to continue further and the patient was discontinued due to protocol deviation.

Eleven patients (7.1%) did not complete the Maintenance period. One patient each in the secukinumab Low dose and secukinumab High dose groups discontinued the Maintenance period due to adverse event and lack of efficacy, respectively. Among the patients originally randomised to placebo who completed the Induction period and were PASI 75 non-responders at Week 12, 16 patients were assigned to secukinumab Low dose and 18 patients were assigned to secukinumab High dose starting at Week 12. The majority of these patients (placebo - secukinumab Low dose: 15 patients [93.8%] and placebo - secukinumab High dose: 16 patients [88.9%]) completed the Maintenance period.

Of the 41 patients who were randomised to the etanercept group during the Induction period, one patient discontinued study treatment due to lack of efficacy. Forty patients entered the Maintenance period, 6 patients in this group (including 3 due to lack of efficacy) discontinued study treatment.

Table 18 ***Patient disposition by treatment - Maintenance period (Randomised set)***

Disposition /Reason	AIN457 Low dose N=40 n (%)	AIN457 High dose N=40 n (%)	Placebo-AIN457 Low dose N=16 n (%)	Placebo-AIN457 High dose N=18 n (%)	Etanercept N=41 n (%)	Total N=155 n (%)
Entered maintenance period	39 (97.5)	38 (95.0)	16 (100.0)	18 (100.0)	40 (97.6)	151 (97.4)
Completed	38 (95.0)	37 (92.5)	15 (93.8)	16 (88.9)	34 (82.9)	140 (90.3)
Discontinued	1 (2.5)	1 (2.5)	1 (6.3)	2 (11.1)	6 (14.6)	11 (7.1)
Primary reason for discontinuation						
Adverse event	1 (2.5)	0 (0.0)	1 (6.3)	0 (0.0)	1 (2.4)	3 (1.9)
Lack of efficacy	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	3 (7.3)	4 (2.6)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (0.6)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	1 (2.4)	3 (1.9)

Current patient disposition in the Extension period at the time of the second data cut-off (September 2019) is displayed in Table below. Overall, 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 (Any secukinumab Low dose group: 53 patients and Any secukinumab High dose group: 53 patients). Ninety-five patients were still continuing in the Extension period at the time of cut-off date for the Week 52 analysis. The current rate of discontinuation during Extension period is 12.5% in the Any secukinumab Low dose group and 6.9% in the Any secukinumab High dose group. It should be noted that patients in the etanercept group are not eligible for the Extension period but enter the Post-treatment follow-up period at the end of the Maintenance period.

Table 19 ***Patient disposition by treatment – Extension period (Randomised set). Current at the time of data cut-off for the Week 52 analysis.***

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)
Ongoing	46 (82.1)	49 (84.5)	95 (83.3)
Discontinued	7 (12.5)	4 (6.9)	11 (9.6)
Primary reason for discontinuation			
Lack of efficacy	5 (8.9)	2 (3.4)	7 (6.1)
Pregnancy	2 (3.6)	0 (0.0)	2 (1.8)
Lost to follow-up	0 (0.0)	2 (3.4)	2 (1.8)

Recruitment

Study A2310 was conducted across 47 Investigator sites in 19 participating countries: 3 centres in Belgium (n=7), 2 centres in Colombia (n=9), 2 centres in Egypt (n=11), 1 centre in Estonia (n=11), 3 centres in France (n=3), 7 centres in Germany (n=25), 3 centres in Guatemala (n=10), 3 centres in Hungary (n=8), 3 centres in Israel (n=10), 2 centres in Italy (n=2), 1 centre in Japan (n=5), 2 centres in Latvia (n=4), 3 centres in Poland (n=28), 1 centre in Romania (n=4), 5 centres in Russia (n=13), 3 centres in Spain (n=8), 1 centre in Switzerland (n=1), 1 centre in the United Kingdom (n=1), and 1 centre in the United States (n=2).

Conduct of the study

The original protocol for Study A2310 had an effective date of 26 March 2015, and first patient first visit took place on 29 September 2015. The first data cut-off date for the current submission was 7 March 2019; a second cut-off was done on 18 September 2019 to enable analysis of the full Week 52 dataset.

The study protocol was amended on three occasions. In Amendment 1, dated 1 April 2015, further detail and clarification was added on the duration of contraception requested during the study and to give option to align the duration on local label requirements.

Within Amendment 2, dated 10 February 2016, inclusion criterion #5 (characterisation of a patient being a candidate for systemic therapy) was modified to align with text agreed with PDCO. The CHAQ was also added for subjects with a history of psoriatic arthritis, following a request by the Japanese Health Authority. At the time of Amendment 2, 4 patients had been randomised into the study.

The purpose of Amendment 3 was to introduce an additional Interim Analysis prior to the Week 24 analysis once sufficient safety and pharmacokinetic data had been collected. At the time of this Amendment, a total of 120 patients were enrolled. However, the MAH ultimately decided that the analysis was not warranted and was thus not performed.

Overall, 75% of the randomised patients had at least one protocol deviation until the time of the Week 52 analysis data cut-off. Protocol deviations were reported more frequently in the secukinumab High dose group (92.5%) followed by placebo - secukinumab Low dose group (83.3%) compared to the etanercept group (73.2%), secukinumab Low dose group (70%) and placebo - secukinumab Low dose (56.3%) group. In the placebo group (*i.e.*, the 7 placebo patients who did not enter Maintenance), 3 (42.9%) patients had at least one protocol deviation.

The most common protocol deviation was "treatment deviation" (84 patients, 51.9% overall), which was most frequent in the secukinumab High dose group (70%) and the secukinumab Low dose group (60%). The most common treatment deviation was "active medication instead of placebo administered to patient following IRT error" (36 patients, 22% overall), being reported for 20 patients in the secukinumab High dose group and 16 patients in the secukinumab Low dose group. The underlying reason was an error in the Interactive Response Technology (IRT) system used in the study, leading to additional dosing of patients. Specifically, 36 patients who were assigned to the Low dose (16 patients) and High dose (20 patients) secukinumab groups were dispensed active medication at the Week 13, 14 and 15 visits. At these visits, the patients who were randomised to active treatment groups were expected to receive placebo medication as to maintain the blind. However, 5 patients in the secukinumab High dose group (25 - < 50 kg/150 mg dose) were dispensed in error secukinumab 150 mg at these visits; 16 patients in the secukinumab Low dose group (≥ 50 kg/150 mg dose) were dispensed in error secukinumab 300 mg at these visits; and 15 patients in the secukinumab High dose group (≥ 50 kg/300 mg dose) were dispensed in error secukinumab 300 mg at these visits. The dosing errors happened after the primary endpoint (Week 12) assessment and thus did not impact the primary endpoint analysis. Furthermore, the error was rectified before enrolment of patients into the younger age stratum was commenced and thus only affected the older age stratum.

The second most common protocol deviation was "other deviation" (61 patients, 37.7% overall). The most common other deviations were "central laboratory analyses not conducted at a scheduled visit" and "patient reported outcome (PRO) assessment done after study medication administration" (reported in 21 and 20 patients, respectively). Prohibited concomitant medication use was more frequent in the secukinumab High dose group compared to other groups. According to the MAH, only 6 patients used prohibited concomitant medication prior to the Week 12 assessment, and the majority of patients using prohibited concomitant medications after Week 12 either used them only after Week 52 or after premature discontinuation and while in the follow-up period.

There were no protocol deviations leading to exclusion from any analysis population. Protocol deviations by deviation category are summarised in Table below.

Table 20 ***Protocol Deviations by deviation category (Randomised Set)***

Protocol deviation	AIN457 Low dose N=40 n (%)	AIN457 High dose N=40 n (%)	Placebo N=7 n (%)	Etanercept N=41 n (%)	Placebo-AIN457 Low dose N=16 n (%)	Placebo-AIN457 High dose N=18 n (%)	Total N=162 n (%)
Patients with at least one protocol deviation	28 (70.0)	37 (92.5)	3 (42.9)	30 (73.2)	9 (56.3)	15 (83.3)	122 (75.3)
Selection criteria not met	1 (2.5)	3 (7.5)	1 (14.3)	3 (7.3)	1 (6.3)	2 (11.1)	11 (6.8)
Treatment deviation	24 (60.0)	28 (70.0)	2 (28.6)	18 (43.9)	6 (37.5)	6 (33.3)	84 (51.9)
Treatment deviation, excluding IRT error	12 (30.0)	10 (25.0)	2 (28.6)	18 (43.9)	6 (37.5)	6 (33.3)	54 (33.3)
Prohibited concomitant medication	6 (15.0)	10 (25.0)	1 (14.3)	7 (17.1)	1 (6.3)	3 (16.7)	28 (17.3)
Other deviation	17 (42.5)	14 (35.0)	1 (14.3)	14 (34.1)	6 (37.5)	9 (50.0)	61 (37.7)

A patient with multiple occurrences of a protocol deviation category is counted only once in the protocol deviation category.
Patients may have protocol deviations in more than one protocol deviation category.

Baseline data

The demographic characteristics of the study patients are summarised in Table below. In the entire study population, mean age was approximately 13.5 years, and 77% of patients were in the age stratum 12 years or above. Overall mean weight was about 53 kg; 7% of patients (N=12) were in the weight stratum <25 kg, 40% of patients (N=65) in the weight stratum 25- <50 kg, and 53% of patients (N=85) in the weight stratum ≥ 50 kg. The patients were predominantly Caucasian, with a 60:40 female:male split.

Table 21 ***Demographic and background characteristics – Induction period groups (Randomised set)***

Characteristic	AIN457 Low dose N=40	AIN457 High dose N=40	Placebo N=41	Etanercept N=41	Total N=162
Age group (years) - n (%)					
< 12	8 (20.0)	9 (22.5)	10 (24.4)	10 (24.4)	37 (22.8)
>= 12	32 (80.0)	31 (77.5)	31 (75.6)	31 (75.6)	125 (77.2)
Age (years)					
N	40	40	41	41	162
Mean	13.7	13.2	13.7	13.5	13.5
SD	2.92	3.21	3.27	2.94	3.06
Median	14.5	14.0	15.0	14.0	14.0
Min – Max	7 – 17	6 - 17	6 - 17	6 - 17	6 - 17
Sex – n (%)					
Male	13 (32.5)	17 (42.5)	19 (46.3)	16 (39.0)	65 (40.1)
Female	27 (67.5)	23 (57.5)	22 (53.7)	25 (61.0)	97 (59.9)
Race – n (%)					
Caucasian	34 (85.0)	34 (85.0)	36 (87.8)	30 (73.2)	134 (82.7)
Black	1 (2.5)	1 (2.5)	0 (0.0)	0 (0.0)	2 (1.2)
Asian	1 (2.5)	2 (5.0)	1 (2.4)	3 (7.3)	7 (4.3)
Native American	3 (7.5)	3 (7.5)	3 (7.3)	8 (19.5)	17 (10.5)
Other	1 (2.5)	0 (0.0)	1 (2.4)	0 (0.0)	2 (1.2)
Weight (kg)					
N	40	40	41	41	162
Mean	52.60	53.61	55.68	51.96	53.47
SD	15.263	20.179	22.280	19.430	19.345
Median	51.45	50.95	50.50	50.00	50.60
Min – Max	21.0 - 85.0	20.5 - 116.0	17.6 - 104.0	20.5 - 105.5	17.6 - 116.0
Weight strata (kg) - n (%)					
<25	2 (5.0)	3 (7.5)	3 (7.3)	4 (9.8)	12 (7.4)
25 - <50	17 (42.5)	15 (37.5)	17 (41.5)	16 (39.0)	65 (40.1)
>= 50	21 (52.5)	22 (55.0)	21 (51.2)	21 (51.2)	85 (52.5)
Height (cm)					
N	40	40	41	41	162
Mean	159.14	156.45	155.59	154.60	156.43
SD	14.833	18.547	16.459	16.464	16.557
Median	160.00	159.00	161.00	158.00	160.00
Min – Max	121.0 - 185.0	115.0 - 194.0	118.0 - 184.0	118.0 - 183.0	115.0 - 194.0
BMI (kg/m^2)					
N	40	40	41	41	162
Mean	20.32	21.16	22.19	21.00	21.17
SD	3.595	4.368	6.199	4.799	4.845
Median	19.50	20.45	20.60	21.00	20.50
Min – Max	14.1 - 30.7	11.1 - 33.9	12.6 - 42.5	13.7 - 31.5	11.1 - 42.5
Child Bearing status - n (%)					
Able to bear children	17 (63.0)	16 (69.6)	18 (81.8)	16 (64.0)	67 (69.1)
Premenarche	10 (37.0)	7 (30.4)	4 (18.2)	9 (36.0)	30 (30.9)

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.

Disease characteristics and history at baseline are summarised in Table below. Mean PASI score was 28 and mean % of affected body surface area was 40%. Patients had a mean history of 5.2 years since first diagnosis of plaque psoriasis, and all patients had received previous treatment for their psoriasis.

Table 22 ***Disease history and baseline disease characteristics – Induction period groups (Randomised set)***

Background Characteristics	AIN457 Low dose N=40	AIN457 High dose N=40	Placebo N=41	Etanercept N=41	Total N=162
Baseline PASI score					
N	40	40	41	41	162
Mean	27.6	28.0	28.0	28.4	28.0
SD	6.89	8.67	8.09	9.05	8.15
Median	25.6	25.5	25.8	24.8	25.5
Min - Max	20 - 48	17 - 59	20 - 55	20 - 60	17 - 60
Baseline PASI, n (%)					
<= 20	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	1 (0.6)
> 20	40 (100.0)	39 (97.5)	41 (100.0)	41 (100.0)	161 (99.4)
Baseline total BSA					
N	40	40	41	41	162
Mean	37.59	40.26	38.99	43.13	40.01
SD	13.860	17.559	17.647	19.557	17.258
Median	36.65	36.75	34.50	37.70	36.00
Min - Max	12.0 - 72.5	16.0 - 94.0	17.9 - 77.0	13.1 - 90.5	12.0 - 94.0
Baseline IGA mod 2011 score, n (%)					
3 = Moderate disease	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	1 (0.6)
4 = Severe disease	40 (100.0)	39 (97.5)	41 (100.0)	41 (100.0)	161 (99.4)
Diagnosis of plaque-type psoriasis - n (%)					
Yes	40 (100.0)	40 (100.0)	41 (100.0)	41 (100.0)	162 (100.0)
No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Time since first diagnosis of plaque-type psoriasis (years)					
N	40	40	41	41	162
Mean	4.85	5.44	6.03	4.55	5.22
SD	4.291	4.665	5.093	3.733	4.468
Median	3.78	3.31	4.95	3.86	3.97
Min - Max	0.3 - 17.0	0.4 - 17.3	0.5 - 17.5	0.3 - 14.0	0.3 - 17.5
Psoriasis History - n (%)					
Generalized pustural psoriasis	1 (2.5)	2 (5.0)	0 (0.0)	0 (0.0)	3 (1.9)
Palmoplantar pustural psoriasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Erythrodermic psoriasis	0 (0.0)	1 (2.5)	0 (0.0)	1 (2.4)	2 (1.2)
Diagnosis of psoriatic arthritis - n (%)					
Yes	5 (12.5)	3 (7.5)	3 (7.3)	3 (7.3)	14 (8.6)
No	35 (87.5)	37 (92.5)	38 (92.7)	38 (92.7)	148 (91.4)
Time since first diagnosis of psoriatic arthritis (years)					
N	5	3	3	3	14
Mean	4.72	1.89	2.16	1.38	2.85
SD	3.407	1.992	3.237	1.146	2.858
Median	3.51	0.79	0.45	1.23	1.86
Min - Max	1.6 - 9.7	0.7 - 4.2	0.1 - 5.9	0.3 - 2.6	0.1 - 9.7
Previous psoriasis therapies- n (%)					
Yes	40 (100.0)	40 (100.0)	41 (100.0)	41 (100.0)	162 (100.0)
No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

BSA: body surface area affected by plaque-type psoriasis

The most commonly used previous psoriasis therapies were topical (88.9%) and phototherapy (43.2%). About 53% of patients had received prior systemic therapies for psoriasis, and 84% of these patients

had failed on these therapies. The most commonly used prior systemic therapies were methotrexate (26.5%), acitretin (11.7%) and ciclosporin (9.9%); prior use of methotrexate was more frequent in the secukinumab Low dose group than in the secukinumab High dose, placebo or etanercept groups (42.5%, 22.5%, 22.0% and 19.5%, respectively). The majority of patients (97.5% overall) had no previous exposure to biologic psoriasis therapies.

Numbers analysed

The numbers of patients included in analysis data sets for the various treatment periods are summarised in Table below. According to the MAH, no patients were excluded from any analysis set.

Table 23 ***Analysis sets by treatment period (All subjects enrolled)***

Treatment period: Induction period					
Analysis Set	**AIN457 Low dose**	**AIN457 High dose**	**Placebo**	**Etanercept**	**Total**
Screened					187
Randomized set	40	40	41	41	162
Full analysis set	40	40	41	41	162
Safety set	40	40	41	41	162

Treatment period: Maintenance period						
Analysis Set	**AIN457 Low dose**	**AIN457 High dose**	**Placebo-AIN457 Low dose**	**Placebo-AIN457 High dose**	**Etanercept**	**Total**
Completed induction period						156
Randomized set	40	40	16	18	41	155
Full analysis set	40	40	16	18	41	155
Safety set	39	38	16	18	40	151

Treatment period: Entire treatment period								
Analysis Set	**AIN457 Low dose**	**AIN457 High dose**	**Placebo**	**Etanercept**	**Any AIN457 Low dose**	**Any AIN457 High dose**	**Any AIN457 dose**	**Total**
Randomized set	40	40	41	41	56	58	114	162
Full analysis set	40	40	41	41	56	58	114	162
Safety set	40	40	41	41	56	58	114	162

Outcomes and estimation

Primary Analysis

As seen in Table below, the study achieved its primary and key secondary objectives at Week 12. Both Low and High dose secukinumab groups were superior to placebo with respect to the co-primary endpoints of PASI 75 response and IGA mod 2011 0 or 1 response and the key secondary endpoint of PASI 90 at Week 12 ($p < 0.0001$ for all comparisons).

Table 24 ***Results of hypothesis tests within testing strategy (Full analysis set)***

Hypothesis	Endpoint	Comparison	One-sided P-value	Outcome
H1	PASI 75 response at Week 12	AIN457 Low dose vs. Placebo	<0.0001	Superior vs Placebo
H2	PASI 75 response at Week 12	AIN457 High dose vs. Placebo	<0.0001	Superior vs Placebo
H3	IGA 0/1 response at Week 12	AIN457 Low dose vs. Placebo	<0.0001	Superior vs Placebo
H4	IGA 0/1 response at Week 12	AIN457 High dose vs. Placebo	<0.0001	Superior vs Placebo
H5	PASI 90 response at Week 12	AIN457 Low dose vs. Placebo	<0.0001	Superior vs Placebo
H6	PASI 90 response at Week 12	AIN457 High dose vs. Placebo	<0.0001	Superior vs Placebo

Co-Primary Endpoints

Both secukinumab dose levels (Low and High) were superior to placebo with respect to PASI 75 response and IGA 0/1 response at Week 12 (Table 25; Figure 12). In the primary statistical analyses, performed using multiple imputation for missing data, a PASI 75 response at Week 12 was achieved by 80.1% of patients in the secukinumab Low dose group and 80.2% of patients in the secukinumab High dose group compared with 14.9% of patients in the placebo group. Similarly, at Week 12, an IGA 0/1 response was achieved by 69.8% of patients in the secukinumab Low dose group and 62.6% of patients in the secukinumab High dose group compared with 6.3% of patients in the placebo group. Sensitivity analyses based on a pure non-responder imputation strategy demonstrated similar differences between the treatment groups.

In the etanercept group, a PASI 75 response was achieved by 65.7% of patients, and an IGA 0/1 response by 36.3% of patients. Statistical comparisons between etanercept and secukinumab were not part of the formal testing strategy.

Table 25 ***Logistic regression analysis of IGA 0/1, PASI 75, and PASI 90 response at Week 12 (multiple imputation) (Full analysis set)***

Response criterion	Treatment comparison 'test' vs. 'control'	'test' n*/m (%)	'control' n*/m (%)	odds ratio estimate (95% CI)	p-value
IGA 0/1	AIN457 Low dose vs. Placebo	28/40(69.8)	3/41(6.3)	40.39 (8.37,194.87)	<.0001
	AIN457 High dose vs. Placebo	25/40(62.6)	3/41(6.3)	28.35 (6.00,133.92)	<.0001
	AIN457 Low dose vs. Etanercept	28/40(69.8)	15/41(36.3)	4.04 (1.51,10.79)	0.0053
	AIN457 High dose vs. Etanercept	25/40(62.6)	15/41(36.3)	2.89 (1.12,7.41)	0.0276
PASI 75	AIN457 Low dose vs. Placebo	32/40(80.1)	6/41(14.9)	25.97 (7.31,92.22)	<.0001
	AIN457 High dose vs. Placebo	32/40(80.2)	6/41(14.9)	26.55 (7.57,93.09)	<.0001
	AIN457 Low dose vs. Etanercept	32/40(80.1)	27/41(65.7)	2.05 (0.69,6.13)	0.1989
	AIN457 High dose vs. Etanercept	32/40(80.2)	27/41(65.7)	2.04 (0.69,6.01)	0.1942
PASI 90	AIN457 Low dose vs. Placebo	28/40(71.1)	1/41(2.5)	121.86 (14.23,1043.28)	<.0001
	AIN457 High dose vs. Placebo	28/40(69.3)	1/41(2.5)	110.14 (12.98,934.72)	<.0001
	AIN457 Low dose vs. Etanercept	28/40(71.1)	13/41(31.4)	5.78 (2.06,16.25)	0.0009
	AIN457 High dose vs. Etanercept	28/40(69.3)	13/41(31.4)	5.16 (1.88,14.15)	0.0014

n* is the rounded mean number of responders for 100 imputations, m = number of subjects evaluable. Odds ratio, 95% confidence interval, and p-value are from an exact logistic regression model with treatment group, baseline body-weight category and age category as factors.

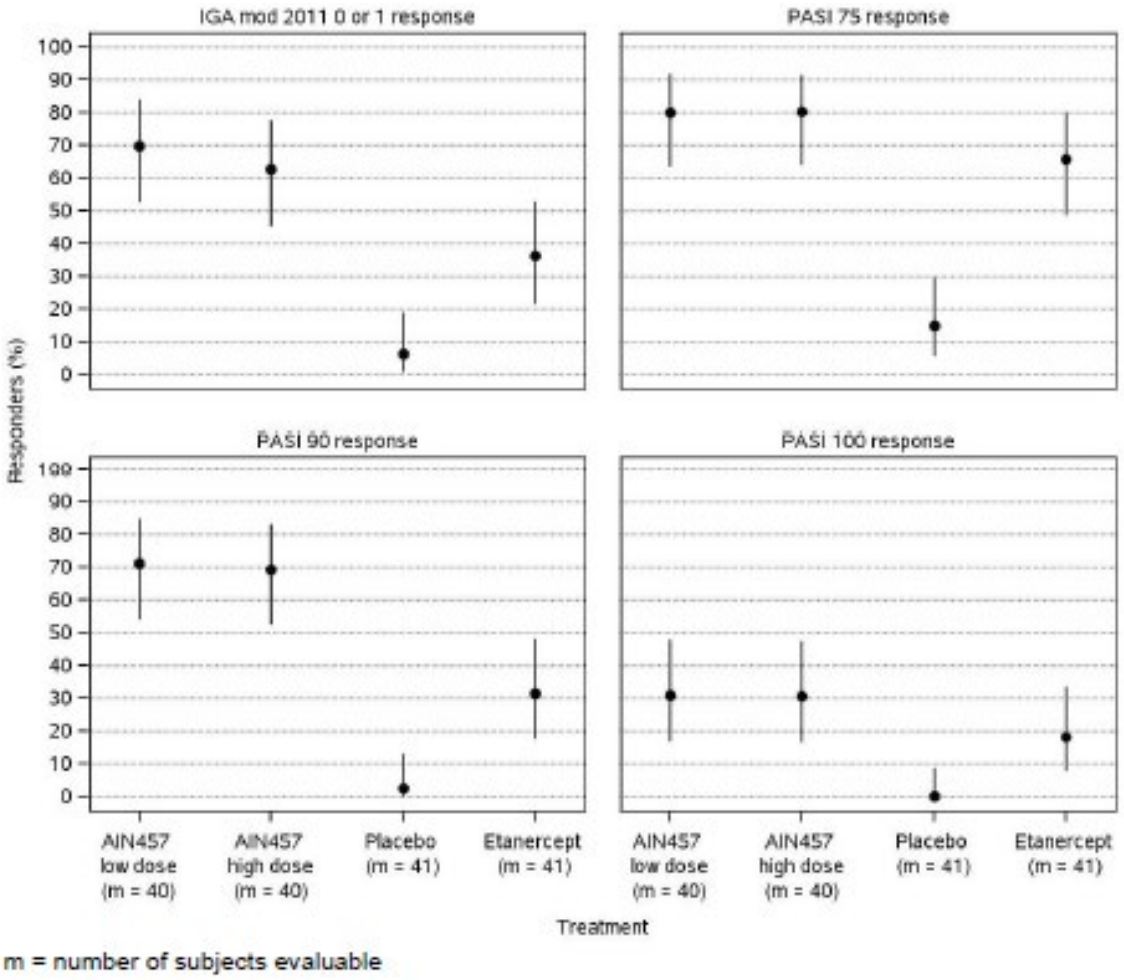


Figure 12 ***IGA 0/1, PASI 75, PASI 90 and PASI 100 response (estimate ± 95% CI) at Week 12 (Multiple imputation) (Full analysis set)***

Key Secondary Endpoint

At Week 12, PASI 90 response rates were also statistically significantly superior to placebo for both secukinumab dose levels (Table 25and Figure 12); in the multiple imputation dataset, a PASI 90 response at Week 12 was achieved by 71.1% of patients in the secukinumab Low dose group and 69.3% of patients in the secukinumab High dose group compared with 2.5% of patients in the placebo group. A 31.4% response rate was seen in the etanercept group.

Additional analysis using extended visit window

As indicated above, upon performing the pure non-responder imputation the MAH noticed that many Week 12 efficacy assessments were noted as missing and thus patients were accounted as non-responders for the analysis at Week 12, whereas an assessment was in fact available somewhat outside the pre-specified Week 12 visit window. Consequently, an additional analysis with an extended Week 12 analysis visit window was performed using a Week 12 visit window of Day 72 - 102 instead of Day 72 - 88. Results from this analysis using non-responder imputation are displayed in Table below.

Table 26 ***Logistic regression analysis of IGA 0/1, PASI 75, and PASI 90 response at Week 12 based on extended Week 12 visit window (pure non-responder imputation) (Full analysis set)***

Response criterion	Treatment comparison 'test' vs. 'control'	'test' n/m (%)	'control' n/m (%)	odds ratio estimate (95% CI)	p-value
IGA 0/1	AIN457 Low dose vs. Placebo	28/ 40 (70.0)	2/ 41 (4.9)	51.77 (10.02,538.64)	<.0001
	AIN457 High dose vs. Placebo	24/ 40 (60.0)	2/ 41 (4.9)	32.52 (6.48,329.52)	<.0001
	AIN457 Low dose vs. Etanercept	28/ 40 (70.0)	14/ 41 (34.1)	4.49 (1.60,13.42)	0.0027
	AIN457 High dose vs. Etanercept	24/ 40 (60.0)	14/ 41 (34.1)	2.86 (1.05,8.13)	0.0395
PASI 75	AIN457 Low dose vs. Placebo	32/ 40 (80.0)	6/ 41 (14.6)	25.78 (7.08,114.66)	<.0001
	AIN457 High dose vs. Placebo	31/ 40 (77.5)	6/ 41 (14.6)	22.65 (6.31,98.93)	<.0001
	AIN457 Low dose vs. Etanercept	32/ 40 (80.0)	26/ 41 (63.4)	2.25 (0.73,7.38)	0.1819
	AIN457 High dose vs. Etanercept	31/ 40 (77.5)	26/ 41 (63.4)	1.92 (0.64,6.07)	0.2919
PASI 90	AIN457 Low dose vs. Placebo	29/ 40 (72.5)	1/ 41 (2.4)	133.67 (16.83,6395.22)	<.0001
	AIN457 High dose vs. Placebo	27/ 40 (67.5)	1/ 41 (2.4)	102.86 (13.22,4850.13)	<.0001
	AIN457 Low dose vs. Etanercept	29/ 40 (72.5)	12/ 41 (29.3)	7.03 (2.34,23.19)	0.0002
	AIN457 High dose vs. Etanercept	27/ 40 (67.5)	12/ 41 (29.3)	5.32 (1.82,16.75)	0.0011

Other Secondary Endpoints

Effects on IGA 0/1, PASI 75 and PASI 90 responses over time

IGA 0/1, PASI 75 and PASI 90 response rates from randomisation until Week 52 are displayed in Figure13. Depending on the endpoint, responses in both secukinumab groups were detected from Week 2 to Week 4 onward, with further increases observed until Week 12. A consistent pattern (from Week 12 to Week 52) was seen among patients switching from placebo to secukinumab at Week 12.

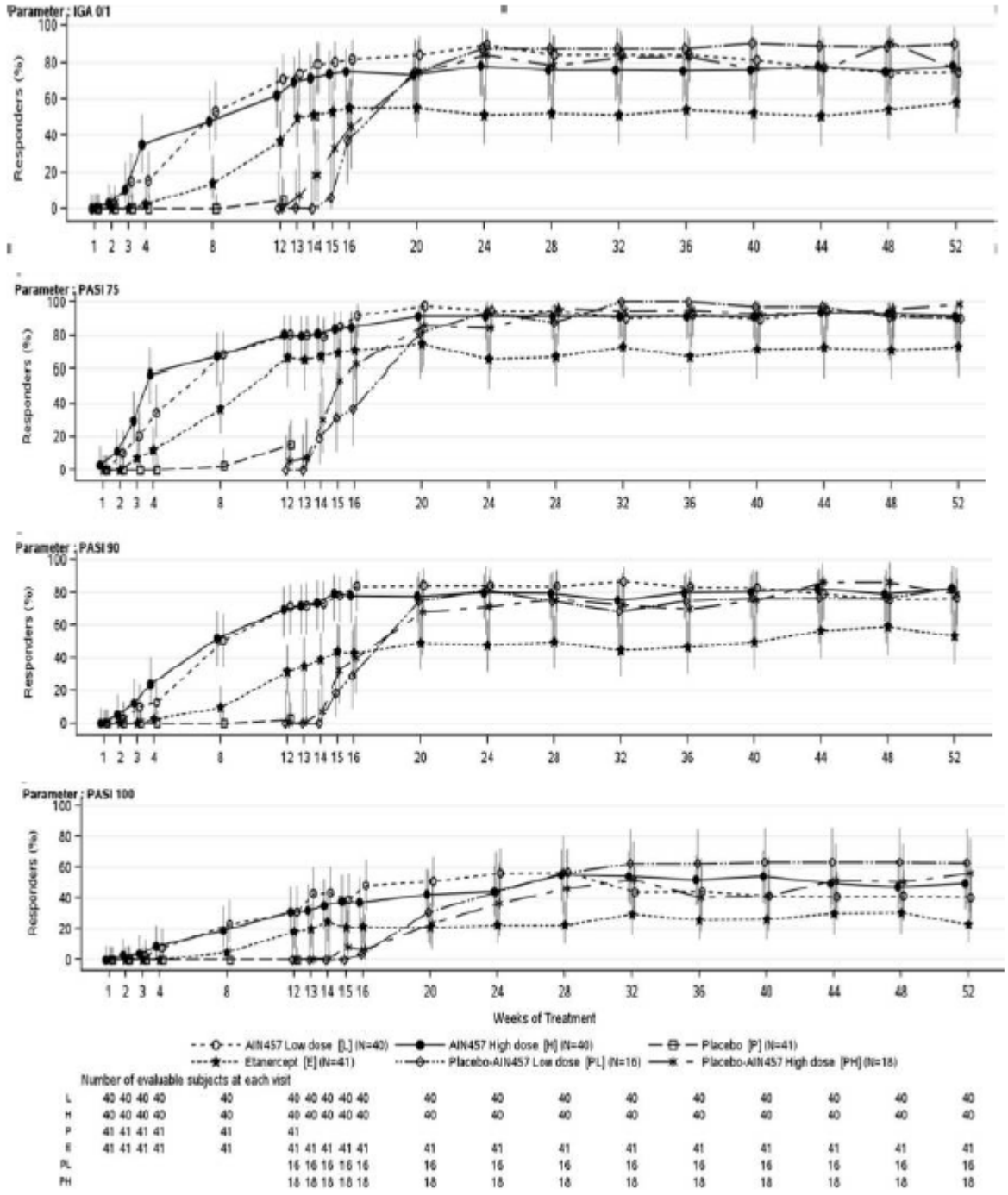


Figure 13 Time course of IGA 0/1, PASI 75, PASI 90 and PASI 100 responders over time (estimate ± 95% CI, multiple imputation, FAS)

Patient Reported Outcomes (CDLQI, CHAQ)

At Week 12, the proportions of patients achieving a CDLQI 0 or 1 response (indicating no or little impairment) were 44.7% in the secukinumab Low dose group and 50% in the High dose group, compared with 36.6% in the etanercept group and 15% in the placebo group. Mean decrease (improvement) in CDLQI total score from baseline to Week 12 was:

-9.05 (-67.43%) in the secukinumab Low dose group,

-7.71 (-62.50%) in the secukinumab High dose group,

-6.49 (-62.80%) in the etanercept group, and

-3.79 (-18.48%) in the placebo group.

Summary statistics for CHAQ were not computed due to the low number of patients with psoriatic arthritis.

Maintenance of Effect

As seen in Figure 13 above, response rates achieved by Week 12 were generally maintained or increased further during maintenance. At Week 52, numerically highest response rates were observed in the secukinumab High dose group (Table below). Response rates in both secukinumab groups were higher than in the etanercept group at all visits up to Week 52. High response rates at Week 52 were also seen for patients switching from placebo to secukinumab at Week 12, although patient numbers in these groups are smaller.

Table 27 ***Number (%) of patients with PASI 50, PASI 75, PASI 90, PASI 100 and IGA 0 or 1 response by visit (multiple imputation) - Maintenance period (Full Analysis set)***

		AIN457 Low dose N=40		AIN457 High dose N=40		Placebo-AIN457 Low dose N=16		Placebo-AIN457 High dose N=18		Etanercept N=41	
Visit	Criterion	n*/m	(%)	n*/m	(%)	n*/m	(%)	n*/m	(%)	n*/m	(%)
Week 12	IGA 0/1	28/40	(70.6)	25/40	(62.0)	0/16	(0.3)	0/18	(0.0)	15/41	(37.0)
	PASI 50	34/40	(85.7)	35/40	(87.2)	1/16	(9.2)	3/18	(16.8)	36/41	(88.3)
	PASI 75	32/40	(80.5)	32/40	(80.5)	0/16	(0.2)	1/18	(5.6)	27/41	(66.9)
	PASI 90	29/40	(71.6)	28/40	(69.8)	0/16	(0.0)	0/18	(0.0)	13/41	(31.5)
	PASI 100	12/40	(30.9)	12/40	(31.0)	0/16	(0.0)	0/18	(0.0)	7/41	(18.2)
Week 16	IGA 0/1	33/40	(82.1)	30/40	(74.9)	6/16	(37.4)	8/18	(45.4)	23/41	(55.1)
	PASI 50	38/40	(95.0)	38/40	(94.6)	12/16	(76.3)	17/18	(92.1)	34/41	(83.8)
	PASI 75	37/40	(92.1)	34/40	(84.8)	6/16	(37.0)	11/18	(63.0)	29/41	(71.0)
	PASI 90	34/40	(83.9)	31/40	(78.0)	5/16	(29.2)	7/18	(40.3)	18/41	(43.2)
	PASI 100	19/40	(48.2)	15/40	(37.1)	1/16	(3.5)	1/18	(6.8)	9/41	(21.8)
Week 24	IGA 0/1	36/40	(89.7)	31/40	(78.3)	14/16	(87.5)	15/18	(84.3)	21/41	(51.3)
	PASI 50	39/40	(97.5)	39/40	(97.4)	15/16	(93.8)	18/18	(98.3)	33/41	(79.6)
	PASI 75	38/40	(94.9)	37/40	(91.3)	15/16	(93.8)	15/18	(84.4)	27/41	(65.6)
	PASI 90	34/40	(84.4)	32/40	(80.3)	13/16	(81.3)	13/18	(71.4)	20/41	(47.7)
	PASI 100	23/40	(56.5)	18/40	(44.5)	7/16	(43.8)	7/18	(36.7)	9/41	(22.6)
Week 36	IGA 0/1	34/40	(84.2)	30/40	(75.4)	14/16	(87.5)	15/18	(83.3)	22/41	(54.2)
	PASI 50	39/40	(97.5)	39/40	(97.2)	16/16	(100.0)	18/18	(98.9)	33/41	(81.2)
	PASI 75	37/40	(92.4)	36/40	(91.2)	16/16	(100.0)	17/18	(95.3)	28/41	(67.2)
	PASI 90	33/40	(83.6)	32/40	(80.3)	12/16	(75.0)	13/18	(69.9)	19/41	(46.6)
	PASI 100	18/40	(44.3)	21/40	(52.0)	10/16	(62.5)	7/18	(40.6)	11/41	(26.0)
Week 52	IGA 0/1	30/40	(74.5)	31/40	(78.1)	14/16	(89.9)	14/18	(76.1)	24/41	(58.2)
	PASI 50	40/40	(100.0)	39/40	(97.2)	16/16	(98.9)	18/18	(99.8)	36/41	(87.7)
	PASI 75	36/40	(89.8)	36/40	(91.2)	14/16	(90.4)	18/18	(98.3)	30/41	(73.1)
	PASI 90	31/40	(76.5)	33/40	(82.6)	13/16	(82.5)	14/18	(79.3)	22/41	(53.5)
	PASI 100	16/40	(40.7)	20/40	(49.4)	10/16	(63.1)	10/18	(56.1)	10/41	(23.2)

n* is the rounded mean number of responders for 100 imputations, m = number of patients evaluable.
Percentages are calculated based on n and m values, for each treatment groups.

As the study remains ongoing and many patients remain on treatment, opportunities to evaluate relapse and rebound are limited. In the analysis of Week 52 data, 6 patients (1 patient in the placebo group, one patient in the secukinumab High dose group, one patient in the placebo-Low dose switch group, and

three patients in the etanercept group) met criteria for relapse after treatment discontinuation. Three patients experienced a rebound event; one patient in secukinumab High dose group reported an event of erythrodermic psoriasis during the Follow up Period, 34 days after the last secukinumab dose; one patient in etanercept group also reported an event of erythrodermic psoriasis; the event started 7 days after the last etanercept dose; and one patient in the placebo group had new pustular psoriasis starting on Day 9, one day after the unique placebo dose.

Ancillary analyses

Subgroup Analyses: Weight and Age Strata, Previous Exposure to Systemic Therapy

Results of a subgroup analysis of primary and key secondary endpoints at Week 12 by weight strata used to define the dosing regimens, based on a pure non-responder imputation strategy, are displayed in Table 28. For weight stratum < 25 kg, it should be noted that the same 75 mg dose was used in both the Low and High dose groups.

A corresponding subgroup analysis was undertaken by age stratum, and the results are displayed in Table below.

A subgroup analysis was also undertaken to assess response among patients with and without previous exposure to systemic therapy, and the results are displayed in Table 30.

Table 28 ***PASI 75, IGA 0/1 and PASI 90 response at Week 12 by weight strata - pure non-responder imputation (FAS)***

	AIN457 Low dose N=40		AIN457 High dose N=40		Placebo N=41		Etanercept N=41	
	n/m (%)	95%CI	n/m (%)	95%CI	n/m (%)	95%CI	n/m (%)	95%CI
Weight:< 25 kg								
	N=2		**N=3**		**N=3**		**N=4**	
PASI 75	1/2 (50.0)	2.7,97.3	2/3 (66.7)	12.5,98.2	0/3 (0.0)	0.0,69.0	3/4 (75.0)	21.9,98.7
IGA 0/1	1/2 (50.0)	2.7,97.3	0/3 (0.0)	0.0,69.0	0/3 (0.0)	0.0,69.0	2/4 (50.0)	9.2,90.8
PASI 90	1/2 (50.0)	2.7,97.3	0/3 (0.0)	0.0,69.0	0/3 (0.0)	0.0,69.0	2/4 (50.0)	9.2,90.8
Weight:≥ 25 kg to < 50 kg								
	N=17		**N=15**		**N=17**		**N=16**	
PASI 75	9/17 (52.9)	28.5,76.1	9/15 (60.0)	32.9,82.5	2/17 (11.8)	2.1,37.7	7/16 (43.8)	20.8,69.4
IGA 0/1	6/17 (35.3)	15.3,61.4	8/15 (53.3)	27.4,77.7	1/17 (5.9)	0.3,30.8	4/ 16 (25.0)	8.3,52.6
PASI 90	8/17 (47.1)	23.9,71.5	8/15 (53.3)	27.4,77.7	1/17 (5.9)	0.3,30.8	3/16 (18.8)	5.0,46.3
Weight:≥ 50 kg								
	N=21		**N=22**		**N=21**		**N=21**	
PASI 75	18/21 (85.7)	62.6,96.2	19/22 (86.4)	64.0,96.4	4/21 (19.0)	6.3,42.6	15/21 (71.4)	47.7,87.8
IGA 0/1	17/21 (81.0)	57.4,93.7	15/22 (68.2)	45.1,85.3	1/21 (4.8)	0.2,25.9	8/ 21 (38.1)	19.0,61.3
PASI 90	17/21 (81.0)	57.4,93.7	18/22 (81.8)	59.0,94.0	0/21 (0.0)	0.0,19.2	7/ 21 (33.3)	15.5,56.9

n = number of patients with response, m = number of patients evaluable.

Table 29 ***PASI 75, IGA 0/1 and PASI 90 response at Week 12 by age strata - pure non-responder imputation (FAS)***

	AIN457 Low dose N=40		AIN457 High dose N=40		Placebo N=41		Etanercept N=41	
	n/m (%)	95%CI	n/m (%)	95%CI	n/m (%)	95%CI	n/m (%)	95%CI
Age: 6 to < 12 years								
	N=8		**N=9**		**N=10**		**N=10**	
PASI 75	3/8 (37.5)	10.2,74.1	6/9 (66.7)	30.9,91.0	1/10 (10.0)	0.5,45.9	7/10 (70.0)	35.4,91.9
IGA 0/1	2/8 (25.0)	4.5,64.4	4/9 (44.4)	15.3,77.3	1/10 (10.0)	0.5,45.9	4/10 (40.0)	13.7,72.6
PASI 90	3/8 (37.5)	10.2,74.1	4/9 (44.4)	15.3,77.3	1/10 (10.0)	0.5,45.9	5/10 (50.0)	20.1,79.9
Age: 12 to < 18 years								
	N=32		**N=31**		**N=31**		**N=31**	
PASI 75	25/32 (78.1)	59.6,90.1	24/31 (77.4)	58.5,89.7	5/31 (16.1)	6.1,34.5	18/31 (58.1)	39.3,74.9
IGA 0/1	22/32 (68.8)	49.9,83.3	19/31 (61.3)	42.3,77.6	1/31 (3.2)	0.2,18.5	10/31 (32.3)	17.3,51.5
PASI 90	23/32 (71.9)	53.0,85.6	22/31 (71.0)	51.8,85.1	0/31 (0.0)	0.0,13.7	7/31 (22.6)	10.3,41.5

n = number of patients with response, m = number of patients evaluable.

Table 30 ***PASI 75, IGA 0/1 and PASI 90 response at Week 12 by previous systemic therapy - pure non-responder imputation (FAS)***

	AIN457 Low dose N=40		AIN457 High dose N=40		Placebo N=41	
	n/m (%)	95%CI	n/m (%)	95%CI	n/m (%)	95%CI
Previous systemic therapy: Yes						
	N=26		**N=21**		**N=20**	
PASI 75	17/26 (65.4)	44.4,82.1	13/21 (61.9)	38.7,81.0	3/20 (15.0)	4.0,38.9
IGA 0/1	16/26 (61.5)	40.7,79.1	9/21 (42.9)	22.6,65.6	1/20 (5.0)	0.3,26.9
PASI 90	16/26 (61.5)	40.7,79.1	11/21 (52.4)	30.3,73.6	0/20 (0.0)	0.0,20.0
Previous systemic therapy: No						
	N=14		**N=19**		**N=21**	
PASI 75	11/14 (78.6)	48.8,94.3	17/19 (89.5)	65.5,98.2	3/21 (14.3)	3.8,37.4
IGA 0/1	8/14 (57.1)	29.6,81.2	14/19 (73.7)	48.6,89.9	1/21 (4.8)	0.2,25.9
PASI 90	10/14 (71.4)	42.0,90.4	15/19 (78.9)	53.9,93.0	1/21 (4.8)	0.2,25.9

n = number of patients with response, m = number of patients evaluable.

An analysis of responses over time until Week 52 was also performed for the groups by body weight and dose group. In the ≥25-<50 kg weight category, the patients receiving High (secukinumab 150 mg (n=15)) and Low dose (secukinumab 75 mg (n=17)) reached comparable PASI 75, PASI 90, PASI 100 and IGA mod 2011 0/1 responses at Week 14. From Week 15, the patients on secukinumab Low dose showed higher responses than those receiving secukinumab High dose up to Week 52. At Week 52, the PASI 75/90/100 and IGA mod 2011 0/1 response rates were 80.0%, 66.7%, 26.7% and 60.0%, respectively, for the 150 mg group and 88.2%, 76.5%, 58.8% and 76.5%, respectively, for the 75 mg group.

In the ≥50 kg weight category, throughout the Maintenance period the patients on High dose (secukinumab 300 mg (n=21)) showed higher PASI and IGA responses than those receiving Low dose (secukinumab 150 mg (n=22)). At Week 52, the PASI 75/90/100 and IGA mod 2011 0/1 response rates were 100%, 95.2%, 61.9% and 85.7%, respectively, for the 300 mg group and 86.4%, 72.7%, 27.3% and 68.2%, respectively, for the 150 mg group.

2.4.2.2. 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"

Methods

Study A2311 is an ongoing randomised, open-label, historical controlled study, consisting of a screening period of up to 4 weeks, a 208 week treatment period and a 16 week post-treatment follow-up period. An outline of the study design is displayed in Figure below.

Eligible patients were randomised in a 1:1 ratio to receive either secukinumab Low dose or High dose during the treatment period. Randomisation was stratified by body weight (< 25kg, 25-< 50 kg, ≥ 50kg) and disease severity (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 the Randomisation Visit.

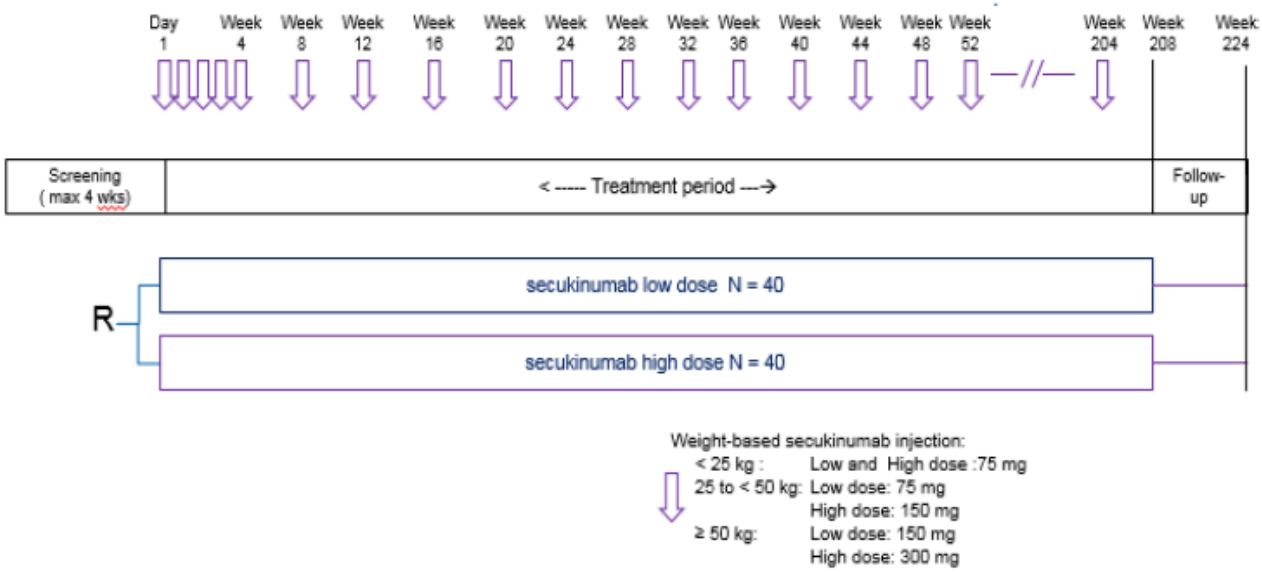


Figure 14 ***Outline of study design for study A2311***

At the time of the current assessment, the study is fully enrolled and all patients have completed the Week 24 visit (or withdrawn).

Study participants

Key inclusion criteria

- Written informed assent and parental permission obtained at screening. Patients reaching the age of consent during the study would also need to sign the corresponding study Informed Consent
- Aged 6 years to <18 years of age at the time of randomization
- Moderate to Severe plaque psoriasis, defined as a PASI score ≥ 12, and IGA score of ≥3, and Body Surface Area (BSA) involvement of ≥10%, at randomization
- History of plaque psoriasis for at least 3 months before randomization
- Patient 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.

Key exclusion criteria

- Forms of psoriasis other than chronic plaque-type (e.g. pustular, erythrodermic and guttate psoriasis), active at randomization
- Female patients of childbearing potential (menarchal or becoming 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 might confound the evaluation of the benefit of secukinumab therapy
- Underlying condition (including, but not limited to metabolic, hematologic, 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 randomization and any infections that reoccur on a regular basis
- Previous exposure to secukinumab or any other biologic drug targeting IL-17 or the IL-17 receptor.

Treatments

Patients weighing < 25 kg received 75 mg (both Low and High dose groups), patients weighing 25 kg to < 50 kg received 75 mg (Low dose group) or 150 mg (High dose group), and patients weighing ≥ 50 kg received 150 mg (Low dose group) or 300 mg (High dose group).

Patients received one s.c. injection at each drug administration of either secukinumab 75 mg or 150 mg Pre-filled Syringe (PFS) according to their treatment group. Only the patients in the ≥ 50 kg High dose treatment groups received two s.c. injections of 150 mg secukinumab PFS at each administration.

All patients visited the study site at Randomisation (Day 1) and at Weeks 1, 2, 3, 4, 8, 12, and 16 during which they received either Low-dose or High-dose secukinumab treatment subcutaneously (s.c.).

There is no within study control drug. A historical placebo control was obtained using data from qualifying trials (adult secukinumab placebo-controlled trials and paediatric placebo-controlled trials with secukinumab or other biologics), and used as the comparator for the primary and key secondary endpoint analysis. According to the MAH, this is in line with the guidance from and discussions with Health Authorities including FDA and EMA (PDCO-Paediatric Committee of the European Medicines Agency) which suggested reducing placebo exposure as well as overall clinical trial burden for paediatric population and suggest/accept use of extrapolation approach.

Objectives

The primary objective of the study was to evaluate the efficacy of secukinumab in pediatric 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).

The secondary objectives defined in the study protocol were:

- To evaluate the efficacy of secukinumab in pediatric patients 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, electrocardiogram (ECG)s, and adverse event monitoring.
- To evaluate the PK of secukinumab in pediatric patients.

The exploratory objectives defined in the study protocol and assessed until Week 16 to support the current assessment 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 Week 16.
- To investigate the effects of treatment with secukinumab with respect to Children's Dermatology Life Quality Index (CDLQI) 0 or 1 score over time, up to Week 12.
- To investigate the development of immunogenicity against secukinumab.

Outcomes/endpoints

The endpoint corresponding to the primary objective was the proportion of patients who achieved PASI 75 and IGA mod 2011 0 or 1 response at Week 12 in each secukinumab treatment group (Low dose and High dose). Placebo data were obtained from adult secukinumab placebo-controlled trials and pediatric placebo-controlled trials with secukinumab or other biologics.

Endpoints for secondary objectives were:

- Proportion of patients who achieved PASI 90 response at Week 12 in each secukinumab treatment group (Low dose and High dose). Placebo data were obtained from adult placebo-controlled trials and pediatric placebo-controlled trials.
- Height and weight, vital signs, laboratory evaluations, ECG and adverse events.
- Secukinumab concentration in serum at various time points.

Endpoints for exploratory objectives were:

- Proportion of patients in PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response over time up to Week 16.
- Proportion of patients achieving CDLQI 0 or 1 over time up to Week 12.
- Development of anti-Drug Antibodies (ADA) to secukinumab.

Sample size

Per the current PIP, at least 60 paediatric patients with moderate psoriasis should be enrolled into the study; the total sample size is not defined in the KBE's. No details concerning sample size calculation have been provided. Based on reported data, 84 patients of whom 61 had moderate disease, were enrolled into the study.

Randomisation

Patients were randomised in a 1:1 ratio to receive either secukinumab Low dose or High dose during the treatment period. Randomisation was stratified by body weight (< 25kg, 25-< 50 kg, ≥ 50kg) and disease severity (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 the Randomisation Visit.

Statistical methods

Primary endpoint analysis

The co-primary efficacy endpoints were the proportion of patients with PASI 75 response and IGA 0/1 response at Week 12. Analysis of the co-primary and secondary endpoint (proportion of PASI 90 responders) was performed on each treatment group separately (secukinumab High dose against historical placebo and secukinumab Low dose against historical placebo) on the Full Analysis Set (FAS).

The statistical hypothesis was that secukinumab (High dose/Low dose) was not superior to historical placebo with respect to co-primary endpoints and key secondary endpoint PASI 90 at Week 12. A Bayesian method was chosen to allow the direct incorporation into the analysis of information about placebo response rates from historical data through a meta-analytic-predictive (MAP) prior.

First, a logistic Bayesian mixed effects model was fitted to the historical placebo data, including terms study and population (adult or paediatric). This was built to predict efficacy outcomes of a future paediatric trial taking into account between study heterogeneity of the control response rate. The adult studies were assigned a smaller weight in comparison to the paediatric studies. This was achieved through allocation to two distinct exchangeability strata which share a common population response rate, but differ in their between-trial heterogeneity parameter $\tau_{s(h)}$. Moderate between-trial heterogeneity (with τ prior set as HalfNormal(0, 0.5)) was defined for paediatric study data and substantial heterogeneity (with τ prior set as HalfNormal(0, 1)) was defined for adult study data, thus allowing paediatric study data to be given a higher weight compared to adult study data. From this model, the MAP prior was derived on the logit scale, and represented the predicted placebo log odds of the paediatric study, which was used in this study as the comparator. For each endpoint the resulting posterior distributions forming the MAP prior were approximated with a parametric distribution.

A separate logistic Bayesian model was fitted for each endpoint on the log odds scale to active data from this study with the term treatment.

These data were used to calculate the Bayesian posterior of the log odds ratio between secukinumab and placebo treatment response rate in this study. For the log odds of the secukinumab treatment groups a non-informative prior was used, whilst the placebo treatment group log odds response rate was represented though the MAP prior as described above.

Comparisons with placebo was performed for the secukinumab Low and High dose group separately on each of the efficacy endpoints (PASI 75, PASI 90 and IGA 0/1 at week 12) using MCMC in Stan version 2.17.1.

The analysis reported the posterior of the mean log odds ratio as point estimate by its median, its 95% credible interval and the probability of a positive treatment effect, which corresponded to the level of evidence for a positive treatment effect.

Missing values with respect to response variables based on PASI score and IGA 0/1 score were imputed with non-response regardless to the reason for missing data (e.g. premature study discontinuation, missed visit, administrative issues). This imputation was used for the primary and secondary endpoint Bayesian analysis.

The key secondary efficacy endpoint of this study is the proportion of patients with a PASI 90 response at Week 12. These data were analysed in the same way as the primary endpoint though a Bayesian framework.

Summary statistics for PASI 75, PASI 90, PASI 100, and IGA 0/1 response by visit were presented in contingency tables and included absolute and relative frequencies. In addition, summaries of the above efficacy endpoints were presented by age, disease severity strata and body weight strata. Missing data were imputed with pure non-responder imputation method (as described above).

All safety evaluations were based on the safety set. Data were presented by the following treatment groups:

- secukinumab Low dose: all patients who were randomized to secukinumab Low dose
- secukinumab High dose: all patients who were randomized to secukinumab High dose
- Any secukinumab dose: data on secukinumab groups above pooled together.

Results

Participant flow

A total of 92 patients were screened of which 84 patients completed the screening phase and were randomised to the two treatment groups in a 1:1 ratio. All except three patients (from secukinumab High dose group) completed the Week 24 visit (81/84 patients; 96.4% overall); thus 81 patients remained ongoing in the study at the time of the data cut-off. The reasons for discontinuations were AEs in two patients (ALT and AST elevations in one patient, and haemorrhagic diarrhoea in one patient) and lack of efficacy in one patient. Patient disposition is displayed in Table below.

Table 31 ***Patient disposition - data up to Week 24 (Randomised set)***

Disposition/Reason	AIN457 Low dose N=42 n (%)	AIN457 High dose N=42 n (%)	Total N=84 n (%)
Randomized	42	42	84
Ongoing at Week 24	42 (100.0)	39 (92.9)	81 (96.4)
Discontinued	0 (0.0)	3 (7.1)	3 (3.6)
Primary reason for discontinuing			
Adverse event	0 (0.0)	2 (4.8)	2 (2.4)
Lack of efficacy	0 (0.0)	1 (2.4)	1 (1.2)

Recruitment

Study A2311 was conducted across 23 Investigator sites in 9 participating countries: 2 centres in Belgium (n=4), 2 centres in Czech Republic (n=5), 1 centre in Estonia (n=7), 2 centres in Germany (n=11), 1 centre in Peru (n=5), 3 centres in Poland (n=17), 4 centres in Russia (n=14), 4 centres in Spain (n=10), and 4 centres in the United States (n=11).

Conduct of the study

The original protocol for Study A2311 had an effective date of 7 February 2018, and first patient first visit took place on 29 August 2018. The last data cut-off date to support the current submission was 14 November 2019, enabling analysis of the Week 24 dataset. According to the MAH, there have been no amendments to the study protocol.

The most common protocol deviation was 'other' deviation (15/84 subjects; 17.9%) which was reported with a similar frequency between the secukinumab Low dose (7/42 subjects; 16.7%) and High dose (8/42 subjects; 19.0%) groups. These 'other' deviations included missing assessments (IGA, PASI, haematology or pregnancy test, haematology being the most common). The second most common protocol deviation was 'treatment deviation' (the study drug was not administered at the scheduled "drug dispensing study visit") in both secukinumab Low dose (2/42 subjects; 4.8%) and High dose (4/42 subjects; 9.5%) groups.

Baseline data

The demographic characteristics of the study patients are summarised in Table below. In the entire study population, mean age was 12.6 years; 61% of patients (N=51) were in the age stratum 12-<18 years and 39% (N=33) in the 6-<12 year stratum. Overall mean weight was about 55 kg; 9.5% of patients (N=8) were in the weight stratum <25 kg, 29.8% (N=25) in the weight stratum 25- <50 kg, and 60.7% (N=51) in the weight stratum >= 50 kg. The patients were predominantly Caucasian, with a 54%:46% female:male split.

Table 32 ***Demographic and background characteristics (Randomised set)***

Characteristic	AIN457 Low dose N=42	AIN457 High dose N=42	Total N=84
Age group (years), -n (%)			
6 - < 12	17 (40.5)	16 (38.1)	33 (39.3)
12 - < 18	25 (59.5)	26 (61.9)	51 (60.7)
Age (years)			
n	42	42	84
Mean	12.5	12.8	12.6
SD	3.39	3.43	3.39
Minimum	6	6	6
Median	12.5	13.5	13.0
Maximum	17	17	17
Gender, -n (%)			
Male	22 (52.4)	17 (40.5)	39 (46.4)
Female	20 (47.6)	25 (59.5)	45 (53.6)
Race, -n (%)			
White	39 (92.9)	38 (90.5)	77 (91.7)
Black or African American	1 (2.4)	0 (0.0)	1 (1.2)
Asian	1 (2.4)	0 (0.0)	1 (1.2)
-Vietnamese	1 (2.4)	0 (0.0)	1 (1.2)
American Indian or Alaska Native	1 (2.4)	4 (9.5)	5 (6.0)
Height (cm)			
n	42	42	84
Mean	155.54	155.93	155.73
SD	17.755	18.635	18.091
Minimum	114.0	112.0	112.0
Median	160.00	159.20	160.00
Maximum	180.0	186.0	186.0
Weight (kg)			
n	42	42	84
Mean	54.34	55.73	55.03
SD	19.703	19.258	19.377
Minimum	20.0	18.0	18.0
Median	55.65	55.50	55.65
Maximum	95.0	110.0	110.0
Weight strata (kg), -n (%)			
<25	4 (9.5)	4 (9.5)	8 (9.5)
25 - <50	13 (31.0)	12 (28.6)	25 (29.8)
≥50	25 (59.5)	26 (61.9)	51 (60.7)
BMI (kg/m^2)			
n	42	42	84
Mean	21.67	22.18	21.92
SD	5.171	4.470	4.811
Minimum	14.5	13.3	13.3
Median	20.65	22.20	21.50
Maximum	32.5	34.4	34.4

Age collected at screening
BMI = body mass index is calculated based on raw data measurements.

Disease characteristics and history at baseline are summarised in Tables below. Overall mean PASI score was 18.86 (range 12.0 - 45.6) and mean % of affected body surface area was 29.9% (range 10.5% - 77.0%). Severity of psoriasis was moderate for 72.6% of patients (N=61) and severe for 27.4% (N=23). Patients had a mean history of 3.9 years since first diagnosis of plaque psoriasis, and only one patient had not received previous treatment for their psoriasis.

Table 33 ***Baseline disease characteristics (Randomised set)***

Background characteristic	AIN457 Low dose N=42	AIN457 High dose N=42	Total N=84
Baseline PASI score			
n	42	42	84
Mean	18.46	19.25	18.86
SD	5.244	6.728	6.009
Minimum	12.0	12.0	12.0
Q1	14.30	13.90	14.10
Median	16.60	18.50	17.70
Q3	22.20	22.20	22.20
Maximum	33.6	45.6	45.6
Baseline PASI, -n (%)			
≤20	27 (64.3)	24 (57.1)	51 (60.7)
>20	15 (35.7)	18 (42.9)	33 (39.3)
Baseline Total BSA			
n	42	42	84
Mean	29.35	30.38	29.86
SD	11.243	16.788	14.210
Minimum	10.5	11.5	10.5
Q1	20.00	17.90	18.95
Median	29.00	26.25	28.00
Q3	36.60	36.00	36.30
Maximum	60.5	77.0	77.0
Baseline IGA mod 2011 score, -n (%)			
3 = Moderate disease	29 (69.0)	29 (69.0)	58 (69.0)
4 = Severe disease	13 (31.0)	13 (31.0)	26 (31.0)
Severity of psoriasis (as per randomization), -n (%)			
Moderate	30 (71.4)	31 (73.8)	61 (72.6)
Severe	12 (28.6)	11 (26.2)	23 (27.4)

Table 34 ***Disease history (Randomised set)***

Background characteristic	AIN457 Low dose N=42	AIN457 High dose N=42	Total N=84
Time since first diagnosis of plaque-type psoriasis (years)			
n	42	42	84
Mean	3.92	3.95	3.94
SD	3.644	3.779	3.689
Minimum	0.3	0.3	0.3
Q1	1.34	0.94	1.08
Median	2.76	2.62	2.67
Q3	6.55	5.84	6.07
Maximum	16.7	14.5	16.7
Generalized pustular psoriasis, -n (%)			
Yes	0 (0.0)	0 (0.0)	0 (0.0)
No	42 (100)	42 (100)	84 (100)
Palmoplantar pustular psoriasis, -n (%)			
Yes	0 (0.0)	0 (0.0)	0 (0.0)
No	42 (100)	42 (100)	84 (100)
Erythrodermic psoriasis, -n (%)			
Yes	0 (0.0)	1 (2.4)	1 (1.2)
No	42 (100)	41 (97.6)	83 (98.8)
Psoriatic arthritis history, -n (%)			
Yes	1 (2.4)	0 (0.0)	1 (1.2)
No	41 (97.6)	42 (100)	83 (98.8)
Previous psoriasis therapies, -n (%)			
Yes	42 (100)	41 (97.6)	83 (98.8)
No	0 (0.0)	1 (2.4)	1 (1.2)

Numbers analysed

All 84 randomised patients were included in the FAS and Safety set (Table below).

Table 35 ***Analysis sets (All patients enrolled)***

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

Outcomes and estimation

Primary efficacy results: PASI 75 and IGA mod 2011 0/1 at Week 12

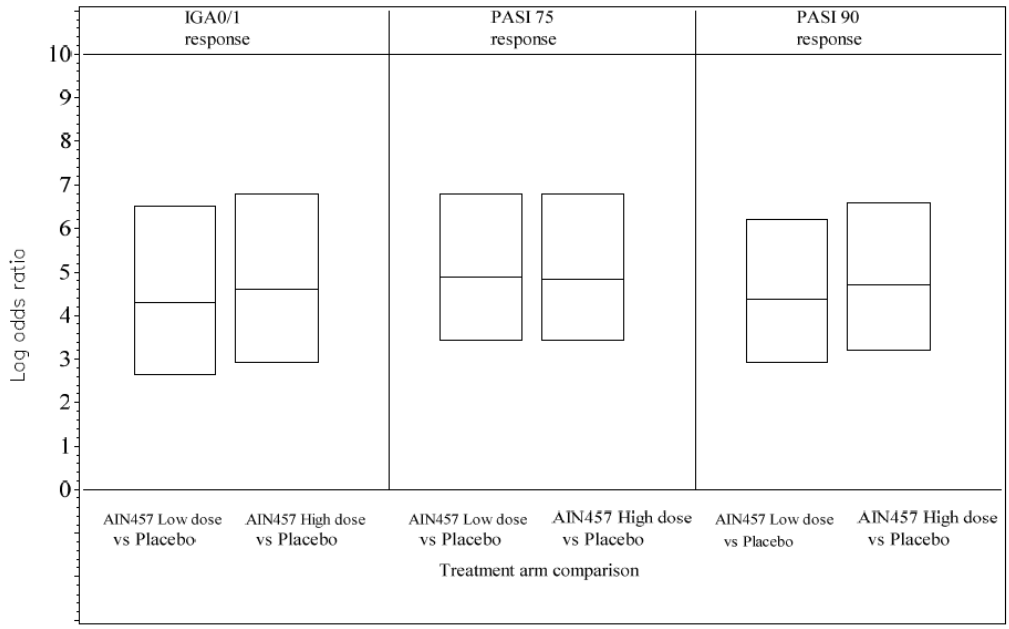
Both secukinumab doses (Low and High) were superior to historical placebo with respect to PASI 75 response and IGA 0/1 response at Week 12. Estimates for the log odds ratios and credible intervals from the Bayesian analysis are displayed in Table and Figure below. The estimated probability of a positive treatment effect (i.e., log OR >0) for secukinumab Low or High dose compared to historical placebo is 1 (100%). This supports the conclusion that efficacy response rates on secukinumab are better than historical placebo.

Table 36 ***Predicted log-odds ratio for PASI 75, PASI 90 and IGA 0 or 1 response at Week 12 (Pure non-responder imputation) (Full analysis set)***

Criterion	AIN457 Low dose N=42	AIN457 High dose N=42
IGA 0/1		
Predicted log-OR (95% CrI)	4.292 (2.638, 6.513)	4.606 (2.919, 6.780)
Probability of (log-OR > 0) *	1.0000	1.0000
PASI 75		
Predicted log-OR (95% CrI)	4.862 (3.422, 6.782)	4.836 (3.422, 6.772)
Probability of (log-OR > 0) *	1.0000	1.0000
PASI 90		
Predicted log-OR (95% CrI)	4.367 (2.916, 6.202)	4.709 (3.201, 6.580)
Probability of (log-OR > 0) *	1.0000	1.0000

OR = odds ratio, 95% CrI = 95% credible interval.

* Posterior probability of a positive treatment effect for secukinumab high or low dose compared to historical placebo. 1 = 100% probability.



Box represents 95% credible interval and the bar represents the median of the mean predictive log odds ratio for study A2311.

Treatment comparison to historical placebo.

Figure 15 ***Predictive response rates in PASI 75, PASI 90 and IGA 0 or 1 response at Week 12 by treatment (Pure non-responder imputation) (Full analysis set) (All patients enrolled)***

Both secukinumab dose levels (Low and High) displayed very high response rates on the primary endpoints of PASI 75 response and IGA 0/1 response at Week 12 (Figure below). Using non-responder imputation for missing data, the PASI 75 response at Week 12 was 92.9% (39/42) in both secukinumab Low dose and High dose group. The IGA 0/1 response at Week 12 was 78.6% (33/42 patients) in the Low dose group and 81.0% (34/42 patients) in the High dose group.

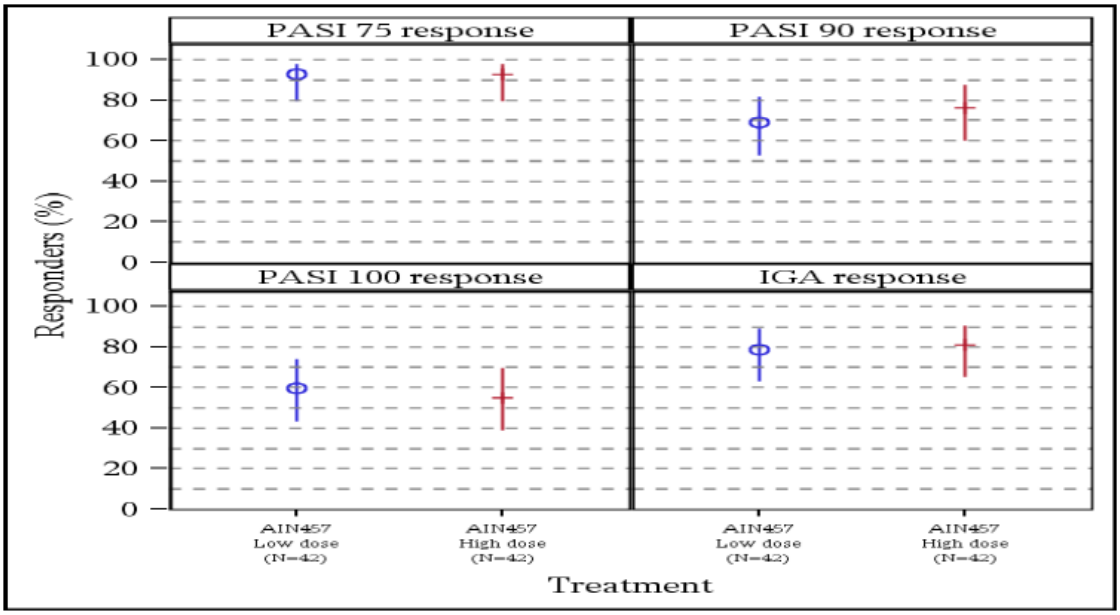


Figure 16 ***PASI 75, PASI 90, PASI 100 and IGA 0/1 response (estimate ± 95% CI) at Week 12 (Pure non-responder imputation) (Full analysis set)***

Secondary efficacy endpoint: PASI 90 at Week 12

Using non-responder imputation, a PASI 90 response at Week 12 was achieved by 69.0% of patients (N=29/42) in the secukinumab Low dose group and 76.2% of patients (N=32/42) in the secukinumab High dose group (Figure above).

Exploratory endpoints: Responses over time until Week 24

Effects on IGA 0/1, PASI 75, PASI 90 and PASI 100 responses over time

IGA 0/1, PASI 75, PASI 90 and PASI 100 response rates from randomisation until Week 24 are displayed in Figure below. Depending on the endpoint, responses in both secukinumab groups were detected from Week 2 to Week 4 onward, with further increases observed until Week 24.

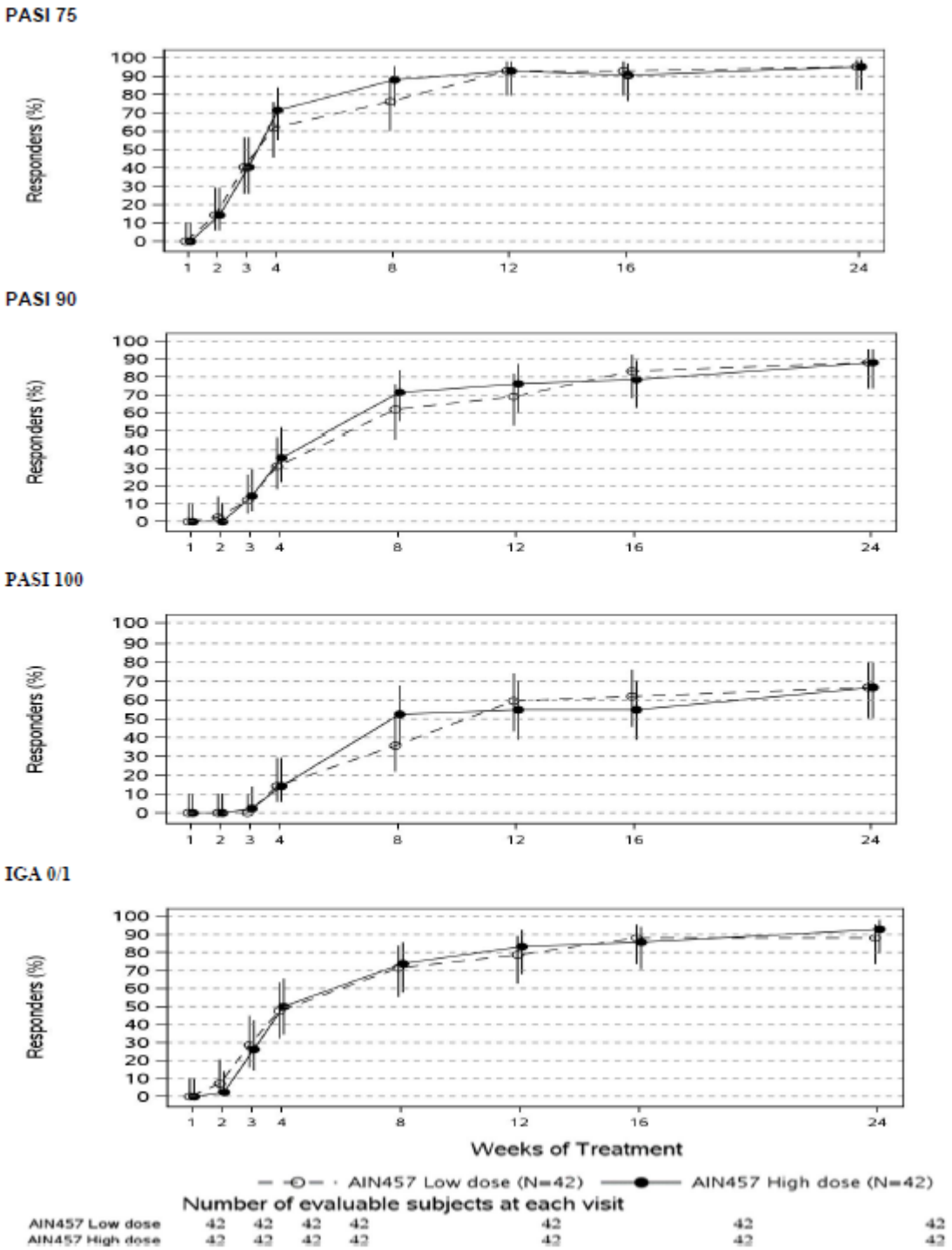


*Figure 17**PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response (estimate + 95% CI) by visit (Pure non-responder imputation)- Data up to Week 24 (Full analysis set)***

Patient Reported Outcomes (CDLQI)

At Week 12, the proportions of patients achieving a CDLQI 0 or 1 response (indicating no or little impairment) were 50.0% (21/42 patients) in the secukinumab Low dose group and 61.9% (26/42 patients) in the High dose group. Further improvement until Week 24 was observed in the Low dose group: at Week 24, the corresponding proportions were 70.7% (29/42 patients) in the secukinumab Low dose group and 60.5% (23/38 patients) in the High dose group.

Ancillary analyses

Subgroup Analyses: Weight and age strata, Baseline disease severity

Results of a subgroup analysis of primary and key secondary endpoints by weight strata used to define the dosing regimens, based on a pure non-responder imputation strategy, are displayed in Table 37. For weight stratum < 25 kg, it should be noted that the same 75 mg dose was used in both the Low and High dose groups.

A corresponding subgroup analysis was undertaken by age stratum, and the results are displayed in Table 38.

Lastly, a subgroup analysis was also undertaken to assess response by baseline disease severity. The results are displayed in Table 39.

Table 37 ***IGA 0/1, PASI 75, PASI 90 and PASI 100 response at Week 12 by weight strata - pure non-responder imputation (Full analysis set)***

Visit	Criterion	AIN457 Low dose N=4 n/m (%)	AIN457 High dose N=4 n/m (%)
Weight stratum: <25 kg			
Week 12	IGA 0/1	2/4 (50.0)	3/4 (75.0)
	PASI 75	4/4 (100.0)	4/4 (100.0)
	PASI 90	2/4 (50.0)	3/4 (75.0)
	PASI 100	2/4 (50.0)	1/4 (25.0)
Weight stratum: 25 - <50 kg			
Visit	**Criterion**	**AIN457 Low dose N=13 n/m (%)**	**AIN457 High dose N=12 n/m (%)**
Week 12	IGA 0/1	11/13 (84.6)	9/12 (75.0)
	PASI 75	13/13 (100.0)	10/12 (83.3)
	PASI 90	10/13 (76.9)	8/12 (66.7)
	PASI 100	8/13 (61.5)	7/12 (58.3)
Weight stratum: ≥50 kg			
Visit	**Criterion**	**AIN457 Low dose N=25 n/m (%)**	**AIN457 High dose N=26 n/m (%)**
Week 12	IGA 0/1	20/25 (80.0)	22/26 (84.6)
	PASI 75	22/25 (88.0)	25/26 (96.2)
	PASI 90	17/25 (68.0)	21/26 (80.8)
	PASI 100	15/25 (60.0)	15/26 (57.7)

Table 38 ***IGA 0/1, PASI 75, PASI 90 and PASI 100 response at Week 12 by age strata - pure non-responder imputation (Full analysis set)***

Age group: 6-<12 years of age					
		AIN457 Low dose N=17		AIN457 High dose N=16	
Visit	Criterion	n/m	(%)	n/m	(%)
Week 12	IGA 0/1	14/17	(82.4)	13/16	(81.3)
	PASI 75	17/17	(100.0)	15/16	(93.8)
	PASI 90	14/17	(82.4)	12/16	(75.0)
	PASI 100	12/17	(70.6)	9/16	(56.3)
Age group: 12-<18 years of age					
		AIN457 Low dose N=25		AIN457 High dose N=26	
Visit	Criterion	n/m	(%)	n/m	(%)
Week 12	IGA 0/1	19/25	(76.0)	21/26	(80.8)
	PASI 75	22/25	(88.0)	24/26	(92.3)
	PASI 90	15/25	(60.0)	20/26	(76.9)
	PASI 100	13/25	(52.0)	14/26	(53.8)

Table 39 ***IGA 0/1, PASI 75, PASI 90 and PASI 100 response at Week 12 by baseline dsease severity - pure non-responder imputation (Full analysis set)***

Disease Severity: MODERATE			
		AIN457 Low dose N=30	AIN457 High dose N=31
Visit	Criterion	n/m (%)	n/m (%)
Week 12	IGA 0/1	25/30 (83.3)	26/31 (83.9)
	PASI 75	28/30 (93.3)	29/31 (93.5)
	PASI 90	21/30 (70.0)	25/31 (80.6)
	PASI 100	17/30 (56.7)	18/31 (58.1)
Disease Severity: SEVERE			
		AIN457 Low dose N=12	AIN457 High dose N=11
Visit	Criterion	n/m (%)	n/m (%)
Week 12	IGA 0/1	8/12 (66.7)	8/11 (72.7)
	PASI 75	11/12 (91.7)	10/11 (90.9)
	PASI 90	8/12 (66.7)	7/11 (63.6)
	PASI 100	8/12 (66.7)	5/11 (45.5)

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 40 ***Summary of Efficacy for trial A2310***

Title: 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	
Study identifier	CAIN457A2310

Design	Randomised, double-blind placebo- and active-controlled study				
	Duration of Induction phase: 12 weeks (time point for primary analysis) Duration of Maintenance phase: 40 weeks (Week 12 to 52) Duration of Extension phase: 184 weeks (Week 52 to 236)				
Hypothesis	Superiority to placebo				
Treatment groups	Secukinumab Low dose		According to the weight category, s.c. secukinumab 75 mg (in <25 kg and 25 to <50 kg) or 150 mg (⩾50 kg) injections at Randomization, Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and placebo at Weeks 13, 14 and 15 during the blinded phase of the study; thereafter at Week 52 and every 4 weeks during the Extension period until Week 232. N = 40 + 16 transitioning from placebo for Maintenance.		
	Secukinumab High dose		According to the weight category , s.c. secukinumab 75mg (in <25 kg), 150mg (25 to <50 kg), 300 mg (⩾50 kg) injections at Randomization, Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and placebo at Weeks 13, 14 and 15 during the blinded phase of the study; thereafter at Week 52 and every 4 weeks during the extension treatment epoch until Week 232. N = 40 + 18 transitioning from placebo for Maintenance.		
	Placebo		s.c. placebo once per week for four weeks (at Randomization, Weeks 1, 2 and 3), followed by dosing every four weeks (Weeks 4 and 8). N = 41. Placebo non-responders transition to secukinumab at completion of Induction period.		
	Etanercept (open-label arm)		s.c. etanercept 0.8 mg/kg (up to a maximum dose of 50 mg) once per week, for 51 weeks. N = 41.		
Endpoints and definitions	Co-primary endpoint	PASI 75 response	Improvement of ⩾75% on the PASI score, at week 12.		
	Co-primary endpoint	IGA mod 2011 0 or 1 response	A score of 0 (clear) or 1 (almost clear) on the IGA mod 2011 scale, at week 12.		
	Key secondary endpoint	PASI 90 response	Improvement of ⩾90% on the PASI score, at week 12.		
Data cut-off	7 March 2019 (all patients having completed Week 24) 18 September 2019 (all patients having completed Week 52)				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Full Analysis Set; Multiple Imputation for missing data Week 12				
Descriptive statistics and estimate variability	Treatment group	Secukinumab Low dose	Secukinumab High dose	Placebo	Etanercept
	Number of subjects	40	40	41	41
	PASI 75 (%)	80.1%	80.2%	14.9%	65.7%
	95% CI	63.6, 91.8	64.1, 91.5	5.7, 29.6	48.7, 80.3

	IGA 0/1 (%)	69.8%	62.6%	6.3%	36.3%
	95% CI	52.6, 83.9	45.5, 77.7	0.8, 18.9	21.6, 53.0
	PASI 90 (%)	71.1%	69.3%	2.5%	31.4%
	95% CI	54.1, 84.8	52.4, 83.2	0.0, 13.0	17.6, 48.0

Effect estimate per comparison	Co-primary endpoint: PASI 75 response	Comparison groups	Secukinumab Low dose vs. placebo
		OR	25.97
		95% CI	7.31, 92.22
		P-value	<.0001
	Co-primary endpoint: PASI 75 response	Comparison groups	Secukinumab High dose vs. placebo
		OR	26.55
		95% CI	7.57, 93.09
		P-value	<.0001
	Co-primary endpoint: IGA 0/1 response	Comparison groups	Secukinumab Low dose vs. placebo
		OR	40.39
		95% CI	8.37, 194.87
		P-value	<.0001
	Co-primary endpoint: IGA 0/1 response	Comparison groups	Secukinumab High dose vs. placebo
		OR	28.35
		95% CI	6.00, 133.92
		P-value	<.0001
	Key secondary endpoint: PASI 90 response	Comparison groups	Secukinumab Low dose vs. placebo
		OR	121.86
		95% CI	14.23, 1043.28
		P-value	<.0001
	Key secondary endpoint: PASI 90 response	Comparison groups	Secukinumab High dose vs. placebo
		OR	110.14
		95% CI	12.98, 934.72
		P-value	<.0001
Notes	Comparisons against etanercept are not tabulated as they were not part of formal testing strategy		

Table 41 ***Summary of Efficacy for trial A2311***

Title: 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		
Study identifier	CAIN457A2311	
Design	Randomised, open-label study with historical placebo control group	
	Duration of Treatment:	208 weeks (interim analysis at Week 24)
Hypothesis	Superiority to historical placebo	
Treatment groups	Secukinumab Low dose	According to the weight category, s.c. secukinumab 75 mg (in <25 kg and 25 to <50 kg) or 150 mg (⩾50 kg) injections at Randomization, Weeks 1, 2, 3, 4, and every 4 weeks thereafter N = 42

	Secukinumab High dose		According to the weight category , s.c. secukinumab 75mg (in <25 kg), 150mg (25 to <50 kg), 300 mg (⩾50 kg) injections at Randomization, Weeks 1, 2, 3, 4, and every 4 weeks thereafter N = 42
Endpoints and definitions	Co-primary endpoint	PASI 75 response	Improvement of ⩾75% on the PASI score, at week 12.
	Co-primary endpoint	IGA mod 2011 0 or 1 response	A score of 0 (clear) or 1 (almost clear) on the IGA mod 2011 scale, at week 12.
	Secondary endpoint	PASI 90 response	Improvement of ⩾90% on the PASI score, at week 12.
Data cut-off	14 November 2019 (all patients having completed Week 24)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set; Non-responder imputation for missing data Week 12		
Descriptive statistics and estimate variability	Treatment group	Secukinumab Low dose	Secukinumab High dose
	Number of subjects	42	42
	PASI 75 (%)	92.9%	92.9%
	95% CI	79.4, 98.1	79.4, 98.1
	IGA 0/1 (%)	78.6%	81.0%
	95% CI	62.8, 89.2	65.4, 90.9
	PASI 90 (%)	69.0%	76.2%
	95% CI	52.8, 81.9	60.2, 87.4
Effect estimate per comparison	Co-primary endpoint: PASI 75 response	Comparison groups	Secukinumab Low dose vs. historical placebo
		Log OR	4.862
		95% CrI	3.422, 6.782
		Posterior probability of (log-OR > 0) *	100%
	Co-primary endpoint: PASI 75 response	Comparison groups	Secukinumab High dose vs. historical placebo
		Log OR	4.836
		95% CrI	3.422, 6.772
		Posterior probability of (log-OR > 0) *	100%
	Co-primary endpoint: IGA 0/1 response	Comparison groups	Secukinumab Low dose vs. historial placebo
		Log OR	4.301
		95% CrI	2.657, 6.509
		Posterior probability of (log-OR > 0) *	100%
	Co-primary endpoint: IGA 0/1 response	Comparison groups	Secukinumab High dose vs. historical placebo
		Log OR	4.434
		95% CrI	2.846, 6.612
		Posterior probability of (log-OR > 0) *	100%
Notes	* Posterior probability of a positive treatment effect for secukinumab High or Low dose compared to historical placebo.		

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Supportive studies

Comparison of efficacy results from study A2310 vs. previously completed secukinumab studies in adult psoriasis patients is discussed in Section 2.3.

2.4.3. Discussion on clinical efficacy

The current variation application is based on interim analyses of two ongoing studies:

1) Analysis of data up to Week 52 in study A2310, a randomised, double-blind, placebo and etanercept controlled study in paediatric patients with severe chronic plaque psoriasis. The study consists of a screening period of up to 4 weeks, a placebo- and active-controlled 12 week induction period, an active-controlled 40 week maintenance period, a non-controlled 184 week extension period, and a 16 week post-treatment follow-up period. The study is referred to as "Study 3" in the currently agreed PIP for secukinumab in paediatric psoriasis.
2) Analysis of data up to Week 24 in study A2311, a randomised open-label study with a historical placebo control group and a treatment period of 208 weeks in paediatric patients with moderate to severe chronic plaque psoriasis. The study is referred to as "Study 4" in the PIP.

Design and conduct of clinical studies

Study A2310

The general design features of this double-blind placebo- and active-controlled study are in accordance with the EU Guideline on psoriasis (CHMP/EWP/2454/02 corr) and are also in agreement with the PIP (recognising that the study remains ongoing, and possibilities to assess remission and relapse are therefore limited). According to the MAH, etanercept was chosen as an active comparator, since it was the first biologic medication approved for use in children and adolescents with severe psoriasis in the European Union and elsewhere. This justification is acceptable to CHMP. Placebo responders were discontinued from the study at Week 12. While this may be justifiable from an efficacy assessment perspective, it is noted that continuing these already enrolled patients on active medication could have provided useful further data regarding the safety of secukinumab.

The inclusion criteria are appropriate for defining a paediatric population with severe plaque psoriasis. According to the MAH, the definition of severe disease was also agreed with PDCO during the psoriasis PIP discussions. Exclusion criteria are acceptable and not unduly restrictive. The definition of a patient being "a candidate for systemic therapy" was analogous to that used in the adult program, essentially permitting use as first-line systemic therapy.

Secukinumab dosing regimens were based on modelling and simulation from adult psoriasis data; separate dose response studies in paediatric patients were not performed. Etanercept was administered according to its approved posology in paediatric plaque psoriasis; the duration of treatment per current etanercept SmPC is capped at 24 weeks, but re-treatment is permitted.

It is noted that a 75 mg pre-filled syringe was used for administration of secukinumab in the study. Commercial availability of this presentation would facilitate treatment of patients in the < 50 kg weight range, and considering that the 150 mg vial may is not available across all Member States, might even

be critical to enable adequate treatment of these patients. The MAH was invited to comment on plans to introduce such a presentation and how the 75 mg dose envisioned in the SmPC would be administered for patients in Member States where the 150 mg vial has not been introduced. In its response, the MAH assured that the secukinumab 150 mg lyophilised vial can be made available to patients in all the Member States, where needed. Furthermore, the MAH indicated that it is currently planning to submit in EU the extension application for the registration of the Cosentyx 75 mg/0.5 mL PFS by the end of 2020.

The pre-defined primary endpoints are in accordance with Guideline requirements; the MAH-developed IGA mod 2011 scale was deemed acceptable during assessment of the adult psoriasis indication for secukinumab. A large number of secondary and exploratory objectives were defined; however, they were not included within the hierarchical statistical testing strategy. All comparisons to etanercept were included within exploratory objectives, and references to statistical significance and p values for comparisons vs. etanercept were therefore removed from the SmPC proposal.

The sample size was based on a power calculation that confirms a high likelihood of meeting the study aims based on the assumed response rates. The sample size is also in agreement with binding elements of the current PIP. The sample size calculation does not include the element of stratification; however as it is likely that it would increase the power, the sample size calculation is acceptable to CHMP.

Forced randomisation was used, which typically forces a deviation from the randomisation scheme. The use of forced randomisations is not included in the protocol deviation list, which suggests that this conduct was according to the protocol; however, with strict ITT principle, these patients should have been treated according to the randomisation scheme, not according to the treatment available at the site. The MAH clarified that the decision to permit the use of forced randomisation was based primarily on ethical grounds. Actual use of forced randomisation was limited to a few cases and based on an additional sensitivity analysis presented by the MAH, did not have any significant influence on the results of the study. The clarification was acceptable to the CHMP.

IRT technology was utilised in the randomisation procedure. Due to an error caused by the IRT system, dosing errors were recognised, for which further clarification was requested. According to the MAH, the unfortunate IRT error affected only subjects that were initially randomised to active drug and was only limited to weeks 13, 14 and 15. However, as the error indeed happened, the MAH was requested to clarify the reason for the error, and to further explain how it has been ascertained that this error was limited to dosing of secukinumab patients dosed at weeks 13, 14 and 15 and that the possibility of additional mix-ups, *e.g.*, for dosings prior to week 12 can be excluded. Based on additional details provided by the MAH, the CHMP agreed that the IRT error was unlikely to have affected pre-Week 12 dosings or the integrity of the Week 12 data.

The blinding procedures of the double-blind treatment arms are acceptable in general. The CHMP noted that the open-label use of etanercept was unfortunate, as it may introduce a bias in any data collected in this group.

The analysis populations as defined are commonly used and acceptable to the CHMP. The used statistical analysis method is suitable for binary response data. The multiple testing strategy is appropriate to protect type-I-error rate on acceptable level.

For missing data of the primary endpoints, two methods were planned to be used, multiple imputation assuming MAR and non-responder imputation. 75% of the missing data (18/24) was caused by a narrow visit window at week 12, the rest (6/24) was due to treatment discontinuations. The assumption of MAR is realistic for the missing caused by narrow visit window, but unlikely for the discontinuations, and the non-responder imputation is too conservative for missing caused by narrow visit window, thus neither of the planned methods is optimal. A data driven analysis was conducted using extended visit window, in which actual observed data was used for all except for missing due to discontinuations. At the CHMP

request, the extended time-window analysis with non-responder imputation for discontinuations was used to present the results in Section 5.1 of the SmPC.

The study was conducted across 47 Investigator sites in 19 countries. Of the total of 162 patients enrolled, the largest numbers were recruited in Poland (28), Germany (25), Russia (13), Egypt (11) and Estonia (11). More than 60% of the study patients were enrolled at sites located within EU Member States.

The overall attrition rate during the initial 12 week induction period was low, with 95 % of patients completing Week 12 in all treatment groups. Similarly, over 90 % of patients entering the maintenance period completed Week 52.

An error in the IRT system led to incorrect dosing of a significant proportion of patients in the Maintenance period. The primary endpoint analysis (Week 12) was not affected by the error, but it cannot be excluded that Week 24 analyses were impacted by exposures that are higher than intended. However, subsequent to full Week 52 data becoming available during assessment, Week 24 data is considered of limited importance.

Use of prohibited concomitant medication was reported in a substantial proportion of patients (e.g., 25% in the secukinumab High dose group). However, based on additional details provided by the MAH, it is unlikely that these medications would have a significant influence on the reported efficacy results.

The majority of enrolled patients were in the older age stratum and in the higher weight categories; 37 patients (23%) were under 12 years, and 12 patients (7%) in the weight category < 25 kg. Mean PASI score was 28 and mean BSA affected was 40%, consistent with severe disease. Less than 10% of patients overall had a diagnosis of psoriatic arthritis.

In principle, the patients seem to meet the protocol definition "candidate for systemic therapy"; the use was essentially second line after failure on a previous systemic therapy in a substantial proportion of patients. About 53% of patients had received prior systemic therapies for psoriasis; the most commonly used prior systemic therapies were methotrexate (26.5%), acitretin (11.7%) and ciclosporin (9.9%). The majority of patients (97.5% overall) had no previous exposure to biologic psoriasis therapies.

Study A2311

The design features of this study are in agreement with the PIP. Although data is currently available only through Week 24, the results can be considered to provide relevant additional information to support the overall assessment.

The eligibility criteria are appropriate for defining a paediatric population with moderate to severe plaque psoriasis. The definition of a patient being "a candidate for systemic therapy" was analogous to that used in the adult program and study A2310, essentially permitting use as first-line systemic therapy.

Secukinumab dosing regimens and body weight categories to guide dose selection in study A2311 were identical to A2310. The absence of a concurrent control group is noted, and the use of a historical placebo control group had been agreed beforehand with the PDCO. The endpoints for this study were aligned with study A2310 and represent recognised endpoints in the EU Guideline. Based on reported enrolment numbers, the sample size is in accordance with the PIP KBE.

Randomisation was stratified by body weight category and disease severity. A Bayesian approach was used for statistical testing. Considering the context with a historical control group, the described methods are acceptable. Non-responder imputation represents a conservative approach to missing data.

The study was conducted across 23 Investigator sites in 9 countries. Of the total of 84 patients enrolled, the largest numbers were recruited in Poland (17), Russia (14), Germany (11), United States (11), and

Spain (10). More than 60% of the study patients were enrolled at sites located within EU Member States. There have been no amendments to the original study protocol and reported protocol deviations seem unlikely to jeopardise data integrity.

Of the 84 enrolled patients, 81 patients completed the Week 24 visit. The attrition rate during the early stages of the study was thus low, with over 90 % of patients completing Week 24 in both treatment groups.

Similar to study A2310, the majority of enrolled patients were in the older age stratum and in the higher weight categories; 33 patients (39.3%) were under 12 years, and 8 patients (9.5%) in the weight category <25 kg. Consistent with the overall aim of the study, the majority of patients (72.6%; N=61) had disease of moderate severity at baseline, and study A2311 thus provides useful insight into the actual performance of secukinumab in this subpopulation.

Efficacy data and additional analyses

Study A2310

Statistically significant and clinically relevant treatment effects were seen with both secukinumab dosages on the co-primary endpoints as well as the key secondary endpoint; there was no numeric difference between the dose levels. Although not part of the formal statistical testing strategy, both dosages also demonstrated numerically better response rates compared to the active comparator etanercept on the co-primary and key secondary endpoints. Sensitivity analyses based on non-responder imputation supported robustness of the observation. The study provides good evidence of the short-term efficacy of secukinumab in paediatric patients with severe psoriasis.

There was no numeric difference in any efficacy parameter assessed at Week 12 and actual up-titration data is not available. In Week 52 data, some incremental efficacy with the higher 300 mg dose could be observed in the ≥50 kg weight stratum. In contrast, long-term response rates in the ≥25-<50 kg weight stratum were higher with the 75 mg dose than the 150 mg dose, questioning whether a recommendation to double the dose to achieve additional benefit would be appropriate in this weight stratum. Hence, the MAH proposed SmPC posology wording to indicate that the recommended dose can be increased from 150 to 300 mg within weight stratum ≥50 kg and that some patients may derive additional benefit from a higher dose was endorsed by the CHMP. However, at the CHMP request, the MAH removed this recommendation for the 25-50 kg weight stratum from the SmPC. See also discussions on clinical safety (Section 2.5.1).

Onset of activity of secukinumab was rapid, with responses detected from Week 2 onward, and a consistent pattern was observed among placebo non-responders switching to secukinumab at Week 12.

Results on the CDLQI indicated a favourable effect on subjectively experienced quality of life. Summary statistics for CHAQ were not computed due to the low number of patients with psoriatic arthritis.

Assessment of Week 24 data was hampered by the IRT dosing error affecting a significant proportion of subjects in both secukinumab groups. However, Week 52 data is less likely to be affected by the error and the CHMP concluded that long-term maintenance of effect until Week 52 has been demonstrated. Hence, a long-term indication has therefore been accepted by the CHMP.

In subgroup analyses of Week 12 data based on age stratum, weight category and previous exposure to systemic therapy, substantially better response rates were generally observed in both secukinumab dose groups compared to placebo across all subgroups. It should be noted that the number of patients in the lowest weight group (<25 kg) is very small (total N=12), and conclusions regarding the younger age stratum are also limited by the small sample size (total N=37). Consistent with the main analyses, there

was generally little difference between the secukinumab dose groups in response rates when assessed by the different subgroups although the younger age and lowest weight cohorts in this study alone are too small for robust conclusions. See discussion below for general conclusion on that point.

Study A2311

The overall results of Study A2311 are well aligned with those of study A2310. Bayesian analysis of co-primary endpoints (PASI 75 and IGA 0/1) at Week 12 demonstrated superiority over historical placebo for both secukinumab High dose and Low dose groups, and very high response rates with rapid onset of activity were observed in both treatment groups. Furthermore, similar to A2310, there was no difference between the dose levels. Results on the CDLQI indicated a favourable effect on subjectively experienced quality of life. The study thus complements the results of A2310 and can be considered to provide evidence supportive of short-term efficacy of secukinumab in paediatric patients with moderate to severe psoriasis.

The Week 24 data, provided in response to the 2nd Request for Supplementary Information, support maintenance of effect and the claim for a long-term indication. Whereas an interim analysis of Week 52 data has been pre-specified in the study protocol and is also part of the agreed PIP, an analysis of Week 24 data is not specifically mentioned in the protocol. The MAH should replace the Week 24 data in the Section 5.1 SmPC with Week 52 data when they become available.

In subgroup analyses based on age and weight strata as well as baseline disease severity, high response rates were generally observed for both dose levels. Similar to study A2310, the number of patients in the lowest weight stratum (< 25 kg) is very small (total N=8), and conclusions regarding the younger age stratum are also limited by the small sample size (total N=33).

Nevertheless, consistent with study A2310 and the main analyses, there was generally little difference between the secukinumab dose groups in response rates when assessed by the different subgroups. Furthermore, in the analysis by weight strata, it is noted that similar to A2310, efficacy in the 25-<50 kg stratum in fact appears to be higher in the Low dose group than the High dose group supporting again the removal of the initially proposed posology recommendation to allow dose doubling in this weight stratum.

2.4.4. Conclusions on the clinical efficacy

Secukinumab is being studied in a randomised, double-blind, placebo- and etanercept -controlled study in paediatric patients with severe psoriasis. In an interim analysis, the study met its co-primary and key secondary endpoints and demonstrated responses rates exceeding those observed with an appropriate active comparator. The CHMP concluded that short-term efficacy of secukinumab in the studied population has been demonstrated. Maintenance of effect until Week 52 was also shown, supporting a long-term indication.

Data until Week 24 from study A2311, which is an open-label study in paediatric patients with moderate to severe psoriasis, corroborates findings from the placebo-controlled study.

Results up to Week 24 in study A2311 were consistent with study A2310 and support efficacy in patients with disease of moderate severity.

Although the limited dataset in patients under 25 kg in body weight is recognised, together, studies A2310 and A2311 provide efficacy and safety data from 58 patients <12 years receiving at least a single dose of secukinumab, and 16 patients <25 kg receiving at least a single dose of secukinumab. Total exposure to secukinumab was reported as 35.02 patient-years in patients <12 years and 13.2 patient-years in patients weighing <25 kg. The CHMP considered that sufficient data was available for patients

under 25 kg in body weight and that no weight restriction below 25 kg was deemed necessary in the indication.

In conclusion, the CHMP considered that the efficacy was adequately described in the claimed indication.

2.5. Clinical safety

Introduction

The presented paediatric safety data set presented in this dossier is comprised of patients enrolled in Studies A2310 and A2311. These were male and female, 6 to < 18 years (at the start of study treatment), with moderate (Study A2311) or severe (Study A2310 and Study A2311) plaque psoriasis, a history of plaque psoriasis for at least 3 months and psoriasis that was poorly controlled by topical treatments and/or phototherapy and/or previous systemic therapy. These paediatric patients were candidates for systemic therapy. The lower age of enrolment was limited to 6 years since, according to the MAH, the prevalence of psoriasis in children under 6 years is very low (with the highest prevalence published of 0.3%), and the proportion of children with a severe condition in need of a systemic treatment is 4%, giving a final prevalence of the condition to be about 1 per 10,000 in this age group.

Severe psoriasis criteria were agreed with PDCO during the psoriasis PIP discussions and subsequently moderate psoriasis criteria were defined. These severity definitions are used in both ongoing paediatric studies for psoriasis and in the adult data comparison. The disease severity classification is outlined in Table below.

Table 42 ***Definition of psoriasis severity by IGA and PASI score***

IGA	PASI score	Psoriasis severity
3	12-< 20	Moderate
3	≥ 20	Moderate
4	12-< 20	Moderate
4	≥ 20	Severe

- IGA = Investigator's global assessment
- PASI = Psoriasis area and severity index

The adult safety dataset used for comparison with Studies A2310 and A2311 paediatric data was based on the 4 pivotal studies (see Table below) that were previously used to demonstrate the safety and efficacy of secukinumab 150 mg or 300 mg administered s.c. in the adult patients: Studies CAIN457A2302, CAIN457A2303, CAIN457A2308 and CAIN457A2309 (first 12 week placebo controlled data and up to Week 52 for all studies; referred hereafter as Studies A2302, A2303, A2308 and A2309 in this AR). These were male and female adults (≥ 18 years) with moderate to severe plaque psoriasis, and a history of plaque psoriasis for at least 3 months before randomisation that was poorly controlled by topical treatments and/or phototherapy and/or previous systemic therapy. These adult patients were candidates for systemic therapy.

Table 43 ***Overview of supportive studies in psoriasis (adult pool)***

Study	Design, objectives	Population	Number of patients randomised	Treatments and treatment duration
A2302	Phase III, randomised, double blind, placebo-controlled, parallel group studies. To demonstrate superiority of secukinumab 150 mg and 300 mg compared to placebo with respect to both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at 12 weeks of treatment	Adult patients (≥ 18 years) with moderate to severe chronic plaque-type psoriasis who were candidates for systemic treatment	150 mg: N=245 300 mg: N=245 Placebo: N=248	150 , 300 mg AIN457, placebo qw till Week 4, then q4w to Week 48
A2303			150 mg: N=327 300 mg: N=327 Placebo: N=326 Etanercept*: N=326	150 mg or 300 mg AIN457, placebo qw till Week 4, then q4w until Week 48 Etanercept 50 mg twice per week to Week 12, then qw to Week 51
A2308			150 mg: N=59 300 mg: N=59 Placebo: N=59	150, 300 mg AIN457, placebo qw till Week 4, then q4w until Week 48
A2309			150 mg: N=61 300 mg: N=60 Placebo: N=61	150 mg or 300 mg AIN457, placebo qw till Week 4, then q4w until Week 48

- * Etanercept, active control, non-inferiority.

Safety considerations arisen from prior experience with secukinumab are addressed in the currently approved RMP. Identified risks include infections and infestations, neutropenia and hypersensitivity. Potential risks include malignant or unspecified tumours, major adverse cardiovascular events (MACE), immunogenicity, inflammatory bowel disease, hepatitis B reactivation, suicidal ideation and behaviour, and interactions with live vaccines.

Study A2310 was designed to enrol 160 paediatric patients aged 6 to < 18 years with severe plaque psoriasis. The recruitment started in September 2015 and was completed in September 2018 with 162 patients enrolled globally. The study is ongoing.

This study consists of 5 epochs:

- Screening: up to 4 weeks to assess eligibility and to taper patients off prohibited medications.
- Induction period: up to Week 12, both active and placebo-controlled and at its completion the primary endpoint was assessed.
- Maintenance period: of 40 weeks (after Week 12 up to Week 52), it was active-controlled and the objectives focused on the maintenance of the response observed at Week 12
- Extension period: open-label (only after the Week 52 data base lock) of 184 weeks, all treated with secukinumab, and the purpose was the collection of long-term safety and efficacy data.
- Post-treatment follow-up of 16 weeks.

Patients were randomised using a 1:1:1:1 ratio into one of the treatment arms: secukinumab Low dose, secukinumab High dose, etanercept or placebo. Patients randomised to secukinumab treatment arms (Low dose and High dose) received a dose based on the weight category (< 25 kg, 25 to < 50 kg, ≥ 50 kg). Patients in the two secukinumab arms weighing < 25 kg received 75 mg secukinumab in both low and High dose groups, 25 to < 50 kg received 75 mg (Low dose group) and 150 mg (High dose group) and ≥ 50 kg received 150 mg (Low dose group) and 300 mg (High dose group).

The following analysis periods were used for safety assessment of paediatric Study A2310:

- Induction period: Day 1 through Week 12 visit and included patients who completed the Week 12 visit or discontinued the study treatment before Week 12 and completed the treatment discontinuation visit;

- Up to Week 24: Day 1 through Week 24 visit; and included all patients completing the Week 24 visit as of the cut-off date or who discontinued the study treatment before the Week 24 visit and completed the treatment discontinuation visit.
- Up to Week 52: Day 1 through Week 52 visit; and included patients who completed the Week 52 as of the cut-off date 18 Sep 2019 or who discontinued the study treatment before the Week 52 visit and completed the treatment discontinuation visit.
- Entire treatment period: included all safety data up to the cut-off date of 18 Sep 2019. For adult studies (A2302, A2303, A2308 and A2309), data from the Induction period and up to Week 52 were considered for safety analysis.

The following treatment groups were used and compared side-by-side where appropriate:

For the paediatric Study A2310:

- Induction period (up to Week 12): secukinumab Low dose (< 25 kg – 75 mg; 25 to <50 kg – 75 mg; ≥ 50 kg – 150 mg), secukinumab High dose (< 25 kg – 75 mg; 25 to <50 kg – 150 mg; ≥ 50 kg – 300 mg), Any secukinumab, placebo and etanercept.
- Up to Week 52: Any secukinumab Low dose, Any secukinumab High dose, Any secukinumab and etanercept.

For the adult studies pool:

- Induction period (up to Week 12): Secukinumab 150 mg, secukinumab 300 mg, Any secukinumab, placebo and etanercept;
- Up to Week 52: Any secukinumab 150 mg, Any secukinumab 300 mg, Any secukinumab and etanercept.

The MAH has supplemented an interim report from **Study A2311** up until 24 weeks of study treatments. This study consisted only one analysis period up to week 16.

Patients weighing < 25 kg received 75 mg (both Low and High dose groups), patients weighing 25 kg to < 50 kg received 75 mg (Low dose group) or 150 mg (High dose group), and patients weighing ≥ 50 kg received 150 mg (Low dose group) or 300 mg (High dose group). Patients received one s.c. injection at each drug administration of either secukinumab 75 mg or 150 mg Pre-filled Syringe (PFS) according to their treatment group. Only the patients in the ≥ 50 kg High dose treatment groups received two s.c. injections of 150 mg secukinumab PFS at each administration.

Forty-two (42) patients were randomised both to the low dose group and the high dose group. Two patients discontinued the study until week 16, one for adverse event and another for lack of efficacy.

Patient exposure

The mean age of the patients was approximately 13.5 years in the paediatric group in Study 2310 and 45 years in the adult population. Majority of the patients in both populations were Caucasian. In the paediatric population, approximately 60% of the patients were females, whereas in the adult pool, majority were males (approx. 70%). Mean body weight of patients in the paediatric population was approx. 53 kg, and the mean body weight in the adult population was 86 kg.

For Study 2310, characteristics were typical of a population with severe disease; for the adult pool, the characteristics were representative of patients with moderate or severe psoriasis.

In Study 2311, the mean age was 12.5 years (17 + 16 patients from 6 to 12 years in low + high dose groups, and 25 + 26 from 12 to 18 years in low + high dose groups). The mean weight was 54.34 kg in the low dose group and 55.73 kg in the high dose group. By the weight strata, there were 4 + 4 patients in the <25 kg group, 13 + 12 patients in the 25- <50 kg group, and 25 + 26 patients in the ≥ 50 kg group.

On the basis of baseline IGA mod 2011 score, 58/84 patients (69.0%) in Study 2311 had moderate disease (IGA=3) and 26/84 patients (31.0%) had severe disease (IGA=4).

Study A 2310

Induction period (up to week 12)

A total of 162 patients were randomised to receive Low or High doses of secukinumab, placebo or etanercept with an allocation ratio of 1:1:1:1. Of these, 6 patients (3.7%) discontinued study treatment during the Induction Period (up to Week 12) with 2 patients discontinuing due to Adverse Events (AEs) 1 each from the High dose and the placebo group), see Table below.

Table 44 ***Patient disposition by treatment – Study A2310- Induction period (Randomised set)***

Disposition /Reason	AIN457 Low dose N=40 n (%)	AIN457 High dose N=40 n (%)	Placebo N=41 n (%)	Etanercept N=41 n (%)	Total N=162 n (%)
Randomised	40 (100)	40 (100)	41 (100)	41 (100)	162 (100)
Completed	39 (97.5)	38 (95.0)	39 (95.1)	40 (97.6)	156 (96.3)
Discontinued	1 (2.5)	2 (5.0)	2 (4.9)	1 (2.4)	6 (3.7)
Primary reason for discontinuation					
Adverse event	0 (0.0)	1 (2.5)	1 (2.4)	0 (0.0)	2 (1.2)
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (0.6)
Protocol deviation	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.6)
Subject/guardian decision	1 (2.5)	1 (2.5)	0 (0.0)	0 (0.0)	2 (1.2)

At the end of the Induction period, PASI75 non-responder placebo patients (n=34) were re-randomised to receive either Low or High doses of secukinumab. Six patients from the placebo group were PASI75 responders at Week 12 and thus completed the study. One of these 6 patients continued in the study in error up to Week 16 due to wrong responder status recorded by the study site.

Maintenance period (weeks 13 to 52)

Patient disposition by treatment is presented in Table below.

Table 45 ***Patient disposition by treatment – Study A2310 – Maintenance period (Randomised set)***

Disposition /Reason	AIN457 Low dose N=40 n (%)	AIN457 High dose N=40 n (%)	Placebo-AIN457 Low dose N=16 n (%)	Placebo-AIN457 High dose N=18 n (%)	Etanercept N=41 n (%)	Total N=155 n (%)
Entered maintenance period	39 (97.5)	38 (95.0)	16 (100.0)	18 (100.0)	40 (97.6)	151 (97.4)
Completed	38 (95.0)	37 (92.5)	15 (93.8)	16 (88.9)	34 (82.9)	140 (90.3)
Discontinued	1 (2.5)	1 (2.5)	1 (6.3)	2 (11.1)	6 (14.6)	11 (7.1)
Primary reason for discontinuation						
Adverse event	1 (2.5)	0 (0.0)	1 (6.3)	0 (0.0)	1 (2.4)	3 (1.9)
Lack of efficacy	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	3 (7.3)	4 (2.6)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (0.6)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	1 (2.4)	3 (1.9)

Extension period (weeks 52 to 236)

Overall, of the 114 patients who received secukinumab at initial randomization visit or switched from placebo to secukinumab at Week 12, 106 patients (93.0%) entered the Extension period (Any secukinumab low dose group: 53 patients and Any secukinumab high dose group: 53 patients). 95 patients were still continuing in the Extension period at the time of cut-off date (18-Sep-2019) for the Week 52 analysis. There were more patients discontinuing during the Extension period in the Any secukinumab low dose group (7 patients, 12.5%) compared to the Any secukinumab high dose group (4 patients, 6.9%). The most common reason for discontinuation was lack of efficacy; this was more frequent in the Any secukinumab low dose group (5 patients, 8.9%) than in the Any secukinumab high dose group (2 patients, 3.4%), refer to Table below.

The median duration of exposure was lower in the < 12 years stratum (Any secukinumab low dose: 365.0 days, Any secukinumab high dose: 364.5 days and etanercept group: 370.0 days) when compared to the ≥ 12 years stratum (Any secukinumab low dose group: 895.0 days, Any secukinumab high dose group: 896.0 days and etanercept group: 391.0 days).

Table 46 ***Patient disposition by treatment – Study A2310 - 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)
Ongoing	46 (82.1)	49 (84.5)	95 (83.3)
Discontinued	7 (12.5)	4 (6.9)	11 (9.6)
Primary reason for discontinuation			
Lack of efficacy	5 (8.9)	2 (3.4)	7 (6.1)
Pregnancy	2 (3.6)	0 (0.0)	2 (1.8)
Lost to follow-up	0 (0.0)	2 (3.4)	2 (1.8)

Study A2311

All except two patients (both from secukinumab High dose group, see Table below) completed the Week 16 visit (82/84 patients; 97.6% overall). The reasons for discontinuations were AEs in one patient (ALT and AST elevations and lack of efficacy in another.

Table 47 ***Patient disposition by treatment - Study A2311 - interim at 16 weeks***

Disposition/Reason	AIN457 Low dose N=42 n (%)	AIN457 High dose N=42 n (%)	Total N=84 n (%)
Randomized	42	42	84
Ongoing at Week 16	42 (100.0)	40 (95.2)	82 (97.6)
Discontinued	0 (0.0)	2 (4.8)	2 (2.4)
[1]Primary reason for discontinuing			
Adverse event	0 (0.0)	1 (2.4)	1 (1.2)
Lack of efficacy	0 (0.0)	1 (2.4)	1 (1.2)

[1] Two patients discontinued due to AE. Whilst the AE for both patients started prior to the Week 16 cut off, second patient from secukinumab High Dose group discontinued after Week 16 cut off and thus not reported in this table.

Concomitant medications or treatments

In Study 2310, the most commonly used concomitant medication was paracetamol, used more frequently in the Any secukinumab low dose group (35.7%) than the Any secukinumab high dose group (31.0%). In the etanercept group, paracetamol was used by 24.4% patients. The second most common concomitant medication was ibuprofen, used at a comparable frequency in the Any secukinumab low dose group (23.2%) and Any secukinumab high dose group (24.1%). In the etanercept group, ibuprofen was used by 19.5% patients. Other most commonly used concomitant medications (>10% in Any secukinumab dose group) were amoxicillin and amoxicillin-clavulanic acid. The use of amoxicillin was similar in the Any secukinumab low dose group and the Any secukinumab high dose group (12.5% vs 13.8%).

Adverse events

Adverse events were evaluated by primary system organ class (SOC) and preferred term (PT), and according to severity of AEs (mild, moderate and severe) and Investigator's assessment of the possible relationship to study drug. They were classified as common AEs, Serious Adverse Events (SAEs) including deaths, and AEs causing permanent discontinuation of study treatment.

Adverse events are presented as absolute and relative frequencies (*i.e.*, absolute incidence) for the treatment periods. The comparison of absolute incidence rates vs. placebo is limited only to the Induction period of Study A2310. Side-by-side comparison of paediatric data (Study A2310) to adult pooled data is presented for the Induction period and Up to Week 52.

In addition, AEs are also expressed as incidence rate per 100 patient years (PY) of exposure (calculated as the number of AEs divided by the PY in the treatment group × 100). Exposure Adjusted Incidence Rate (EAIR) was calculated for the long-term safety summary to adjust for patient exposure. The PY denominator was the sum of total exposure on study drug in patients with no event and the time to first event divided by 365.25. Given the much shorter duration of placebo exposure, since patients were

switched to secukinumab treatment groups after Week 12, the EAIR allows for comparison of AEs over the longer term.

All safety analyses were based on the Safety set. The safety set includes all patients who took at least one dose of study drug during the treatment period. Patients were analysed according to the treatment received. If a patient received the wrong treatment during the Entire study period, the treatment received was set to this wrong treatment. If a patient received intermittent wrong treatment, the treatment received was set to the original randomised treatment.

To assess the consistency of the safety profile of secukinumab and to evaluate the effect of secukinumab in younger and/or lighter body weight patients, below subgroup analyses were performed in the paediatric patients (Study A2310) for selected study periods. Crude incidence of treatment emergent AEs (TEAEs) for these subgroups of interest for selected study periods are presented in this section:

- Age at randomisation (< 12 years and ≥ 12 years)
- Body weight < 25 kg at randomisation
- Body weight and secukinumab dose group stratum
- Secukinumab exposure percentile stratum at Week 4

In Study A2310, an Interactive Response Technology (IRT) error, which occurred early in the study, led to additional dosing of some patients in the ≥ 12 age group. The dosing error happened after the primary endpoint (Week 12) assessment. Specifically, 36 patients who were assigned to the Low dose (16 patients) and High dose (20 patients) secukinumab groups were dispensed active medication at Week 13, 14, 15 visits. At these visits, the patients who were randomised to active treatment groups were expected to receive placebo medication to maintain the blind. Five patients in the secukinumab High dose group (25-<50 kg/150 mg dose) were dispensed in error secukinumab 150 mg at these visits; 16 patients in the secukinumab Low dose group (≥50 kg/150 mg dose) were dispensed in error secukinumab 300 mg at these visits; and 15 patients in the secukinumab High dose group (≥50 kg/300 mg dose) were dispensed in error secukinumab 300 mg at these visits.

The incident was communicated to Investigators and Health Authorities, was presented to internal Novartis boards and a corrective action plan was put in place by the IRT vendor. The unblinded DMC Board also reviewed data from the affected patients and expressed no safety concerns. The dosing error was taken into account in additional efficacy, safety and pharmacokinetic reports, and its impact on the results was assessed and documented appropriately in the study report.

Induction period

Study A2310

During the active and placebo-controlled Induction period, the overall incidence of AEs was similar between the active treatment groups (57.5% and 62.5% in the low and high dose secukinumab groups, respectively and 61% in the etanercept group). The incidence of AEs was slightly lower in the placebo group (53.7%) compared to the active treatment groups. Refer to Tables 48 and 49.

Table 48 ***Absolute and relative frequencies for treatment emergent adverse events, by primary SOC in Study A2310 - Induction period (Study A2310, Safety set)***

Primary system organ class	AIN457 Low dose N=40 n (%)	AIN457 High dose N=40 n (%)	Any AIN457 dose N=80 n (%)	Placebo N=41 n (%)	Etanercept N=41 n (%)
Any primary system organ class	23 (57.5)	25 (62.5)	48 (60.0)	22 (53.7)	25 (61.0)
Infections and infestations	13 (32.5)	15 (37.5)	28 (35.0)	16 (39.0)	11 (26.8)

Primary system organ class	AIN457 Low dose N=40 n (%)	AIN457 High dose N=40 n (%)	Any AIN457 dose N=80 n (%)	Placebo N=41 n (%)	Etanercept N=41 n (%)
Gastrointestinal disorders	6 (15.0)	7 (17.5)	13 (16.3)	6 (14.6)	10 (24.4)
General disorders and administration site conditions	4 (10.0)	5 (12.5)	9 (11.3)	3 (7.3)	4 (9.8)
Skin and subcutaneous tissue disorders	5 (12.5)	3 (7.5)	8 (10.0)	3 (7.3)	1 (2.4)
Respiratory, thoracic and mediastinal disorders	3 (7.5)	4 (10.0)	7 (8.8)	3 (7.3)	1 (2.4)
Nervous system disorders	3 (7.5)	3 (7.5)	6 (7.5)	5 (12.2)	1 (2.4)
Investigations	2 (5.0)	2 (5.0)	4 (5.0)	2 (4.9)	5 (12.2)
Reproductive system and breast disorders	1 (2.5)	2 (5.0)	3 (3.8)	1 (2.4)	2 (4.9)
Blood and lymphatic system disorders	1 (2.5)	1 (2.5)	2 (2.5)	1 (2.4)	0 (0.0)
Eye disorders	0 (0.0)	2 (5.0)	2 (2.5)	1 (2.4)	3 (7.3)
Injury, poisoning and procedural complications	1 (2.5)	1 (2.5)	2 (2.5)	2 (4.9)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	2 (5.0)	2 (2.5)	1 (2.4)	2 (4.9)
Renal and urinary disorders	2 (5.0)	0 (0.0)	2 (2.5)	2 (4.9)	2 (4.9)
Ear and labyrinth disorders	1 (2.5)	0 (0.0)	1 (1.3)	0 (0.0)	2 (4.9)
Metabolism and nutrition disorders	0 (0.0)	1 (2.5)	1 (1.3)	0 (0.0)	1 (2.4)
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)

- Primary system organ classes are sorted in decreasing order of frequency in Any AIN457 dose group.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the "Any AIN457 dose".
- MedDRA version 22.0 was used for reporting.

Table 49 ***Most frequent (≥4% in any treatment group) treatment emergent adverse events, by PT in Study A2310 - Induction period (Safety set)***

Preferred term	AIN457 Low dose N=40 n (%)	AIN457 High dose N=40 n (%)	Any AIN457 dose N=80 n (%)	Placebo N=41 n (%)	Etanercept N=41 n (%)
Any preferred term	23 (57.5)	25 (62.5)	48 (60.0)	22 (53.7)	25 (61.0)
Nasopharyngitis	7 (17.5)	6 (15.0)	13 (16.3)	1 (2.4)	4 (9.8)
Headache	2 (5.0)	3 (7.5)	5 (6.3)	4 (9.8)	1 (2.4)
Abdominal pain	2 (5.0)	2 (5.0)	4 (5.0)	0 (0.0)	3 (7.3)
Pharyngitis	2 (5.0)	2 (5.0)	4 (5.0)	4 (9.8)	0 (0.0)
Asthenia	1 (2.5)	2 (5.0)	3 (3.8)	1 (2.4)	0 (0.0)
Conjunctivitis	1 (2.5)	2 (5.0)	3 (3.8)	0 (0.0)	0 (0.0)
Cough	1 (2.5)	2 (5.0)	3 (3.8)	0 (0.0)	0 (0.0)
Diarrhea	2 (5.0)	1 (2.5)	3 (3.8)	0 (0.0)	1 (2.4)
Abdominal pain upper	0 (0.0)	2 (5.0)	2 (2.5)	1 (2.4)	2 (4.9)
Aspartate aminotransferase increased	1 (2.5)	1 (2.5)	2 (2.5)	0 (0.0)	2 (4.9)
Dry skin	2 (5.0)	0 (0.0)	2 (2.5)	0 (0.0)	0 (0.0)
Nausea	1 (2.5)	1 (2.5)	2 (2.5)	2 (4.9)	3 (7.3)
Upper respiratory tract infection	2 (5.0)	0 (0.0)	2 (2.5)	3 (7.3)	1 (2.4)
Oral herpes	0 (0.0)	1 (2.5)	1 (1.3)	1 (2.4)	2 (4.9)
Rhinitis	0 (0.0)	1 (2.5)	1 (1.3)	4 (9.8)	1 (2.4)
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	2 (4.9)
Bronchitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.9)	0 (0.0)
Conjunctivitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.9)
Influenza	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.3)	1 (2.4)

Preferred term	AIN457 Low dose N=40 n (%)	AIN457 High dose N=40 n (%)	Any AIN457 dose N=80 n (%)	Placebo N=41 n (%)	Etanercept N=41 n (%)
- Preferred terms are sorted in descending order of frequency in the any AIN457 column.					
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.					
- MedDRA version 22.0 was used for reporting.					

Age

The number of patients < 12 years was low (N=37) compared to the ≥ 12 years stratum (N=125) and therefore the results should be interpreted with caution.

The overall incidence of AEs in secukinumab treated patients aged < 12 years was lower compared to ≥ 12 years (35.3% vs. 66.7% in Any secukinumab group) and the placebo group but not for the etanercept group. The incidence of AEs in <12 years and ≥ 12 years, respectively, was:

- secukinumab Low dose: 2 (25%) patients and 21 (65.6%) patients,
- secukinumab High dose: 4 (44.4%) and 21 patients (67.7%),
- placebo: 4 (40%) patients and 18 (58.1%) patients, and
- etanercept: 7 (70%) and 18 (58.1%) patients.

The incidence of AEs related to the SOC of Infections and infestations in patients treated with secukinumab was lower in patients < 12 years compared to the older patients (≥ 12 years) and was comparable to patients treated with etanercept and placebo within the same age group (< 12 years). The incidence of the most commonly reported AE of nasopharyngitis was (in patient < 12 years and ≥ 12 years, respectively): 0 and 7 (21.9%) in the secukinumab Low dose group, 1 (11.1%) and 5 (16.1%) in the secukinumab High dose group, 1 (10%) and 0 in the placebo group and 1 (10%) and 3 (9.7%) in the etanercept group.

Weight

In both secukinumab low and High dose groups, the incidence of AEs was slightly higher in the ≥ 50 kg weight stratum compared to the other two strata within same dose group. Similar trend was observed for the most commonly reported SOC of Infections and infestations. Thus patients ≥ 50 kg had higher incidence of AEs irrespective of the dose administered (low secukinumab or high secukinumab dose) compared to paediatric patients from other weight groups in same dose level (secukinumab Low or High dose). Within the stratum of patients ≥ 50 kg, the High dose group patients had higher incidence of AEs during the Induction period but infections were comparable in incidence. In the 5 paediatric patients < 25 kg treated with secukinumab, there were no different safety findings than higher weight group patients.

The overall incidence of treatment emergent AEs was lower in secukinumab treated patients < 25 kg compared to heavier patients. In the secukinumab treated patients ≥ 50 kg the incidence rates of overall treatment emergent were comparable to placebo.

The incidence of the most commonly reported AE of nasopharyngitis was:

- secukinumab Low dose group: none in the 75 mg and < 25 kg strata, 2 (11.8%) patients in the 75 mg and ≥ 25 - < 50 kg strata, ; and 5 (23.8%) patients in the 150 mg and ≥ 50 kg strata.
- secukinumab High dose group: 1 (33.3%) in the 75 mg and < 25 kg strata; 1 (6.7%) patients in the 150 mg and ≥ 25 - < 50 kg strata; and 4 (19%) patients in the 300 mg and ≥50 kg strata.

The incidence of another commonly reported AE of headache was:

- secukinumab Low dose group: none in the 75 mg and < 25 kg strata, 1 (5.9%) patients in the 75 mg and ≥ 25 - < 50 kg strata; and 1 (4.8%) patients in the 150 mg and ≥ 50 kg strata.
- secukinumab High dose group: none in the 75 mg and < 25 kg strata; 1 (6.7%) patients in the 150 mg and ≥ 25 - < 50 kg strata; and 2 (9.5%) patients in the 300 mg and ≥ 50 kg strata.

Secukinumab exposure

The overall incidence of AEs was higher in the higher quartile (≥ 75th percentile) of secukinumab exposure as defined by trough concentration at all time points (63.2% up to Week 4, 68.4% up to Week 8 and 73.7% up to Week 12) compared to other percentile categories. This was also true for the most frequently occurring SOCs, Infections and infestations and Gastrointestinal disorders. By Week 12 when more events have occurred, these differences are less apparent, see Table 50.

The incidence of most commonly reported AEs were generally low and similar across the secukinumab exposure percentile at all time points (up to Week 4, up to Week 8 and up to Week 12). The number of patients in each the exposure categories are small and therefore these results should be interpreted carefully.

Table 50 ***Adverse events (by SOC) by secukinumab exposure percentile at Week 4 – Study A2310***

System organ class	< 25th percentile: N=18 n (%)	25th - < 50th percentile N=19 n (%)	50th - < 75th percentile N=18 n (%)	≥ 75th percentile N=19 n (%)
Up to Week 4				
Any SOCs	6 (33.3)	9 (47.4)	6 (33.3)	12 (63.2)
Infections and infestations	3 (16.7)	2 (10.5)	2 (11.1)	4 (21.1)
Gastrointestinal disorders	1 (5.6)	2 (10.5)	2 (11.1)	4 (21.1)
Up to Week 8				
Any SOCs	10 (55.6)	11 (57.9)	9 (50.0)	13 (68.4)
Infections and infestations:	6 (33.3)	5 (26.3)	6 (33.3)	7 (36.8)
Gastrointestinal disorders	2 (11.1)	2 (10.5)	2 (11.1)	4 (21.1)
Up to Week 12				
Any SOCs	12 (66.7)	11 (57.9)	10 (55.6)	14 (73.7)
Infections and infestations	7 (38.9)	6 (31.6)	6 (33.3)	8 (42.1)
Gastrointestinal disorders	4 (22.2)	2 (10.5)	3 (16.7)	4 (21.1)
General disorders and administration site conditions	2 (11.1)	1 (5.3)	3 (16.7)	3 (15.8)

- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- MedDRA version 22.0 was used for reporting.

Study A2311

Overall, 57.1% (48/84) of subjects had AEs. The incidence of TEAEs was same in secukinumab Low dose and High dose (24/42 subjects in each; 57.1%) groups, see Table 51.

The most commonly affected SOCs (> 10% in any secukinumab dose group) were the infections and infestations (33/84 subjects; 39.3% overall) and gastrointestinal disorders (12/84 subjects; 14.3% overall). A single event from either of these SOCs was serious (AE of infectious mononucleosis in one subject from Low dose group (150 mg)), a single event led to study drug discontinuation (AE of hemorrhagic diarrhea in one subject from High dose group (300 mg)), and two AEs led to study drug interruptions (influenza and pharyngotonsillitis in one subject each from Low dose group (75 mg and 150 mg respectively).

The incidences of AEs were similar in secukinumab Low dose and High dose groups under infections and infestations (Low dose group: 15/42 subjects; 35.7%; High dose group: 18/42 subjects; 42.9%) whilst incidence of AEs under gastrointestinal disorders were higher in secukinumab High dose compared to Low dose group (High dose group: 8/42 subjects; 19.0%; Low dose group: 4/42 subjects; 9.5%).

Table 51 ***Treatment emergent adverse events by primary system organ class – Up to Week 24 (Safety set)***

Primary system organ class	AIN457 Low dose N=42 n (%)	AIN457 High dose N=42 n (%)	Any AIN457 dose N=84 n (%)
-Any primary system organ class	24 (57.1)	24 (57.1)	48 (57.1)
Infections and infestations	15 (35.7)	18 (42.9)	33 (39.3)
Gastrointestinal disorders	4 (9.5)	8 (19.0)	12 (14.3)
Skin and subcutaneous tissue disorders	4 (9.5)	4 (9.5)	8 (9.5)
Blood and lymphatic system disorders	3 (7.1)	3 (7.1)	6 (7.1)
General disorders and administration site conditions	4 (9.5)	2 (4.8)	6 (7.1)
Cardiac disorders	2 (4.8)	2 (4.8)	4 (4.8)
Respiratory, thoracic and mediastinal disorders	2 (4.8)	2 (4.8)	4 (4.8)
Injury, poisoning and procedural complications	3 (7.1)	0 (0.0)	3 (3.6)
Investigations	0 (0.0)	2 (4.8)	2 (2.4)
Nervous system disorders	1 (2.4)	1 (2.4)	2 (2.4)
Reproductive system and breast disorders	1 (2.4)	1 (2.4)	2 (2.4)
Eye disorders	1 (2.4)	0 (0.0)	1 (1.2)
Immune system disorders	1 (2.4)	0 (0.0)	1 (1.2)
Musculoskeletal and connective tissue disorders	1 (2.4)	0 (0.0)	1 (1.2)
Psychiatric disorders	0 (0.0)	1 (2.4)	1 (1.2)
Vascular disorders	1 (2.4)	0 (0.0)	1 (1.2)

Primary system organ are sorted in descending frequency of AEs in the Any AIN457 dose column.
A subject with multiple AEs within a primary system organ class is counted only once in the system organ class.
MedDRA version 22.1 was used for reporting.

The most commonly reported AE was nasopharyngitis in both Low dose (6/42 subjects; 14.3%) and High dose (4/42 subjects; 9.5%) groups (Table 12-4). The event of upper respiratory tract infection (3/42 subjects; 7.1%) was reported only in the High dose group.

The AEs of pyrexia (3/42 subjects; 7.1%), atrioventricular block first degree (2/42 subjects; 4.8%), folliculitis (2/42 subjects; 4.8%), gastroenteritis (2/42 subjects; 4.8%), influenza (2/42 subjects; 4.8%), and otitis media (2/42 subjects; 4.8%) were reported only in the secukinumab Low dose group.

The upper respiratory tract infections (3/42 subjects; 7.1%), diarrhea (3/42 subjects; 7.1%), upper abdominal pain (2/42 subjects; 4.8%), hordeolum (2/42 subjects; 4.8%), rhinitis (2/42 subjects; 4.8%) and viral respiratory tract infections (2/42 subjects; 4.8%) were reported only in the secukinumab High dose group.

Leukopenia was reported as AE in 3 subjects, and neutropenia was reported as AE in 3 subjects.

Table 52 ***Most frequent (≥4% in any treatment group) treatment emergent adverse events, by preferred term – Data up to week 24 (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	24 (57.1)	24 (57.1)	48 (57.1)
Nasopharyngitis	6 (14.3)	4 (9.5)	10 (11.9)
Acne	3 (7.1)	1 (2.4)	4 (4.8)
Diarrhea	0 (0.0)	3 (7.1)	3 (3.6)
Leukopenia	2 (4.8)	1 (2.4)	3 (3.6)
Neutropenia	2 (4.8)	1 (2.4)	3 (3.6)
Pyrexia	3 (7.1)	0 (0.0)	3 (3.6)
Upper respiratory tract infection	0 (0.0)	3 (7.1)	3 (3.6)
Abdominal pain upper	0 (0.0)	2 (4.8)	2 (2.4)
Atrioventricular block first degree	2 (4.8)	0 (0.0)	2 (2.4)
Folliculitis	2 (4.8)	0 (0.0)	2 (2.4)
Gastroenteritis	2 (4.8)	0 (0.0)	2 (2.4)
Hordeolum	0 (0.0)	2 (4.8)	2 (2.4)
Influenza	2 (4.8)	0 (0.0)	2 (2.4)
Otitis media	2 (4.8)	0 (0.0)	2 (2.4)
Rhinitis	0 (0.0)	2 (4.8)	2 (2.4)
Viral upper respiratory tract infection	0 (0.0)	2 (4.8)	2 (2.4)

Preferred terms are sorted in descending frequency of AEs in the Any AIN457 dose column.
A subject with multiple AEs with the same PT is counted only once for that PT.
MedDRA version 22.1 was used for reporting.

Weight

A total of 8 subjects (Low dose 75 mg: 4 subjects; High dose 75 mg: 4 subjects) were enrolled in the weight group of **<25 kg**. TEAEs were reported in 6 out of the 8 evaluable subjects (secukinumab low dose + secukinumab high dose). The commonly affected SOCs in any secukinumab treatment group were:

1. infections and infestations (3/8 subjects, 37.5%; AEs: folliculitis, nasopharyngitis, upper respiratory tract infection and viral upper respiratory tract infection)
2. blood and lymphatic system disorders (2/8 subjects, 25.0%; AE: leukopenia)
3. cardiac disorders (2/8 subjects; 25.0%, AEs: first degree atrioventricular block and intraventricular conduction defect in one subject each).

All the AEs were mild in severity (except leukopenia of grade 2 which was moderate in severity in patient A2311-1604004 with severe disease from High dose group) and resolved without any treatment. None of the events were serious, none led to study drug interruption or discontinuation of study drug

A total of 25 subjects (Low dose: 13 subjects; High dose: 12 subjects) were enrolled in the age group of **25-<50 kg** of which 8/13 (61.5%) subjects from Low dose and 7/12 (58.3%) subjects from High dose group had TEAEs. The most commonly affected SOC in any secukinumab treatment group were infections and infestations (9/25 subjects; 36.0%, AEs: conjunctivitis, enterobiosis, gastroenteritis, gastroenteritis viral, influenza, nasopharyngitis, otitis media, pharyngitis, tonsillitis, upper respiratory tract infection, and viral upper respiratory tract infection). None of the events were serious, none led to

discontinuation of study drug, and none led to study drug interruption (except for an AE of mild influenza in one subject from Low dose group.

A total of 51 subjects were enrolled in the age group of ≥**50 kg** and TEAEs were reported in 14/25 (56.0%) subjects from Low dose and 13/26 (50.0%) subjects from High dose groups. The most commonly affected SOC in Any secukinumab treatment group for this weight group were the infections and infestations (21/51 subjects; 41.2%), and the most common AE was nasopharyngitis (8/51 subjects; 15.7%) with similar incidence in both Low dose (4/25 subjects; 16.0%) and High dose (4/26 subjects; 15.4%) groups. None of these events of nasopharyngitis were serious, and none led to study drug discontinuation/ interruptions.

Disease severity:

The frequency of TEAEs in any secukinumab dose group were comparable in both moderate (35/61; 57.4% subjects) and severe disease severity subjects (13/23 subjects; 56.5%). The most commonly affected SOC was infections and infestations in both moderate (26/61 subjects; 42.6%) and severe (7/23 subjects; 30.4%) subjects.

None of these events were serious (except for an event of mild infectious mononucleosis in A2311 for one patient from Low dose (150 mg) group with moderate disease), none led to discontinuation of study drug, and none led to study drug interruption (except for an AE of mild influenza in one subject from Low dose group.

Age:

The frequency of TEAEs in any secukinumab dose group were comparable between 6-<12 years age (20/33, 60.6%) and 12-<18 years age (28/51 subjects; 54.9%) group. The most commonly affected SOC was infections and infestations with similar incidence in both 6-< 12 years (13/33 subjects; 39.4%) and 12 - <18 years (20/51 subjects; 39.2%) age groups.

Comparison with adult patients: During the Induction period, treatment emergent AEs in paediatric patients treated with secukinumab were comparable to that of adults with moderate psoriasis and were slightly higher compared to the adults with severe psoriasis. As expected, the AEs related to Infections and infestations SOC occurred at a slightly higher frequency in the paediatric population with severe psoriasis (35%) compared to the adult population with severe psoriasis (26.9%). Other SOCs that were affected more frequently in the paediatric population compared to the adults were Gastrointestinal disorders and General disorders and administration site conditions, see Tables 53 and 54.

Table 53 ***Treatment emergent adverse events, by primary SOC, population (paediatric and adult) and baseline disease severity – Induction period (Safety set)***

	Any AIN457		
	Paediatric (Study A2310)	**Adult (Moderate psoriasis)**	**Adult (Severe psoriasis)**
Primary system organ class	**N=80 n(%)**	**N=991 n(%)**	**N=390 n(%)**
Any system organ class	48 (60.0)	596 (60.1)	209 (53.6)
Infections and infestations	28 (35.0)	297 (30.0)	105 (26.9)
Skin and subcutaneous tissue disorders	8 (10.0)	107 (10.8)	50 (12.8)
Gastrointestinal disorders	13 (16.3)	120 (12.1)	45 (11.5)
Musculoskeletal and connective tissue disorders	2 (2.5)	90 (9.1)	40 (10.3)
General disorders and administration site conditions	9 (11.3)	64 (6.5)	26 (6.7)
Nervous system disorders	6 (7.5)	103 (10.4)	25 (6.4)
Respiratory, thoracic and mediastinal disorders	7 (8.8)	78 (7.9)	20 (5.1)

	Any AIN457		
	Paediatric (Study A2310)	Adult (Moderate psoriasis)	Adult (Severe psoriasis)
Primary system organ class	N=80 n(%)	N=991 n(%)	N=390 n(%)
Metabolism and nutrition disorders	1 (1.3)	35 (3.5)	19 (4.9)
Injury, poisoning and procedural complications	2 (2.5)	63 (6.4)	11 (2.8)
Vascular disorders	0 (0.0)	29 (2.9)	10 (2.6)
Blood and lymphatic system disorders	2 (2.5)	22 (2.2)	8 (2.1)
Investigations	4 (5.0)	25 (2.5)	7 (1.8)
Psychiatric disorders	0 (0.0)	23 (2.3)	7 (1.8)
Cardiac disorders	0 (0.0)	10 (1.0)	6 (1.5)
Reproductive system and breast disorders	3 (3.8)	15 (1.5)	6 (1.5)
Eye disorders	2 (2.5)	22 (2.2)	5 (1.3)
Hepatobiliary disorders	0 (0.0)	4 (0.4)	3 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	13 (1.3)	3 (0.8)
Renal and urinary disorders	2 (2.5)	12 (1.2)	3 (0.8)
Ear and labyrinth disorders	1 (1.3)	12 (1.2)	2 (0.5)
Congenital, familial and genetic disorders	0 (0.0)	0 (0.0)	1 (0.3)
Immune system disorders	0 (0.0)	8 (0.8)	1 (0.3)
Endocrine disorders	0 (0.0)	2 (0.2)	0 (0.0)
Social circumstances	0 (0.0)	1 (0.1)	0 (0.0)

- A patient with multiple adverse events within a primary system organ class is counted only once in the system organ class.
- Primary system organ classes are sorted in descending order of frequency in Any AIN457 column of Adult (Severe).

Table 54 ***Most frequent (≥2% in any treatment group) treatment emergent AEs, by PT, population (paediatric and adult) and baseline disease severity – Induction period (Safety set)***

	Any AIN457		
	Paediatric (Study A2310)	Adult (Moderate psoriasis)	Adult (Severe psoriasis)
Preferred term	N=80 n(%)	N=991 n(%)	N=390 n(%)
Any preferred term	48 (60.0)	596 (60.1)	209 (53.6)
Nasopharyngitis	13 (16.3)	119 (12.0)	44 (11.3)
Pruritus	1 (1.3)	29 (2.9)	17 (4.4)
Headache	5 (6.3)	67 (6.8)	16 (4.1)
Diarrhea	3 (3.8)	33 (3.3)	14 (3.6)
Arthralgia	0 (0.0)	19 (1.9)	11 (2.8)
Upper respiratory tract infection	2 (2.5)	30 (3.0)	9 (2.3)
Cough	3 (3.8)	21 (2.1)	8 (2.1)
Hypertension	0 (0.0)	22 (2.2)	8 (2.1)
Pain in extremity	0 (0.0)	10 (1.0)	8 (2.1)
Rhinitis	1 (1.3)	12 (1.2)	8 (2.1)
Nausea	2 (2.5)	19 (1.9)	7 (1.8)
Oropharyngeal pain	2 (2.5)	25 (2.5)	7 (1.8)
Pharyngitis	4 (5.0)	9 (0.9)	6 (1.5)
Pyrexia	2 (2.5)	9 (0.9)	5 (1.3)
Back pain	1 (1.3)	22 (2.2)	4 (1.0)
Abdominal pain	4 (5.0)	5 (0.5)	2 (0.5)
Abdominal pain upper	2 (2.5)	9 (0.9)	2 (0.5)
Asthenia	3 (3.8)	6 (0.6)	2 (0.5)
Conjunctivitis	3 (3.8)	5 (0.5)	2 (0.5)
Dysmenorrhea	2 (2.5)	4 (0.4)	2 (0.5)

	Any AIN457		
	Paediatric (Study A2310)	Adult (Moderate psoriasis)	Adult (Severe psoriasis)
Preferred term	N=80 n(%)	N=991 n(%)	N=390 n(%)
Eczema	2 (2.5)	8 (0.8)	2 (0.5)
Dry skin	2 (2.5)	3 (0.3)	1 (0.3)
Aspartate aminotransferase increased	2 (2.5)	3 (0.3)	0 (0.0)

- A patient with multiple AEs with the same PT is counted only once for that PT.
- Preferred terms are sorted in descending order of frequency in Any AIN457 column of Adult (Severe).

Up to Week 24

Consistent with the Induction period, Infections and infestations was the most commonly affected SOC overall. The incidence of AEs in this SOC was slightly higher in the Any secukinumab Low dose group (51.8%) compared to the Any secukinumab High dose group (46.6%) and the etanercept group (48.8%). The higher incidence of AEs in this SOC was mainly driven by PTs of nasopharyngitis and pharyngitis.

The most commonly reported AEs (≥ 10% in the Any secukinumab group) up to Week 24 were nasopharyngitis and headache. The incidence of nasopharyngitis was slightly higher in the Any secukinumab high dose group (22.4%) compared to the Any Low dose group (17.9%) and the etanercept group (17.1%). The incidence of headache was similar between the Any secukinumab Low dose and High dose group (12.5% and 10.3%, respectively) and was lower in the etanercept group (2.4%).

Up to Week 52

Up to Week 52, patients in the Any secukinumab low dose (45 patients, 80.4%) and Any secukinumab high dose groups (47 patients, 81.0%) had AEs, which was similar to the number of patients with AEs in the etanercept group (34 patients, 82.9%). The incidence of AEs was also similar between the secukinumab low and high dose groups (34 patients, 85.0% each).

Overall, the most commonly affected SOC was Infections and infestations. The incidence of AEs in this SOC was numerically higher in the Any secukinumab low dose group (69.6%) compared to the Any secukinumab high dose group (62.1%) and the etanercept group (65.9%). The higher incidence of AEs in this SOC was mainly driven by non-serious nasopharyngitis, pharyngitis, rhinitis and upper respiratory tract infections (Table 55)

Table 55 ***Absolute and relative frequencies for treatment emergent adverse events by primary system organ class - Up to Week 52 (Safety set).Treatment emergent adverse events, by primary system organ class, population (paediatric and adult) and baseline disease severity – Up to Week 52 (Study 2310, Safety set)***

Primary system organ class	AIN457 Low dose N=40 n (%)	AIN457 High dose N=40 n (%)	Etanercept N=41 n (%)	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	34 (85.0)	34 (85.0)	34 (82.9)	45 (80.4)	47 (81.0)	92 (80.7)
Infections and infestations	30 (75.0)	27 (67.5)	27 (65.9)	39 (69.6)	36 (62.1)	75 (65.8)
Gastrointestinal disorders	12 (30.0)	13 (32.5)	14 (34.1)	14 (25.0)	17 (29.3)	31 (27.2)
Skin and subcutaneous tissue disorders	12 (30.0)	12 (30.0)	10 (24.4)	14 (25.0)	17 (29.3)	31 (27.2)
General disorders and administration site conditions	9 (22.5)	9 (22.5)	8 (19.5)	9 (16.1)	13 (22.4)	22 (19.3)
Respiratory, thoracic and mediastinal disorders	6 (15.0)	10 (25.0)	4 (9.8)	8 (14.3)	13 (22.4)	21 (18.4)
Nervous system disorders	6 (15.0)	6 (15.0)	4 (9.8)	9 (16.1)	9 (15.5)	18 (15.8)
Musculoskeletal and connective tissue disorders	1 (2.5)	3 (7.5)	5 (12.2)	4 (7.1)	7 (12.1)	11 (9.6)
Injury, poisoning and procedural complications	4 (10.0)	4 (10.0)	1 (2.4)	4 (7.1)	6 (10.3)	10 (8.8)
Reproductive system and breast disorders	3 (7.5)	5 (12.5)	3 (7.3)	4 (7.1)	6 (10.3)	10 (8.8)
Blood and lymphatic system disorders	6 (15.0)	2 (5.0)	2 (4.9)	6 (10.7)	3 (5.2)	9 (7.9)
Investigations	5 (12.5)	2 (5.0)	6 (14.6)	5 (8.9)	4 (6.9)	9 (7.9)
Eye disorders	2 (5.0)	4 (10.0)	3 (7.3)	2 (3.6)	4 (6.9)	6 (5.3)
Psychiatric disorders	2 (5.0)	0	1 (2.4)	3 (5.4)	1 (1.7)	4 (3.5)
Renal and urinary disorders	2 (5.0)	2 (5.0)	3 (7.3)	2 (3.6)	2 (3.4)	4 (3.5)
Vascular disorders	1 (2.5)	2 (5.0)	1 (2.4)	1 (1.8)	3 (5.2)	4 (3.5)
Immune system disorders	1 (2.5)	1 (2.5)	0	1 (1.8)	2 (3.4)	3 (2.6)
Cardiac disorders	1 (2.5)	0	2 (4.9)	1 (1.8)	0	1 (0.9)
Ear and labyrinth disorders	1 (2.5)	0	2 (4.9)	1 (1.8)	0	1 (0.9)
Metabolism and nutrition disorders	0	1 (2.5)	1 (2.4)	0	1 (1.7)	1 (0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (2.5)	0	0	1 (1.7)	1 (0.9)
Hepatobiliary disorders	0	0	1 (2.4)	0	0	0
Pregnancy, puerperium and perinatal conditions	0	0	1 (2.4)	0	0	0
Social circumstances	0	0	1 (2.4)	0	0	0

Primary system organ classes are sorted in decreasing order of frequency in Any AIN457 dose group.
A patient with multiple adverse events within a primary system organ class is counted only once in the "Any AIN457 dose".
MedDRA version 22.0 was used for reporting.

Table 56 ***Most frequent (≥4% in any treatment group) treatment emergent adverse events, by preferred term – Up to Week 52 (Safety set)***

Preferred term	AIN457 Low dose N=40 n (%)	AIN457 High dose N=40 n (%)	Etanercept N=41 n (%)	Any AIN457 Low dose N=56 n (%)	Any AIN457 High dose N=58 n (%)	Any AIN457 dose N=114 n (%)
Any preferred term	34 (85.0)	34 (85.0)	34 (82.9)	45 (80.4)	47 (81.0)	92 (80.7)
Nasopharyngitis	12 (30.0)	16 (40.0)	11 (26.8)	14 (25.0)	20 (34.5)	34 (29.8)
Headache	5 (12.5)	6 (15.0)	4 (9.8)	8 (14.3)	9 (15.5)	17 (14.9)
Pharyngitis	4 (10.0)	4 (10.0)	3 (7.3)	6 (10.7)	6 (10.3)	12 (10.5)
Rhinitis	2 (5.0)	3 (7.5)	1 (2.4)	3 (5.4)	6 (10.3)	9 (7.9)
Abdominal pain	3 (7.5)	4 (10.0)	5 (12.2)	3 (5.4)	5 (8.6)	8 (7.0)

Abdominal pain upper	4 (10.0)	3 (7.5)	4 (9.8)	4 (7.1)	4 (6.9)	8 (7.0)
Cough	2 (5.0)	4 (10.0)	2 (4.9)	3 (5.4)	5 (8.6)	8 (7.0)
Diarrhoea	4 (10.0)	4 (10.0)	1 (2.4)	4 (7.1)	4 (6.9)	8 (7.0)
Upper respiratory tract infection	3 (7.5)	1 (2.5)	3 (7.3)	6 (10.7)	2 (3.4)	8 (7.0)
Oropharyngeal pain	2 (5.0)	4 (10.0)	1 (2.4)	2 (3.6)	5 (8.6)	7 (6.1)
Tonsillitis	4 (10.0)	3 (7.5)	1 (2.4)	4 (7.1)	3 (5.2)	7 (6.1)
Eczema	1 (2.5)	4 (10.0)	1 (2.4)	1 (1.8)	5 (8.6)	6 (5.3)
Fatigue	3 (7.5)	1 (2.5)	0	3 (5.4)	3 (5.2)	6 (5.3)
Gastroenteritis	5 (12.5)	0	1 (2.4)	5 (8.9)	1 (1.7)	6 (5.3)
Pyrexia	3 (7.5)	3 (7.5)	2 (4.9)	3 (5.4)	3 (5.2)	6 (5.3)
Acne	3 (7.5)	1 (2.5)	0	3 (5.4)	2 (3.4)	5 (4.4)
Arthralgia	0	1 (2.5)	2 (4.9)	2 (3.6)	3 (5.2)	5 (4.4)
Dysmenorrhoea	1 (2.5)	4 (10.0)	2 (4.9)	1 (1.8)	4 (6.9)	5 (4.4)
Vomiting	1 (2.5)	4 (10.0)	1 (2.4)	1 (1.8)	4 (6.9)	5 (4.4)
Asthenia	1 (2.5)	2 (5.0)	0	1 (1.8)	3 (5.2)	4 (3.5)
Conjunctivitis	2 (5.0)	2 (5.0)	1 (2.4)	2 (3.6)	2 (3.4)	4 (3.5)
Folliculitis	1 (2.5)	2 (5.0)	0	2 (3.6)	2 (3.4)	4 (3.5)
Gastroenteritis viral	2 (5.0)	0	2 (4.9)	3 (5.4)	1 (1.7)	4 (3.5)
Nausea	2 (5.0)	2 (5.0)	4 (9.8)	2 (3.6)	2 (3.4)	4 (3.5)
Pharyngotonsillitis	2 (5.0)	1 (2.5)	0	3 (5.4)	1 (1.7)	4 (3.5)
Pruritus	1 (2.5)	1 (2.5)	1 (2.4)	1 (1.8)	3 (5.2)	4 (3.5)
Seborrhoeic dermatitis	1 (2.5)	1 (2.5)	1 (2.4)	1 (1.8)	3 (5.2)	4 (3.5)
Viral upper respiratory tract infection	1 (2.5)	2 (5.0)	2 (4.9)	1 (1.8)	3 (5.2)	4 (3.5)
Bronchitis	1 (2.5)	0	3 (7.3)	2 (3.6)	1 (1.7)	3 (2.6)
Dry skin	2 (5.0)	0	0	2 (3.6)	1 (1.7)	3 (2.6)
Eosinophilia	3 (7.5)	0	0	3 (5.4)	0	3 (2.6)
Nasal congestion	3 (7.5)	0	0	3 (5.4)	0	3 (2.6)
Neutropenia	2 (5.0)	1 (2.5)	1 (2.4)	2 (3.6)	1 (1.7)	3 (2.6)
Respiratory tract infection	1 (2.5)	2 (5.0)	0	1 (1.8)	2 (3.4)	3 (2.6)
Sinusitis	2 (5.0)	0	1 (2.4)	3 (5.4)	0	3 (2.6)
Aspartate aminotransferase increased	1 (2.5)	1 (2.5)	2 (4.9)	1 (1.8)	1 (1.7)	2 (1.8)
Blood bilirubin increased	2 (5.0)	0	0	2 (3.6)	0	2 (1.8)
Depression	2 (5.0)	0	0	2 (3.6)	0	2 (1.8)
Enteritis	0	2 (5.0)	0	0	2 (3.4)	2 (1.8)
Herpes virus infection	0	2 (5.0)	0	0	2 (3.4)	2 (1.8)
Hordeolum	2 (5.0)	0	0	2 (3.6)	0	2 (1.8)
Impetigo	0	2 (5.0)	1 (2.4)	0	2 (3.4)	2 (1.8)
Influenza	2 (5.0)	0	3 (7.3)	2 (3.6)	0	2 (1.8)
Injection site erythema	0	2 (5.0)	1 (2.4)	0	2 (3.4)	2 (1.8)
Injection site pain	2 (5.0)	0	1 (2.4)	2 (3.6)	0	2 (1.8)
Oral herpes	1 (2.5)	1 (2.5)	4 (9.8)	1 (1.8)	1 (1.7)	2 (1.8)
Pityriasis rosea	0	2 (5.0)	0	0	2 (3.4)	2 (1.8)
Psoriasis	1 (2.5)	1 (2.5)	3 (7.3)	1 (1.8)	1 (1.7)	2 (1.8)
Conjunctivitis allergic	0	1 (2.5)	2 (4.9)	0	1 (1.7)	1 (0.9)
Malaise	0	0	2 (4.9)	0	0	0

Preferred terms are sorted in descending order of frequency in the Any AIN457 dose column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
MedDRA version 22.0 was used for reporting.

The most commonly reported AEs were nasopharyngitis, headache and pharyngitis (Table 56). The incidence of nasopharyngitis was higher in the Any secukinumab high dose group (34.5%) compared to the Any secukinumab low dose group (25.0%) and the etanercept group (26.8%). The incidence of headache was similar between the Any secukinumab high dose group (15.5%), Any secukinumab low dose group (14.3%), and the etanercept group (9.8%). The incidence of pharyngitis was similar in the

Any secukinumab low dose group (10.7%), Any secukinumab high dose group (10.3%) and the etanercept group (7.3%).

The Any secukinumab high dose group had a higher incidence (>5% difference) for eczema, dysmenorrhea and vomiting compared to the Any secukinumab low dose group. The incidence of upper respiratory tract infection, gastroenteritis, eosinophilia, nasal congestion and sinusitis was higher (>5% difference) in the Any secukinumab low dose group compared to the Any secukinumab high dose group. The incidence of oral herpes was lower in Any secukinumab high and Any secukinumab low dose group (1.7% and 1.8%, respectively) compared to the etanercept group (9.8%). All other AEs had comparable incidence in both secukinumab dose groups.

Entire treatment period

The overall exposure in the etanercept group was considerably lower than secukinumab groups for the Entire treatment period, hence for comparison purposes safety data are expressed as exposure adjusted incidence rate (EAIR) per 100 patient years of exposure. Overall, the incidence rate of treatment emergent AEs was lower in the Any secukinumab dose group compared to the etanercept group (Table 57). The EAIRs of the most commonly affected SOC 'infections and infestation' was higher in the Any secukinumab low dose group (112.3) than in the Any secukinumab high dose group (85.7) but was similar to the etanercept group (118.5). This SOC consisted mainly of nasopharyngitis, pharyngitis, and tonsillitis related AEs. The SOC 'skin and subcutaneous tissue disorders' had similar EAIRs in the secukinumab treatment groups (24.2 in Any low dose and 23.2 in Any high dose) which was lower compared to the etanercept group (33.2). Similarly, the EAIRs of gastrointestinal disorders were comparable between the Any secukinumab low dose group (21.2) and the Any secukinumab high dose group (26.1) which were lower compared to etanercept group (45.2, Table 57).

The most common AEs during the entire treatment period were nasopharyngitis, headache and pharyngitis (Table 57). The EAIRs of tonsillitis, diarrhea, and rhinitis were higher in the Any secukinumab dose groups compared to the etanercept group, while the EAIRs of abdominal pain, abdominal pain upper and oral herpes were higher in the etanercept group. The EAIRs of upper respiratory tract infection and psoriasis were similar between the Any secukinumab low dose group and etanercept group and comparatively lower in the Any secukinumab high dose group.

The EAIRs (per 100 patient years) of AEs in patients aged < 12 years compared to ≥ 12 years were: 165.6 vs. 197.2 in the Any secukinumab low dose group, 177.7 vs. 176.6 in the Any secukinumab high dose group and 211.5 vs. 267.2 in the etanercept group. However, since the number of patients in the < 12 years age stratum was low (N=35) these incidence rates should be interpreted with caution.

In patients aged ≥ 12 years, the EAIRs of AEs were similar to that in the overall population.

No particular trend was observed in EAIRs when analysed in body weight strata between the treatment groups.

In < 25 kg stratum the incidence rate was higher in the secukinumab treatment group (Any low dose: 142.9 and Any high dose: 161.4) when compared to the etanercept group (92.4). However, since the number of patients in the 25 kg age stratum was low (N=12), these incidence rates should be interpreted with caution.

'≥ 25 kg and < 50 kg' stratum: the incidence rate was lower in the secukinumab treatment group (Any low dose: 161.6 and Any high dose: 179.2) when compared to the etanercept group (304.9).

Table 57 ***Exposure adjusted incidence rates for most frequent treatment emergent adverse events (≥4.0% or with incidence rate per 100 patient years ≥5.0 in any of the AIN457 treatment groups for preferred terms), 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)	Etanercept N=41 n/EX (IR)
Any preferred term	**46/0.24 (189.4)**	**49/0.28 (176.8)**	**95/0.52 (182.7)**	**34/0.13 (253.4)**
Nasopharyngitis	15/0.79 (18.9)	25/0.75 (33.4)	40/1.54 (26.0)	11/0.35 (31.1)
Headache	10/0.90 (11.1)	12/1.02 (11.7)	22/1.93 (11.4)	4/0.39 (10.2)
Pharyngitis	9/0.90 (10.0)	6/1.04 (5.8)	15/1.94 (7.7)	3/0.40 (7.5)
Tonsillitis	7/0.99 (7.1)	6/1.10 (5.4)	13/2.10 (6.2)	1/0.41 (2.5)
Cough	4/1.02 (3.9)	8/1.08 (7.4)	12/2.10 (5.7)	2/0.40 (5.0)
Diarrhoea	6/1.00 (6.0)	6/1.11 (5.4)	12/2.11 (5.7)	1/0.40 (2.5)
Rhinitis	4/1.02 (3.9)	6/1.08 (5.6)	10/2.10 (4.8)	1/0.41 (2.5)
Upper respiratory tract infection	7/0.95 (7.3)	3/1.13 (2.7)	10/2.08 (4.8)	3/0.39 (7.8)
Abdominal pain	4/1.05 (3.8)	6/1.10 (5.5)	10/2.15 (4.7)	5/0.37 (13.4)
Abdominal pain upper	4/1.02 (3.9)	5/1.09 (4.6)	9/2.12 (4.3)	4/0.39 (10.2)
Oropharyngeal pain	3/1.03 (2.9)	6/1.08 (5.6)	9/2.11 (4.3)	1/0.41 (2.5)
Acne	5/1.02 (4.9)	4/1.12 (3.6)	9/2.14 (4.2)	0/0.41 (0.0)
Bronchitis	3/1.07 (2.8)	5/1.15 (4.4)	8/2.21 (3.6)	3/0.40 (7.5)
Psoriasis	7/1.04 (6.8)	1/1.18 (0.8)	8/2.22 (3.6)	4/0.40 (9.9)
Arthralgia	3/1.06 (2.8)	4/1.12 (3.6)	7/2.19 (3.2)	2/0.39 (5.1)
Conjunctivitis	2/1.05 (1.9)	5/1.13 (4.4)	7/2.18 (3.2)	1/0.41 (2.5)
Eczema	2/1.06 (1.9)	5/1.12 (4.5)	7/2.18 (3.2)	1/0.41 (2.5)
Gastroenteritis	5/1.00 (5.0)	2/1.17 (1.7)	7/2.17 (3.2)	1/0.40 (2.5)
Pruritus	2/1.06 (1.9)	5/1.11 (4.5)	7/2.16 (3.2)	1/0.41 (2.4)
Viral upper respiratory tract infection	3/1.07 (2.8)	4/1.10 (3.6)	7/2.17 (3.2)	2/0.40 (5.0)
Respiratory tract infection	3/1.07 (2.8)	4/1.17 (3.4)	7/2.24 (3.1)	0/0.41 (0.0)
Fatigue	3/1.05 (2.8)	3/1.13 (2.7)	6/2.18 (2.8)	0/0.41 (0.0)
Pyrexia	3/1.03 (2.9)	3/1.13 (2.7)	6/2.16 (2.8)	2/0.40 (5.0)
Vomiting	1/1.07 (0.9)	5/1.11 (4.5)	6/2.18 (2.8)	1/0.40 (2.5)
Folliculitis	3/1.03 (2.9)	3/1.15 (2.6)	6/2.18 (2.7)	0/0.41 (0.0)
Gastrointestinal infection	2/1.04 (1.9)	4/1.15 (3.5)	6/2.19 (2.7)	0/0.41 (0.0)
Influenza	5/1.01 (4.9)	1/1.19 (0.8)	6/2.20 (2.7)	3/0.40 (7.6)
Seborrhoeic dermatitis	2/1.05 (1.9)	4/1.14 (3.5)	6/2.19 (2.7)	1/0.41 (2.5)
Dysmenorrhoea	1/1.06 (0.9)	4/1.12 (3.6)	5/2.18 (2.3)	2/0.40 (5.0)
Toothache	1/1.08 (0.9)	4/1.15 (3.5)	5/2.23 (2.2)	1/0.40 (2.5)
Aspartate aminotransferase increased	1/1.08 (0.9)	3/1.15 (2.6)	4/2.23 (1.8)	2/0.39 (5.1)
Asthenia	1/1.07 (0.9)	3/1.13 (2.6)	4/2.21 (1.8)	0/0.41 (0.0)
Gastroenteritis viral	3/1.02 (2.9)	1/1.17 (0.9)	4/2.19 (1.8)	2/0.40 (5.0)
Neutropenia	3/1.07 (2.8)	1/1.19 (0.8)	4/2.26 (1.8)	1/0.41 (2.5)
Oral herpes	3/1.05 (2.9)	1/1.16 (0.9)	4/2.21 (1.8)	4/0.39 (10.4)
Pharyngotonsillitis	3/1.03 (2.9)	1/1.19 (0.8)	4/2.21 (1.8)	0/0.41 (0.0)
Sinusitis	3/1.02 (2.9)	1/1.19 (0.8)	4/2.22 (1.8)	1/0.41 (2.4)
Nasal congestion	3/1.02 (3.0)	0/1.19 (0.0)	3/2.21 (1.4)	0/0.41 (0.0)
Eosinophilia	3/1.04 (2.9)	0/1.19 (0.0)	3/2.23 (1.3)	0/0.41 (0.0)
Impetigo	0/1.09 (0.0)	3/1.16 (2.6)	3/2.25 (1.3)	1/0.41 (2.4)

The overall incidence of AEs possibly related to the study medication was higher in the Any secukinumab high dose group (24 patients, 41.4%) compared to Any secukinumab low dose group (16 patients, 28.6%) and etanercept group (14 patients, 34.1%).

The frequency of most commonly affected SOC Infections and infestations and AE nasopharyngitis were similar to those reported up to Week 52.

Exposure adjusted incidence rates (per 100 patient-years) of AEs possibly related to the study drug were 18.9 in Any secukinumab low dose group and 31.8 in Any secukinumab high dose group, which were lower than the etanercept group (42.5).

Exposure adjusted incidence rates of AEs possibly related to the study drug in the most commonly affected SOC Infections and infestations were similar between the secukinumab treatment groups (13.3 in the Any low dose group and 14 in the Any high dose) and lower compared to the etanercept group (18.9); and was mainly driven by AEs of nasopharyngitis and upper respiratory tract infection.

Long-term safety, including the safety data until the Week 52, has been compared between the paediatric and the adult populations using exposure-adjusted incidence rates. The overall incidence rates of AEs in the paediatric population up to Week 52 was 294 per 100 PY in Any secukinumab treated paediatric patients with severe psoriasis which was slightly higher than the adults with severe psoriasis (223.0 per 100 PY). Consistent with the trends seen in the Induction period there was an increase in incidence rates for infections with the paediatric population (147.5 per 100 PY) compared to the adult with severe psoriasis (86.1 per 100 PY), mainly driven by nasopharyngitis, pharyngitis, and upper respiratory tract infection.

Serious adverse event/deaths/other significant events

Deaths

There were no deaths in either of the Studies A2310 and A2311.

Serious adverse events (SAEs)

Study A2310

Up to week 12

During the Induction period, 1 patient (2.5%) each in the two secukinumab treatment arms had SAEs (alanine aminotransferase increased and toxic shock syndrome) compared to 4 patients (9.8%) in the etanercept arm (Table 58). The increase in alanine aminotransferase was transient and the patient continued the study treatment; in the case of toxic shock syndrome, the study treatment was discontinued. The investigators consider none of these SAEs related to study treatment.

Table 58 ***Treatment emergent serious adverse events, by preferred term – Induction period (Study A2310, Safety set)***

Preferred term	AIN457 Low dose N=40 n (%)	AIN457 High dose N=40 n (%)	Any AIN457 dose N=80 n (%)	Placebo N=41 n (%)	Etanercept N=41 n (%)
Any preferred term	1 (2.5)	1 (2.5)	2 (2.5)	0 (0.0)	4 (9.8)
Alanine aminotransferase increased	1 (2.5)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)
Toxic shock syndrome	0 (0.0)	1 (2.5)	1 (1.3)	0 (0.0)	0 (0.0)
Autoimmune pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Gallbladder polyp	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Gastrointestinal toxicity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Syncope	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)

-Preferred terms are sorted in decreasing order of frequency in Any AIN457 dose group.
- A patient with multiple occurrences of an serious AE under one treatment is counted only once in the serious AE category for that treatment.
- MedDRA version 22.0 was used for reporting.

During the Induction period, the overall incidence of SAEs in the secukinumab-treated paediatric population was low and similar to the adult population (2.5% in the paediatric vs. 2.1% in adults with moderate psoriasis and 2.3% in adults with severe psoriasis). All events (PTs) were reported in one

patient each except for overdose, which was reported in 2 patients in adult patients with moderate psoriasis.

Up to week 24

In addition to the SAEs reported during the Induction period, 3 more patients had SAEs up to Week 24, *i.e.*, 1 patient each in the secukinumab Low dose group (bronchitis), secukinumab High dose group (lymphadenopathy) and etanercept group (abdominal pain). The SAEs of bronchitis and lymphadenopathy were suspected to be related to the study drug did not lead to study drug discontinuation. Additionally, 1 patient in the placebo-secukinumab Low dose group (reactive arthritis and worsening of psoriasis) and 1 patient in the placebo–secukinumab High dose group (pneumonia and thrombophlebitis) reported SAEs. The SAE of reactive arthritis was suspected to be related to the study drug and led to study drug discontinuation.

Entire treatment period

After adjusting for exposure, the incidence rates of non-fatal SAEs and AEs leading to discontinuation of the study drug were lower in the Any secukinumab dose group compared to the etanercept group (Table 59). The EAIRs for non-fatal SAEs and AEs leading to discontinuation were similar between the Any secukinumab low dose group and Any secukinumab high dose group.

Table 59 ***Exposure adjusted incidence rate for deaths, other serious adverse events and adverse events related discontinuations – Entire treatment period (Study A2310, Safety set)***

	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)	Etanercept N=41 n/EX (IR)
Patients with AEs	46/0.24 (189.4)	49/0.28 (176.8)	95/0.52 (182.7)	34/0.13 (253.4)
Patients with serious or other significant events				
Death	0/1.09 (0.0)	0/1.19 (0.0)	0/2.28 (0.0)	0/0.41 (0.0)
Non-fatal SAEs	5/1.06 (4.7)	6/1.11 (5.4)	11/2.17 (5.1)	6/0.37 (16.1)
Discontinued study treatment due to any AEs	2/1.08 (1.8)	1/1.19 (0.8)	3/2.27 (1.3)	1/0.41 (2.4)

EX=exposure in 100 patient years. IR=incidence rate per 100 patient years.
For patients with event, exposure time is censored at time of first event.

Treatment emergent serious adverse events are presented In Table 60.

The EAIRs of SAEs in patients aged <12 years compared to ≥12 years were: 7.6 vs. 4.3 in the Any secukinumab low dose group, 19.0 vs. 4.0 in the Any secukinumab high dose group and 11.5 vs. 17.5 in the etanercept group. However, since the number of patients in the <12 years age stratum was low (N=35) these incidence rates should be interpreted with caution.

Table 60 ***Treatment emergent serious adverse events, by preferred term – Entire treatment period (Study A2310, 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)	Etanercept N=41 n/EX (IR)
Any preferred term	**5/1.06 (4.7)**	**6/1.11 (5.4)**	**11/2.17 (5.1)**	**6/0.37 (16.1)**
Abdominal hernia	0/1.09 (0.0)	1/1.18 (0.8)	1/2.27 (0.4)	0/0.41 (0.0)
Alanine aminotransferase increased	1/1.08 (0.9)	0/1.19 (0.0)	1/2.27 (0.4)	0/0.41 (0.0)
Arthritis reactive	1/1.09 (0.9)	0/1.19 (0.0)	1/2.28 (0.4)	0/0.41 (0.0)
Bronchitis	1/1.08 (0.9)	0/1.19 (0.0)	1/2.27 (0.4)	0/0.41 (0.0)
Clavicle fracture	0/1.09 (0.0)	1/1.17 (0.9)	1/2.26 (0.4)	0/0.41 (0.0)
Concussion	0/1.09 (0.0)	1/1.19 (0.8)	1/2.28 (0.4)	0/0.41 (0.0)
Contusion	0/1.09 (0.0)	1/1.19 (0.8)	1/2.28 (0.4)	0/0.41 (0.0)
Enterocolitis bacterial	0/1.09 (0.0)	1/1.17 (0.9)	1/2.26 (0.4)	0/0.41 (0.0)
Infectious pleural effusion	0/1.09 (0.0)	1/1.17 (0.9)	1/2.26 (0.4)	0/0.41 (0.0)
Lung abscess	0/1.09 (0.0)	1/1.17 (0.9)	1/2.26 (0.4)	0/0.41 (0.0)
Lymphadenopathy	0/1.09 (0.0)	1/1.19 (0.8)	1/2.27 (0.4)	0/0.41 (0.0)
Major depression	1/1.09 (0.9)	0/1.19 (0.0)	1/2.28 (0.4)	0/0.41 (0.0)
Pneumonia	0/1.09 (0.0)	1/1.17 (0.9)	1/2.26 (0.4)	0/0.41 (0.0)
Suicidal ideation	1/1.09 (0.9)	0/1.19 (0.0)	1/2.28 (0.4)	0/0.41 (0.0)
Testicular torsion	1/1.09 (0.9)	0/1.19 (0.0)	1/2.28 (0.4)	0/0.41 (0.0)
Thrombophlebitis	0/1.09 (0.0)	1/1.17 (0.9)	1/2.26 (0.4)	0/0.41 (0.0)
Toxic shock syndrome	0/1.09 (0.0)	1/1.19 (0.8)	1/2.28 (0.4)	0/0.41 (0.0)
Venous thrombosis limb	0/1.09 (0.0)	1/1.17 (0.9)	1/2.26 (0.4)	0/0.41 (0.0)
Abdominal pain	0/1.09 (0.0)	0/1.19 (0.0)	0/2.28 (0.0)	1/0.41 (2.5)
Autoimmune pancreatitis	0/1.09 (0.0)	0/1.19 (0.0)	0/2.28 (0.0)	1/0.40 (2.5)
Ectopic pregnancy	0/1.09 (0.0)	0/1.19 (0.0)	0/2.28 (0.0)	1/0.41 (2.4)
Gallbladder polyp	0/1.09 (0.0)	0/1.19 (0.0)	0/2.28 (0.0)	1/0.41 (2.4)
Gastrointestinal toxicity	0/1.09 (0.0)	0/1.19 (0.0)	0/2.28 (0.0)	1/0.40 (2.5)
Pilonidal cyst	0/1.09 (0.0)	0/1.19 (0.0)	0/2.28 (0.0)	1/0.41 (2.4)
Syncope	0/1.09 (0.0)	0/1.19 (0.0)	0/2.28 (0.0)	1/0.41 (2.5)

Study A2311

There were no deaths in Study A2311 up to week 24. The SAEs are presented in Table 61.

Table 61 ***Exposure adjusted incidence rate for deaths, other serious or clinically significant AEs or related discontinuations - Entire treatment period (Safety set))***

	AIN457 Low dose N=42 n/EX (IR)	AIN457 High dose N=42 n/EX (IR)	Any AIN457 dose N=84 n/EX (IR)
Subjects with any AEs	28/0.17 (161.6)	25/0.14 (173.4)	53/0.32 (167.0)
Subjects with serious or other significant events			
Death	0	0	0
Non fatal SAE(s)	1/0.31 (3.2)	0/0.28 (0.0)	1/0.59 (1.7)
Discontinued study treatment due to any AE(s)	0/0.31 (0.0)	2/0.28 (7.2)	2/0.59 (3.4)

One SAE (infectious mononucleosis) was reported in one patient randomized to secukinumab Low dose (150 mg). The event started on Day 93 (on 7th day after patient received the 7th dose of study drug). The event was mild in severity and was not considered to be related to the study drug.

One Patient had Grade 1 ALT elevation (73 U/L, normal range: 5-30 U/L) and Grade 2 AST elevation (116 U/L; ULN: 37 U/L) on Day 1 (Randomization/Day 1). At screening as well, the patient had high ALT

(62 U/L) and AST (106 U/L) levels. On Day 2, one day after the first dose of study drug, these ALT and AST elevations were recorded as AEs. The events were mild in severity and were not considered to be related to study drug.

Adverse events of special interest (AESI)

Study A2310

Searches for events that represent each of AEs of special interest were made for paediatric Study A2310 as well as for the adult pool using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs), standardized MedDRA query (SMQ), Novartis MedDRA query (NMQ) or high level term (HLT), as listed below.

- Infections: Infections and infestations SOC
- Hypersensitivity: Hypersensitivity (SMQ) (narrow)
- Neutropenia: Neutropenia (NMQ) (narrow)
- Malignant or unspecified tumour: Malignant or unspecified tumours (SMQ)
- Major adverse cardiovascular events (MACE): MACE (myocardial infarction, stroke, cardiovascular death) (NMQ)
- Inflammatory bowel disease: Inflammatory bowel disease (NMQ) (narrow)
- Hepatitis B reactivation: Hepatitis viral infections (HLT)
- Immunogenicity: Drug specific antibody present (PT)
- Interaction with live vaccines: Vaccination related complications (HLT)
- Suicidal ideation and behaviour: Suicide/self-injury (SMQ)

<u>Up to week 12</u>

During the Induction period, only infections and hypersensitivity related AESI were reported. No events related to the AESI of neutropenia, Crohn's disease, MACE and malignancy were reported during the Induction period in the paediatric population.

The incidences of infection related AEs in the secukinumab and etanercept groups were comparable to the placebo group (32.5% in the secukinumab Low dose, 37.5% in the High dose, 26.8% in the etanercept group and 39% in the placebo group). The higher incidence of infection related AEs in the paediatric population compared to adults was mainly driven by nasopharyngitis, pharyngitis and upper respiratory tract infection. None of the infection related AEs were serious or led to the discontinuation of the study drug.

- Nasopharyngitis was reported in 7 (17.5%) patients in the Low dose and 6 (15%) patients in the High dose group, 1 (2.4%) patient in the placebo group, and 4 (9.8%) patients in the etanercept group.
- Pharyngitis was reported in 2 (5%) patients each in the secukinumab Low dose and the High dose group, 4 (9.8%) patients in placebo group and none in the etanercept group.
- Upper respiratory tract infections were reported in 2 (5%) patients in the secukinumab Low dose group, 3 (7.3%) patients in the placebo, 1 (2.4%) patient in the etanercept group and none in the secukinumab High dose group.

Hypersensitivity related AEs were also low and were reported in 3 (7.5%) patients in the secukinumab Low dose group, 2 patients each in the secukinumab High dose (5%) and etanercept group (4.9%) and 1 (2.4%) patient in the placebo group. All hypersensitivity related events including eczema, injection site hypersensitivity, allergic rhinitis, and urticaria were reported in 1 patient each. Allergic conjunctivitis was the only hypersensitivity related event that occurred in 2 (4.9%) patients in the etanercept group.

A total of 483 serum samples from 118 patients were analysed for anti-drug antibodies (ADA). Treatment-emergent ADAs were detected in only one patient in the secukinumab Low dose at Week 12. This was not associated with clinically relevant AEs or loss of efficacy.

In the < 12 years age stratum, there were no cases of hypersensitivity AEs in the secukinumab treatment groups. The incidence of Infections was 3 (17.6%) patients in the Any secukinumab group compared to 2 (20%) patients in the placebo and 3 (30%) in the etanercept group. In the ≥ 12 years age stratum, the incidence of infection was 25 (39.7%) patients in the Any secukinumab group compared to 14 (45.2%) patients in the placebo and 8 (25.8%) patients in the etanercept group; hypersensitivity was 5 (7.9%) patients in the Any secukinumab group compared to none in the placebo or etanercept group.

In patients with body weight < 25 kg, the only identified risk that was reported was infection with 1 patient each in the Any secukinumab (nasopharyngitis) and the placebo (influenza) groups.

The incidences of AESI in the paediatric population did not increase compared to the adult population during the Induction period with the exception of increased rate of infections in paediatric patients, which is expected this patient population.

Entire treatment period

The potential risk of suicide/self-injury (SMQ) occurred in one patient in the secukinumab low dose group. No events related to the risks of hepatitis B reactivation, inflammatory bowel disease, interaction with live vaccines, MACE and malignant or unspecified tumours were reported

The EAIR for AEs related to the risk of infections and infestations'(SOC) was higher in the Any secukinumab low dose group compared to the Any secukinumab high dose group but not higher compared to etanercept group. The EAIR for Hypersensitivity (SMQ) (narrow) was higher in the Any secukinumab high dose group compared to the Any secukinumab low dose group but not compared to etanercept group. The EAIR for neutropenia (NMQ) (narrow) was low across treatment groups (Table 62).

An additional case of neutropenia was reported in Any secukinumab low dose. This patient was 14-year old male with normal neutrophil count at baseline (3.20 x 10^9/L, NR: 1.54 - 7.04 x 10^9/L), developed Grade 2 neutropenia (1.32 x 10^9/L) on Day 198 (Week 28 visit) which was fluctuating till Day 303 (Week 44). On Day 338 (Week 48), the neutrophil count returned to normal (1.67 x 10^9/L). In the Extension period, the patient reported Grade 2 neutropenia (1.17 x 10^9/L), which was reported as a non-serious AE. The patient's neutrophil count was 1.21 x 10^9/L (Grade 2) at the time of data cut-off. The event was resolved and the event of neutropenia was considered as related to the study drug.

Table 62 ***Exposure adjusted incidence rates for important identified and potential risks (level 1) based on all adverse events – Entire treatment period (Study A2310, Safety set)***

Risk category Level 1	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)	Etanercept N=41 n/EX (IR)
Important identified risk				
Infections and infestations (SOC)	40/0.36 (112.5)	40/0.46 (87.4)	80/0.81 (98.4)	27/0.23 (118.5)
Hypersensitivity (SMQ) (narrow)	5/0.98 (5.1)	12/1.01 (11.8)	17/1.99 (8.5)	5/0.37 (13.4)
Neutropenia (NMQ) (narrow)	3/1.07 (2.8)	1/1.19 (0.8)	4/2.26 (1.8)	1/0.41 (2.5)
Important potential risk				
Hepatitis viral infections (HLT)	0/1.09 (0.0)	0/1.19 (0.0)	0/2.28 (0.0)	0/0.41 (0.0)
Inflammatory bowel disease (NMQ) (narrow)	0/1.09 (0.0)	0/1.19 (0.0)	0/2.28 (0.0)	0/0.41 (0.0)
MACE (MI, Stroke, Cardiovascular death) (NMQ)	0/1.09 (0.0)	0/1.19 (0.0)	0/2.28 (0.0)	0/0.41 (0.0)
Malignant or unspecified tumours (SMQ)	0/1.09 (0.0)	0/1.19 (0.0)	0/2.28 (0.0)	0/0.41 (0.0)
Vaccination related complications (HLT)	0/1.09 (0.0)	0/1.19 (0.0)	0/2.28 (0.0)	0/0.41 (0.0)
Suicide/self-injury (SMQ)	1/1.09 (0.9)	0/1.19 (0.0)	1/2.28 (0.4)	0/0.41 (0.0)

Risk category and risk name are sorted alphabetically, Level 1 is sorted within risk name in descending order of IR in the any AIN457 column.
MedDRA version 22.0 has been used for reporting.
For patients with event, exposure time is censored at time of first event.
EX = exposure in 100 patient years. IR=incidence rate per 100 patient years.

Over the entire treatment period, 13 patients were presented with injection sites reactions as defined above. Three were in the secukinumab low dose group, 4 in the secukinumab high dose group, 4 in the etanercept group and 2 in the placebo group. All AEs were mild in intensity and required no treatment, except in 2 cases: application site erythema in the etanercept group was treated with loratadine (1 day) and injection site hematoma in the placebo group.

The EAIRs of important and potential risks in patients aged < 12 years compared to ≥ 12 years at study entry are described below:

- Infections and infestations (SOC): 65.2 vs. 129.0 in any secukinumab low dose group, 118.0 vs. 82.1 in any secukinumab high dose group and 79.6 vs. 133.3 in etanercept group.
- Hypersensitivity (SMQ) (narrow): 0 vs. 5.9 in any secukinumab low dose group, 19.3 vs. 11.0 in Any secukinumab high dose group and 42.7 vs. 6.6 in etanercept group.
- Neutropenia (NMQ) (narrow): 16.5 vs 1.1 in any secukinumab low dose group, 9.2 vs. 0 in Any secukinumab high dose group and 0 vs. 3.2 in etanercept group.

The EAIRs of important and potential risks in patients by body weight < 25 kg, ≥ 25 kg and < 50 kg, and ≥ 50 kg at study entry were:

- Infections and infestations (SOC): 35.5 vs. 102.2 vs. 134.5 in the any secukinumab low dose group, 141.9 vs. 63.0 vs. 101.7 in the any secukinumab high dose group and 30.5 vs. 133.5 vs. 133.1 in the etanercept group.
- Hypersensitivity (SMQ) (narrow): 0 vs. 2.9 vs. 6.8 in the any secukinumab low dose group, 26.4 vs. 17.7 vs. 8.7 in the any secukinumab high dose group and 0 vs. 23.9 vs. 9.6 in the etanercept group.
- Neutropenia (NMQ) (narrow): 28.9 vs. 5.5 vs. 0 in the any secukinumab low dose group, 0 vs. 2.8 vs. 0 in the any secukinumab high dose group and 0 vs. 0 vs. 4.7 in the etanercept group.

Study A2311

The incidence of AEs related to the 'Infections and infestations' was seen in 42.9% (18/42 subjects) in the secukinumab High dose group and 35.7% (15/42 subjects; 35.7%) in the Low dose group (Table 63). The incidence of AEs related to neutropenia (NMQ) were comparable between Low dose (3/42 subjects; 7.1%) and High dose (2/42 subjects; 4.8%) groups.

Upper respiratory tract infections (HLT): The most frequently reported infections were upper respiratory tract infections [HLT]) in both secukinumab Low dose (8/42 subjects, 19.0%) and High dose (11/42 subjects, 26.2%) groups.

The higher incidence of upper respiratory tract infections was mainly driven by the PT nasopharyngitis (Low dose group: 6/42 subjects; 14.3% and High dose group: 4/42 subjects; 9.5%) which was mild in severity in all subjects except in one subject from High dose group who experienced a severe AE of nasopharyngitis. The event resolved in 6 days with treatment. The event of nasopharyngitis that was reported in 10 subjects overall resolved completely in all while the subjects were still on treatment.

Table 63 ***Absolute and relative frequencies for Important identified and potential risks based on all AEs - Data up to Week 24 (Safety set)***

Risk Category Risk name Level 1	AIN457 Low dose N=42 n (%)	AIN457 High dose N=42 n (%)	Any AIN457 dose N=84 n (%)
Important identified risk			
Hypersensitivity			
Hypersensitivity (SMQ) (narrow)	1 (2.4)	0 (0.0)	1 (1.2)
Infections			
Infections and infestations (SOC)	15 (35.7)	18 (42.9)	33 (39.3)
Neutropenia			
Neutropenia (NMQ) (narrow)	3 (7.1)	2 (4.8)	5 (6.0)
Important potential risk			
Inflammatory Bowel Disease			
[1]Inflammatory bowel disease (NMQ) (narrow)	0 (0.0)	1 (2.4)	1 (1.2)
Diarrhea hemorrhagic (PT)	0 (0.0)	1 (2.4)	1 (1.2)

Risk levels are not mutually exclusive.
Preferred terms are sorted within risk level 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.
[1]Level 2 (PT) was mentioned only for Inflammatory Bowel disease
MedDRA version 22.1 and NMQs as of 03-Nov-2019 have been used for reporting.

Three patients (3/42 patients; 7.1%) in the secukinumab low dose group and 2 patients (2/42 patients; 4.8%) in the secukinumab High dose group had AEs related to neutropenia (NMQ narrow) (PTs: neutropenia and leukopenia).

One patient randomized to secukinumab High Dose group (300 mg) had an AE of haemorrhagic diarrhoea on Day 98 (6 days after the patient received the most recent dose of study drug) which was captured under the NMQ of inflammatory bowel disease. The event was mild in severity and was considered to be

related to the study drug. The study drug was permanently discontinued due to this event. The event resolved at Day 177 with treatment.

One patient randomized to secukinumab High Dose group (300 mg) had short episodes of vulvovaginal candidiasis (2 episodes; episode 1: Day 9 to Day 10; episode 2: Day 13 to Day 21), that were considered to be mild in severity and related to the study drug. Both the episodes resolved completely with treatment. The events did not lead to interruption or discontinuation of study drug. The patient continued treatment and remained on trial at the time of Week 16 data cut-off.

None of the patients in the study developed treatment emergent ADAs until the Week 24 cut-off. Patient randomized to secukinumab High dose (300 mg) group was positive for ADA (Anti-AIN457 antibodies (titer): 7.98) at Randomization (Day 1). The patient did not have ADA at Week 16 and 24.

Laboratory findings

Study A2310

Up to week 12

Haematology: All newly occurring or worsening laboratory abnormalities in haematology parameters during the Induction period were common technical criteria for adverse events (CTCAE) Grade 1 or 2. The most commonly reported haematology abnormalities during the Induction period were Grade 1 decreased haemoglobin and Grade 1 decreased leukocyte count. Most patients had haematology values within normal range at baseline and remained within normal range post-baseline during the Induction period. The majority of CTCAE category shifts were from Normal to Grade 1 or Grade 2 or Grade 1 to Grade 2. None of the increase or decreases or shifts in haematological parameters were considered clinical significant by the investigator.

The majority of the population were ≥ 12 years of age and the incidence of newly occurring or worsening haematology parameters were similar to that observed in the overall population. In the patient population < 12 years of age, the incidence of haematological abnormalities was low and sporadic. One patient weighing < 25 kg each in the Any secukinumab, placebo and etanercept group had neutrophils < 1.5-1.0x 10E9/L, haemoglobin < lower limit of normal (LLN) -100 g/L, and neutrophils < LLN - 1.5x 10E9/L, respectively.

Newly occurring haematological abnormalities in the paediatric population were not increased compared to the adult population during the Induction period except for decreased haemoglobin (Grade 1) and decreased leukocytes (Grade 1) which were reported at a slightly higher rates in the paediatric population compared to the adult population.

Biochemistry: All newly occurring or worsening biochemistry parameters in the paediatric population during the Induction period were CTCAE Grade 1 or 2, except 1 patient in the secukinumab Low dose group who had increased aspartate amino transferase (AST) of Grade 3 (had normal AST at baseline). The majority of CTCAE category shifts were from Normal to Grade 1 or Grade 2 or Grade 1 to Grade 2. One patient in the etanercept group had Grade 3 increased gamma glutamyl transferase (GGT) at baseline and post-baseline (not newly occurring or worsening after baseline).

During the Induction period, the incidence of liver enzyme abnormalities was generally low and comparable between the Any secukinumab dose group, placebo group and etanercept group. No patient had abnormalities that met the Hy's law criteria. Two patients in secukinumab Low dose group and 1 patient in etanercept group had alanine amino transferase (ALT) or AST > 3x upper limit of normal (ULN). One patient in secukinumab Low dose group had ALT or AST > 5x ULN. This patient with ongoing Gilbert's syndrome at baseline had an elevated level of ALT and AST during the study. During the

Induction period (Visit 8, Day 48) the AST level increased to 256 U/L with ALT level at 62 U/L. The patient's ALT and AST returned to normal levels of 13 U/L and 19 U/L, respectively, on Day 92 (Week 12 visit).

Newly occurring chemistry abnormalities in the paediatric population during the Induction period were similar compared to the adult population with no clinically meaningful differences between the treatment groups or any dose-related trends between the secukinumab treatment groups.

Up to week 24

Haematology: All newly occurring or worsening laboratory abnormalities in haematology parameters up to Week 24 were CTCAE Grade 1 or 2, except 1 patient in the Any secukinumab Low dose (150 mg) group with Grade 3 decrease in neutrophil count. This patient had normal neutrophil count at baseline, which decreased on Day 57 (Week 8 visit) and further worsened to Grade 3 on Day 141 (Week 20 visit). From Day 127 to Day 134, the patient presented with a non-serious AE of viral upper respiratory tract infection. Neutrophil count returned to normal on Day 225 (Week 32 visit) and the event of neutropenia was considered as resolved (without any treatment). The event of neutropenia was considered related to the study drug; however, no action was taken with the study treatment.

Biochemistry: The majority of newly occurring or worsening abnormalities in biochemistry parameters up to Week 24 were CTCAE Grade 1 or 2. In addition to 1 patient with Grade 3 increase in AST in the Induction period (discussed above), 1 patient each in the secukinumab High dose and etanercept group had Grade 3 AST increase up to Week 24. One patient each had Grade 3 increase in ALT and ALP in the etanercept group up to Week 24.

No patient had abnormalities that met the Hy's law criteria up to Week 24. One in the etanercept group had ALT or AST > 10x ULN. One patient each in secukinumab Low dose group and etanercept group had ALT or AST > 5x ULN. Two patients in secukinumab Low dose group and one patient in etanercept group had ALT or AST > 3x ULN. One patient in the secukinumab Low dose group had ALT or AST > 3x ULN and total bilirubin (TBL) > 1.5x ULN. One patient in the etanercept group had alkaline phosphatase (ALP) > 5x ULN.

Up to week 52

Haematology: All newly occurring or worsening laboratory abnormalities in haematology parameters up to Week 52 were CTCAE Grade 1 or 2, except for 2 patients in the secukinumab low dose group and in the etanercept group) with Grade 3 decrease in neutrophil count and two patients in the etanercept group with Grade 4 decreased platelet count.

The most commonly reported haematology abnormality up to Week 52 was Grade 1 decreased leukocyte count and Grade 1 decreased haemoglobin count. Grade 1 decreased leukocyte count occurred more frequently in the Any secukinumab low dose group (13 patients, 24.1%) than the Any secukinumab high dose group (9 patients, 16.4%) and etanercept group (8 patients, 20.5%).

Grade 3 neutropenia occurred in 1 patient each in the Any secukinumab low dose and etanercept group (1.8% in Any secukinumab low dose group and 2.4% in etanercept group). Grade 2 neutropenia was similar between Any secukinumab low dose group (7 patients, 12.7%) and etanercept group (5 patients, 12.2%) and high compared to the Any secukinumab high dose group (5 patients, 9.1%). Grade 1 neutropenia was high in Any secukinumab low dose group (9 patients, 16.7%) compared to Any secukinumab high dose group (5 patients, 9.1%) and etanercept group (4 patients, 9.8%).

Grade 1 decreased lymphocyte count occurred more frequently in the Any secukinumab low dose group compared to Any secukinumab high dose group and etanercept group.

There were no clinically meaningful differences in the newly occurring or worsening haematology abnormalities across the treatment groups up to Week 52.

Up to Week 52, the majority of CTCAE category shifts were from Normal to Grade 1 or Grade 2 and a few were from Grade 1 to Grade 2, consistent with the new or worsening post-baseline abnormalities shown in Table 12-11. All patients with Grade 3 or Grade 4 laboratory abnormality in haematology parameters had a shift from Normal at baseline.

Biochemistry: All newly occurring or worsening laboratory abnormalities in chemistry parameters up to Week 52 were CTCAE Grade 1 or 2 (Table 12-13). Grade 3 increased AST and ALT was reported for one patient in the etanercept group and one patient each in secukinumab low dose group and in the switchers to secukinumab high dose group had Grade 3 increased AST. One patient in the etanercept group had Grade 3 increased ALP.

Grade 2 increased ALT was reported in 1 patient (2.6%) in secukinumab low dose group. Grade 2 increased bilirubin was reported in 4 patients (10.3%) in the secukinumab low dose group and 2 patients (4.9%) in the etanercept group. Grade 1 increased ALT was the most commonly reported chemistry abnormality up to Week 52. There were no clinically meaningful differences in the newly occurring or worsening chemistry abnormalities across the treatment groups up to Week 52.

Entire treatment period

Haematology: The majority of newly occurring or worsening laboratory abnormalities in haematology parameters during Entire treatment period were CTCAE Grade 1 or 2. One patient in the Any secukinumab high dose had Grade 3 decreased lymphocyte count. Consistent with the observations up to Week 52, the most commonly reported haematology abnormality during Entire treatment period was Grade 1 decreased leukocyte count.

There were no clinically meaningful differences between the secukinumab treatment groups in the newly occurring or worsening haematology abnormalities during Entire treatment period.

Most patients had haematology values within normal range at baseline and also post-baseline during Entire treatment period. The majority of CTCAE category shifts during the Entire treatment period were from Normal to Grade 1 or Grade 2 and a few were from Grade 1 to Grade 2, consistent with the new or worsening post-baseline abnormalities. The single patient with a Grade 3 abnormality mentioned above, had a shift from Normal at Baseline.

Biochemistry: The majority of newly occurring or worsening laboratory abnormalities in chemistry parameters during Entire treatment period were CTCAE Grade 1 or 2. There were no additional Grade 3 or Grade 4 cases in the Entire treatment period. Consistent with the observations up to Week 52, the most commonly reported chemistry abnormality during Entire treatment period was Grade 1 increased ALT occurring more frequently in the Any secukinumab high dose group (10 patients, 19.6%) than the Any secukinumab low dose group (7 patients, 13.5%). Grade 2 increased bilirubin was reported for 4 (7.3%) patients in the Any secukinumab low dose group and 2 (4.9%) in the etanercept group.

Vital signs and ECGs

The most commonly reported vital signs abnormality was high pulse rate, which was less frequently reported in the Any secukinumab low dose group compared to Any secukinumab high dose group and the etanercept group.

The differences in the frequency of the vital sign abnormalities between the treatment groups were not clinically significant.

The non-serious AEs of increased systolic blood pressure (Day 294), orthostatic hypotension (Day 333) and hypotension (Day 203) were reported for single patient in the secukinumab low dose group, secukinumab high dose group and etanercept group, respectively. The events of increased systolic blood pressure and orthostatic hypotension resolved on the same day, while the event of hypotension resolved after 28 days. All events were considered as not related to study drug and no action was taken with study drug.

High pulse rate continued to be the most commonly reported vital signs abnormalities during Entire treatment period. The frequency of high pulse rate was lower in the Any secukinumab low dose group (7 patients, 13.2%) than the Any secukinumab high dose group (15 patients, 27.3%); and it was (10 patients, 25.6%) in the etanercept group. There were no clinically meaningful differences in the frequency of vital sign abnormalities between the treatment groups.

A non-serious AE of low diastolic blood pressure was reported for one patient in the secukinumab low dose group. The event was ongoing at the time of data cut off for this analysis (18-Sep-2019). This event was considered as not related to study drug and no action was taken with study drug.

Up until 52 weeks, one patient (2.6%) in the secukinumab high dose group had QTcF changes from baseline > 450 msec. Three patients (7.7%) in the secukinumab high dose group, 3 patients (7.3%) in the etanercept group and one patient in the switcher from placebo to secukinumab high dose group had QTcF changes from baseline > 30 msec. One patient (2.4%) in the etanercept group had QTcF changes from baseline > 60 msec. These ECG abnormalities were considered not clinically significant.

One patient in the secukinumab low dose group had a non-serious AE of intraventricular conduction defect (mild) on Day 85, which was considered as related to study treatment but no action was taken with the study drug and event resolved on Day 108.

During the entire treatment period, one patient (1.8%) in the Any secukinumab high dose group had QTcF > 450 msec. Four patients (7%) in the Any secukinumab high dose group and 4 patients (9.8%) in the etanercept group had QTcF changes from baseline > 30 msec. One patient (2.4%) in the etanercept group had QTCF changes from baseline > 60 msec. These ECG abnormalities were not clinically significant.

Study A2311

Haematology

Only grade 1 or 2 haematological abnormalities were reported in any secukinumab dose group up to Week 24 with the most commonly reported being grade 1 decreased leukocyte count. There were no clinically meaningful differences in the newly occurring or worsening hematology abnormalities between the treatment groups.

Most subjects in both the treatment groups had haematology values within normal range at baseline and also at post-baseline up to Week 24. Of the few CTCAE categoryshifts reported, the most frequent was Normal at baseline to grade 1 as the most extreme post baseline in both treatment groups. Two subjects had shift from grade 1 to grade 2 (one each from Low dose (Leukopenia) and High dose group (neutropenia) up to Week 24.

Grade 2 neutropenia were reported in 4 subjects from Low dose and 4 subjects from High dose group. Of these 8 subjects, the grade 2 neutropenia in subject with moderate disease, grade 2 neutropenia in a subject enrolled in A2311 with severe disease, and grade 1 neutropenia in a subject enrolled in A2311 with moderate disease were reported as AEs.

All the subjects with grade 2 neutropenia continued study treatment and remained on trial except for subject a subject enrolled in A2311 who discontinued study treatment due to AE of haemorrhagic

diarrhoea. In six out of 8 subjects, the ANC values returned to normal by Week 24. For a subject enrolled in A2311, the ANC values returned to normal by Week 32 (3.57 10E9/L; normal range: 2.03 to 8.36 10E9/L) and in subject a subject enrolled in A2311, the grade 2 neutropenia persisted at Week 24.

Clinical chemistry

All newly occurring or worsening chemistry abnormalities are presented in Table 64. Majority of the chemistry abnormalities reported in any secukinumab dose group till Week 24 were of grade 1. Grade 1 ALT elevation was the commonly reported (6/74 subjects; 8.1%) chemistry abnormality up to Week 24 followed by grade 1 ALP and AST elevations.

The ALT and AST elevation in one subject from High dose group were reported as AEs that led to discontinuation of study treatment.

Grade 2 TBL elevation was reported in one subject from High dose group. Grade 2 increased eGFR was reported for one subject each in Low dose and High dose groups. Grade 2 GGT elevation was reported only in the Low dose group (2/42 subjects; 4.8%) (Table 64).

Most subjects in both the treatment groups had chemistry values within normal range at baseline and also at post-baseline up to Week 24. Of the few CTCAE category shifts reported, the most frequent was Normal at baseline to grade 1 or grade 2 as the most extreme post baseline in both treatment groups.

Post-baseline variations in the chemistry parameters were seen in both the treatment groups, with no meaningful treatment-specific or dose-related trends.

Table 64 ***Number (%) of patients with newly occurring or worsening after baseline abnormalities in*** *clinical chemistry parameters* ***- Data Up to Week 24 (Study A2311, Safety set)***

Variable	Criterion	CTCAE	AIN457 Low dose N=42 n/m	(%)	AIN457 High dose N=42 n/m	(%)	Any AIN457 dose N=84 n/m	(%)
Alanine Aminotransferase	> ULN - 3.0 x ULN	Grade 1	3/35	(8.6)	3/39	(7.7)	6/74	(8.1)
Alkaline Phosphatase	> ULN - 2.5 x ULN	Grade 1	3/38	(7.9)	3/39	(7.7)	6/77	(7.8)
Aspartate Aminotransferase	> ULN - 3.0 x ULN	Grade 1	3/41	(7.3)	2/39	(5.1)	5/80	(6.3)
Bilirubin	> ULN - 1.5 x ULN	Grade 1	1/38	(2.6)	3/41	(7.3)	4/79	(5.1)
	> 1.5 - 3.0 x ULN	Grade 2	0/39	(0.0)	1/41	(2.4)	1/80	(1.3)
Creatinine	> ULN - 1.5 x ULN	Grade 1	2/41	(4.9)	1/40	(2.5)	3/81	(3.7)
Gamma Glutamyl Transferase	> ULN - 2.5 x ULN	Grade 1	1/40	(2.5)	1/40	(2.5)	2/80	(2.5)
	> 2.5 - 5.0 x ULN	Grade 2	2/42	(4.8)	0/42	(0.0)	2/84	(2.4)
Glomerular Filtration Rate, Estimated	< 60 - 30 ml/min/1.73m2	Grade 2	1/41	(2.4)	1/41	(2.4)	2/82	(2.4)

ULN=upper limit of normal.
- n: number of subjects with most extreme value meeting the criterion post-baseline and that is newly occurring or worsening compare to baseline.
- m: number of subjects with evaluable criterion who were better than the criterion at baseline.
- A subject with multiple variable measurements is counted only once under the worst condition.

Vital signs and ECGs

The most commonly reported vital signs abnormality up to Week 24 was high pulse rate, which was reported with a slightly higher frequency in secukinumab Low dose (8/42 subjects; 19.0%) compared to the High dose (6/42 subjects; 14.3%) group. The second most common vital signs abnormality was diastolic BP (category: Low only) that was noted with a slightly higher frequency in High dose (8/41 subjects; 19.5%) compared to Low dose (4/42 subjects; 9.5%) group.

Post-baseline small variations in the vital signs parameters were seen in both the treatment groups, with no meaningful treatment-specific or dose related trends and none of them were reported as AEs.

Safety in special populations

Three cases of pregnancy were observed in the study. A 17-year (at randomisation) patient had an ectopic pregnancy, discontinued the study on Day 282, and proceeded to salpingectomy. A 16-year (at randomisation) patient discontinued the study on extension period on Day 540, and delivered a healthy child with initial jaundice. A 15 year (at randomisation) patient discontinued the study on Day 504 and underwent elective termination of the pregnancy.

Growth and development

The male and female paediatric patients enrolled in this study did not have any notable effect of the study treatment on their growth and development and most remained between 5th and 95th percentile of weight and height expected for age.

At Baseline, the majority of male and female patients in the Any secukinumab low dose group, Any secukinumab high dose group and etanercept group were pubertal (Tanner stage ≥ 2), see Figure 18. The Any secukinumab high dose group had a higher proportion of pre-pubertal (Tanner stage 1) male and female patients at Baseline compared to the Any secukinumab low dose group and the etanercept group.

By Week 52, majority of the evaluable male and female patients in all three treatment groups were pubertal (Tanner stage ≥ 2) except for approximately 20% pre-pubertal (Tanner stage 1) patients in the Any secukinumab high dose group which was not unexpected given higher percentage of pre-pubertal patients in this group at baseline. Except for males in Any secukinumab high dose group, the majority of patients had reached Tanner stage 4 or 5.

By Week 104, the majority of evaluable male and female patients in the Any secukinumab low dose group and the Any secukinumab high dose group had reached Tanner stage 5 (full sexual maturation).

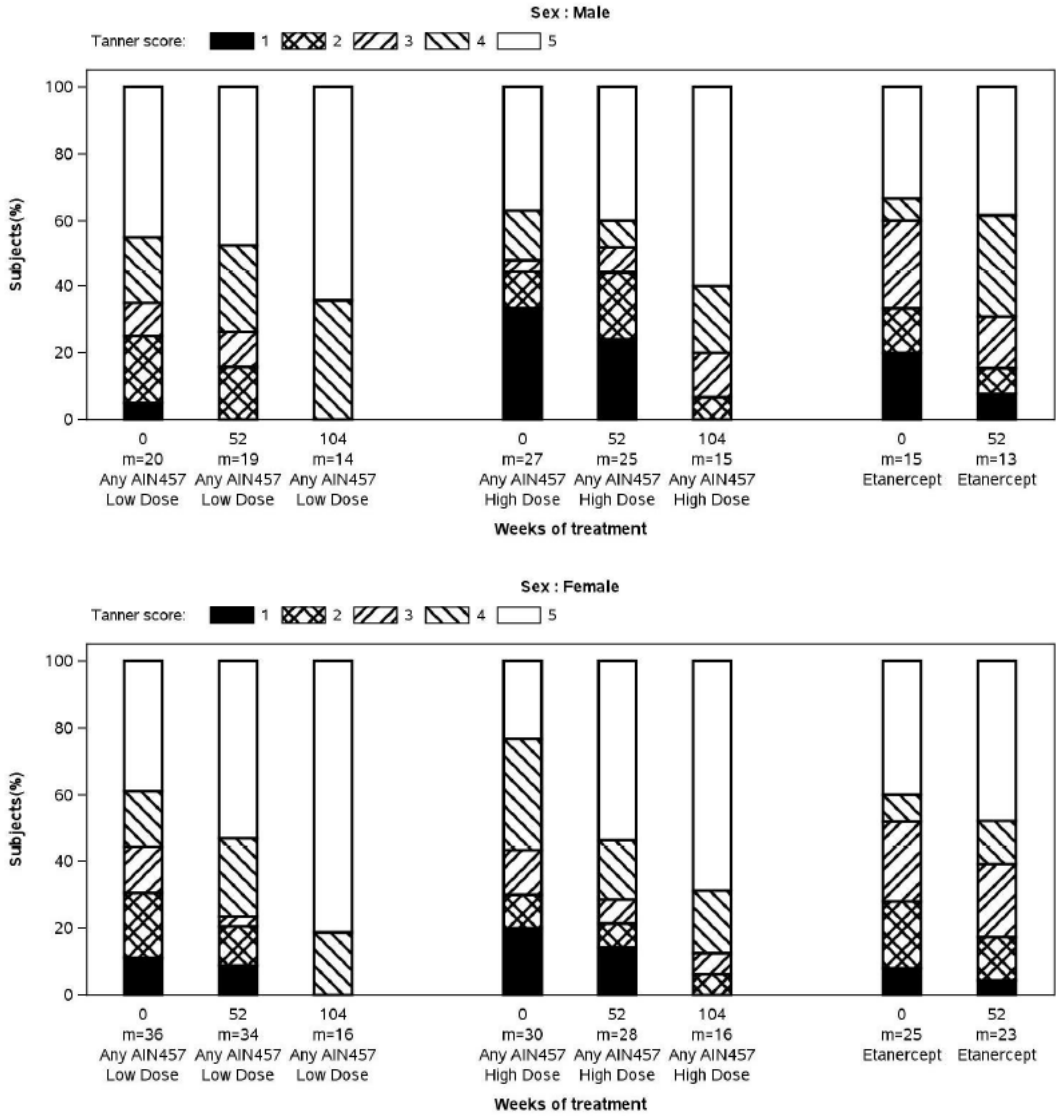


Figure 18 ***Changes in percentages of subjects in Tanner staging scores over time, by gender and treatment (Study A2310)***

Safety related to drug-drug interactions and other interactions

No new information. The concomitant medications used in Study A2310 are discussed above in Section "Patient exposure" of this AR.

Discontinuation due to adverse events

Study A2310 up to Week 52

The 4 patients reporting AEs leading to study treatment discontinuation up to Week 52 are described below:

- One Patient in the secukinumab low dose group had behavior disorder, major depression, mental disorder and suicidal ideation. Major depression and suicidal ideation were serious and suspected to be related to the study drug.
- One Patient in the secukinumab high dose group had toxic shock syndrome.
- One Patient in the placebo – secukinumab low dose group had arthritis reactive (SAE) suspected to be related to the study drug.
- One Patient in the etanercept group had hepatic enzyme increased suspected to be related the study drug.

Study A2310 entire treatment period

Exposure adjusted incidence rates (per 100 patient-years) for treatment emergent AEs leading to study treatment discontinuation for the Entire treatment period were slightly lower in the secukinumab treatment groups (1.8 in any low dose and 0.8 in any high dose) compared to the etanercept group (2.4).

Study A2311 up to week 24

Two subjects in the high dose secukinumab group discontinued treatment due to AEs, one due to ALT and AST elevations and the other due to hemorrhagic diarrhea. Both the AEs resolved and the subjects resumed study treatment.

Post marketing experience

Secukinumab is not approved for use in the paediatric population. Secukinumab is approved in more than 90 countries worldwide for the treatment of adult moderate to severe plaque psoriasis, ankylosing spondylitis, and psoriatic arthritis. In addition, secukinumab is being evaluated in other inflammatory conditions such as non-radiographic axial spondylarthritis, juvenile idiopathic arthritis, and hidradenitis suppurativa. As of 25-Dec-2018, a total of 17,942 patients and healthy volunteers received secukinumab treatment in Novartis sponsored investigational clinical trials. As of the same date, the secukinumab cumulative patient exposure since the International Birth Date (26-Dec-2014) is over 285,000 PY and secukinumab has been evaluated in more than 100 studies.

2.5.1. Discussion on clinical safety

Introduction

The presented paediatric safety data set presented in this application is comprised of patients enrolled in Studies A2310 and A2311. These were male and female, 6 to < 18 years (at the start of study

treatment), with moderate (Study A2311) or severe (Study A2310 and Study A2311) plaque psoriasis, a history of plaque psoriasis for at least 3 months and psoriasis that was poorly controlled by topical treatments and/or phototherapy and/or previous systemic therapy. These paediatric patients were candidates for systemic therapy.

The results from Study A2310 were analysed and presented in intervals of induction period with initial weekly injections of secukinumab up to week 12, where the safety findings could be compared from all groups receiving placebo, low dose of secukinumab, high dose of secukinumab, or etanercept; up to week 24 until which the patients on placebo were switched to secukinumab with initial weekly injections; up to week 52, where treatment with etanercept stops, and the entire study period including also the secukinumab patients in the extension phase.

Further safety information was provided from Study A2311 interim analysis up to week 24.

In the paediatric population in Study 2310, the mean age was 13.5 years and the mean weight 53 kg. There were 17 patients aged 6 to <12 years and 63 patients aged 12 to <18 years receiving initially secukinumab. There were only 8 patients weighing less than 25 kg, 32 patients weighing 25 to <50 kg, and 43 patients weighing over 50 kg receiving initially secukinumab. All with severe presentation of psoriasis.

A dosing error involved 36 patients in the low and high dose secukinumab groups, resulting in extra up titration doses of active medication instead of placebo on weeks 13, 14, and 15, took place. The effect of this error on the safety findings was separately evaluated.

In the paediatric population in Study 2311, the mean age was 12.5 years and the mean weight 55 kg. There were altogether 33 patients aged 6 to <12 years and 51 patients aged 12 to <18 years. There were only 8 patients weighing less than 25 kg, 25 patients weighing 25 to <50 kg, and 51 patients weighing over 50 kg. 69% of the patients had moderate psoriasis and 31% severe psoriasis.

Adherence to the study protocol and treatments was good as evidenced by low number of drop-outs from both of the studies. In Study A2310 93% of the patients receiving secukinumab either low or high dose, entered the extension period beyond week 52. In Study A2311, 98.9% of the patients carried on at week 16 interim analysis point and also further to 24 week analysis point.

Concomitant medications during the study included paracetamol, ibuprofen, and some antibiotics. Locally applied emollients were also used. No new drug interactions were reported. There were single cases of patients in Study A2310 reported using also topical betamethasone (one in low dose group) or topical hydrocortisone (one in low dose group and one in high dose group). This seemed to be a minor deviation and not significantly alter the efficacy or safety interpretations.

Adverse events

At 52 weeks, the TEAEs in the paediatric patients vs. adult patients with moderate or severe psoriasis slightly increased incidences were observed in SOCs infections and infestations (61.4% vs. 57.7% vs. 49.6%), skin and subcutaneous tissue disorders (24.6% vs. 21.6% vs. 21.1%), gastrointestinal disorders (26.3% vs. 21.9% vs. 21.0%), general disorders and administration site conditions (18.4% vs. 15.1% vs. 13.1%), blood and lymphatic disorders (7.9% vs. 4.7% vs. 3.8%), and reproductive system, and breast disorders (7.9% vs. 2.9% vs. 3.4%).

From preferred terms, nasopharyngitis, headache, cough, pharyngitis, pyrexia, rhinitis, fatigue, abdominal pain, gastroenteritis, tonsillitis, eczema, vomiting, acne, and dysmenorrhoea were slightly more common in the paediatric population compared to adults.

During the induction period in Study A2310, infections and infestations were equally common in both secukinumab groups and placebo group, 32.5% low doses, 37.5% high doses, 39.0% placebo, but

somewhat lower in the etanercept group 26.8%. The gastrointestinal disorders were the second most common AEs being more common in the etanercept group, in 15.0%, 17.5%, 14.6%, and 24.4%, respectively. Skin and subcutaneous disorders were more frequent in the secukinumab group, in 12.5%, 7.5%, 7.3% and 2.4%, respectively.

Nasopharyngitis and pharyngitis were the most common infections in all study groups in Study A2310. Gastrointestinal symptoms in the etanercept group consisted of abdominal pain and nausea. Both in the secukinumab and etanercept groups two AST elevations were reported in each - refer below to "Laboratory findings". Most other adverse events as preferred term were present in single or double occurrences only. The overall tolerability of secukinumab was not worse compared to etanercept, judged from the TEAE incidences.

Number of patients <12 years of age was low (37) compared to older patients (137). Further, this young population was subdivided into four treatment groups (8 low doses, 9 high doses, 10 placebo, and 10 etanercept) which makes the number of observations very small. However, no clinically meaningful differential trends in the incidence of infections could be observed between the age groups.

The same applied to the safety findings by the weight strata, as the number of patients in the group <25 kg was equally low (2, 3, 3, and 4 respectively).

The effect of secukinumab exposure by percentiles (<25, 25 to <50, 50 to <75, and 75 to 100) up to week 12 implied to a dose dependence in some extent regarding the overall incidence of AEs, infections and infestations, and gastrointestinal AEs. From a safety perspective, the lowest efficacious dose would be preferential for the paediatric psoriasis patients. In Week 52 data, some incremental efficacy with the higher 300 mg dose could be observed in the ≥50 kg weight stratum. In contrast, long-term response rates in the ≥25-<50 kg weight stratum were higher with the 75 mg dose than the 150 mg dose. The MAH proposed SmPC posology wording to indicate that the recommended dose can be increased from 150 to 300 mg within weight stratum ≥50 kg and that some patients may derive additional benefit from a higher dose was endorsed by the CHMP. However, at the CHMP request, the MAH removed this recommendation for the 25-50 kg weight stratum from the SmPC. See also discussions on clinical efficacy (Section 2.4.3).

Observation of the patient groups by disease severity (moderate or severe), age group (6 to <12 or 12 to <18 years) or weight (<25, 25 to <50, or ≥50 kg) did not reveal remarkable differences in the AE profiles.

The most common AEs during the entire treatment period in Study A2310 were nasopharyngitis, headache and pharyngitis. The Exposure adjusted incidence rates of tonsillitis, diarrhoea, and rhinitis were higher in the secukinumab dose groups compared to the etanercept group, while the EAIRs of abdominal pain, abdominal pain upper and oral herpes were higher in the etanercept group.

Higher dose induced more treatment emergent adverse events possibly related to study medication (41.4% vs 28.6%) in Study A2310. In Study A2311 the incidence of TEAEs were comparable in secukinumab low dose group (28/42; 59.5%) and secukinumab high dose group (25/42; 60.0%).

No significant differences could be pointed out between the different weight strata, age groups, or dose levels regarding Study A2311. When comparing the paediatric psoriasis patient findings with adult moderate or severe psoriasis patients, slightly increased incidences of TEAEs in the SOCs of infections and infestations (35.0% vs 30.0% vs. 26.9%), gastrointestinal disorders (16.3% vs. 12.1% vs. 11.5%), general disorders and administration site conditions (11.3% vs 6.5% vs. 6.7%), and investigations (5.0% vs. 2.5% vs. 1.8%) were observed. Looking at the most common preferred terms, the incidences of nasopharyngitis (16.3% vs. 12.0% vs. 11.3%), abdominal pain (7.5% vs. 1.4% vs. 1.0%) were

observed. These differences did not seem clinically significant to CHMP. It was also observed, that the TEAE profile in adult patients was similar in both moderate and severe psoriasis groups.

Deaths and serious adverse events

During induction period in Study A2310, two SAEs were reported from secukinumab group: ALT increased in the low dose group (due to viral gastroenteritis, no suspected causality, continued in study), and toxic shock syndrome (MRSA infection in the right calf, no suspected causality, discontinued the study) in the high dose group.

Until week 24, two more SAEs were reported from secukinumab group: bronchitis in the low dose group (erroneous extra doses during weeks 13, 14, and 15, treated with amoxicillin, suspected causality, continued in study), and lymphadenopathy (due to skin infection treated with cephalexin and trimethoprim, suspected causality, temporary dosing cessation, continued in study) in the high dose group.

From etanercept group four SAEs emerged: autoimmune pancreatitis (no suspected causality, discontinued the study), gallbladder polyp (previously diagnosed, gallbladder ectomy, no suspected causality, continued the study), GI toxicity ("poisoning", no further information, no suspected causality, continued the study), and syncope (during physical education class, no suspected causality, continued the study). Up to week 24 one episode of abdominal pain was reported as SAE.

Further, one patient in placebo to low dose group had reactive arthritis and worsening of psoriasis (suspected causality to reactive arthritis but not to worsening of psoriasis, discontinued the study), and one patient in placebo to high dose group experienced pneumonia and thrombophlebitis (co-existing morbidity including immunodeficiency, history of pneumonia and thrombophlebitis, atrial septal defect, etc., no suspected causality, continued in study) as SAEs.

There were no distinctive differences in the SAE profiles in Study A2310 attributable to dose level of secukinumab. But the EAIRs of SAEs in patients aged <12 years compared to ≥12 years were: 7.6 vs. 4.3 in the secukinumab low dose group, 19.0 vs. 4.0 in the secukinumab high dose group. Analysis of the TEAE and SAE profiles by age, weight, or dose groups did not reveal any safety concerns in any of the groups, even in those weighing less than 25 kg.

Hypersensitivity reactions were reported from several secukinumab patients but the specific manifestations were single occurrences. Treatment emergent anti-drug antibodies were observed in one secukinumab low dose patient on week 12 and there was no associated AE or loss of efficacy. Neutropenia is discussed below under "Laboratory findings". There were no malignancies, MACEs, or hepatitis B reactivations in patients receiving secukinumab. One case of IBD was reported from Study A2311. One case of suicidal ideation in Study A2310 has been discussed thoroughly by the MAH and did not awake concern of causality to the CHMP.

Cautionary language is already included in section 4.4 of the SmPC of Cosentyx relating to the risk of inflammatory bowel disease (IBD). Exclusion criteria number 10 of trial CAIN457A2310 addresses active ongoing inflammatory diseases other than psoriasis that might confound the evaluation of the benefit of secukinumab and/or etanercept therapy. Therefore, the CHMP understood that no patient with active ongoing IBD were allowed entering the trial. It is noted that although there were reported cases of abdominal pain and diarrhoea, no specific diagnosis of IBD was registered during the trial CAIN457A2310. The MAH has evaluated these cases and there were no verified cases of IBD in Study A2310.

Laboratory findings

During induction period in Study A2310, one patient receiving secukinumab and one patient receiving etanercept had neutropenia < 1.5 x 10E9/L. One secukinumab patient had Grade 3 AST elevation and one etanercept patient Grade 3 GGT elevation. ALT or AST elevations > 3x ULN were seen in two secukinumab low dose patients. One patient had ALT and AST elevations > 5x ULN - due to Gilbert´s syndrome.

Up to week 24, one patient in secukinumab low dose had a reversible Grade 3 neutropenia due to viral infection. Several other ALT, AST, ALP, and TBL elevations were observed, but none of them met Hy´s law criteria. In the entire duration of Study A2310 only two patients secukinumab had reversible Grade 3 neutropenias. During rest of the study there were only single cases of transient Grade 3 abnormalities in all of the study groups. Up until 52 weeks, one patient (2.6%) in the secukinumab high dose group had QTcF changes from baseline > 450 msec.

In study A2311 haematology, clinical chemistry, and ECG abnormalities were rare. Analysis of the laboratory and vital sign findings by age, weight, or dose groups did not reveal any safety concerns in any of the groups, even in those weighing less than 25 kg.

Other issues

There were no patients with hepatic or renal insufficiency in the study population. Secukinumab has not been studied either in adult populations with hepatic or renal insufficiency. The SmPC is up to date in this respect.

Three cases of pregnancies imply to a breach of the exclusion criteria of the study. However, this issue was not pursued further by the CHMP.

There were no apparent effects on the growth and development of the populations in either of the studies.

No new information arises from Study 2310 concerning the drug interactions.

2.5.2. Conclusions on clinical safety

Over 17,900 patients have been treated with secukinumab in blinded and open-label clinical studies in various indications (plaque psoriasis, psoriatic arthritis, ankylosing spondylitis and other autoimmune conditions), representing 29,978 PY of exposure. Of these, over 11,700 patients were exposed to secukinumab for at least one year. The safety profile of secukinumab is consistent across all indications. The most frequently reported adverse drug reactions (ADRs) are upper respiratory tract infections (most frequently nasopharyngitis, rhinitis). No new ADRs were identified in the paediatric patients other than those seen in the adults.

In the paediatric populations, the mean age was 13.5 years, mean weight 53 kg, and there was a female predominance in Study A2310. In study A2311, the mean age was 12.5 years and the mean weight 55 kg. There were 16 patients weighing less than 25 kg in both studies altogether. There were no patients with moderate plaque psoriasis in the presented paediatric population in Study A2310. In Study A2311 69% of the patients had moderate psoriasis and 31% severe psoriasis.

In general, the AE profiles observed in studies A2310 and A2311 do not reveal new safety concerns. Secukinumab in the studied paediatric population appeared equally well tolerated as in adult psoriatic patients. No clinically significant differences regarding safety were observed between the low and high dose groups in either of the studies. Compared to etanercept, the tolerability was not worse either.

Based on the data from Studies A2310 and A2311 the CHMP concluded, that there seems to be no specific safety concerns preventing treatment of patients 6 years of age or older, weighing less than 25

kg, with moderate or severe plaque psoriasis, with secukinumab. Consequently, the wording of the indication, as originally proposed by the MAH, was considered supported from a safety perspective.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 6.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 6.1 with the following content:

Safety concerns

Important identified risks	Infections and infestations Neutropenia Hypersensitivity
Important potential risks	Malignant or unspecified tumors Major Adverse Cardiovascular Events (MACE) Inflammatory bowel disease Hepatitis B reactivation Suicidal ideation and behavior Interaction with live vaccines
Missing information	Fetal exposure in utero Long-term safety data Long-term efficacy data Patients with severe hepatic impairment Patients with severe renal impairment Patients with severe cardiac disease or uncontrolled hypertension

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances.				
Category 3 - Required additional pharmacovigilance activities.				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Corrona Psoriasis Registry Ongoing	The primary goal of the registry is to assess the incidence and nature of malignancies in a real-world population of moderate-to-severe psoriasis patients (including PsA patients) on secukinumab therapy.	Malignant or unspecified tumors Long-term safety, Suicidal ideation and behavior	Final study report submission	June-2033

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important Identified Risks		
Infections and infestations	**Routine risk minimization measures** SmPC Section 4.3, 4.4, 4.8 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Neutropenia	**Routine risk minimization measures** SmPC Section 4.8 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Hypersensitivity	**Routine risk minimization measures** SmPC Section 4.3, 4.4, 4.8 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Important Potential Risks		
Malignant or unspecified tumors	**Routine risk minimization measures** None **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Registry to assess incidence and nature of malignancies in a real-world population of moderate-to-severe psoriasis patients (including PsA patients) on secukinumab therapy; estimated sample size 3000, follow up period of 8 years

Safety concern	Risk minimization measures	Pharmacovigilance activities
Major Adverse Cardiovascular Events (MACE)	**Routine risk minimization measures** None **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Inflammatory bowel disease	**Routine risk minimization measures** SmPC Section 4.4 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Hepatitis B reactivation	**Routine risk minimization measures** None **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Suicidal ideation and behavior	**Routine risk minimization measures** None **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Registry to assess incidence and nature of malignancies in a real-world population of moderate-to severe psoriasis patients (including PsA) on secukinumab therapy will also be utilized to assess long-term safety, including SIB; estimated sample size 3000, follow up period of 8 years.
Interaction with live vaccines	**Routine risk minimization measures** SmPC Section 4.4 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Missing Information		
Fetal exposure in utero	**Routine risk minimization measures** SmPC 4.6 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Long-term safety data	**Routine risk minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	None proposed **Additional risk minimization measures** None	None **Additional pharmacovigilance activities:** Registry to assess incidence and nature of malignancies in a real-world population of moderate-to-severe psoriasis patients (including PsA patients) on secukinumab therapy; estimated sample size 3000, follow up period of 8 years.
Long-term efficacy data	**Routine risk minimization measures** None proposed **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Patients with severe hepatic impairment	**Routine risk minimization measures** None **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Patients with severe renal impairment	**Routine risk minimization measures** None **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Patients with severe cardiac disease or uncontrolled hypertension	**Routine risk minimization measures** None proposed **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 5.3 of the SmPC are updated. Section 6.6 of the SmPC for the solution for injection is also updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI (Annex II) to bring it in line with the current QRD template version 10.1, which were reviewed and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of the Netherlands.

Section 4.4 of the SmPC was updated to indicate that, prior to initiating therapy with Cosentyx, it is recommended that paediatric patients receive all age-appropriate immunisations as per current immunisation guidelines. This change was endorsed by the CHMP.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Psoriasis is a multifactorial skin disorder, caused by the combined action of multiple disease genes, and is also triggered by environmental factors. T-cells are clearly involved, as psoriasis responds to treatment with calcineurin inhibitors, which inhibit T-cell activity (e.g., cyclosporine, tacrolimus). Successful psoriasis therapy correlates with inhibition of IL-17 signalling and is seen, e.g., after IL-17A blockade with secukinumab, and it can therefore be concluded that IL-17A contributes to the disease process.

Psoriasis is one of the most common human skin diseases affecting 2 to 3% of the general population. Plaque psoriasis affects 80% to 90% of all psoriasis patients of all age groups and is also the most common variant of the disease in paediatric patients. Most children manifest with plaque psoriasis in patterns similar to adult patients, and it is accepted that paediatric and adult psoriasis represent manifestations of the same disease process, as opposed to being distinct disease entities.

Disease prevalence in children varies depending on study population and age, with 1% as a commonly quoted figure. Worldwide, the incidence of paediatric psoriasis is increasing, affecting up to 2% of children in some populations. In Europe, psoriasis is reported to affect 0.5-1% of children, and chronic plaque psoriasis is also common among adolescents.

3.1.2. Available therapies and unmet medical need

Topical treatments are the mainstay of therapeutic approaches in paediatric psoriasis, and a significant proportion of patients can be adequately treated with topical therapies such as emollients, vitamin D analogues, corticosteroids or calcineurin inhibitors. Various forms of phototherapy are also successfully used in many patients. Available systemic treatments include methotrexate, cyclosporine and retinoids. It should however be recognised that many of these products have no formal authorisation for use in paediatric psoriasis and can be associated with significant safety concerns. In this respect, and apart from the better studied biological agents, paediatric psoriasis patients can still be considered a significantly underserved patient population.

Three biological agents are currently authorised in the EU for the treatment of plaque psoriasis in the paediatric population: etanercept (authorised in 2009), adalimumab (authorised in 2015), and ustekinumab (authorised in 2015). Etanercept is currently authorised for severe disease from 6 years of age; adalimumab is authorised for severe disease from 4 years of age, and ustekinumab is authorised for moderate to severe disease from 6 years of age. All three products are authorised as second-line therapies, for use in patients who are inadequately controlled by or are intolerant to other systemic therapies or phototherapies (the exact wording varies slightly by individual product).

On 28 May 2020, the CHMP adopted a positive opinion for the following new indication for Taltz (ixekizumab) another medicinal product targeting IL-17: "Paediatric plaque psoriasis: Taltz is indicated for the treatment of moderate to severe plaque psoriasis in children from the age of 6 years and with a body weight of at least 25 kg and adolescents who are candidates for systemic therapy."

3.1.3. Main clinical studies

The main studies within the submission are:

- Study A2310, an ongoing randomised, double-blind, placebo- and etanercept -controlled study in paediatric patients 6-17 years of age with severe plaque psoriasis. An interim study report, containing efficacy data until Week 52 as well as summaries of safety data over various periods of time in study, including a summary of all safety data until data cut-off, has been provided.

- Study A2311, an ongoing randomised, open-label study with a historical placebo control in paediatric patients 6-17 years of age with moderate to severe plaque psoriasis. An interim study report, containing efficacy data until Week 24 and a summary of all safety data until last data cut-off has been provided.

Study A2310, evaluating treatment of severe plaque psoriasis in children and adolescents over 6 years of age with low or high dose of secukinumab and comparator etanercept has progressed to 52 week cut-off with all enrolled patients. Patients have continued in the extension, open phase until up to week 236. Secukinumab was administered at two dose levels and the dose is further adjusted by the weight of the patients (< 25 kg, 25 - < 50 kg, and ≥ 50 kg). It is to be noted, that there were no patients with moderate plaque psoriasis in this study population.

Study A2311 involved also subjects with moderate psoriasis and evaluated the efficacy and safety of two dose levels of secukinumab in similar weight groups as above.

Pooled safety results from the studies of secukinumab in treatment of moderate to severe plaque psoriasis in adult patients ≥ 18 years of age (Studies A2302, A2303, A2308, and A2309) were used for comparison. Presenting the adult data separately for "moderate" and "severe" adult patients enabled comparison for "severe" paediatric patients, and helps in extrapolation of the safety conclusions from "severe" paediatric patients to "moderate" paediatric patients.

The results from the adult studies were compared with the results from the induction period up to 12 weeks, and from the start of medication up to 52 weeks.

3.2. Favourable effects

Secukimab PK has been studied with population pharmacokinetic methodology and the appropriateness of the paediatric doses has been evaluated. The modelling steps have been appropriately conducted.

The MAH has conducted a statistical extrapolation of efficacy from moderately psoriatic adults to moderately psoriatic children which was considered acceptable by the CHMP.

The main favourable effects in study A2310 are as follows:

At Week 12 (time point for primary analysis), both secukinumab dose levels (Low and High) were superior to placebo with respect to the co-primary endpoints of PASI 75 response and IGA 0/1 response as well as the key secondary endpoint of PASI 90 response ($p<0.0001$ for all comparisons).

In the primary statistical analyses, performed using multiple imputation for missing data, a PASI 75 response at Week 12 was achieved by 80.1% of patients in the secukinumab Low dose group and

80.2% of patients in the secukinumab High dose group compared with 14.9% of patients in the placebo group. Similarly, at Week 12, an IGA mod 2011 0 or 1 response was achieved by 69.8% of patients in the secukinumab Low dose group and 62.6% of patients in the secukinumab High dose group compared with 6.3% of patients in the placebo group.

In the multiple imputation dataset, a PASI 90 response at Week 12 was achieved by 71.1% of patients in the secukinumab Low dose group and 69.3% of patients in the secukinumab High dose group compared with 2.5% of patients in the placebo group.

In the etanercept group, a PASI 75 response was achieved by 65.7% of patients, an IGA mod 2011 0 or 1 response by 36.3% of patients, and a PASI 90 response by 31.4% of patients. Statistical comparisons between etanercept and secukinumab were not part of the formal testing strategy.

Among other endpoints at Week 12, the proportions of patients achieving a CDLQI 0 or 1 response (indicating no or little impairment) were 44.7% in the secukinumab Low dose group and 50% in the High dose group, compared with 36.6% in the etanercept group and 15% in the placebo group.

Depending on the endpoint, responses in both secukinumab groups were detected from Week 2 to Week 4 onward, with further increases observed until Week 12.

Maintenance of effect until Week 52 was demonstrated supporting a long-term indication.

Results up to Week 24 in study A2311 were consistent with study A2310 supporting efficacy in patients with disease of moderate severity.

3.3. Uncertainties and limitations about favourable effects

Although the limited dataset in patients under 25 kg in body weight is recognised, together, studies A2310 and A2311 provide efficacy and safety data from 58 patients <12 years receiving at least a single dose of secukinumab, and 16 patients <25 kg receiving at least a single dose of secukinumab. Total exposure to secukinumab was reported as 35.02 patient-years in patients <12 years and 13.2 patient-years in patients weighing <25 kg. The CHMP considered that sufficient data was available for patients under 25 kg in body weight and that no weight restriction below 25 kg was deemed necessary in the indication.

3.4. Unfavourable effects

In general, the AE and SAE profiles observed in Study A2310 do not reveal new safety concerns. Secukinumab appears equally well tolerated as in adult psoriatic patients and not less tolerable than the comparator etanercept.

The effect of secukinumab exposure by percentiles (<25, 25 to <50, 50 to <75, and 75 to 100) up to week 12 implied to a dose dependence in some extent regarding the overall incidence of AEs, infections and infestations, and gastrointestinal AEs. In Week 52 data, some incremental efficacy with the higher 300 mg dose could be observed in the ≥50 kg weight stratum. Hence, the MAH proposed SmPC posology wording to indicate that the recommended dose can be increased from 150 to 300 mg within weight stratum ≥50 kg and that some patients may derive additional benefit from a higher dose was endorsed by the CHMP. In contrast, long-term response rates in the ≥25-<50 kg weight stratum were higher with the 75 mg dose than the 150 mg dose. Hence, at the CHMP request, the MAH removed this recommendation for the 25-50 kg weight stratum from the SmPC.

At 52 weeks, the TEAEs in the paediatric patients vs. adult patients with moderate or severe psoriasis slightly increased incidences were observed in SOCs infections and infestations (61.4% vs. 57.7% vs.

49.6%), skin and subcutaneous tissue disorders (24.6% vs. 21.6% vs. 21.1%), gastrointestinal disorders (26.3% vs. 21.9% vs. 21.0%), general disorders and administration site conditions (18.4% vs. 15.1% vs. 13.1%), blood and lymphatic disorders (7.9% vs. 4.7% vs. 3.8%), and reproductive system, and breast disorders (7.9% vs. 2.9% vs. 3.4%). From preferred terms, nasopharyngitis, headache, cough, pharyngitis, pyrexia, rhinitis, fatigue, abdominal pain, gastroenteritis, tonsillitis, eczema, vomiting, acne, and dysmenorrhoea were slightly more common in the paediatric population compared to adults. These differences did not seem clinically significant to CHMP.

It was also observed, that the TEAE profile in adult patients was similar in both moderate and severe psoriasis groups.

In conclusion, the safety profile in paediatric patients is largely consistent with extensive experience gained in adult patients.

3.5. Uncertainties and limitations about unfavourable effects

The current experience in children under 12 years of age as well as children weighing under 25 kg remains limited. Long-term experience is mostly available from study A2310, in which 15 children in the age cohort 6-<12 years, and 5 children weighing under 25 kg had been exposed for 52 weeks or more at the time of data cut-off. However, based on the data from Studies A2310 and A2311 the CHMP concluded, that there seem to be no specific safety concerns preventing treatment of patients 6 years of age or older, weighing less than 25 kg, with moderate or severe plaque psoriasis, with secukinumab.

3.6. Effects Table

Table 65 ***Effects Table for secukinumab in the treatment of severe plaque psoriasis in paediatric patients (data cut-off: 07 March 2019)***

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PASI 75 Wk 12	% patients with PASI 75 response at Week 12, low dose vs placebo	%	80.1%	14.9%	p<.0001	Study A2310
PASI 75 Wk 12	% patients with PASI 75 response at Week 12, High dose vs placebo	%	80.2%	14.9%	p<.0001	Study A2310
IGA 0/1 Wk 12	% patients with IGA 0/1 response at Week 12, Low dose vs placebo	%	69.8%	6.3%	p<.0001	Study A2310
IGA 0/1 Wk 12	% patients with IGA 0/1 response at Week 12, High dose vs placebo	%	62.6%	6.3%	p<.0001	Study A2310
PASI 90 Wk 12	% patients with PASI 90 response at Week 12, Low dose vs placebo	%	71.1%	2.5%	p<.0001	Study A2310
PASI 90 Wk	% patients with	%	69.3%	2.5%	p<.0001	Study

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
12	PASI 90 response at Week 12, High dose vs placebo					A2310
Unfavourable Effects						
AE rate Wk 12	% patients with AE, Low dose vs placebo	%	57.5%	53.7%		Study A2310
AE rate Wk 12	% patients with AE,High dose vs placebo	%	62.5%	53.7%		Study A2310
AE rate long-term	Incidence rate - all secukinumab exposure	Incident events/ 100 PY	Low dose: 233.1 / 100 PY; High dose: 194.5 / 100 PY			Study A2310
SAE rate Wk 12	% patients with SAE, Low dose vs placebo	%	2.5%	0%		Study A2310
SAE rate Wk 12	% patients with SAE, High dose vs placebo	%	2.5%	0%		Study A2310
SAE rate long-term	Incidence rate - all secukinumab exposure	Incident events/ 100 PY	Low dose: 4.9 / 100 PY; High dose: 5.7 / 100 PY			Study A2310

Abbreviations: AE: Adverse Event; IGA: Investigator's Global Assessment; PASI: Psoriasis Area and Severity Index; PY: Patient Years; SAE: Serious Adverse Event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Secukimab PK has been studied with population pharmacokinetic methodology and the appropriateness of the paediatric doses has been evaluated. The MAH has conducted a statistical extrapolation of efficacy from moderately psoriatic adults to moderately psoriatic children which was considered acceptable by the CHMP.

Based on the co-primary and key secondary efficacy endpoints, secukinumab has statistically significant and clinically relevant efficacy in the treatment of severe chronic plaque psoriasis among paediatric patients. Maintenance of effect until Week 52 was demonstrated supporting a long-term indication. Favourable efficacy against an already authorised active comparator was also seen, although formal statistical comparisons against the active comparator were not undertaken. Results up to Week 24 in study A2311 were consistent with study A2310 supporting efficacy in patients with disease of moderate severity.

The general safety profile observed is largely consistent with previous experience in adult patients.

Overall, it can be concluded that secukinumab could be a valuable alternative for the treatment of moderate to severe paediatric plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy.

3.7.2. Balance of benefits and risks

Overall, the reported studies provide adequate evidence of efficacy of secukinumab in the treatment of moderate to severe paediatric plaque psoriasis, and response rates with the studied dosages match or even exceed those previously reported among adult patients. The safety profile is largely consistent with extensive experience gained in adult patients. A favourable overall profile has been demonstrated among patients over 6 years of age and weighing less than 25 kg.

3.7.3. Additional considerations on the benefit-risk balance

The MAH has proposed an essentially first-line systemic indication for secukinumab in paediatric psoriasis, with wording matching the already authorised adult indication. Whereas all currently authorised biological therapies for paediatric psoriasis still carry indications consistent with second-line therapy, it is recognised that first-line indications are currently being increasingly accepted and have been consistently authorised for recent approvals in the adult population. Taking into account the favourable experience gained in the adult population to date and the data submitted as part of this application, the CHMP considered that this wording is also acceptable for the paediatric population.

3.8. Conclusions

The overall B/R of Cosentyx in the following indication is positive:

Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 5.3 of the SmPC are updated. Section 6.6 of the SmPC for the solution for injection is also updated.
The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Netherlands in the Package Leaflet. The RMP was updated to version 6.1.
Furthermore, the Annex II is brought in line with the latest QRD template version 10.1.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0352/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion "Cosentyx EMEA/H/C/003729/II/0057"