22 October 2015
EMA/CHMP/665427/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cosentyx

International non-proprietary name: SECUKINUMAB

Procedure No. EMEA/H/C/003729/II/0001/G

Note

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

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List of abbreviations

ACR	American College of Rheumatology
ADA	Anti-drug antibodies
ADR	Adverse drug reaction
AE	Adverse event
AI	Autoinjector /pen
AIN457	Secukinumab
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AS	Ankylosing spondylitis
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_{inf}	Area under the curve from time 0 to infinity
AUC_{last}	Area under the curve from time 0 to last measurable timepoint
AUC_{tau}	Area under the curve between time interval
BSA	Body surface area
CASPAR	Classification criteria for psoriatic arthritis
C_{avg}	Average concentration
CHD	Coronary heart disease
CL	Clearance
C_{max}	Maximum concentration
$C_{max,ss}$	Maximum concentration at steady-state
$C_{min,ss}$	Minimum concentration at steady-state
CRP	C-reactive protein
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
CYP	Cytochrome
DAS28	Disease activity score
DAS28-CRP	Disease activity score - C-reactive protein
DAS28-ESR	Disease activity score - erythrocyte sedimentation rate
DDI	Drug-drug interaction
DLQI	Dermatology life quality index
DMARD	Disease modifying anti-rheumatic drug
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European Union
EULAR-CRP	European league against rheumatism - C-reactive protein
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good clinical practice
GI	Gastrointestinal
HAQ-DI	Health assessment questionnaire – disability index
hsCRP	High sensitivity C-reactive protein
HLT	High level term
IBD	Inflammatory bowel disease
IGA mod 2011	Investigator's global assessment modified 2011
IL-17	Interleukin 17
IR	Incidence rate
iv	Intravenous
LoQ	List of questions
LYO	Lyophilisate
MACE	Major adverse cardiovascular event
MedDRA	Medical dictionary for regulatory activities
MCID	Minimum clinically important difference
MTX	Methotrexate
NMQ	Novartis MedDRA Query
NSAID	Non-steroidal anti-inflammatory drug
PASI	Psoriasis area and severity index
PCS	Physical component summary

PFS	Pre-filled syringe
PD	Pharmacodynamic
PK	Pharmacokinetic
PoC	Proof of concept
PPK	Population pharmacokinetic
PsA	Psoriatic arthritis
PT	Preferred term
q4w	Once every 4 weeks
RA	Rheumatoid arthritis
RMP	Risk management plan
SAE	Serious adverse event
sc	Subcutaneous
SCE	Summary of clinical efficacy
SCP	Summary of clinical pharmacology
SCS	Summary of clinical safety
SD	Standard deviation
SF-36	Medical outcome short form (36) health survey
SmPC	Summary of product characteristics
SMQ	Standardized MedDRA Query
SOC	System organ class
t_{max}	Time to maximum concentration
$t_{1/2}$	Terminal half-life
TNFα	Tumour necrosis factor alpha
TNFα-IR	TNFα inhibitor inadequate responder
ULN	Upper limit of normal
URTI	Upper respiratory tract infections
US	United States
vdH-mTSS	van der Heijde-modified Total Sharp Score
VPC	Visual predictive check
V_z	Volume of distribution during terminal phase
WPAI-GH	Work productivity and activity impairment – general health

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 6 March 2015 an application for a group of variations.

The following variations were requested in the group:

Variations 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 and IIIB
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None

Extension of Indication to include new indication for Cosentyx in the treatment of active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate as monotherapy or in combination with methotrexate (MTX); as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 of the SmPC are updated in order to update the safety and efficacy information. The Package Leaflet is updated in accordance. Furthermore, minor editorial changes have been introduced throughout the PI and updated RMP has been also submitted. In addition, the MAH proposed to update the due date of the Psoriasis registry in the RMP (category 3 study).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0247/2014 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP EMEA-000380-PIP02-09-M02 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 applicant 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.

MAH request for additional one year marketing protection

With this application, the MAH requested an additional one year marketing protection in accordance with Article 14(11) of Regulation (EC) No 726/2004. In view of a positive opinion on an additional year of marketing protection granted for the parallel extension of indication procedure

(EMEA/H/C/0003729/II/02) the MAH withdrew the request.

Scientific advice

The applicant 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 and the evaluation teams were:

Rapporteur: Tuomo Lapveteläinen Co-Rapporteur: Kristina Dunder

Timetable	Actual dates
Submission date	6 March 2015
Start of procedure:	28 March 2015
CHMP Rapporteur Assessment Report	26 May 2015
CHMP Co-Rapporteur Assessment Report	26 May 2015
PRAC Rapporteur Assessment Report	26 May 2015
PRAC members comments	4 June 2015
PRAC Outcome	11 June 2015
Updated PRAC Rapporteur Assessment Report	16 June 2015
CHMP members comments	15 June 2015
Updated CHMP Rapporteur Assessment Report	18 June 2015
Request for supplementary information (RSI)	25 June 2015
CHMP Rapporteur Assessment Report	28 September 2015
PRAC Rapporteur Assessment Report	28 September 2015
PRAC members comments	30 September 2015
Updated PRAC Rapporteur Assessment Report	2 October 2015
PRAC Outcome	8 October 2015
CHMP members comments	12 October 2015
Updated CHMP Rapporteur Assessment Report	16 October 2015
Opinion	22 October 2015

2. Scientific discussion

2.1. Introduction

Cosentyx (secukinumab, AIN457) belongs to the Pharmacotherapeutic group of Interleukin inhibitors (ATC Code: L04AC10). Secukinumab is a first in class recombinant high-affinity, fully human monoclonal anti-human antibody of the IgG1/kappa isotype that selectively targets interleukin 17A (IL-17A). IL-17A, produced by a subset of T helper cells, named Th17, but also by other T cells, neutrophils and mast cells, promotes the expression of other pro-inflammatory cytokines as well as effector proteins. This cascade results in the activation of neutrophils and macrophages as well as epithelial cells and fibroblasts, and is considered to play an important role in the pathophysiology of many autoimmune diseases, including psoriasis and psoriatic arthritis (PsA). This new mechanism of action offers greater specificity and selectivity in targeting the specific downstream cytokine.

Cosentyx (secukinumab) was approved on 15 Jan 2015 for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Cosentyx is available in three different pharmaceutical forms: 150 mg powder for solution for injection (also referred to as Lyo in vial), 150 mg solution for injection in pre-filled syringe (also referred to as PFS), and 150 mg solution for injection in pre-filled pen (also referred to as AI or Pen). The recommended dose in psoriasis is 300 mg of secukinumab by subcutaneous injection with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4. Each 300 mg dose is given as two subcutaneous injections of 150 mg.

The current type II variation application was to register a new indication of psoriatic arthritis (PsA). PsA is a chronic debilitating disease which afflicts peripheral synovial, axial, and entheseal structures and is associated with nail involvement and skin psoriasis in up to 30 % of patients. Current therapies include non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs) and tumor necrosis factor alpha (TNFα) inhibitors. Although TNFα inhibitor therapy has dramatically improved the treatment, 30% to 40% of patients fail to respond to these therapies. There are new agents with alternate mechanisms of action such as ustekinumab and apremilast but there still remains an unmet need for agents with novel mechanism of action.

The PsA clinical development program for secukinumab included patients with active PsA disease despite current or previous NSAIDs, DMARDs, and/or TNFα inhibitor therapy. The proposed new indication was:

Cosentyx, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

The proposed posology was:

For patients with concomitant moderate to severe plaque psoriasis or who are anti TNFα inadequate responders (TNFa-IR), the recommended dose is 300 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4. Each 300 mg dose is given as two subcutaneous injections of 150 mg.

For other patients, the recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4.

The PsA clinical development program included two phase II studies (A2206 in PsA patients and F2201 in a related arthritic condition RA) and two pivotal phase III studies in the target indication and population (F2306 and F2312).

The development of new products for the treatment of psoriatic arthritis is covered in the Guideline on clinical investigation of medicinal products indicated for the treatment of psoriatic arthritis (CHMP/EWP/438/04). Recommendations of this guideline were mostly taken into account.

2.2. Non-clinical aspects

2.2.1. Pharmacology

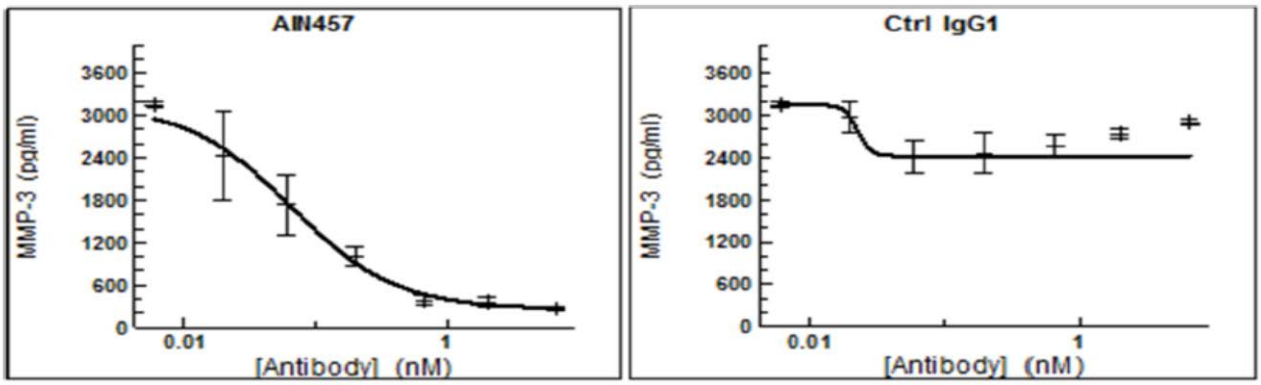
Primary pharmacodynamic studies

Neutralization of human IL-17A-, IL-17AF-dependent production of MMP-3 by human synovial fibroblasts

The *in vitro* neutralising activity of secukinumab for IL-17-induced metalloproteinase production was evaluated by studying the inhibition of human MMP-3 release from primary human fibroblast-like synoviocytes (FLS) stimulated with either human IL-17A or IL-17AF in combination with a fixed concentration of 60 pM of human TNFα.

FLS were costimulated with 30 pM IL17A and 60 pM TNFa. Secukinumab neutralised the induction of MMP-3 secretion potently and in a dose-dependent manner with an IC_{50} value of 0.067 ± 0.004 nM (mean ± SEM, n=3; **Figure 1**). The heterodimer IL-17AF, which is less potent than IL-17A, was used at a 33-fold higher concentration (1 nM IL-17AF vs 30 pM IL-17A) to achieve comparable MMP-3 levels. Under these conditions, secukinumab neutralized IL-17AF-dependent effects in the nanomolar range with an IC_{50} value of 4.471 ± 0.595 nM (mean ± SEM, n=3; **Figure 2**).

Figure 1. Inhibitory effect of secukinumab (AIN457) on MMP-3 secretion by human FLS costimulated with IL-17A/ TNFa

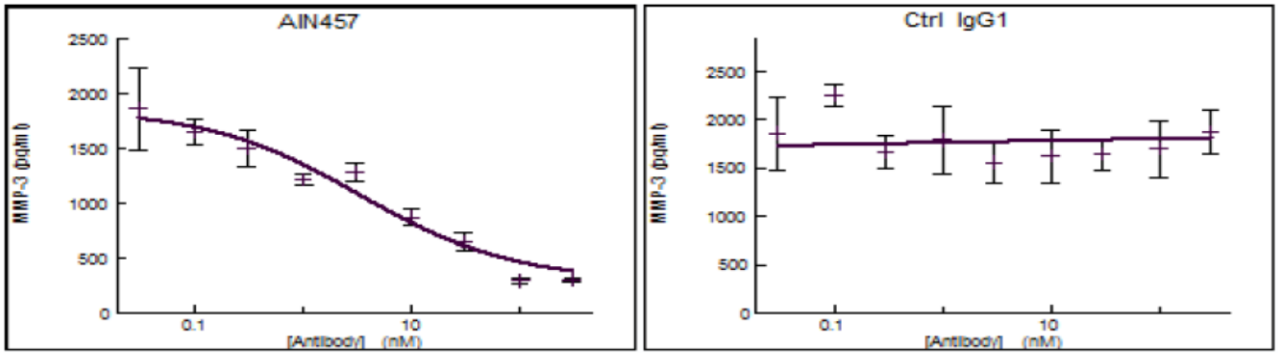


Primary human FLS were co-stimulated overnight with IL-17A (30pM)/ TNFa (60pM) in the presence of increasing concentration of secukinumab (AIN457) or control IgG1. MMP-3 release was measured by AlphaLISA.

Overall, the inhibition of MMP-3 release by secukinumab is in the similar range as the previously described inhibition of IL-6 release from FLS by the antibody, where an IC50 value of 0.14 ± 0.02 nM was determined for IL-17A (30 pM)/ TNFα co-stimulation, and an IC_{50} value of 3.30 ± 0.20 nM for IL-17AF (1 nM)/ TNFα-induced effects (RD-2013-00026). Therefore, sub-nanomolar or nanomolar concentrations of secukinumab were sufficient to neutralize human IL-17A- and IL-17AF-dependent release, respectively, of pro-inflammatory and tissue-degrading mediators from human primary FLS. Since MMP-3 plays a role in

tissue degradation (Burrage *et al*, 2006), these data suggest that neutralization of the bioactivity of IL-17A and/or IL-17AF may contribute to the inhibition of the structural damage in inflammatory and autoimmune diseases including rheumatoid arthritis and psoriatic arthritis.

Figure 2. Inhibitory effect of secukinumab (AIN457) on MMP-3 secretion by human FLS costimulated with IL-17AF/ TNFa



Primary human FLS were co-stimulated overnight with IL-17AF (1nM)/ TNFa (60pM) in the presence of increasing concentration of secukinumab (AIN457) or control IgG1. MMP-3 release was measured by AlphaLISA.

2.2.2. Pharmacokinetics

A comparison of PK parameters in cynomolgus monkeys and humans after intravenous administration is presented in **Table 1**. The similar PK characteristics observed in the cynomolgus monkey and PsA and AS patients are in line with the comparable binding activities of secukinumab to cynomolgus monkey and human neonatal Fc receptor (FcRn).

Human exposure multiples

Using a population PK model based on pharmacokinetic data from several i.v. and s.c. studies in PsA and AS patients, mean concentration-time profiles resulting from the dose regimens in the phase III program were simulated. This allowed the calculation of human exposure multiples for the 300 or 150 mg s.c. dosing regimens in PsA patients with loading doses at Weeks 0, 1, 2, and 3, followed by maintenance doses every four weeks (q4w) starting at Week 4 until week 48.

For the calculation of human exposure multiples, use was made of i) the experimental maximum concentration at steady-state, Cmax,ss, (5455 µg/mL) and ii) the experimental AUCtau at steady-state divided by the dosing interval tau to obtain the average steady-state concentration Cav,ss (4824 µg/mL) for the 13 week toxicology study in cynomolgus monkey with single weekly s.c. administration at the NOAEL of 150 mg/kg. Exposure data and exposure multiples for the loading and maintenance phases are given in **Table 2**.

Table 1. Comparative PK in cynomolgus and PsA and AS patients

Parameters	Cynomolgus monkey		PsA patients [c]	AS patients [d]
	Sp2/0 [a]	CHO [b]	CHO	CHO
Dose	10 mg/kg i.v.	10 mg/kg i.v.	2x10 mg/kg i.v.	2x10 mg/kg i.v.
Cmax (µg/mL)	253 [e]	319 [e]	424	364
CL (mL/day/kg)	2.76	1.8	1.9	2.0
Vz (mL/kg)	n.a.	n.a.	81.1	78.7
Vss (mL/kg)	74.5	59.0	n.a.	n.a.
T1/2 (day)	20.1	24.0	29.8	28.1
F (%) (s.c. bioavailability)	94 (15 mg/kg s.c)	62 (15 mg/kg s.c.)	85 [f]	79 [f]

a) Parameters from [DMPK R0400373]
b) Parameters from [DMPK R0600743-1]
c) Results from [Study CAIN457A2206] with CHO-derived material, clearance and distribution volume normalized for a typical PsA patient with a mean body weight of 84 kg
d) Results from [Study CAIN457A2209] with CHO-derived material, clearance and distribution volume normalized for a typical AS patient with a mean body weight of 77 kg
e) values are C(0) = extrapolated initial drug level after i.v. administration
f) Source: [SCP – section 1.2.1]
n.a.: not available

Table 2. Comparative systemic exposure in cynomolgus monkey and PsA patients

Patients			Exposure multiples		
			Loading	Maintenance	
Dose regimen	Cav,ss (µg/mL)[a,e]	Cmax,ind/ Cmax,ss (µg/mL)[b,e]	Based on Cmax,ss of 5455 µg/mL at 150 mg/kg s.c [c]	Based on AUC7d,ss/7d (Cav,ss) of 4824 µg/mL at NOAEL of 150 mg/kg s.c [d]	Based on Cmax,ss of 5455 µg/mL at 150 mg/kg s.c. [d]
150 mg s.c. at w 0,1,2,3 then 150 mg s.c. q4w starting at week 4	25.1	61.2 / 31.8	89	192	172
300 mg s.c. at w 0,1,2,3 then 300 mg s.c. q4w starting at week 4	50.3	122 / 63.6	45	96	86

a) Cav,ss is the average secukinumab concentration (=AUCtau/tau; tau = 28 days) during maintenance at steady-state.
b) Cmax,ind is the maximum secukinumab concentration after the 5th dose in the loading phase; Cmax,ss is the maximum secukinumab concentration during maintenance at steady state.
c) Predicted Cmax,ind in patients were compared with Cav,ss and Cmax,ss, respectively, at the NOAEL of 150 mg/kg s.c. in the 13 weeks tox study in cynomolgus monkey in order to calculate the exposure multiple during loading; tau (dosing interval) is 7 days in the cynomolgus tox study and in the clinical studies in patients.
d) Predicted Cav,ss and Cmax,ss in patients were compared with Cav,ss and Cmax,ss, respectively, at the NOAEL of 150 mg/kg s.c. in 13 weeks study in cynomolgus monkey in order to calculate the exposure multiple during maintenance; tau (dosing interval) is 7 days in the cynomolgus tox study and 28 days in patients in the maintenance phase.
e) Derived PK characteristics for mean simulated human exposure profiles

The average serum concentrations at steady-state observed in monkeys after 13 weekly s.c. doses were 192- and 96-fold higher than the predicted average serum concentrations expected in PsA patients treated with monthly maintenance s.c. doses of 150 mg and 300 mg respectively. At the end of the loading phase, human exposure is approximately 2-fold higher than during the maintenance phase. Therefore, exposure multiples are approximately half of those described above during the maintenance phase.

For assessment of non-target related toxicity the species difference in binding affinity to the IL-17A receptor is not important, therefore human exposure multiple calculations on the basis of the exposure in man and animals were considered valid.

2.2.3. Toxicology

No new toxicity data were submitted in this application, which was considered acceptable by the CHMP.

2.2.4. Ecotoxicity / environmental risk assessment

Secukinumab is a high-affinity fully human monoclonal anti-human Interleukin-17A antibody and in accordance with the CHMP guideline on the environmental risk assessment (EMEA/CHMP/SWP/4447/00) is exempted from testing because of its chemical structure.

2.2.1. Discussion on non-clinical aspects

One new pharmacodynamics study addressing the neutralising effect of secukinumab on IL-17A and IL-17AF-dependent production of MMP-3 by human synovial fibroblasts was included. The new data support the role of secukinumab in prevention of cartilage damage in PsA, AS and RA patients.

The CHMP considered that the comparison of PK characteristics and systemic exposure to humans demonstrate significant exposure margin to PsA and AS patients and that the nonclinical safety data generated to support the initial marketing authorisation of Cosentyx for treatment of psoriasis patients were adequate and sufficient to support the indication in PsA

2.2.2. Conclusion on the non-clinical aspects

Non clinical data submitted in this application, are sufficient to support the use of secukinumab in the new indication

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The applicant 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

Summary of Phase 2 studies used for dose selection

Study	Description	N	Treatments	Key Efficacy	Key Conclusions
Psoriatic Arthritis					
A2206	PoC (iv) in PsA	42	10 mg/kg secukinumab iv at R, Day 22 PBO iv at R, Day 22	ACR20 (Wk 6)	Secukinumab demonstrated preliminary evidence for therapeutic benefit in patients with PsA
Rheumatoid Arthritis					
F2201	Dose-ranging (sc) in RA	237	25, 75, 150 or 300 mg secukinumab sc at R, Wks 4, 8, 12 PBO at R, Wks 4, 8, 12	ACR20 (Wk 16)	Secukinumab 75-300 mg sc showed efficacy in RA

Summary of Phase 3 controlled, randomized, blinded trials

Study	Description	N	Treatments	Primary endpoint
F2306 *(PE: 24 Wk)*	Efficacy/safety in target population (iv load / sc every 4 weeks)	606	10 mg/kg iv secukinumab, PBO at Wks 0, 2, 4, followed by 75, 150 mg sc q4w from Wk 8 to Wk 104 PBO iv at Wks 0, 2, 4, followed by sc q4w at Wks 8 and 12[a] or Wks 8 to 20[b]	ACR20 at Wk 24
F2312 *(PE: 24 Wk)*	Efficacy/safety in target population (sc load / sc every 4 weeks)	397	75, 150, 300 mg sc secukinumab in pre-filled syringe (PFS) at Wks 0, 1, 2 and 3, then q4w from Wk 4 to Wk 256 PBO sc at Wks 0, 1, 2 and 3 then q4w at Wks 4 to 12[c] or Wks 4 to 20[d]	ACR20 at Wk 24

ACR = American College of Rheumatology; iv =intravenous; N = number of patients included in efficacy analysis (Full Analysis Set); PBO = placebo; PE = Primary Endpoint analysis at Week 24; PFS = pre-filled syringe; PoC =proof of concept; R = randomization (baseline); sc = subcutaneous; q4w = once every 4 weeks; Wks = weeks

[a] PBO non-responders (<20% improvement from baseline in both tender and swollen joint counts) were re-randomized 1:1 to receive either secukinumab 75 or 150 mg sc q4w starting at Wk 16

[b] PBO responders (≥20% improvement from baseline in both tender and swollen joint counts) were re-randomized 1:1 to receive either secukinumab 75 or 150 mg sc q4w starting at Wk 24

[c] PBO non-responders (<20% improvement from baseline in both tender and swollen joint counts) were re-randomized 1:1 to receive either secukinumab 150 or 300 mg sc q4w starting at Wk 16

[d] PBO responders (≥20% improvement from baseline in both tender and swollen joint counts) were re-randomized 1:1 to receive either secukinumab 150 or 300 mg sc q4w starting at Wk 24

2.3.2. Pharmacokinetics

Secukinumab displays PK properties typical of a human IgG1-type immunoglobulin interacting with a soluble target, i.e. a low clearance and a low total volume of distribution. The PK properties of secukinumab in patients with PsA were described using population PK analysis. The studies included in the analysis are described in **Table 3**.

Table 3. Studies included in the PPK analysis.

Study	Description	Regimens	Note
A2206	PoC PD study of efficacy of AIN457	• 2 x 10 mg/kg i.v. q3w • placebo	PK samples taken pre-dose, 2, 3, 4 and 24 hours after infusion, and then at weeks 1, 2, 3, 4, 6, 8 ,10, 12, 16, 20 and 24/end of study
F2306*	Phase III efficacy safety and tolerability	• 3 x 10 mg/kg i.v. q2w + 150 mg s.c. q4w from week 8 • 3 x 10 mg/kg i.v. q2w + 75 mg s.c. q4w from week 8 • placebo + 150 mg s.c. q4w from week 24 • placebo + 75 mg s.c. q4w from week 24 • placebo + 150 mg s.c. q4w from week 16 • placebo + 75 mg s.c. q4w from week 16 • placebo	PK samples at weeks 0, 4, 16, 24, 52
F2312**	Phase III efficacy, safety and tolerability	• 4 x 300 mg s.c. q1w + 300 mg s.c. q4w from week 4 • 4 x 150 mg s.c. q1w + 150 mg s.c. q4w from week 4 • 4 x 75 mg s.c. q1w + 75mg s.c. q4w from week 4 • placebo + 300 mg s.c. q4w from week 24 • placebo + 150 mg s.c. q4w from week 24 • placebo + 300 mg s.c. q4w from week 16 • placebo + 150 mg s.c. q4w from week 16 • placebo	PK samples at weeks 0, 4, 16, 24

* F2306: Week 52 interim lock
** F2312: Week 24 interim lock

Based on the final model and parameter estimates (**Table 4**), PK profiles were simulated and secondary exposure metrics such as AUC, Cavg, Cmin, Cmax, Tmax, and t1/2 were derived.

Table 4. Parameters of the final PK model

Name	Value	%RSE	Shrinkage (%)
Structural parameters			
CL [L/day]	0.19	2	
V_c [L]	3.66	4	
Q_1 [L/day]	0.54	10	
V_{p1} [L]	2.45	5	
k_a [1/day]	0.18 (fixed)	-	
F_{abs1} (bioavailability)	85%	2	
Covariate effect			
WT0 on CL	0.71	8	
WT0 on V_c	0.44	37	
WT0 on V_{p1}	0.72	25	
Inter-individual variability(std)			
IIV on CL	0.32	3	7.9
IIV on V_c	0.36	8	33
IIV on Q_1	-	-	-
IIV on V_{p1}	0.3	11	53
IIV on k_a	-	-	-

IIV on F_{abs1}	-	-	-
Covariance			
CL-V_c (corr)	0.66	8	
Residual variability			
Additive error (std)	2.37	5	
Proportional error (std)	0.11	4	
Objective Function Value (BIC)	21604		
Objective Function Value (-2xLL)	20511		

A two-compartment model, with first-order absorption (for sc drug administration) and zero-order infusion (for iv drug administration) adequately described secukinumab PK profiles.

Absorption

On the basis of the PPK model the mean maximum concentrations (Cmax) at steady-state following sc loading + 150 mg sc and 300 mg sc maintenance dose were estimated to be 31 µg/ml and 62.1 µg/ml and occurred at approximately 6 days after dose in PsA patients. The Cmax at steady-state is approximately 2 times higher than the Cmax after the single-dose.

Bioavailability

On the basis of the PPK model, the bioavailability after sc administration is 85% in PsA patients.

Distribution

Estimation from the PPK model indicated a low total volume of distribution (central compartment volume of 3.66 l (CV% 30.5) and peripheral compartment volume of 2.45 l (CV% 30.6) in a typical PsA patient weighing 84 kg.

Elimination

Secukinumab has a terminal half-life (t1/2) averaging 25 days with an inter-patient variability of 27.5% and secukinumab has slow serum clearance (CL = 0.19 l/day, CV% 32.5%) on the basis of the PPK model.

Clearance and volumes of secukinumab vary with body weight in an allometric relationship. For CL and central volume of distribution the allometric exponents were estimated to be 0.8 and 0.4 respectively. CRP at baseline, race (non-Asian vs Asian), and anti-TNFα response status did not have a clinically relevant influence on CL (after adjusting for bodyweight).

Excretion

No specific elimination studies have been performed and this is acceptable because secukinumab is not expected to be excreted in urine or secreted into the bile.

Metabolism

The majority of IgG elimination occurs via intracellular catabolism, following fluid-phase or receptor mediated endocytosis.

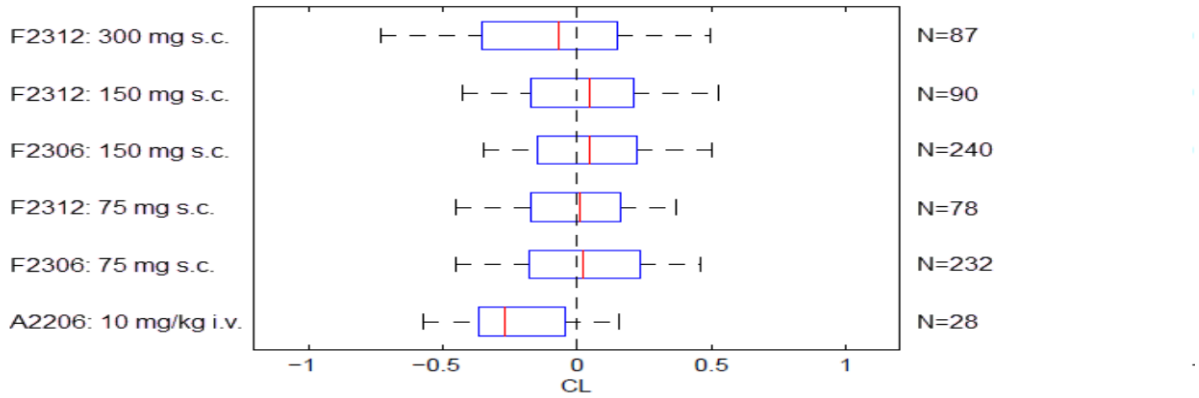
Dose proportionality and time dependencies

On the basis of the PPK model the PK of secukinumab is linear with no evidence of a time dependent change in the CL. There is also no evidence of a dose-dependence of CL. On the basis of the study

CAIN457F2312 there was an evidence of dose-proportionality in exposure (mean concentrations at steady-state) across the 75 mg, 150 mg and 300 mg during the sc administration.

Dose-independency of secukinumab CL was demonstrated by plotting the individual estimates of CL from the PPK model against the treatment regimens (**Figure 3**).

Figure 3. Relative CL by treatment group (after adjusting for bodyweight)



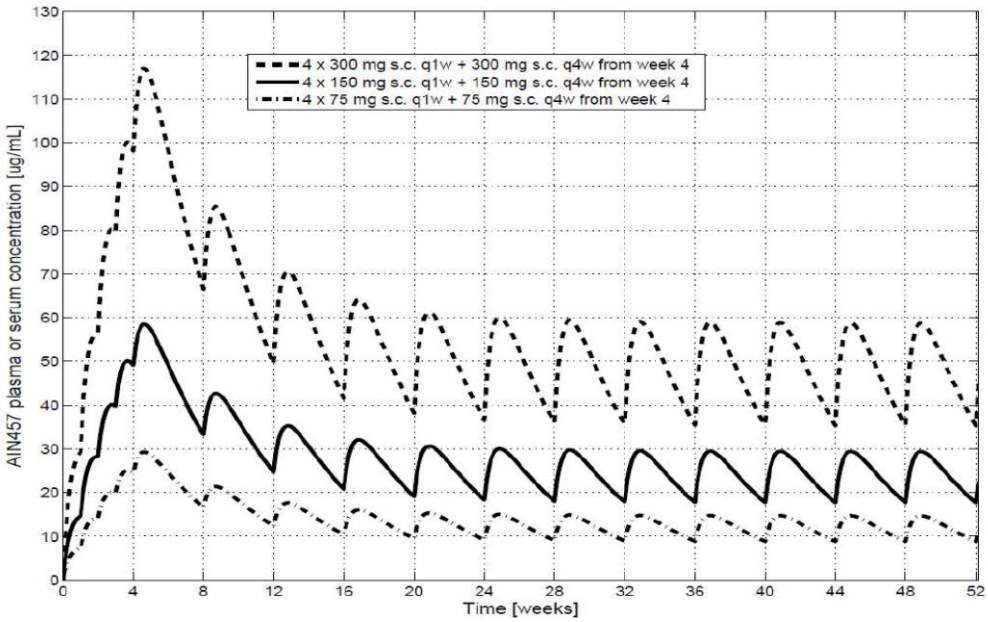
Relative CL indicates relative to the CL of 0.19 l/day in a "typical subject" (e.g., a value of 0.1 indicates a 10% relative increase in CL).

The estimated CL in the clinical phase III studies CAIN457F2306 and CAIN457F2312 was generally consistent across the active study groups. In the study CAIN457A2206 the CLs were lower (exposures were higher) compared to the other phase III studies, but this was considered to be a chance finding.

Exposure in target population

No clinically relevant differences in secukinumab PK were observed between the various autoimmune diseases studied (AS, PsA, PsO, RA, CD, AS, non-infectious uveitis). PK is also similar when compared between healthy volunteers, PsA and AS patients. Furthermore, PK similarity was observed between the lyophilisate formulation (LYO) and solution and between the three forms LYO, prefilled syringe (PFS) and auto-injector/pen (AI). The exposure profiles of a typical patient given the proposed dosing are illustrated in **Figure 4**.

Figure 4. Simulated concentration profiles of s.c. loading + s.c. maintenance 300 mg, 150 mg and 75 mg phase III regimens



Special populations

No clinical studies were performed in patients with impaired hepatic or renal function and that was considered acceptable because no great effect on exposure is anticipated on the assumption that secukinumab has typical IgG pharmacokinetic properties.

Pharmacokinetic interaction studies

No *in vitro* or *in vivo* drug-drug interaction studies were performed.

The PPK results in PsA patients with secukinumab indicated that MTX had no impact on the disposition of secukinumab. However, as no data of concomitant use of MTX (and glucocorticoids) in PsA patients (or in AS patients) were available in the initial submission the MAH was requested to justify that MTX and glucocorticoids have no impact on the disposition of secukinumab. The MAH provided further analyses from the phase III studies for patients with and without concomitant methotrexate or glucocorticoid use which showed that there were no systematic trends, either downward or upward, in concentrations of one subgroup versus the other. Therefore, the following sentence was proposed to be added to the Cosentyx SmPC: "No interaction was seen when Cosentyx was administered concomitantly with MTX and/or corticosteroids in arthritis studies (including in patients with PsA and AS)", which was accepted by the CHMP.

2.3.3. Pharmacodynamics

Mechanism of action

The pharmacodynamic effect of secukinumab in binding to IL-17A, and inhibiting IL-17A signalling, is linked with the reduction of the inflammatory processes of PsA. Based on the data provided within the initial MAA, the engagement of IL-17A was seen as an increase in serum total IL-17A levels after secukinumab treatment, followed by a slow release of the IL-17A-secukinumab complex.

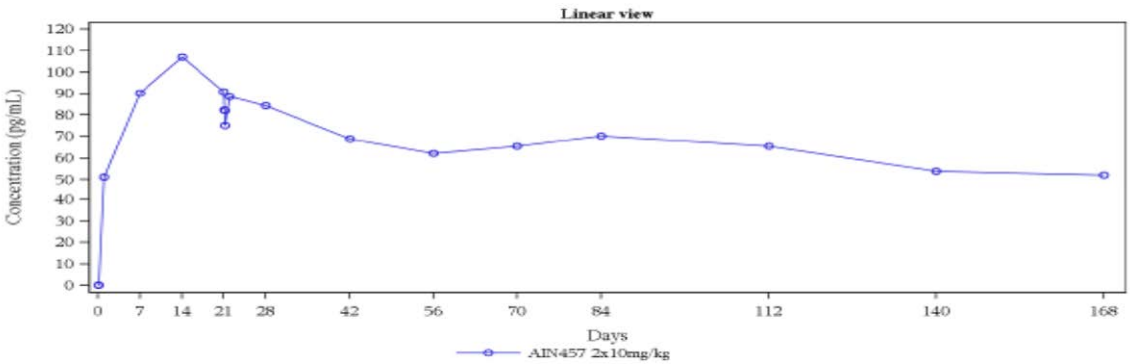
Primary and secondary pharmacology

A meta-analysis entitled Total Interleukin 17A analysis report (Release date: 06-Feb-2015 was provided in order to assess the total IL-17A levels from eight phase I, IIb and phase III clinical trials which were either not part of the clinical study reports or only partly summarized in the CSR (Studies A1101, A2206, A2209, A2212, A2220, A2309, F2201 and F2208).

Pharmacodynamic blood samples for quantification of total IL-17A (i.e., the sum of free and secukinumab bound IL-17 in serum) were taken at the same time points as for pharmacokinetic. The MESO Scale Discovery electrochemiluminescence assay was used.

Study A2206 i.e., the Proof-of-Concept study in PsA was included in the meta-analysis. The median total IL-17A concentration-time profile after a dose of 10 mg/kg iv on Days 0 and 22 is shown in **Figure 5**. The highest median concentration was 107 pg/mL, observed 2 weeks after the first dose, followed by slowly declining concentrations from 90 to 50 pg/mL during a half year time.

Figure 5. Median total IL-17A serum concentration-time profiles (A2206)



Based on the meta-analysis, the increase in total IL-17A concentrations at post dose time points is due to binding to secukinumab to form an IL-17A-secukinumab complex which has slower clearance than that of uncomplexed IL-17A. The decrease after treatment reflects the decrease in secukinumab concentrations.

In summary, total IL-17A profiles across studies in both healthy subjects and patient populations (psoriasis, psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis) show concentration-time patterns that are consistent with target engagement of secukinumab.

2.3.4. PK/PD modelling

The MAH provided a population PK (PPK) modelling report with the pooled PPK analysis of Cosentyx in PsA. The data were collected l from the following studies: CAIN457A2206, CAIN457F2306 and CAIN457F2312. Graphical exploratory analysis of Cosentyx exposure –response of efficacy, adverse events (AEs) and radiographic assessments in PsA patients were also provided. The focus was on describing exposure-response trend at a fixed time point, rather than through longitudinal PK/PD modelling.

The 2-compartment PK model adequately described the observed concentration-time profiles for sc and iv secukinumab in PsA patients. The influence of covariates on the individual PK was explored. The following covariates were investigated: bodyweight, age, gender, race (non-Asian vs. Asian), disease activity assessed by the PASI score, DAS28 score and CRP level at baseline, previous use of biologics, response status to anti-TNFα therapy, concomitant use of methotrexate, and time since first diagnosis of psoriatic arthritis. They were tested using a full covariate modelling approach. Only the effect of bodyweight was considered clinically relevant based on an assumption that only changes in typical parameter estimates >20% are clinically important. Dose dependency or time dependency was not seen. The PK properties were as expected for an IgG antibody and the PPK model parameters were similar to a previous PPK analysis of secukinumab in psoriasis patients.

In the graphical analysis, a comparison of Cmin concentrations between patients < 90 kg and ⩾ 90 kg showed that the heavier patient the lower exposure. This is in line with findings from the PPK analysis and the known impact of body weight on the PK of mAbs. Also in the clinical studies with psoriasis patients, the body weight of the patients was demonstrated to have an effect on the exposure. The results of this exploratory analysis were limited to the sc loading regimen tested in study CAIN457F2312 (loading dose on weeks 0, 1, 2, 3, 4, followed by Q4W dosing).

Clear exposure-response relationships were observed in all efficacy parameters (ACR, PASI, DAS and HAQ-DI), with a trend for increased response with higher Cmin concentrations. The exposure-response relationship of endpoints reflecting the arthritic components of the disease (ACR20/50/70, DAS28-CRP) appeared to plateau at Cmin level higher than ca. 20 µg/ml. This concentration (20 µg/ml) generally corresponds to the typical steady-state Cmin achieved following a 150 mg sc Q4W dosing.

Exposure-response relationships of PASI75/90 and HAQ-DI demonstrated a trend for a monotonous increase in response over the concentration range.

No evidence of an effect of Cmin was observed on AE rates for the following categories: any AE, infections and infestations, upper respiratory tract infections, nasopharyngitis, and urinary tract infection. There was an increasing trend with exposure for SAEs and oral herpes. However, its interpretation was complicated by the fact that it appeared to be driven by lower AE rates in the first two exposure categories ([0, 10] and [10, 20] µg/mL) and higher AE rate in the last exposure category (>30 µg/mL) when compared to the placebo group (0 µg/mL). Also, the slope coefficients were not statistically significant at the 0.1 level for those AE categories. It was therefore difficult to conclude for a Cmin-related effect in both cases.

2.3.5. Discussion on clinical pharmacology

The PK data of secukinumab in PsA patients were provided from 3 clinical studies. In addition, simulated PK data from the PPK model and a graphical exploratory analysis of exposure-response of efficacy, AEs and radiographic assessments were presented.

In the clinical study CAIN457A2206, the studied secukinumab dose was 10 mg/kg as an iv infusion administered twice by 3 weeks interval (also placebo group). For evaluation of the PK of secukinumab, the chosen dosing regimen was not optimal because the 2nd dose was administered, while there were still substantial amounts of drug from the 1st dose. The reported PK parameters for secukinumab were quite similar as earlier seen in the study with similar dosing regimen and route with psoriasis patients.

In the extension study (CAIN457A2206E1), the studied secukinumab dose was 3 mg/kg administered as an iv infusion monthly up to 6 months (with a possible extension of a further 6 months).The steady-state was reached on the basis of the pre-dose and post-dose infusion serum concentrations after week 16. The Cmax,ss and Cmin,ss values of secukinumab were lower in the samples from patients, which received placebo in the study CAIN457A2206.

In the clinical study CAIN457F2306, the studied loading dose of secukinumab was 10 mg/kg iv at baseline, weeks 2 and 4, and thereafter the studied secukinumab doses were 75 mg and 150 mg s.c monthly (starting at week 8). At week 4, serum concentrations reflected the rise in exposure (the mean concentrations were about equal both after 75 mg and 150 mg sc). At week 16, mean concentrations declined due to the less-frequent sc dosing as the iv dosing. The mean secukinumab concentrations declined still at weeks 24 and 52. The mean secukinumab concentrations with 75 mg sc dose were 16.2 µg/ml and 10.2 µg/ml at weeks 24 and 52 and with 150 mg sc dose 24.4 µg/ml and 18.6 µg/ml, respectively. In this study, there were also patients who received placebo as the loading dose and at week 16 were classified as responder or non-responders. The non-responders received secukinumab 75 mg or 150 mg sc monthly and the responders remained on placebo until week 24 and thereafter received either secukinumab 75 mg or 150 mg sc. The mean secukinumab concentrations were at week 52 very close to those seen in the active secukinumab groups.

In the pivotal clinical study CAIN457F2312 the studied secukinumab doses were 75 mg or 150 mg or 300 mg sc weekly up to 4 week and thereafter monthly starting at week 4. In this study, there were also patients receiving placebo in the same study design as in the study CAIN457F2306, except the doses after the re-randomisation were 150 mg or 300 mg sc The dose-proportionality in the secukinumab concentrations was found at week 4 and also at steady-state (weeks 16 and 24). The mean secukinumab concentrations were in the expected range i.e., with 75 mg sc ~10 µg/ml , with 150 mg sc ~ 20 µg/ml and with 300 mg ~ 40 µg/ml.

The inter-subject variation in the PK parameters of secukinumab after iv administration was low or moderate (16-33%). Based on the PPK model in PsA, the derived inter-subject variability for PK parameters such as Cmin,ss, Cmax,ss, Cavg,ss, AUCtau,ss for the 150 mg and 300 mg sc regimens was in the range of 31.4% and 45.0%. Estimates of intra-subject variability were not available from PsA patients. In the Cmin values the inter-subject variation was usually moderate (> 30%).

On the basis of the PPK model, the PK of secukinumab is linear with no evidence of a time dependent change in the CL or dose-dependence of CL (CL = 0.19 l/day, CV% 32.5%).

On the basis of the PPK model, the bioavailability after sc administration was 85% in PsA patients being better than in psoriasis patients (66-77%).

The body weight of the patients was found to have an impact on secukinumab serum concentrations and also on efficacy. On the basis of the PPK model and graphical analysis the heavier the patient, the lower the Cmin concentrations were observed. There was also a trend that the higher the Cmin concentrations, the better response in efficacy. The Cmin,ss of secukinumab needed for the therapeutic effect was estimated to be about 20 µg/ml. This steady-state concentration is achieved for most patients with the proposed dosing regimen with 150 mg or 300 mg sc. The 75 mg sc was demonstrated to be not sufficiently effective. The applicant provided adequate secukinumab concentration data separately for patients < 90 kg and ⩾90 kg and discussion about the secukinumab concentrations and efficacy variables (i.e., ACR, PASI, DAS and HAQ-DI) in the pivotal clinical study CAIN457F2312. On the basis of the simulations etc. no consistent clinically meaningful benefit could be observed for the 300 mg dose over 150 mg in heavier patients.

Regarding the covariate effect in anti TNFa-IR patients, this appears to affect Emax rather than EC50 suggesting that these patients are likely to have a lower treatment effect even at the higher exposures. In contrast, the lower effect observed in patients in the upper weight category (>90kg) appears to be attributed to a lower exposure as both EC50 and Emax are similar across weight groups.).

Age and gender do not appear to be significant predictors of secukinumab PK, why the tendency for age and gender related differences in response appear to be related to PD for these sub-groups.

In all clinical studies with PsA patients, there were pre-dose samples with quantifiable concentrations of secukinumab. The number of these samples; however, was relatively small and did not impact on interpretation of PK results.

2.3.6. Conclusions on clinical pharmacology

The pharmacokinetics of secukinumab in PsA patients was very similar as in the psoriatic patients.

2.4. Clinical efficacy

2.4.1. Dose response studies

Study A2206

A randomized, double-blind placebo-controlled multi-center proof-of-concept study to assess the efficacy of AIN457 in patients with psoriatic arthritis.

Study A2206 was a proof of concept study in patients with diagnosis of active psoriatic arthritis based on Classification Criteria or Psoriatic Arthritis (CASPAR). The patients received secukinumab 10 mg/kg iv or matching placebo on Days 1 and 22.

ACR20 response rates on secukinumab and placebo at Week 6 did not differ significantly and the primary endpoint of the study was therefore not met. However, preliminary evidence for therapeutic benefit of secukinumab in PsA patients was observed as numerically greater responses on secukinumab were seen.

Study A2206E1

An open label non-randomized extension study to evaluate the safety and tolerability of AIN457 (anti interleukin-17 monoclonal antibody) in patients with psoriatic arthritis.

Study A2206E1 was an open-label extension of the phase II proof of concept study A2206, with iv dosing 3 mg/kg q4w. The primary objective was to assess safety and tolerability of secukinumab. Patients previously treated with placebo in the core study achieved response rates similar to those initially treated with secukinumab, and the efficacy was maintained during the 52-week treatment period.

Study F2201

A 16-week multicenter, randomized, double-blind, placebo-controlled, parallel group, dose-finding study to evaluate the efficacy, safety and tolerability of subcutaneous secukinumab (AIN457) followed by an extension phase up to a total of 60 weeks in patients with active rheumatoid arthritis despite stable treatment with methotrexate.

F2201 was a study in patients with active RA, with treatment up to Week 48 and a 12-week follow-up period. Secukinumab was administered sc q4w with a dose range of 25 mg, 75 mg, 150 mg or 300 mg. No loading dose was given.

Although the primary efficacy endpoint (ACR20 response of secukinumab compared to placebo at Week 16) was not achieved, there was a clear numerical trend in favour of secukinumab 75-300 mg within the primary and the secondary efficacy variables.

Taken together, the initial doses and the dosing regimen in phase II studies were based on preclinical in vivo efficacy data in animal models from the initial MAA. The two phase II studies A2206 and F2201 provided preliminary evidence of efficacy in two arthritic disease models, PsA and RA. The posology carried forward to the phase III studies was mainly based on pK/PD modelling and simulation of different treatment regimens as well as data in psoriasis.

2.4.2. Main studies

Study CAIN457F2306 (also referred to as F2306)

A randomized, double-blind, placebo-controlled, multicentre study of secukinumab to demonstrate the efficacy at 24 weeks and to assess the long term safety, tolerability and efficacy up to 2 years in patients with active psoriatic arthritis.

Methods

Study participants

The main inclusion criteria are summarised below:

1. Male or non-pregnant, non-lactating female patients at least 18 years of age.

2. Diagnosis of PsA classified by CASPAR criteria and with symptoms for at least 6 months with moderate to severe PsA who must have at Baseline ≥ 3 tender joints out of 78 and ≥3 swollen joints out of 76 (dactylitis of a digit counts as one joint each).

3. RF and anti-CCP antibodies negative.

4. Diagnosis of active plaque psoriasis, with at least one psoriatic plaque of ≥ 2 cm diameter (but not in intertriginous areas such as armpits, or chest between breasts, or groin) or nail changes consistent with psoriasis or a documented history of plaque psoriasis.

5. Patients with PsA should have been on NSAIDs for at least 4 weeks prior to randomization with inadequate control of symptoms or intolerant to NSAIDs.

6. Patients who were regularly taking NSAIDs as part of their PsA therapy were required to be on a stable dose for at least 2 weeks before study randomization and had to remain on a stable dose up to Week 24.

7. Patients taking corticosteroids were to be on a stable dose of ≤10 mg/day prednisone or equivalent for at least 2 weeks before randomization and had to remain on a stable dose up to Week 24.

8. Patients taking MTX (≤ 25 mg/week) were allowed to continue their medication if the dose was stable for at least 4 weeks.

The main exclusion criteria were:

1. Patients taking high potency opioid analgesics (e.g., methadone, hydromorphone, or morphine)

2. Patients who had ever received biologic immunomodulating agents except for those targeting TNF alpha, investigational or approved.

3. Patients who had previously been treated with more than 3 different TNF alpha inhibitors (investigational or approved).

4. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or IL-17 receptor

5. Use of any investigational drug and/or devices within 4 weeks of randomization or 5 half lives of the investigational drug, whichever was longer.

6. Ongoing use of prohibited psoriasis treatments / medications (e.g., topical corticosteroids, UV therapy) at randomization. The following wash out periods were to be observed:

a. Oral or topical retinoids 4 weeks

b. Photochemotherapy (e.g. PUVA) 4 weeks

c. Phototherapy (UVA or UVB) 2 weeks

d. Topical treatments (except in face, scalp and genital area during screening, only corticosteroids with mild to moderate potency) 2 weeks

7. Any intramuscular or i.v. corticosteroid treatment within 4 weeks before randomization

Treatments

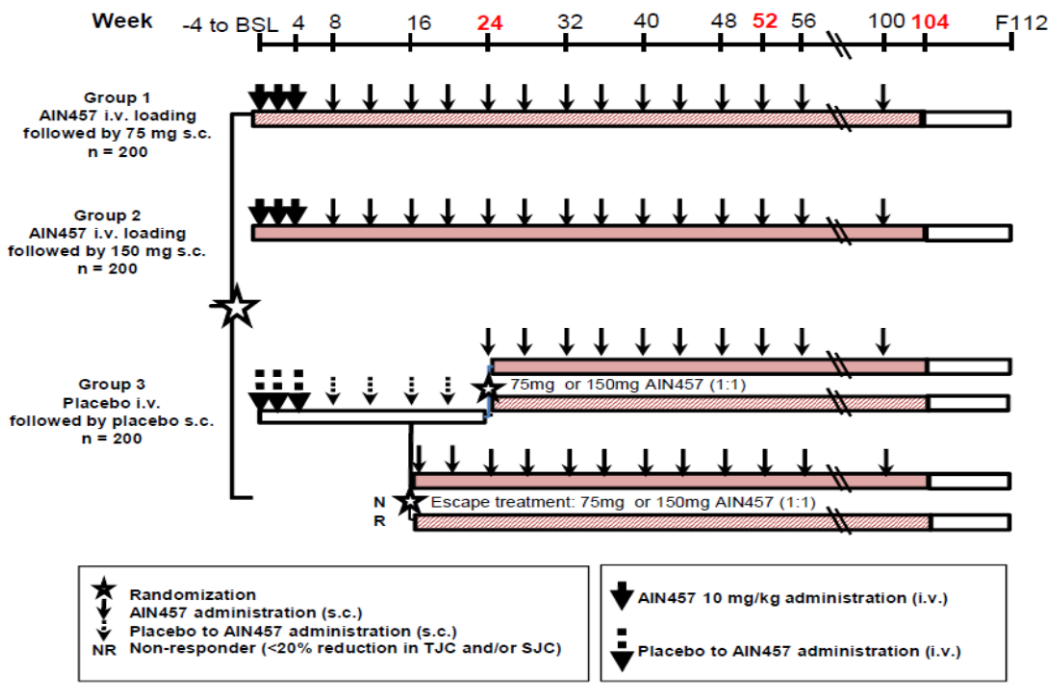
The study design is presented in **Figure 6**.

At baseline, eligible patients were to be randomized to one of the following 3 treatment arms in a ratio of 1:1:1:

- Group 1: Secukinumab i.v. (10 mg/kg) at baseline, Weeks 2 and 4, then secukinumab 75 mg s.c. starting at Week 8 and injected every 4 weeks
- Group 2: Secukinumab i.v. (10 mg/kg) at baseline, Weeks 2 and 4, then secukinumab 150 mg s.c. starting at Week 8 and injected every 4 weeks

- Group 3: Placebo i.v. at baseline, Weeks 2 and 4, then placebo s.c. starting at Week 8 and Week 12.

Figure 6.Schematic of Study F2306



At Week 16, all patients were to be classified as responders (≥20% improvement from baseline in both tender and swollen joint counts) or non-responders. Patients who were randomized to placebo at baseline were to be re-randomized by the IRT to receive double blind treatment up to two years, as follows:

- Patients on placebo (Group 3) who were responders remained on placebo until week 24. At Week 24, these patients received either secukinumab 75 or 150 mg every 4 weeks, regardless of responder status (as dictated by the re-randomization).
- Patients on placebo (Group 3) who were non-responders were to be re-randomized (1:1) at Week 16 to receive either secukinumab 75 mg or 150 mg sc every 4 weeks.

Objectives

The primary objective was to demonstrate that the efficacy of secukinumab 75 or 150 mg at Week 24 was superior to placebo in patients with active psoriatic arthritis (PsA) based on the proportion of patients achieving an American College of Rheumatology 20 (ACR20) response.

The secondary objectives were to demonstrate that:

1. The efficacy of secukinumab 75 or 150 mg at Week 24 was superior to placebo based on the proportion of patients achieving a Psoriasis Area and Severity Index 75 (PASI75) response in the subgroup of patients who have ≥3% skin involvement with psoriasis.
2. The efficacy of secukinumab 75 or 150 mg at Week 24 was superior to placebo based on the proportion of patients achieving a PASI90 response in the subgroup of patients who have ≥3% skin involvement with psoriasis.

3. The improvement (change) from baseline on secukinumab 75 or 150 mg was superior to placebo for the Disease Activity Score 28-CRP (DAS28-CRP) at Week 24.
4. The improvement (change) from baseline on secukinumab 75 or 150 mg was superior to placebo for the Short Form 36 (SF36)- Physical Component Summary (PCS) at Week 24.
5. The improvement (change) from baseline on secukinumab 75 or 150 mg was superior to placebo for the Health Assessment Questionnaire – Disability Index (HAQ-DI©) at Week 24.
6. The efficacy of secukinumab 75 or 150 mg at Week 24 was superior to placebo based on the proportion of patients achieving an ACR50 response.
7. The improvement (change) from baseline to Week 24 on secukinumab pooled regimen (75 mg and 150 mg s.c.) was superior to placebo for joint/bone structural damage (van der Heijde modified total Sharp score [vdH-mTSS]).
8. The efficacy of secukinumab pooled regimen (75 mg and 150 mg s.c.) at Week 24 was superior to placebo based on the proportion of patients with dactylitis in the subset of patients who have dactylitis at baseline.
9. The efficacy of secukinumab pooled regimen (75 mg and 150 mg s.c.) at Week 24 was superior to placebo based on the proportion of patients with enthesitis in the subset of patients who have enthesitis at baseline.
10. The improvement (change) from baseline to Week 24 on secukinumab 75 or 150 mg was superior to placebo for joint/bone structural damage (vdH-mTSS).
11. The overall safety and tolerability of each secukinumab regimen compared to placebo a assessed by vital signs, clinical laboratory values, electrocardiogram (ECG) and adverse events (AEs) monitoring.

Outcomes/endpoints

The primary efficacy endpoint was ACR20 response at Week 24.

The secondary efficacy endpoints were:

- PASI75 response at Week 24 in the subgroup of patients who had ≥3% skin involvement with psoriasis at baseline.
- PASI90 response at Week 24 in the subgroup of patients who had ≥3% skin involvement with psoriasis at baseline.
- Disease activity score DAS28-CRP at Week 24.
- SF36-PCS at Week 24.
- Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 24.
- ACR50 response at Week 24.
- Joint/bone structural damage (van der Heijde-modified total Sharp score [vdH-mTSS]).
- Proportion of patients with dactylitis at Week 24 in the subset of patients who have dactylitis at baseline.
- Proportion of patients with enthesitis at Week 24 in the subset of patients who have enthesitis at baseline.

Sample size

A 5% two-sided type I error rate was used to control for type I error. Two secukinumab doses were tested vs. placebo with respect to the primary endpoint (ACR20 response at Week 24), thus the type-I-error was split to 2.5% two-sided for each comparison. Sample sizes were based on this type I error assumption.

For the primary endpoint, ACR20 in the overall population, 200 patients per group would yield approximately 99% power to detect a treatment difference in the response rates between the secukinumab regimens and placebo with the above assumptions (Fisher's exact test, NQuery 7.0).

A total of 817 patients were screened and 606 patients were randomised to the treatment groups; 202 patients in each treatment group.

Randomisation

At baseline (Visit 2), all eligible patients were randomized via the IRT (Interactive Response Technology) to one of the treatment arms (1:1:1 ratio) At Week 16 (Visit 8), all patients were classified as responders or non-responders. Patients who were randomized to placebo at baseline were re-randomized to receive double blind treatment up to 2 years.

Randomization was stratified according to being either TNFα inadequate responders (TNFa-IR) or TNFα inhibitor naïve patients. 30% of patients were to be TNFa-IR to ensure a representative patient population for the assessment of efficacy and safety.

Blinding (masking)

This was a double-blind study.

Statistical methods

Summary statistics for continuous variables included N, mean, standard deviation minimum, lower quartile, median, upper quartile, and maximum. For binary or discrete variables the absolute number of patients in each category and relative frequencies were provided. If not otherwise specified, p-values and confidence intervals were two-sided and the level of significance was set to 5% (two-sided, family-wise type- I-error).

Statistical analyses of efficacy variables were performed on an intent-to-treat basis, involving all randomized patients who were assigned to study treatment (Full analysis set, FAS). A sequentially rejective testing strategy was used to evaluate the study hypotheses for the primary and secondary variables (hypotheses H1 to H19) while retaining a family-wise type I error of 5%.

For binary variables (*e.g.,* ACR20 response) a logistic regression model was fitted with treatment and TNF-alpha inhibitor status as factors and baseline score (if appropriate) and weight as covariates. Missing responses were considered as non-responders. Continuous variables were evaluated using a mixed-effect model repeated measures (MMRM) which was valid under the missing at random (MAR) assumption.

The MAR assumption for missing data in MMRM analyses for continuous endpoints is questionable. It was defined that the data collected after the placebo patient switched to secukinumab at Week 16 was treated as missing. Thus the occurrence of these missing values at Week 24 is due to the study design and is not at random. The MAH conducted additional sensitivity analyses as requested and confirmed that the conclusions of the clinical study report remain valid.

Results

Participant flow

A total of 817 patients were screened and 606 were randomized to the 3 treatment groups. Of the randomized patients, 515 (85.0%) patients completed 52 weeks of treatment (86.1% in the secukinumab 10 mg/kg-75 mg group, 89.1% in the secukinumab 10 mg/kg-150 mg group and 79.7% in the placebo group (**Table 5**).

Of the 202 patients in the placebo group, 187 patients were re-randomized (1:1). Of these placebo patients, 4 patients discontinued before receiving secukinumab, 123 non-responding patients received secukinumab starting at Week 16 (75 mg: 62 patients and 150 mg: 61 patients) sc every 4 weeks, and 60 patients continued on placebo until Week 24 and then received either secukinumab 75 mg (28 patients) or 150 mg (32 patients) sc every 4 weeks. Overall, 161 patients in the placebo group completed Week 52.

For the 91 patients who discontinued at Week 52, the most common reason for premature discontinuation was lack of efficacy which occurred at a higher rate in the placebo group (6.4%) compared to the secukinumab 10 mg/kg-75 mg group (3.0%) and the secukinumab 10 mg/kg-150 mg group (3.5%).

Similar percentages of patients reported having at least one protocol deviation up to Week 24 (28.7% vs. 23.8% vs. 29.7% in the secukinumab 10 mg/kg-75 mg, secukinumab 10 mg/kg-150 mg and placebo groups, respectively). The most common categories were “key procedures not performed as per-protocol” and “GCP-related deviation”. Percentages of patients reporting at least one protocol deviation during the entire treatment period were 34.7% in secukinumab 10 mg/kg-75 mg, 31.2% in secukinumab 10 mg/kg-150 mg and 34.2% in placebo.

Table 5. Patient disposition-up to Week 52-Randomised set (Study F2306).

Disposition /Reason	AIN457 10mg/kg - 75 mg N=202 n (%)	AIN457 10mg/kg - 150 mg N=202 n (%)	Placebo N=202 n (%)	Placebo Non-responder - AIN457 75 mg N=62 n (%)	Placebo Non-responder - AIN457 150 mg N=61 n (%)	Placebo Responder - AIN457 75 mg N=31 n (%)	Placebo Responder - AIN457 150 mg N=33 n (%)
Randomized	202	202	202	62	61	31	33
Completed Week 52	174 (86.1)	180 (89.1)	161 (79.7)	55 (88.7)	51 (83.6)	27 (87.1)	28 (84.8)
Discontinued Week 52	28 (13.9)	22 (10.9)	41 (20.3)	7 (11.3)	10 (16.4)	4 (12.9)	5 (15.2)
Adverse event	6 (3.0)	5 (2.5)	9 (4.5)	2 (3.2)	2 (3.3)	1 (3.2)	1 (3.0)
Lack of efficacy	6 (3.0)	7 (3.5)	13 (6.4)	1 (1.6)	5 (8.2)	1 (3.2)	0 (0.0)
Lost to follow-up	1 (0.5)	1 (0.5)	4 (2.0)	0 (0.0)	0 (0.0)	1 (3.2)	2 (6.1)
Physician decision	6 (3.0)	4 (2.0)	2 (1.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	1 (0.5)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol deviation	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject /guardian decision	6 (3.0)	5 (2.5)	12 (5.9)	2 (3.2)	3 (4.9)	1 (3.2)	2 (6.1)
Death	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Placebo patients who are not re-randomized are counted in the placebo total only.

Recruitment

Study initiation date: 08 Sep 2011 (first patient first visit)

Study completion date: Not applicable. Last Visit 17 / Week 52 for interim analysis was on 09 Oct 2013.

Conduct of the study

The study protocol was amended 3 times. The amendments are considered minor and occurred prior to study un-blinding.

The following changes were made to the planned analysis:

- Prior to database lock, the baseline definition was revised in the statistical analysis plan to allow X-ray and MRI values collected within 30 days/7 days (respectively) after dosing to be considered as baseline values.

Baseline data

The majority of patients were < 65 years of age (89.1% in both the secukinumab 10 mg/kg-75 mg group and secukinumab 10 mg/kg-150 mg group and 95.0% in the placebo group) with a mean age of 49 years). More than half of the patients were female (54.5%) and more than two-thirds of patients (74.6%) were non- hispanic or latino. Around 20% were smokers at baseline. The mean BMI (±SD) was: 30.05±6.250 kg/m2, in the secukinumab 10 mg/kg-75 mg group, 29.86±6.828 kg/m2 in the secukinumab 10 mg/kg-150 mg group and 28.67±6.476 kg/m2 in the placebo group.

Baseline demographics and disease characteristics are reported in **Table 6**.

Table 6. Demographic and background characteristics by randomised Treatment (Randomised set, Study F2306)

Demographic variable	AIN457 10mg/kg - 75 mg N=202	AIN457 10mg/kg - 150 mg N=202	Placebo N=202
Age group in years, n (%)			
< 65	180 (89.1)	180 (89.1)	192 (95.0)
>= 65	22 (10.9)	22 (10.9)	10 (5.0)
>= 75	1 (0.5)	0 (0.0)	1 (0.5)
Age (Years)			
N	202	202	202
Mean	48.8	49.6	48.5
SD	12.23	11.76	11.19
Median	50.0	51.0	49.0
Min – Max	20 - 76	22 - 73	21 - 77
Gender, n (%)			
Female	118 (58.4)	106 (52.5)	106 (52.5)
Male	84 (41.6)	96 (47.5)	96 (47.5)
Race, n (%)			
White	165 (81.7)	162 (80.2)	154 (76.2)
Black of African American	2 (1.0)	3 (1.5)	0 (0.0)
Asian	33 (16.3)	36 (17.8)	46 (22.8)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	1 (0.5)
Unknown	1 (0.5)	0 (0.0)	0 (0.0)
Other	1 (0.5)	1 (0.5)	1 (0.5)

Ethnicity, n (%)			
Hispanic or Latino	15 (7.4)	16 (7.9)	14 (6.9)
Not Hispanic or Latino	143 (70.8)	150 (74.3)	159 (78.7)
Unknown	23 (11.4)	19 (9.4)	10 (5.0)
Not reported	21 (10.4)	17 (8.4)	19 (9.4)
Height (cm)			
N	201	200	202
Mean	167.51	167.94	166.54
SD	10.127	10.286	10.143
Median	167.00	168.00	167.00
Min – Max	145.0 - 201.0	143.0 - 200.0	144.0 - 190.5
Weight (kg)			
N	202	202	202
Mean	84.45	84.23	80.00
SD	19.608	21.052	20.472
Median	82.00	83.00	79.85
Min - Max	44.0 - 155.1	50.0 - 163.3	32.0 - 152.4
BMI (kg/m2)**			
n	201	200	202
Mean	30.05	29.86	28.67
SD	6.250	6.828	6.476
Median	29.34	28.46	27.47
Min - Max	17.3 - 51.4	16.7 - 58.6	14.6 - 59.5
Current smoker at baseline, n (%)			
No	168 (83.2)	160 (79.2)	162 (80.2)
Yes	34 (16.8)	42 (20.8)	40 (19.8)

Baseline DAS28CRP score			
n	202	201	201
Mean	4.891	4.782	4.929
SD	1.1502	1.0941	1.0994
Minimum	1.52	1.83	2.28
Q1	4.092	3.996	4.062
Median	4.815	4.664	4.844
Q3	5.678	5.478	5.718
Maximum	8.12	7.86	7.54
Presence of enthesitis n (%)			
Yes	129 (63.9)	126 (62.4)	117 (57.9)
No	73 (36.1)	76 (37.6)	85 (42.1)
Presence of dactylitis n (%)			
Yes	104 (51.5)	104 (51.5)	116 (57.4)
No	98 (48.5)	98 (48.5)	86 (42.6)
MTX use at randomization			
Yes	122 (60.4)	121 (59.9)	125 (61.9)
No	80 (39.6)	81 (40.1)	77 (38.1)

Dose of methotrexate at randomization (mg/week)

Background Characteristics	AIN457 10mg/kg - 75 mg N=202	AIN457 10mg/kg - 150 mg N=202	Placebo N=202
n	115	118	122
Mean	15.26	14.56	14.41
SD	5.004	5.267	5.417
Minimum	2.5	2.5	2.5
Q1	10.00	10.00	10.00
Median	15.00	15.00	15.00
Q3	20.00	20.00	20.00
Maximum	30.0	25.0	25.0
Tender joint total score for PsA 78 joints			
n	202	202	202
Mean	23.4	23.8	25.1
SD	17.19	16.40	18.41
Minimum	3	3	1
Q1	11.0	11.0	11.0
Median	19.0	20.5	19.0
Q3	32.0	31.0	35.0
Maximum	75	78	78
Swollen joint total score for PsA 76 joints			
n	202	202	202
Mean	12.7	12.5	14.9
SD	11.11	9.38	13.06
Minimum	3	3	2
Q1	5.0	6.0	6.0
Median	9.0	10.0	10.0
Q3	16.0	16.0	18.0
Maximum	68	56	66
Baseline DAS28ESR score			
n	202	201	201
Mean	5.434	5.373	5.501
SD	1.3072	1.2098	1.2197
Minimum	1.87	2.23	2.56
Q1	4.487	4.704	4.576
Median	5.426	5.274	5.401
Q3	6.438	6.181	6.457
Maximum	8.71	8.49	8.29
Patients global assessment of disease (PsA) activity			
n	202	201	201
Mean	56.1	55.2	55.6
SD	22.62	23.99	21.70
Minimum	0	4	1
Q1	42.0	39.0	44.0
Median	55.0	53.0	57.0
Q3	74.0	73.0	70.0
Maximum	100	100	100

Background Characteristics	AIN457 10mg/kg - 75 mg N=202	AIN457 10mg/kg - 150 mg N=202	Placebo N=202
Physicians global assessment			
n	198	199	200
Mean	54.3	58.3	56.7
SD	18.04	18.88	18.78
Minimum	0	1	1
Q1	43.0	46.0	44.0
Median	56.0	59.0	57.0
Q3	67.0	71.0	70.0
Maximum	100	100	100
Psoriatic arthritis pain today			
n	202	200	201
Mean	55.1	55.7	56.7
SD	22.07	24.22	21.06
Minimum	0	4	3
Q1	41.0	38.5	45.0
Median	56.5	58.0	59.0
Q3	70.0	76.0	71.0
Maximum	100	100	100
Naive to TNF alpha inhibitors			
Yes	142 (70.3)	143 (70.8)	143 (70.8)
No	60 (29.7)	59 (29.2)	59 (29.2)
Proportion of patients with psoriasis of hands and feet			
Yes	102 (50.5)	103 (51.0)	108 (53.5)
No	100 (49.5)	99 (49.0)	93 (46.0)
Proportion of patients with psoriasis of the nail			
Yes	136 (67.3)	145 (71.8)	154 (76.2)
No	66 (32.7)	57 (28.2)	47 (23.3)
Time since first diagnosis of psoriatic arthritis (years)			
n	200	201	201
Mean	7.830	8.337	7.437
SD	8.5695	8.5338	8.0881
Minimum	0.04	0.04	0.02
Q1	2.082	2.045	1.747
Median	5.101	5.342	4.375
Q3	9.900	11.855	11.190
Maximum	49.30	45.68	48.27
CASPAR Total Score			
n	202	202	202
Mean	4.361	4.381	4.391
SD	0.8364	0.9023	0.8584
Minimum	3.00	2.00	3.00
Q1	4.000	4.000	4.000
Median	4.000	4.000	5.000
Q3	5.000	5.000	5.000

Background Characteristics	AIN457 10mg/kg - 75 mg N=202	AIN457 10mg/kg - 150 mg N=202	Placebo N=202
Maximum	6.00	6.00	6.00
Target Lesion Diameter			
n	182	186	183
Mean	8.45	8.12	8.02
SD	11.460	10.017	8.080
Minimum	0.0	0.0	0.0
Q1	3.00	3.00	3.00
Median	5.00	5.00	5.00
Q3	9.00	9.00	10.00
Maximum	90.0	70.0	50.0
Health Assessment Questionnaire - Disability Index (HAQ-DI©)			
n	201	200	201
Mean	1.2512	1.2313	1.1884
SD	0.66568	0.68175	0.64410
Minimum	0.000	0.000	0.000
Q1	0.7500	0.7500	0.7500
Median	1.2500	1.2500	1.1250
Q3	1.7500	1.7500	1.7500
Maximum	2.875	3.000	2.750
Systemic glucocorticoids use at randomization			
Yes	34 (16.8)	34 (16.8)	27 (13.4)
No	168 (83.2)	168 (83.2)	175 (86.6)
Number of prior anti-TNF PsA therapies*			
0	142 (70.3)	143 (70.8)	142 (70.3)
1	35 (17.3)	39 (19.3)	36 (17.8)
>=2	25 (12.4)	20 (9.9)	24 (11.9)
Patients with psoriasis >= 3% of BSA			
Yes	108 (53.5)	108 (53.5)	109 (54.0)
No	94 (46.5)	94 (46.5)	93 (46.0)
Baseline PASI score			
n	108	108	109
Mean	10.67	15.62	15.10
SD	8.833	13.888	11.633
Minimum	0.8	2.4	0.8
Q1	4.60	6.25	7.00
Median	8.20	11.25	11.80
Q3	15.45	19.35	19.20
Maximum	59.1	72.0	62.8
Baseline PASI, n (%)			
<=10	64 (59.3)	50 (46.3)	46 (42.2)
>10	44 (40.7)	58 (53.7)	63 (57.8)
Baseline IGA mod 2011 score, n (%)			

Background Characteristics	AIN457 10mg/kg - 75 mg N=202	AIN457 10mg/kg - 150 mg N=202	Placebo N=202
0 = Clear	0 (0.0)	0 (0.0)	1 (0.9)
1 = Almost clear	1 (0.9)	0 (0.0)	1 (0.9)
2 = Mild disease	26 (24.1)	22 (20.4)	20 (18.3)
3 = Moderate disease	65 (60.2)	64 (59.3)	67 (61.5)
4 = Severe disease	15 (13.9)	21 (19.4)	20 (18.3)
5 = Very severe disease	0 (0.0)	0 (0.0)	0 (0.0)

*Started before the first dosing of study treatment

Numbers analysed

The following analysis sets were used for the data analysis: Randomized set; Full analysis set (FAS); and Safety set. The total number of patients in each analysis set was 606 and the number of patients by treatment group was 202. Efficacy analyses were performed on an intent-to-treat basis, involving all 606 randomized patients who were assigned to study treatment (**Table 7**).

Table 7. Analysis sets by treatment sequence (Randomised set, Study F2306)

Analysis Set	AIN457 10 mg/kg - 75 mg N	AIN457 10 mg/kg - 150 mg N	Placebo N	Placebo Non-responder - AIN457 75 mg N	Placebo Non-responder - AIN457 150 mg N	Placebo Responder - AIN457 75 mg N	Placebo Responder - AIN457 150 mg N
Randomized set	202	202	202	62	61	31	33
Full analysis set	202	202	202	62	61	31	33
Safety set	202	202	202	62	61	31	33
Treated with AIN457 after re-randomization	--	--	183	62	61	28	32

Placebo column include patients randomized to placebo at the beginning and re-randomized to AIN457 later, as well as those prematurely discontinued without taking AIN457.
- Placebo patients who are not re-randomized are counted in the placebo total only.

Outcomes and estimation

The results of the primary efficacy variable ACR20 response using non-responder imputation for the FAS at Week 24 is shown in **Table 8** and **Figure 7**.

Secukinumab at both doses (10 mg/kg-75 mg and 10 mg/kg-150 mg) was statistically significantly superior to placebo for ACR20 response at Week 24 ($p<0.0001$). At Week 24, the ACR20 response rate was 50.5% for secukinumab 10 mg/kg-75 mg, 50.0% for secukinumab 10 mg/kg-150 mg and 17.3% for placebo.

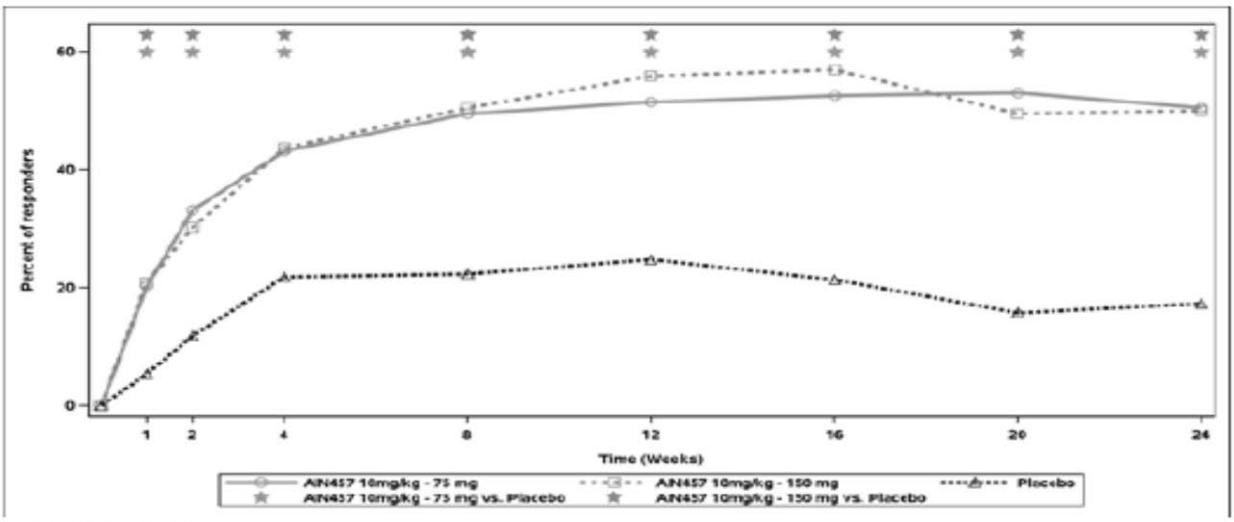
Table 8. ACR20 response using non-responder imputation - up to Week 24 (Full analysis set)

Analysis visit	Treatment Group	n/M (%)	Comparison	Odds ratio	95% Confidence Interval	p-value
Week 1	AIN457 10 mg/kg - 75 mg (N = 202)	41/202 (20.3)	vs. Placebo	4.46	(2.21, 8.97)	<.0001
	AIN457 10 mg/kg - 150 mg (N = 202)	42/202 (20.8)	vs. Placebo	4.59	(2.28, 9.22)	<.0001
	Placebo (N = 202)	11/202 (5.4)				
Week 2	AIN457 10 mg/kg -	67/202 (33.2)	vs. Placebo	3.81	(2.26, 6.42)	<.0001

	75 mg (N = 202)					
	AIN457 10 mg/kg - 150 mg (N = 202)	61/202 (30.2)	vs. Placebo	3.30	(1.95, 5.58)	<.0001
	Placebo (N = 202)	24/202 (11.9)				
Week 4	AIN457 10 mg/kg - 75 mg (N = 202)	87/202 (43.1)	vs. Placebo	2.96	(1.90, 4.61)	<.0001
	AIN457 10 mg/kg - 150 mg (N = 202)	88/202 (43.6)	vs. Placebo	3.00	(1.93, 4.68)	<.0001
	Placebo (N = 202)	44/202 (21.8)				
Week 8	AIN457 10 mg/kg - 75 mg (N = 202)	100/202 (49.5)	vs. Placebo	3.65	(2.36, 5.65)	<.0001
	AIN457 10 mg/kg - 150 mg (N = 202)	102/202 (50.5)	vs. Placebo	3.78	(2.44, 5.86)	<.0001
	Placebo (N = 202)	45/202 (22.3)				
Week 12	AIN457 10 mg/kg - 75 mg (N = 202)	104/202 (51.5)	vs. Placebo	3.57	(2.31, 5.50)	<.0001
	AIN457 10 mg/kg - 150 mg (N = 202)	113/202 (55.9)	vs. Placebo	4.27	(2.77, 6.60)	<.0001
	Placebo (N = 202)	50/202 (24.8)				
Week 16	AIN457 10 mg/kg - 75 mg (N = 202)	106/202 (52.5)	vs. Placebo	4.43	(2.84, 6.91)	<.0001
	AIN457 10 mg/kg - 150 mg (N = 202)	115/202 (56.9)	vs. Placebo	5.31	(3.39, 8.31)	<.0001
	Placebo (N = 202)	43/202 (21.3)				
Week 20	AIN457 10 mg/kg - 75 mg (N = 202)	107/202 (53.0)	vs. Placebo	6.90	(4.25, 11.17)	<.0001
	AIN457 10 mg/kg - 150 mg (N = 202)	100/202 (49.5)	vs. Placebo	5.93	(3.66, 9.60)	<.0001
	Placebo (N = 202)	32/202 (15.8)				
Week 24	AIN457 10 mg/kg - 75 mg (N = 202)	102/202 (50.5)	vs. Placebo	5.53	(3.46, 8.85)	<.0001
	AIN457 10 mg/kg - 150 mg (N = 202)	101/202 (50.0)	vs. Placebo	5.39	(3.37, 8.62)	<.0001
	Placebo (N = 202)	35/202 (17.3)				

Odds ratio, 95% confidence interval, and p-value are from a logistic regression model with treatment and randomization stratum (TNFa status -naive or IR) as factors and baseline weight as a covariate.
Odds ratio > 1 favors AIN457.
M: Number of patients in the treatment group.
n: The number of patients who are ACR20 responders with the corresponding imputation approach in the treatment group.

Figure 7. ACR20 response using non-responder imputation - up to Week 24 (Full analysis set)



*P-value < 0.05

Secondary efficacy results

The results of the hypothesis tests within the testing strategy are shown in **Table 9**. Secukinumab 10 mg/kg-75 mg and 10 mg/kg-150 mg were superior to placebo at Week 24 for all endpoints in the testing hierarchy. All p-values except that for the vdH-mTSS were <0.0001.

Table 9. Results for primary and secondary endpoints based on hierarchical testing sequence

Endpoint	Secukinumab 10 mg/kg - 75 mg (N=202)	Secukinumab 10 mg/kg - 150 mg (N =202)	Pooled Secukinumab (N =404)	Placebo (N =202)
Primary Endpoint: ACR 20	50.5% p < 0.0001	50.0% p < 0.0001	--	17.3%
PASI 75	64.8% p < 0.0001	61.1% p < 0.0001	--	8.3%
PASI 90	49.1% p < 0.0001	45.4% p < 0.0001	--	3.7%
DAS28-CRP	-1.67 p < 0.0001	-1.62 p <0.0001	--	-0.77
SF-36 PCS	5.41 p < 0.0001	5.91 p < 0.0001	--	1.82
HAQ-DI©	-0.41 p < 0.0001	-0.40 p < 0.0001	--	-0.17
ACR 50	30.7% p < 0.0001	34.7% p < 0.0001	--	7.4%
van der Heijde modified total Sharp score**	0.02 p = 0.0132	0.13 p = 0.0212	0.08 p = 0.0113	0.57
Presence of Dactylitis**	43.3% p < 0.0001	51.9% p < 0.0001	47.6% p < 0.0001	84.5%
Presence of Enthesitis**	51.2% p < 0.0001	54.0% p < 0.0001	52.5% p < 0.0001	87.2%

**hierarchy order is first pooled van der Heijde modified total Sharp score, followed by pooled dactylitis and enthesitis scores, lastly van der Heijde modified total Sharp score for individual doses. Individual doses for dactylitis and enthesitis are not in the hierarchy

Study CAIN457F2312 (also referred to as F2312)

A Phase III randomized, double-blind, placebo-controlled multicenter study of subcutaneous secukinumab in prefilled syringes to demonstrate the efficacy at 24 weeks and to assess the long term efficacy, safety and tolerability up to 5 years in patients with Active Psoriatic Arthritis

Methods

Study participants

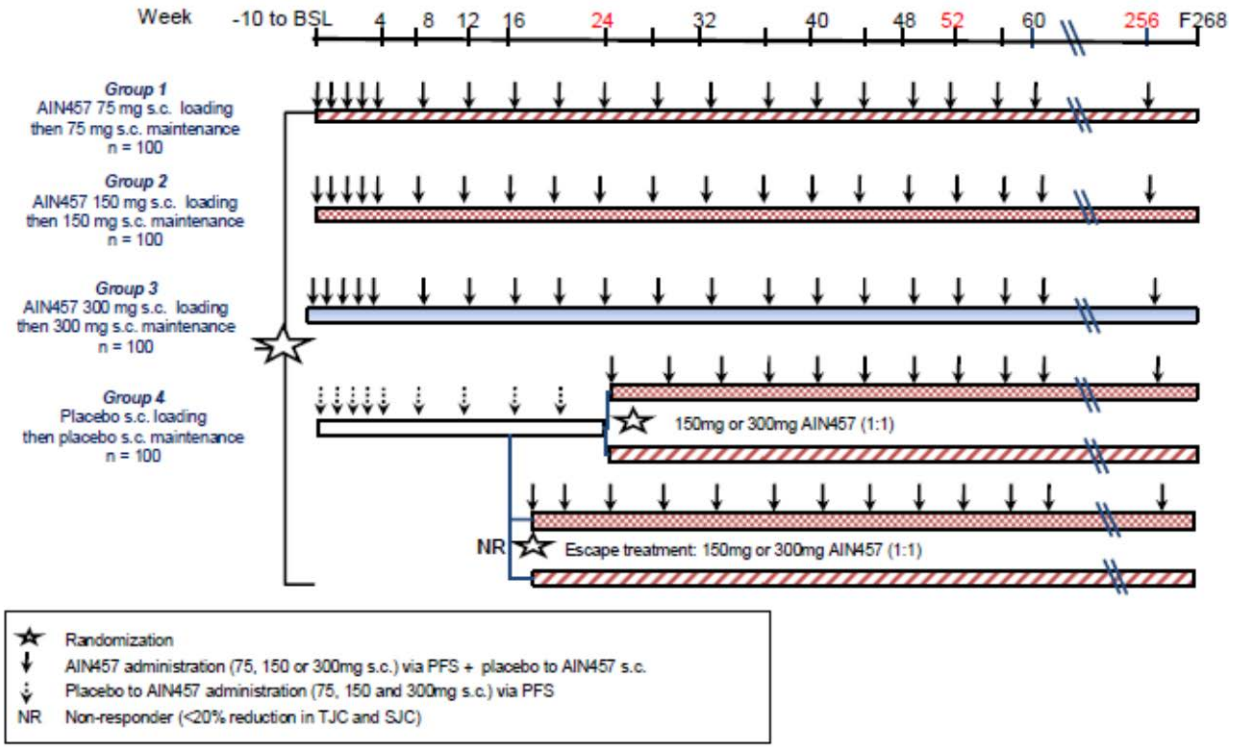
There were 76 study centres in 10 countries (Australia 4 centres, Belgium 3 centres, Canada 6 centres, Czech Republic 4 centres, Germany 9 centres, Poland 6 centres, Russia Federation 10 centres, Thailand 2 centres, United Kingdom 10 centres, United States of America 22 centres).

Inclusion and exclusion criteria were identical to those of Study F2306, with the addition of the following exclusion criterion: History of hypersensitivity to the study drug or its excipient or to drugs of similar chemical classes.

Treatments

The study design is presented in **Figure 8**.

Figure 8. Schematic of Study F2312 design



BSL= baseline; n=number of patients; PFS=pre-filled syringe; sc=subcutaneous; SJC=Swollen Joint Count; TJC=Tender Joint Count

At baseline, patients were randomized to one of the following 4 treatment arms in a ratio of 1:1:1:1:

- Group 1: Secukinumab 75 mg (0.5 mL) plus placebo (2 x 1.0 mL) at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4.
- Group 2: Secukinumab 150 mg (1.0 mL) plus placebo (0.5 mL and 1.0 mL) at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4.
- Group 3: Secukinumab 300 mg (2 × 1.0 mL) plus placebo (0.5 mL) at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4.
- Group 4: Placebo (2 × 1.0 mL and 1× 0.5 mL) at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4.

At Week 16, patients were classified as responders (ACR20 response defined as ≥ 20% improvement from baseline in both tender and swollen joint counts) or non-responders. Patients who were randomized to Groups 1, 2, and 3 continued to receive study treatment as described above regardless of responder status. Patients who were randomized to placebo at baseline were re-randomized by the Interactive Response Technology (IRT) to receive double-blind treatment up to 52 weeks, as follows:

- Group 4: Placebo patients who were non-responders were re-randomized in a 1:1 ratio to receive secukinumab 150 mg sc or 300 mg sc every 4 weeks.
- Group 4: Placebo patients who were responders continued to receive placebo every 4 weeks until Week 24. Starting at Week 24, these patients received secukinumab 150 mg sc or 300 mg sc (1:1) every 4 weeks regardless of responder status (as dictated by the re-randomization).

All study treatments were self-administered by the patients at the study site up to Week 104. After Week 104, the patients were allowed to self-administer the PFS at home during the optional visits in which there were no scheduled site assessments.

At Week 24, efficacy of secukinumab treatment was assessed based on an ACR20 response.

According to the investigational plan, response to study treatment was also assessed at the Week 52 visit. Un-blinding is planned after the Week 52 analysis was conducted in order to eliminate the placebo injection. Responders (ACR20 response) patients continued in the post Week 52 open-label long-term treatment period on the same treatment dose and regimen (secukinumab 75 mg, 150 mg or 300 mg every 4 weeks) until Week 256 and non-responder patients will be discontinued the study.

Objectives, Outcomes/endpoints

The objectives, primary and secondary endpoints of the study were similar to those of study F2306 with an additional comparison between the 300 mg dose and placebo while no assessment of joint/bone structural damage was performed.

Sample size

A 5% two-sided type I error rate was used to control for type I error. Three secukinumab doses were tested versus placebo with respect to the primary endpoint (ACR20 response at Week 24), thus the type-I-error was split to 1.7% two-sided for each comparison. Sample sizes were based on this type I error assumption.

The overall placebo rate was expected to be 21% and the overall rate on a dose of secukinumab was expected to be 47%. For the primary endpoint of ACR20 response in the FAS population, 100 patients per group would yield approximately 92% power to detect a treatment difference of 26% (Fisher's exact test, NQuery 7.0).

Randomisation

At baseline, all eligible patients were randomized via IRT to one of four treatment arms. At Week 16, patients were classified as responders or non-responders. Patients who were randomised to placebo at baseline were re-randomised to receive double-blind treatment up to 52 weeks.

The patients were stratified at randomization according to either TNFα-IR or TNFα inhibitor naïve patients. Approximately 40% of randomized patients should be TNFα-IR to ensure a representative patient population for the assessment of efficacy and safety.

Blinding (masking)

This was a double-blind, double-dummy study.

Statistical methods

See the methods described for study F2306.

For binary variables (*e.g.,* ACR20 response) a logistic regression model was fitted with treatment and TNFα-inhibitor status as factors and baseline score (if appropriate) and weight as covariates. In cases where separation was a concern at Week 24 time-point, *e.g.,* 0% response in one treatment (sub)-

group, an exact logistic regression model was applied. Fisher's exact test was applied for situations where separation issues caused both logistic regression and exact logistic regression to fail.

Results

Participant flow

A total of 397 patients were randomized to 4 treatment groups: secukinumab 75 mg, 150 mg, 300 mg, and placebo. Of the total randomized, 373 (94.0%) patients completed 24 weeks of treatment. More patients in the placebo group (10.2%) discontinued treatment compared with all of the secukinumab groups (range: 3.0%-6.1%). Of the 98 patients in the placebo group, 88 patients completed Week 24 and were re-randomized (1:1) **(Table 10**).

For the 24 patients who discontinued at Week 24, the most common reason for premature discontinuation was AEs, which occurred at a higher rate in the placebo group compared with secukinumab groups.

The number of patients who reported at least 1 protocol deviation up to Week 24 was lower in the secukinumab 75 mg group compared with the rest of the treatment groups (13.1% vs 15.0-18.4%). The most common categories for protocol deviations up to Week 24 were Good Clinical Practices (GCP) related deviations, followed by prohibited concomitant medication and selection criteria not met.

Table 10. Study design Patient disposition - up to Week 24 (Randomised set, Study F2312)

Disposition/Reason	AIN457 75 mg N=99 n (%)	AIN457 150 mg N=100 n (%)	AIN457 300 mg N=100 n (%)	Placebo N=98 n (%)
Randomized	99	100	100	98
Completed Week 24	93 (93.9)	95 (95.0)	97 (97.0)	88 (89.8)
Discontinued Week 24	6 (6.1)	5 (5.0)	3 (3.0)	10 (10.2)
Adverse event	3 (3.0)	0 (0.0)	2 (2.0)	4 (4.1)
Lack of efficacy	2 (2.0)	3 (3.0)	0 (0.0)	3 (3.1)
Physician decision	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Subject/guardian decision	1 (1.0)	1 (1.0)	1 (1.0)	3 (3.1)

Placebo patients who are not re-randomized are counted in the placebo total only.

Recruitment

Study initiation date: 14-Apr-2013 (first patient first visit)

Study completion date: Not applicable (last patient Visit 12/ Week 24 for interim analysis was on 12-May-2014)

The primary endpoint analysis (Week 24 analysis) was performed after all patients had completed Week 24 visit. Additional analyses are planned for regulatory submission and/or publication purposes after all patients have completed year 1, 2, 3, 4 and 5.

Conduct of the study

The original study protocol (dated 15-Oct-2012) was amended once (25-Feb-2014).

There were no changes to study conduct. The following changes were made in the planned analysis:

- Prior to database lock, logistic regression was planned for binary endpoints. However, low response rates due to small sample sizes for a few subgroup analyses (*e.g.,* by TNFα-IR status or concomitant MTX use) caused separation (ie, convergence) issues when applying logistic regression. The planned alternative method, exact logistic regression, was applied but also did not converge. A second alternative method, Fisher's exact test, was therefore proposed and applied for situations where separation issues caused both logistic regression and exact logistic regression to fail.
- An additional data-driven analysis was explored to determine the effect of weight on ACR20 response with a <100 kg and ⩾100 kg cutoff. Interactions between treatment and other baseline covariates for ACR20 response at Week 24 show weight may have a possible association with ACR20 response. Therefore, both a table and a figure were created showing ACR20 response through Week 24 by the 100 kg weight cutoff.

Baseline data

Baseline demographics were generally balanced across the treatment groups. The majority of patients were < 65 years of age with a mean age of approximately 48 years. More than half of the population were female (51.6%). Overall, the female to male ratio was equal in the groups except for the placebo group which had 60.2% female and 39.8% male patients. Over 90% of patients were white and more than 80% were not Hispanic or Latino. Around 20% were smokers at baseline.

Disease history and baseline characteristics are reported in **Table 11.**

Table 11. Disease history and baseline characteristics by randomized treatment (Randomised set, Study F2312)

Demographic variable	AIN457 75 mg N=99	AIN457 150 mg N=100	AIN457 300 mg N=100	Placebo N=98
Age group in years, n(%)				
< 65	93 (93.9)	94 (94.0)	90 (90.0)	87 (88.8)
65-74	6 (6.1)	6 (6.0)	9 (9.0)	9 (9.2)
≥75	0 (0.0)	0 (0.0)	1 (1.0)	2 (2.0)
Age (Years)				
n	99	100	100	98
Mean	48.6	46.5	46.9	49.9
SD	11.42	11.72	12.57	12.53
Median	51.0	46.5	46.5	51.0
Min - Max	21 - 71	20 - 67	23 - 77	20 - 77
Gender, n(%)				
Female	52 (52.5)	45 (45.0)	49 (49.0)	59 (60.2)
Male	47 (47.5)	55 (55.0)	51 (51.0)	39 (39.8)

Race, n(%)				
American Indian or Alaska Native	0 (0.0)	2 (2.0)	0 (0.0)	0 (0.0)
Asian	5 (5.1)	6 (6.0)	2 (2.0)	1 (1.0)
Black or African American	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Native Hawaiian or other Pacific Islander	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
White	90 (90.9)	90 (90.0)	96 (96.0)	94 (95.9)
Unknown	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (2.0)	1 (1.0)	1 (1.0)	3 (3.1)
Ethnicity, n(%)				
Hispanic or Latino	2 (2.0)	5 (5.0)	4 (4.0)	4 (4.1)
Not Hispanic or Latino	84 (84.8)	82 (82.0)	80 (80.0)	79 (80.6)
Not reported	6 (6.1)	9 (9.0)	9 (9.0)	6 (6.1)
Unknown	7 (7.1)	4 (4.0)	7 (7.0)	9 (9.2)
Height (cm)				
Mean	168.47	170.70	170.46	168.90
SD	9.803	9.847	9.601	9.630
Median	167.00	170.80	169.30	168.50
Min - Max	146.0 - 193.0	152.5 - 203.2	142.2 - 198.0	148.0 - 189.2
Weight (kg)				
Mean	85.62	91.22	85.37	86.19
SD	20.558	19.814	18.429	19.802
Median	87.40	91.35	83.00	85.55
Min - Max	47.5 - 132.4	47.3 - 146.5	52.2 - 161.0	54.2 - 147.3
BMI (kg/m^2)				
Mean	30.12	31.18	29.38	30.10
SD	6.958	5.802	5.800	5.963
Median	29.51	30.47	28.26	29.33
Min - Max	18.6 - 59.0	20.1 - 48.1	19.0 - 48.3	19.6 - 50.3
Current smoker at baseline, n (%)				
No	79 (79.8)	79 (79.0)	81 (81.0)	81 (82.7)
Yes	20 (20.2)	21 (21.0)	19 (19.0)	17 (17.3)

Background Characteristics	AIN457 75 mg N=99	AIN457 150 mg N=100	AIN457 300 mg N=100	Placebo N=98
Baseline DAS28CRP score				
n	98	100	99	98
Mean	4.709	4.899	4.763	4.712
SD	1.0022	1.1206	1.0061	1.0467
Median	4.610	4.868	4.744	4.527
Presence of enthesitis, n (%)				
Yes	68 (68.7)	64 (64.0)	56 (56.0)	65 (66.3)
No	30 (30.3)	36 (36.0)	44 (44.0)	33 (33.7)
Presence of dactylitis, n (%)				
Yes	33 (33.3)	32 (32.0)	46 (46.0)	27 (27.6)
No	65 (65.7)	68 (68.0)	54 (54.0)	71 (72.4)
MTX use at randomization, n (%)				
Yes	47 (47.5)	44 (44.0)	44 (44.0)	50 (51.0)
No	52 (52.5)	56 (56.0)	56 (56.0)	48 (49.0)
Dose of methotrexate at randomization (mg/week)				
n	47	44	43	50
Mean	18.032	17.188	16.105	17.600
SD	7.2220	5.1371	5.3258	11.2141
Median	17.500	18.750	15.000	15.000
Tender joint total score for PsA 78 joints				
n	99	100	100	98
Mean	22.2	24.1	20.2	23.4
SD	16.32	19.36	13.33	18.97
Median	18.0	18.0	17.0	17.0
Swollen joint total score for PsA 76 joints				
n	99	100	100	98
Mean	10.8	11.9	11.2	12.1
SD	9.17	10.05	7.77	10.65
Median	8.0	8.0	9.0	8.5
Baseline DAS28ESR score				
n	98	100	99	98
Mean	5.129	5.268	5.180	5.188
SD	1.2165	1.3003	1.2230	1.1927
Median	5.054	5.219	5.131	5.151
Subjects global assessment				
n	98	100	99	98
Mean	59.0	62.0	60.7	57.6
SD	19.09	19.53	18.93	19.77
Median	60.5	65.5	64.0	59.0
Physicians global assessment				
n	98	100	99	98
Mean	59.0	56.7	55.0	55.0
SD	17.86	16.59	14.72	15.98

Background Characteristics	AIN457 75 mg N=99	AIN457 150 mg N=100	AIN457 300 mg N=100	Placebo N=98
Median	60.0	58.5	55.0	57.5
Psoriatic arthritis pain today				
n	98	100	99	98
Mean	56.7	58.9	57.7	55.4
SD	21.11	19.76	19.02	22.11
Median	60.0	61.0	58.0	57.0
Naive to TNF alpha inhibitors, n (%)				
Yes	65 (65.7)	63 (63.0)	67 (67.0)	63 (64.3)
No	34 (34.3)	37 (37.0)	33 (33.0)	35 (35.7)
Proportion of patients with psoriasis of hands and feet, n (%)				
Yes	43 (43.4)	62 (62.0)	39 (39.0)	40 (40.8)
No	56 (56.6)	38 (38.0)	61 (61.0)	58 (59.2)
Proportion of patients with psoriasis of the nail, n (%)				
Yes	76 (76.8)	75 (75.0)	63 (63.0)	65 (66.3)
No	23 (23.2)	25 (25.0)	37 (37.0)	33 (33.7)
Time since first diagnosis of psoriatic arthritis (years)				
n	99	100	100	98
Mean	6.484	6.512	7.381	7.318
SD	7.1775	8.1728	7.4798	7.7610
Median	3.934	4.297	4.705	4.951
CASPAR Total Score				
n	99	100	100	98
Mean	4.222	4.270	4.220	4.031
SD	0.8398	0.8022	0.8713	0.8550
Median	4.000	4.000	4.000	4.000
Disability index score (HAQ-DI)				
n	98	100	99	98
Mean	1.1620	1.2200	1.2828	1.1684
SD	0.63261	0.60174	0.58346	0.66486
Median	1.2500	1.2500	1.2500	1.2500
Systemic glucocorticoids use at randomization, n (%)				
Yes	19 (19.2)	23 (23.0)	18 (18.0)	21 (21.4)
No	80 (80.8)	77 (77.0)	82 (82.0)	77 (78.6)
Number of prior anti-TNF PsA therapies*, n (%)				
=0	65 (65.7)	63 (63.0)	67 (67.0)	63 (64.3)
=1	21 (21.2)	26 (26.0)	16 (16.0)	16 (16.3)
>=2	13 (13.1)	11 (11.0)	17 (17.0)	19 (19.4)
Patients with psoriasis ≥ 3% of BSA, n (%)				
Yes	50 (50.5)	58 (58.0)	41 (41.0)	43 (43.9)
No	49 (49.5)	42 (42.0)	59 (59.0)	55 (56.1)
Distal interphalangeal joint arthritis, n (%)				
Yes	62 (62.6)	57 (57.0	62 (62.0)	49 (50.0)
No	37 (37.4)	43 (43.0)	38 (38.0)	48 (49.0)
Presence of arthritis mutilans, n (%)				
Yes	7 (7.1)	7 (7.0)	5 (5.0)	6 (6.1)

Background Characteristics	AIN457 75 mg N=99	AIN457 150 mg N=100	AIN457 300 mg N=100	Placebo N=98
No	91 (91.9)	93 (93.0)	95 (95.0)	92 (93.9)
Asymetric peripheral arthritis, n (%)				
Yes	61 (61.6)	64 (64.0)	68 (68.0)	61 (62.2)
No	38 (38.4)	36 (36.0)	32 (32.0)	37 (37.8)
Polyarticular arthritis, n (%)				
Yes	89 (89.9)	86 (86.0)	85 (85.0)	81 (82.7)
No	10 (10.1)	14 (14.0)	15 (15.0)	17 (17.3)
Spondylitis, n (%)				
Yes	21 (21.2)	23 (23.0)	24 (24.0)	18 (18.4)
No	77 (77.8)	77 (77.0)	76 (76.0)	80 (81.6)

*Started before the first dosing of study treatment. CASPAR=CIASsification criteria for Psoriatic; MTX=Methotrexate; PsA=Psoriatic Arthritis; Arthritis; HAQ-DI=Health Assessment Questionnaire-Disability Index; TNF=Tumor necrosis factor; BSA=Body surface area

Numbers analysed

The following analysis sets were used for the data analysis: Randomised set; Full analysis set (FAS); and Safety set. The total number of patients in each analysis set was 397. The number of patients by treatment group was 99 in the secukinumab 75 mg group, 100 in the secukinumab 150 mg group, 100 in the secukinumab 300 mg group, and 98 in the placebo group (**Table 12**). Among the 98 placebo-treated subjects, 88 were treated with secukinumab after re-randomization.

Efficacy analyses were performed on an intent-to-treat basis, involving all 397 randomized patients who were assigned to study treatment (FAS).

Table 12. Analysis sets by treatment sequence (Randomised set, Study F2312)

Analysis Set	AIN457 75mg	AIN457 150mg	AIN457 300mg	Placebo	Placebo Non-responder - AIN457 150 mg	Placebo Non-responder - AIN457 300mg	Placebo Responder - AIN457 150 mg	Placebo Responder - AIN457 300mg
Randomized set	99	100	100	98	27	28	16	17
Full analysis set	99	100	100	98	27	28	16	17
Safety set	99	100	100	98	27	28	16	17
Treated with AIN457 after re-randomization	--	--	--	88	27	28	16	17

Placebo column include patients randomized to placebo at the beginning and re-randomized to AIN457 later, as well as those prematurely discontinued without taking AIN457.
Placebo patients who are not re-randomized are counted in the placebo total only.

Outcomes and estimation

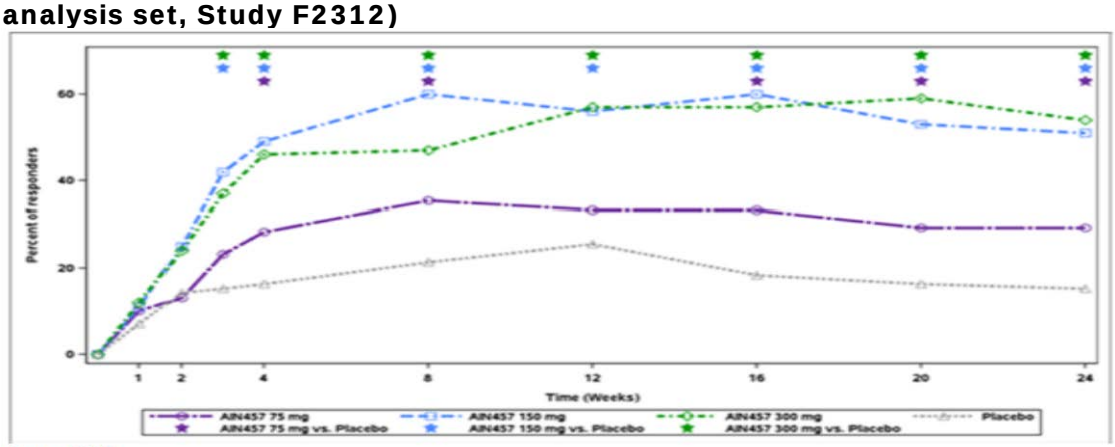
The primary efficacy variable ACR20 response using non-responder imputation for the FAS at Week 24 is shown in **Table 13** and **Figure 9**. Secukinumab 75 mg, 150 mg and 300 mg were statistically superior to placebo at Week 24 using the pre-defined statistical testing hierarchy. Thus, the primary endpoint of this study was met. The ACR20 response rates at Week 24 were 29.3% for secukinumab 75 mg ($p=0.0399$; adjusted p-value), 51.0% for secukinumab 150 mg ($p<0.0001$), and 54.0% for secukinumab 300 mg ($p<0.0001$) compared with 15.3% for placebo. The magnitude of the treatment effect vs placebo was similar between the secukinumab 150 mg and 300 mg dose groups.

Table 13. ACR20 response using non-responder imputation - up to Week 24 (Full analysis set, Study F2312)

Analysis visit	Treatment Group	n/M	(%)	Comparison	Odds ratio	95% Confidence Interval	p-value (unadjusted)
Week 1	AIN457 75 mg (N = 99)	10/ 99	(10.1)	vs Placebo	1.46	(0.53,4.01)	0.4633
	AIN457 150 mg (N = 100)	11/100	(11.0)	vs Placebo	1.55	(0.57,4.19)	0.3903
	AIN457 300 mg (N = 100)	12/100	(12.0)	vs Placebo	1.77	(0.66,4.71)	0.2534
	Placebo (N = 98)	7/ 98	(7.1)				
Week 2	AIN457 75 mg (N = 99)	13/ 99	(13.1)	vs Placebo	0.90	(0.40,2.04)	0.8025
	AIN457 150 mg (N = 100)	25/100	(25.0)	vs Placebo	1.90	(0.92,3.96)	0.0850
	AIN457 300 mg (N = 100)	24/100	(24.0)	vs Placebo	1.90	(0.91,3.96)	0.0876
	Placebo (N = 98)	14/ 98	(14.3)				
Week 3	AIN457 75 mg (N = 99)	23/ 99	(23.2)	vs Placebo	1.67	(0.81,3.45)	0.1651
	AIN457 150 mg (N = 100)	42/100	(42.0)	vs Placebo	4.10	(2.06,8.15)	<.0001
	AIN457 300 mg (N = 100)	37/100	(37.0)	vs Placebo	3.26	(1.64,6.48)	0.0008
	Placebo (N = 98)	15/ 98	(15.3)				
Week 4	AIN457 75 mg (N = 99)	28/ 99	(28.3)	vs Placebo	2.02	(1.01,4.04)	0.0474
	AIN457 150 mg (N = 100)	49/100	(49.0)	vs Placebo	5.17	(2.64,10.12)	<.0001
	AIN457 300 mg (N = 100)	46/100	(46.0)	vs Placebo	4.37	(2.24,8.52)	<.0001
	Placebo (N = 98)	16/ 98	(16.3)				
Week 8	AIN457 75 mg (N = 99)	35/ 99	(35.4)	vs Placebo	2.01	(1.06,3.82)	0.0322
	AIN457 150 mg (N = 100)	60/100	(60.0)	vs Placebo	5.83	(3.08,11.05)	<.0001
	AIN457 300 mg (N = 100)	47/100	(47.0)	vs Placebo	3.27	(1.75,6.14)	0.0002
	Placebo (N = 98)	21/ 98	(21.4)				
Week 12	AIN457 75 mg (N = 99)	33/ 99	(33.3)	vs Placebo	1.47	(0.78,2.75)	0.2353
	AIN457 150 mg (N = 100)	56/100	(56.0)	vs Placebo	4.17	(2.23,7.80)	<.0001
	AIN457 300 mg (N = 100)	57/100	(57.0)	vs Placebo	4.04	(2.18,7.51)	<.0001
	Placebo (N = 98)	25/ 98	(25.5)				
Week 16	AIN457 75 mg (N = 99)	33/ 99	(33.3)	vs Placebo	2.25	(1.15,4.41)	0.0176
	AIN457 150 mg (N = 100)	60/100	(60.0)	vs Placebo	7.76	(3.96,15.22)	<.0001
	AIN457 300 mg (N = 100)	57/100	(57.0)	vs Placebo	6.14	(3.18,11.86)	<.0001
	Placebo (N = 98)	18/ 98	(18.4)				
Week 20	AIN457 75 mg (N = 99)	29/ 99	(29.3)	vs Placebo	2.13	(1.06,4.28)	0.0327
	AIN457 150 mg (N = 100)	53/100	(53.0)	vs Placebo	6.42	(3.25,12.67)	<.0001
	AIN457 300 mg (N = 100)	59/100	(59.0)	vs Placebo	7.60	(3.86,14.94)	<.0001
	Placebo (N = 98)	16/ 98	(16.3)				
Week 24	AIN457 75 mg (N = 99)	29/ 99	(29.3)	vs Placebo	2.32	(1.14,4.73)	0.0200
	AIN457 150 mg (N = 100)	51/100	(51.0)	vs Placebo	6.52	(3.25,13.08)	<.0001
	AIN457 300 mg (N = 100)	54/100	(54.0)	vs Placebo	6.81	(3.42,13.56)	<.0001
	Placebo (N = 98)	15/ 98	(15.3)				

Odds ratio, 95% confidence interval, and p-value are from a logistic regression model with treatment and randomization stratum (TNFα status -naive or IR) as factors and baseline weight as a covariate.
Odds ratio > 1 favors AIN457.
M: Number of subjects in the treatment group.
n: The number of subjects who are ACR20 responders with the corresponding imputation approach in the treatment group.

Figure 9. ACR20 response using non-responder imputation - up to Week 24 (Full analysis set, Study F2312)



p < 0.05

Secondary efficacy results

The results of the hypothesis tests within the testing strategy are shown in **Table 14**. Based on adjusted p-values, all secondary endpoints at Week 24 were met with the secukinumab 300 mg dose group compared with placebo. For secukinumab 150 mg dose group compared with placebo, all secondary endpoints were met with the exception of HAQ-DI and ACR50. The ACR50 treatment effect for secukinumab 150 mg vs placebo was similar to that of the secukinumab 300 mg, but it was not tested because the ACR50 was placed after HAQ-DI in the hierarchy and the HAQ-DI did not achieve statistical significance (p=0.0555). None of the secondary endpoints were met with secukinumab 75 mg dose group compared with placebo. The pooled hypotheses for dactylitis and enthesitis were not tested; however, the nominal p-values for the 150mg and 300mg showed a benefit for secukinumab vs placebo.

Table 14. Results for primary and secondary endpoints based on hierarchical testing sequence (Full Analysis Set – Study F2312)

			p-value		
Hypothesis	Endpoint	Comparison	unadjusted	adjusted	Statistically significant?
H1	ACR20 at Week 24	AIN457 75mg vs Placebo	0.0200	0.0399	Yes
H2	ACR20 at Week 24	AIN457 150mg vs Placebo	<0.0001	<0.0001	Yes
H3	ACR20 at Week 24	AIN457 300mg vs Placebo	<0.0001	<0.0001	Yes
H4	PASI75 at Week 24	AIN457 75mg vs Placebo	0.1650	0.1650	No
H5	PASI75 at Week 24	AIN457 150mg vs Placebo	0.0006	0.0017	Yes
H6	PASI75 at Week 24	AIN457 300mg vs Placebo	<0.0001	<0.0001	Yes
H7	PASI90 at Week 24	AIN457 75mg vs Placebo	0.6421	0.6421	No
H8	PASI90 at Week 24	AIN457 150mg vs Placebo	0.0029	0.0057	Yes
H9	PASI90 at Week 24	AIN457 300mg vs Placebo	0.0002	0.0005	Yes
H10	DAS28CRP at Week 24	AIN457 75mg vs Placebo	0.3763	0.6421	No
H11	DAS28CRP at Week 24	AIN457 150mg vs Placebo	0.0008	0.0057	Yes
H12	DAS28CRP at Week 24	AIN457 300mg vs Placebo	0.0004	0.0013	Yes
H13	SF36-PCS at Week 24	AIN457 75mg vs Placebo	0.0482	0.6421	No
H14	SF36-PCS at Week 24	AIN457 150mg vs Placebo	0.0003	0.0057	Yes
H15	SF36-PCS at Week 24	AIN457 300mg vs Placebo	<0.0001	0.0013	Yes
H16	HAQ-DI at Week 24	AIN457 75mg vs Placebo	0.9195	0.9195	No
H17	HAQ-DI at Week 24	AIN457 150mg vs Placebo	0.0278	0.0555	No
H18	HAQ-DI at Week 24	AIN457 300mg vs Placebo	0.0013	0.0040	Yes
H19	ACR50 at Week 24	AIN457 75mg vs Placebo	0.0245	0.9195	No
H20	ACR50 at Week 24	AIN457 150mg vs Placebo	<0.0001	0.0555	No
H21	ACR50 at Week 24	AIN457 300mg vs Placebo	<0.0001	0.0040	Yes
H22	Dactylitis at Week 24	AIN457 pooled vs Placebo	0.0114	0.9195	No
H23	Enthesitis at Week 24	AIN457 pooled vs Placebo	0.0060	0.9195	No

PASI75 and PASI90 response was assessed in the subgroup of patients who had ≥ 3% of body surface area (BSA) affected by psoriatic skin involvement at baseline. For both PASI75 and PASI90 response, the difference compared with placebo at Week 24 was statistically significant for the secukinumab 150 mg and 300 mg treatment (PASI75: 48.3%, p=0.0006 and 63.4%, p<0.0001; PASI90: 32.8%, p=0.0029 and 48.8%, p=0.0002, respectively).

For DAS28-CRP change from baseline, a statistically significant difference relative to placebo was observed for the secukinumab 150 mg and 300 mg doses at Week 24 (p=0.0008 and p=0.0004) and response for these 2 dose levels were similar (-1,58 and -1.61, respectively, compared to placebo -0.96).

For SF-36 PCS scores, a clear dose-response rate was observed for the 150 mg and 300 mg dose groups relative to placebo at most visits, including the Week 24 visit. Changes in the secukinumab 75 mg, 150 mg and 300 mg groups at Week 24 were 4.38, 6.39 and 7.25, respectively, and 1.95 in the placebo group. Differences in mean change from baseline were statistically significant for all the 3 secukinumab dose levels (p=0.0482, p=0.0003, and p<0.0001, respectively).

The changes from baseline for the HAQ-DI score were higher in the 150 mg and 300 mg dose groups compared with placebo at most visits including the Week 24 visit (-0.48 and -0.56, respectively; p=0.0278 and p=0.0013, respectively).

ACR50 responder rates were highest in the secukinumab 150 mg and 300 mg group compared with placebo ($p<0.0001$ for both 150 mg and 300 mg) and Week 24 responder rates for these 2 dose levels were similar. ACR50 responder rates were also higher in the 75 mg compared with placebo at Week 24 ($p=0.0245$).

Placebo had a greater percentage of patients without dactylitis resolution compared with secukinumab pooled dose in the dactylitis subset (i.e., patients who had dactylitis at baseline) at Week 24 ($p=0.0114$). Overall, the percentage of patients without resolution of dactylitis at Week 24 was 69.7%, 50.0%, 43.5%, 53.2%, and 85.2% for secukinumab 75 mg, 150 mg, 300 mg, secukinumab pooled, and placebo groups, respectively. These differences vs placebo were also greater for the comparison of the 150 mg and 300 mg dose groups vs placebo ($p=0.0056$ and $p=0.0021$, respectively).

Placebo had a greater percentage of patients without resolution of enthesitis compared with secukinumab pooled dose in the enthesitis subset (i.e., patients who had enthesitis at baseline) at Week 24 ($p=0.0060$). Overall, the percentage of patients without resolution of enthesitis at Week 24 was 67.6%, 57.8%, 51.8%, 59.6%, and 78.5% for secukinumab 75 mg, 150 mg, 300 mg, secukinumab pooled, and placebo groups, respectively. At Week 24, these differences vs placebo were also greater for the 150 mg and 300 mg dose groups vs placebo ($p=0.0108$ and $p=0.0025$, respectively). P-values quoted for enthesitis and dactylitis are unadjusted for multiplicity.

Summary of main efficacy results

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 15. Summary of Efficacy for trial CAIN457F2306

Title: A randomized, double-blind, placebo-controlled, multicenter study of secukinumab to demonstrate the efficacy at 24 weeks and to assess the long term safety, tolerability and efficacy up to 2 years in patients with active psoriatic arthritis (Interim analyses at Week 52)			
Study identifier	CAIN457F2306		
Design	Randomized, double-blind, parallel-group, placebo controlled design		
	Duration of main phase:		52 weeks (interim analyses of a 2-year trial) Primary Efficacy analysis at Week 24
Hypothesis	Superiority		
Treatments groups	Secukinumab 10 mg/kg-75 mg		Secukinumab 10 mg/kg iv at baseline and Weeks 2 and 4, then secukinumab 75 mg sc q4w. Number randomized 202.
	Secukinumab 10 mg/kg-150 mg		Secukinumab 10 mg/kg iv at baseline and Weeks 2 and 4, then secukinumab 150 mg sc q4w. Number randomized 202.
	Placebo		Placebo. Number randomized 202.
Endpoints and definitions	Primary endpoint	ACR20 response at Week 24	To demonstrate that the efficacy of secukinumab 75 or 150 mg at Week 24 was superior to placebo in patients with active PsA based on the proportion of patients achieving ACR20 response

	Secondary endpoint	PASI75 response at Week 24	To demonstrate that the efficacy of secukinumab 75 or 150 mg at Week 24 was superior to placebo based on the proportion of patients achieving a PASI75 response in the subgroup of patients who have ≥3% skin involvement with psoriasis
	Secondary endpoint	PASI90 response at Week 24	To demonstrate that the efficacy of secukinumab 75 or 150 mg at Week 24 was superior to placebo based on the proportion of patients achieving a PASI90 response in the subgroup of patients who have ≥3% skin involvement with psoriasis
	Secondary endpoint	DAS28-CRP at Week 24	To demonstrate that the improvement (change) from baseline on secukinumab 75 or 150 mg was superior to placebo for the DAS28-CRP at Week 24
Database lock	09 October 2013 (last Visit 17 / Week 52 for interim analysis)		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat 24 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 10 mg/kg-75 mg	Secukinumab 10 mg/kg-150 mg	Placebo
	Number of subject	202	202	202
	ACR20	50.5 %	50.0 %	17.3 %
	DAS28-CRP	-1.67	-1.62	-0.77
	Number of subjects with ≥3% BSA psorasis skin involvement at baseline	108	108	109
	PASI75	64.8 %	61.1 %	8.3 %
	PASI90	49.1 %	45.4 %	3.7%

Effect estimate per comparison	ACR20	Comparison groups	Secukinumab 10 mg/kg-75 mg vs. Placebo
		Logistic regression model Odds ratio	5.53
		95% CI	3.46, 8.85
		P-value	p<0.0001
	ACR20	Comparison groups	Secukinumab 10 mg/kg-150 mg vs. Placebo
		Logistic regression model Odds ratio	5.39

		95% CI	3.37, 8.62
		P-value	p<0.0001
	PASI75	Comparison groups	Secukinumab 10 mg/kg-75 mg vs. Placebo
		P-value	p<0.0001
	PASI75	Comparison groups	Secukinumab 10 mg/kg-150 mg vs. Placebo
		P-value	p<0.0001
	PASI90	Comparison groups	Secukinumab 10 mg/kg-75 mg vs. Placebo
		P-value	p<0.0001
	PASI90	Comparison groups	Secukinumab 10 mg/kg-150 mg vs. Placebo
		P-value	p<0.0001
	DAS28-CRP	Comparison groups	Secukinumab 10 mg/kg-75 mg vs. Placebo
		P-value	p<0.0001
	DAS28-CRP	Comparison groups	Secukinumab 10 mg/kg-150 mg vs. Placebo
		P-value	p<0.0001
Notes	Results of the primary endpoint as well as the secondary endpoints ranking highest in the testing hierarchy have been included.		

Table 16. Summary of Efficacy for trial CAIN457F2312

Title: A Phase III randomized, double-blind, placebo-controlled multicenter study of subcutaneous secukinumab in prefilled syringes to demonstrate the efficacy at 24 weeks and to assess the long term efficacy, safety and tolerability up to 5 years in patients with Active Psoriatic Arthritis (Interim analyses at Week 24)			
Study identifier	CAIN457F2312		
Design	Randomized, double-blind, parallel-group, placebo controlled design		
	Duration of main phase:		24 weeks (interim analyses of a 5-year trial) Primary Efficacy analysis at Week 24
Hypothesis	Superiority		
Treatments groups	Secukinumab 75 mg		Secukinumab 75 mg sc at baseline, Weeks 1, 2, 3 and 4, followed by 75 mg sc q4w. Number randomized 99.
	Secukinumab 150 mg		Secukinumab 150 mg sc at baseline, Weeks 1, 2, 3 and 4, followed by 150 mg sc q4w.. Number randomized 100.
	Secukinumab 300 mg		Secukinumab 300 mg sc at baseline, Weeks 1, 2, 3 and 4, followed by 300 mg sc q4w. Number randomized 100.
	Placebo		Placebo. Number randomized 98.
Endpoints and definitions	Primary endpoint	ACR20 response at Week 24	To demonstrate that the efficacy of secukinumab 75, 150 or 300 mg at Week 24 is superior to placebo in patients with active PsA based on the proportion of patients achieving ACR20 response

	Secondary endpoint	PASI75 response at Week 24	To demonstrate that the efficacy of secukinumab 75, 150 or 300 mg at Week 24 is superior to placebo based on the proportion of patients achieving a PASI75 response in the subgroup of patients who have ≥3% skin involvement with psoriasis
	Secondary endpoint	PASI90 response at Week 24	To demonstrate that the efficacy of secukinumab 75, 150 or 300 mg at Week 24 is superior to placebo based on the proportion of patients achieving a PASI90 response in the subgroup of patients who have ≥3% skin involvement with psoriasis
	Secondary endpoint	DAS28-CRP at Week 24	To demonstrate that the improvement (change) from baseline on secukinumab 75, 150 or 300 mg is superior to placebo for the DAS28-CRP at Week 24
Database lock	12 May 2014 (last patient Visit 12/ Week 24 for interim analysis)		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat 24 weeks				
Descriptive statistics and estimate variability	Treatment group	Secukinumab 75 mg	Secukinumab 150 mg	Secukinumab 300 mg	Placebo
	Number of subject	99	100	100	98
	ACR20	29.3 %	51.0 %	54.0 %	15.3 %
	DAS28-CRP	-1.12	-1.58	-1.61	-0.96
	Number of subjects with ≥3% BSA psorasis skin involvement at baseline	43	50	58	41
	PASI75	28.0 %	48.3 %	63.4%	16.3 %
	PASI90	12.0 %	32.8 %	48.8%	9.3%

Effect estimate per comparison	ACR20	Comparison groups	Secukinumab 75 mg vs. Placebo
		Logistic regression model Odds ratio	2.32
		95% CI	1.14, 4,73
		P-value	p=0.0200
	ACR20	Comparison groups	Secukinumab 150 mg vs. Placebo
		Logistic regression model Odds ratio	6.52
		95% CI	3.25, 13.08
		P-value	p<0.0001

	ACR20	Comparison groups	Secukinumab 300 mg vs. Placebo
		Logistic regression model Odds ratio	6.81
		95% CI	3.42, 13.56
		P-value	p<0.0001
	PASI75	Comparison groups	Secukinumab 75 mg vs. Placebo
		P-value	p=0.1650
	PASI75	Comparison groups	Secukinumab 150 mg vs. Placebo
		P-value	p=0.0006
	PASI75	Comparison groups	Secukinumab 300 mg vs. Placebo
		P-value	p<0.0001
	PASI90	Comparison groups	Secukinumab 75 mg vs. Placebo
		P-value	p=0.6421
	PASI90	Comparison groups	Secukinumab 150 mg vs. Placebo
		P-value	p=0.0029
	PASI90	Comparison groups	Secukinumab 300 mg vs. Placebo
		P-value	p=0.0002
	DAS28-CRP	Comparison groups	Secukinumab 75 mg vs. Placebo
		P-value	p=0.3763
	DAS28-CRP	Comparison groups	Secukinumab 150 mg vs. Placebo
		P-value	p=0.0008
	DAS28-CRP	Comparison groups	Secukinumab 300 mg vs. Placebo
		P-value	p=0.0004
Notes	Results of the primary endpoint as well as the secondary endpoints ranking highest in the testing hierarchy have been included.		

Analysis performed across trials

The data from the 2 Phase 3 trials (F2306 and F2312) were pooled to evaluate the primary and secondary treatment effect across subgroups. Subgroups examined were age, gender, race, region, weight, TNFα inhibitor status, number of prior TNFα inhibitors, reasons for stopping TNFα inhibitors, baseline DAS28 status, concomitant corticosteroid use, concomitant methotrexate use, baseline HAQ-DI; baseline CRP, baseline BSA. When pooling was performed the 'AIN457 Pooled' group constituted of iv-75 mg, iv-150 mg, 150 mg sc and 300 mg sc, and the 75 mg sc dose from Study CAIN457F2312 was excluded. The MAH justified the pooling of the iv-75 mg, iv-150 mg, 150 mg sc, and 300 mg sc dose groups (while leaving out 75 mg sc) by the similarity in response rates for the primary and key secondary endpoints for these groups.

The results from the pooling approach are briefly summarized in the Forest plots below.

Figure 10. Treatment difference between secukinumab and placebo for ACR20 response at Week 24 stratified by age, gender and race (FAS, for Studies F2306 and F2312)

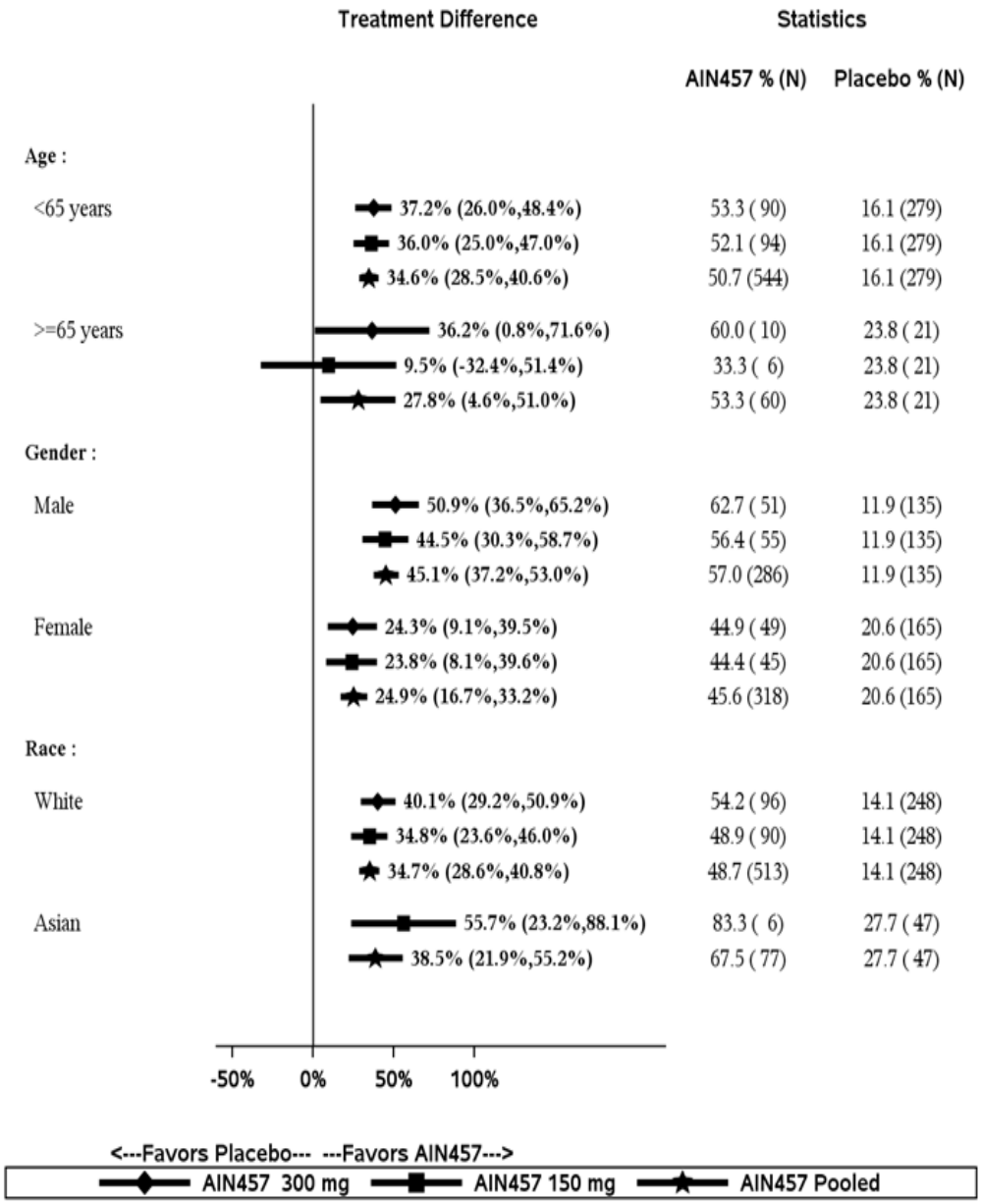
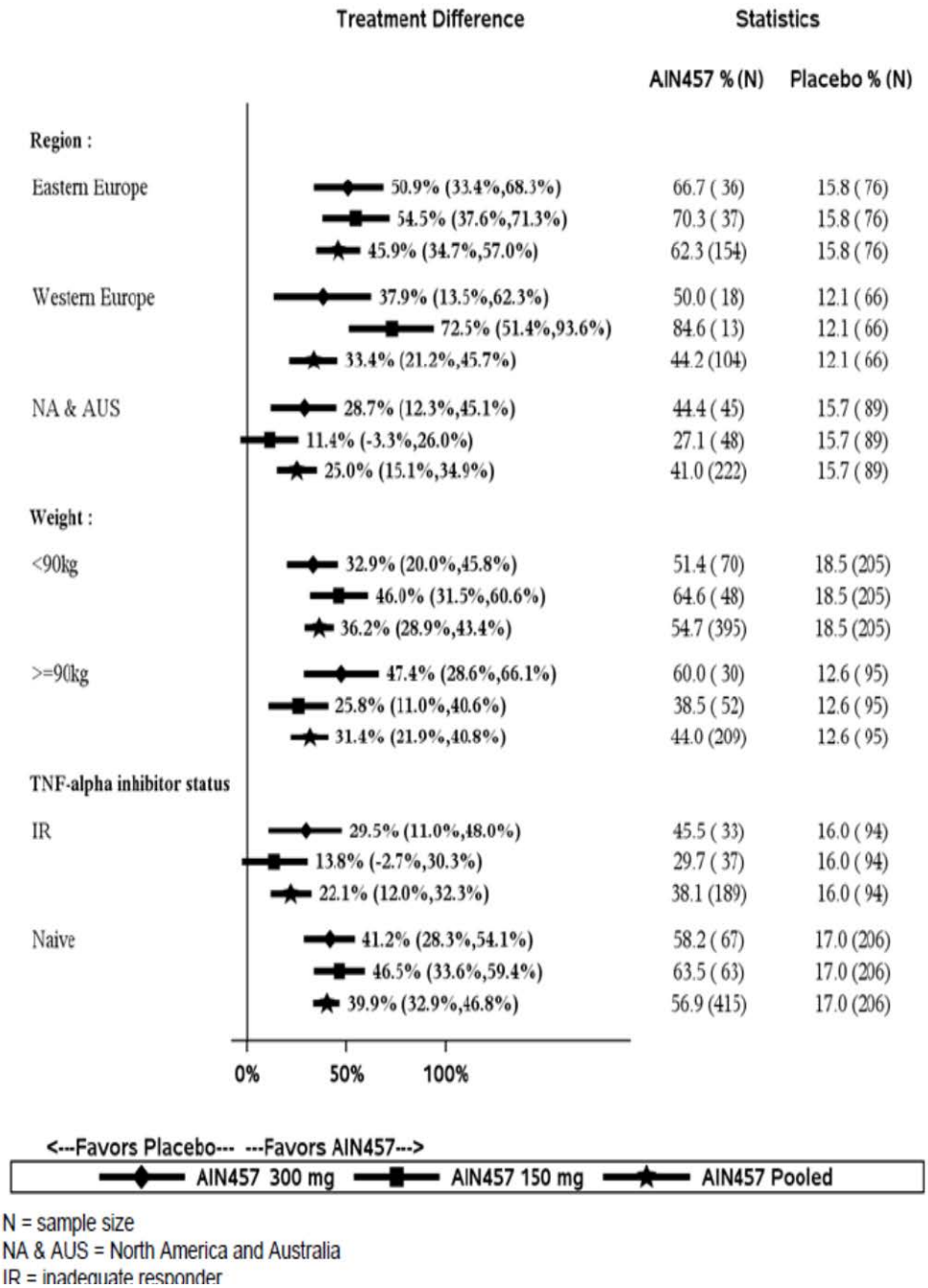


Figure 11. Treatment difference between secukinumab and placebo for ACR20 response at Week 24 stratified by region, body weight and TNF alpha inhibitor status (FAS, for Studies F2306 and F2312)



N = sample size
NA & AUS = North America and Australia
IR = inadequate responder

Figure 12. Treatment difference between secukinumab and placebo for ACR20 response at Week 24 stratified by baseline DAS28-CRP, concomitant corticosteroid use and concomitant methotrexate use (FAS, for Studies F2306 and F2312)

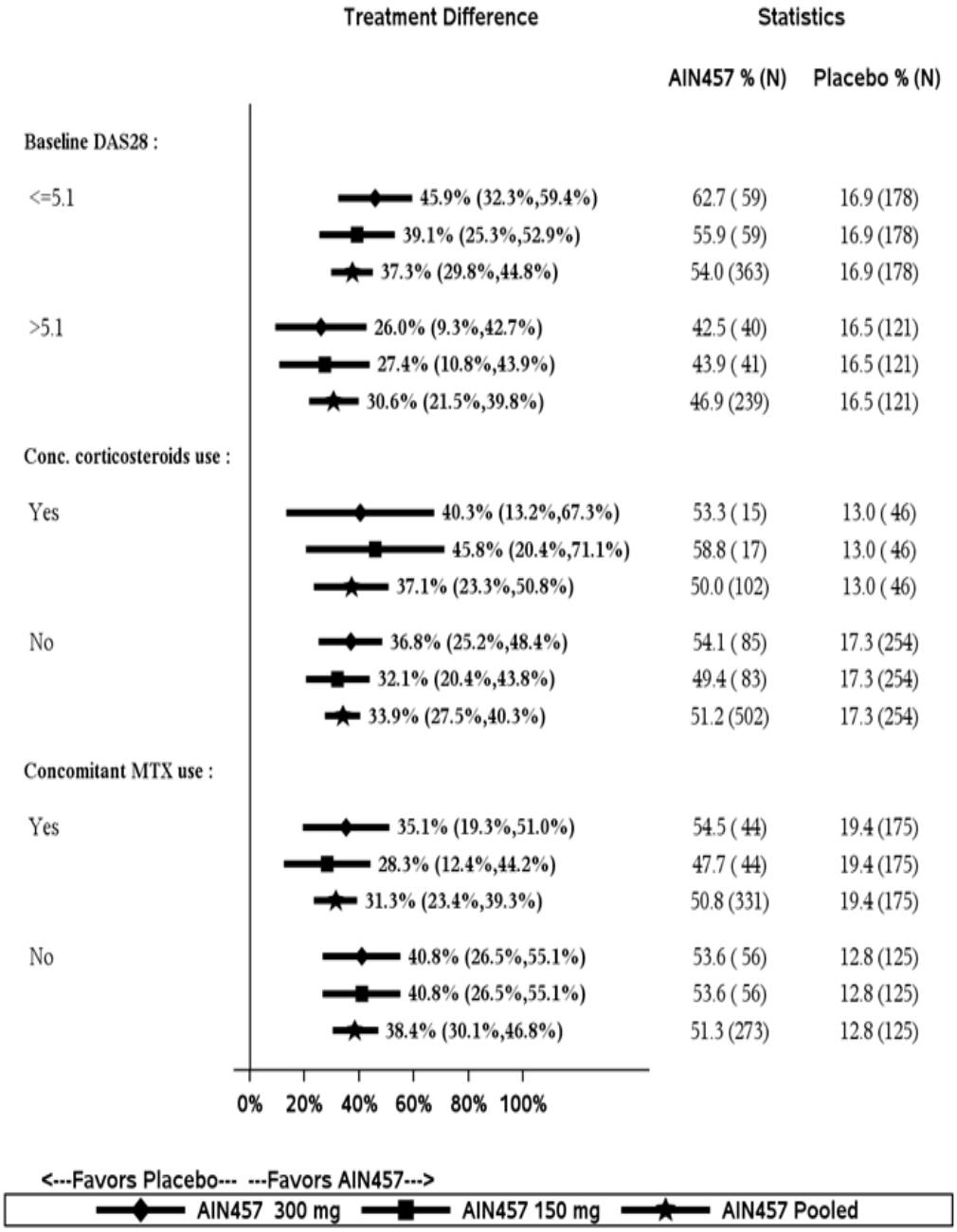
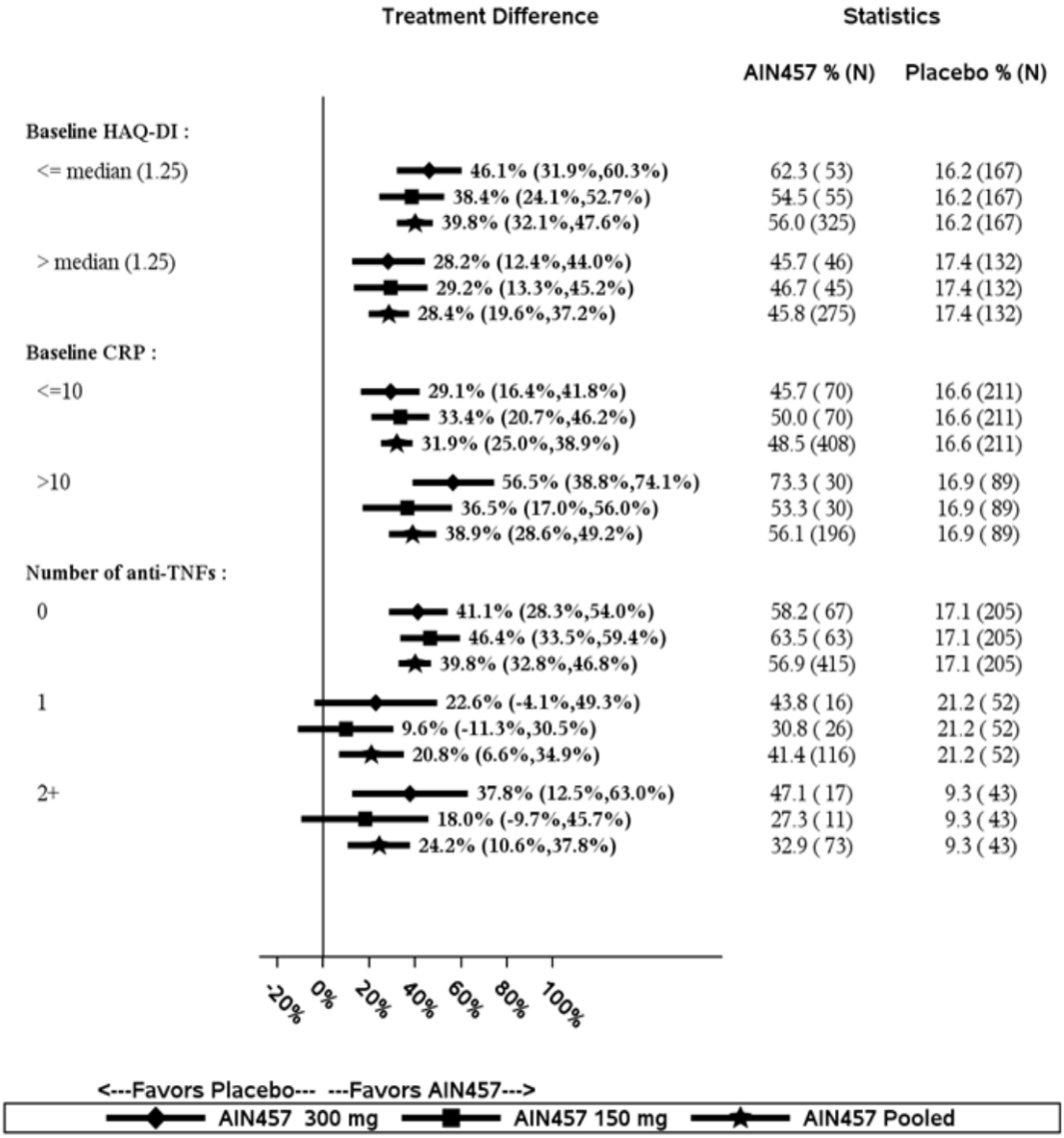


Figure 13. Treatment difference between secukinumab and placebo for ACR20 response at Week 24 stratified by baseline HAQ - DI, baseline hsCRP and number of prior TNF alpha inhibitors (FAS, for Studies F2306 and F2312)



Supportive studies

A subset of 363 (18%) patients with moderate to severe plaque psoriasis and concomitant PsA from 2 phase 3 moderate to severe plaque psoriasis trials (Study CAIN457A2302 and CAIN457A2303) was pooled to provide additional information on selected endpoints (HAQ-DI, PASI75 and PASI90) for secukinumab 150 mg sc and 300 mg sc dose regimens.

Among moderate to severe plaque psoriasis patients with concomitant PsA, greater improvements in physical functioning, as measured by the mean change in HAQ-DI score from baseline (comparison with placebo up to Week 12), were observed with secukinumab 300 mg from both studies A2302 and A2303. For both studies, the mean HAQ-DI score at baseline was comparable across the treatment groups. In Study A2302, the mean change in HAQ-DI score at Week 12 was -0.18, and -0.35 for those patients treated with secukinumab 150 mg and 300 mg, respectively, compared with -0.08 for placebo. In Study A2303, the mean change in HAQ-DI score at Week 12 was -0.19, and -0.41 for those patients treated with secukinumab 150 mg and 300 mg, respectively.

Table 17. Week 12 data for moderate to severe plaque psoriasis patients with concomitant PsA from Study A2302 and Study A2303

	CAIN457A2302				CAIN457A2303			
	Response rate of PASI 75	Response rate of PASI 90	Mean change in HAQ-DI©	% of patients with change of ≥0.3 HAQ-DI© (MCID)	Response rate of PASI 75	Response rate of PASI 90	Mean change in HAQ-DI©	% of patients with change of ≥0.3 HAQ-DI© (MCID)
150 mg	70%	44%	-0.18	26.7%	59%	39%	-0.19	31.7%
300 mg	68%	53%	-0.35	47.1%	72%	44%	-0.41	45.5%
Placebo	4%	0%	-0.08	21.5%	2%	2%	0.02	12.8%
Etanercept*	-	-	-	-	39%	18%	-0.29	38.2%

* EU Sourced

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The PsA clinical development program includes two phase II studies (A2206 in PsA patients and F2201 in a related arthritic indication with RA patients) and two pivotal phase III studies PsA (F2306 and F2312). Pivotal efficacy data up to Week 24 (Study F2312) and up to Week 52 (Study F2306) have been provided. In addition, data on a subset of 363 psoriasis patients with concomitant PsA from psoriasis Studies A2302 and A2303 have been pooled to obtain information on selected endpoints (HAQ-DI, PASI 75/90; the latter study also included active comparator etanercept). In addition, follow-up data from five phase III psoriasis studies have been provided with the target secukinumab doses of 150 mg and 300 mg.

Recommendations of the EMA clinical guidance for psoriatic arthritis (Guideline on clinical investigation of medicinal products indicated for the treatment of psoriatic arthritis, CHMP/EWP/438/04) have mostly been taken into account in the clinical development programme.

The initial doses and the dosing regimen in phase II studies were based on preclinical *in vivo* efficacy data in animal models which were evaluated during the initial MAA for Cosentyx.

The two phase II studies A2206 and F2201 provided preliminary evidence of efficacy in two arthritic disease models, PsA and RA. The posology carried forward to the phase III studies was mainly based on PK/PD modelling and simulation of different treatment regimens as well as data in psoriasis.

The study population in phase III studies consisted of adults with active moderate to severe PsA. They fulfilled the CASPAR diagnostic criteria for PsA and the disease activity was based on 3 or more tender joints and 3 or more swollen joints.

Study F2306 was a double-blind, randomized, parallel-group, placebo-controlled study. The 52-week interim analyses of the 2-year study was provided, with the assessment of the primary efficacy variable of ACR20 response at Week 24. Loading regimen was secukinumab 10 mg/kg iv at baseline and at Weeks 2 and 4, followed by maintenance treatment with 75 mg or 150 mg sc q4w. The efficacy variables chosen covered relevant aspects of the disease except for the lack of dedicated assessment of axial involvement. The MAH was requested to discuss this issue and present any efficacy data available with respect to axial arthritis or any evidence that efficacy can be extrapolated to this sub-group of PsA patients. The MAH noted that only a small number of PsA patients within the studies had axial involvement, and therefore

assessments of axial involvement would have been difficult to demonstrate meaningful data. However, the MAH considered that data from the AS studies which show a clear effect of secukinumab on key measures of efficacy related to axial involvement and overall physical function could be extrapolated to the PsA patients. The CHMP agreed that PsA and AS represent spondyloarthritides with some clinical overlap and therefore considering the overall weight of evidence on the efficacy of secukinumab in both PsA and AS, such extrapolation was considered meaningful. A statement on the low number of PsA patients with axial involvement was included in Section 5.1 of the SmPC.

The design of Study F2312 was identical to that of Study F2306, but the iv loading regimen in the latter study was replaced by a sc loading regimen that is similar to the one approved for the treatment of psoriasis (sc dosing at baseline, Weeks 1, 2, 3 and 4 and then q4w). Also, an additional 300 mg sc dose arm was included. No assessment of progression of structural damage was performed in this study.

Efficacy data and additional analyses

For Study F2306, 202 patients were randomized to each of the 3 treatment groups (secukinumab 10 mg/kg-75 mg, secukinumab 10 mg/kg-150 mg and placebo). Baseline disease activity was consistent with moderate to severe PsA and generally comparable across the treatment groups.

The primary efficacy endpoint was achieved as secukinumab at both 10 mg/kg-75 mg and 10 mg/kg-150 mg doses was statistically significantly superior to placebo for ACR20 response at Week 24 ($p<0.0001$). The ACR20 response rates at Week 24 were 50.5% for secukinumab 75 mg, 50.0% for secukinumab 150 mg and 17.3% for placebo. Superior response rates compared to placebo were seen as early as from Week 1 onwards, with p-values <0.0001 at each time point.

For Study F2312, a total of 397 patients were randomized to 4 treatment groups: secukinumab 75 mg, 150 mg, 300 mg, and placebo. The primary efficacy endpoint was achieved as secukinumab at all doses was statistically significantly superior to placebo for ACR20 response at Week 24 ($p<0.0001$ for secukinumab 150 mg and 300 mg vs. placebo, $p=0.0200$ for secukinumab 75 mg vs. placebo). The ACR20 response rates at Week 24 were 29.3% for secukinumab 75 mg, 51.0% for secukinumab 150 mg, 54.0 for secukinumab 300 mg and 15.3% for placebo. For the 150 mg and 300 mg doses, statistically superior response rates compared to placebo were seen from Week 3 onwards.

All secondary endpoints at Week 24 were met with the 300 mg dose group compared with placebo. For the 150 mg dose group, secondary endpoints within the testing hierarchy were met until HAQ-DI. For ACR50 (placed after HAQ-DI in the hierarchy), the treatment effect was however similar to that of the 300 mg dose. Among exploratory endpoints, relevant improvements in quality of life were noted with both secukinumab 150 mg and 300 mg doses.

ACR20, ACR50 and ACR70 response rates at Week 24 were higher in TNFα inhibitor naïve patients compared with TNFα-IR patients. This is consistent with secukinumab data in psoriasis and also a general phenomenon in biological therapies. The subgroup analysis by TNFα inhibitor status at Week 24 provided evidence that the ACR20 response rates in TNFα-IR patients are better with the 300 mg dose. The updated Week 52 efficacy data confirmed these results. Therefore, for TNFα-IR patients the recommended dose is 300 mg sc.

Based on temporal efficacy data, a time point earlier than 24 weeks could have been chosen for the assessment of the primary endpoint. 55 placebo patients were re-randomized at Week 16 and were treated as MAR at Week 24 in the MMRM analyses. The MAH was requested to discuss the validity of the time point chosen for the primary endpoint analysis.

The MAH responded that the time point for the assessment of the primary endpoint at 24 weeks was based on the EMA guideline and the need to harmonize the efficacy and the structural damage assessments. In addition, it was considered that the more stringent endpoints like ACR70 and DAS-28

remission need longer time to become evident. As the placebo escape for non-responders at Week 16 may have resulted in potential bias, further sensitivity analyses were performed at Week 24 where the actual data from patients who were switched from placebo to active treatment at week 16 were analysed as placebo. In these analyses the conclusions of the clinical study report remained valid.

The MAH proposed a time point of 16 weeks for consideration to discontinue treatment in patients who have shown no response and this was agreed by the CHMP and is reflected in Section 4.2 of the SmPC.

Within analyses performed across trials, similar efficacy at Week 24 based on ACR 20, 50 and 70 responses was seen for both iv-75 mg and iv-150 mg dose groups in Study F2306. These results suggest a significant contribution of the iv loading dose to ACR response at Week 24. However, the doses began to separate around Week 32, and by Week 52, the ACR 20, 50 and 70 responses were approximately 3%, 10% and 3% higher in the iv-150 mg dose group. Similar separation at Week 32 was also seen in PASI 75 and 90 responses. In Study F2312, a clear difference in efficacy between the 75 mg sc regimen and the higher 150/300 mg sc dose regimens was evident. The 75 mg dose was statistically not significantly different to placebo, and it was clinically inferior to the 150 mg and 300 mg doses. The MAH was asked to provide an explanation for these observations. The MAH provided a simulated secukinumab concentration profile, illustrating the overriding contribution of the iv loading regimen towards exposure for the respective 75 mg and 150 mg sc dosing regimens over the first 24 weeks of the study (although minor differences in exposure resulting from these regimens are predicted starting from Week 8). The CHMP agreed that this obscured the possibility to observe a dose-response during this period of time.

Several analyses were done in subpopulations across secukinumab 150 mg (n=100), secukinumab 300 mg (n=100), secukinumab pooled (n=604) and placebo pooled (n=300) groups.

In the analysis by weight, ACR20 response was decreased in patients weighing ≥90 kg. However, it seemed that other endpoints including the more clinically relevant and more stringent ACR 50 and 70 responses were similar between the doses of 150 mg and 300 mg. The MAH provided further data based on weight groups, stratified by TNF-a status from study F2312. For the TNF-alpha inhibitor naïve subgroup of patients ⩾90 kg, there was a difference in ACR 20 response at Week 24 in the 150 mg and 300 mg dose groups (50.0% and 65.0%, respectively) but not in the more stringent endpoint ACR50 (43.3% and 40.0%, respectively). In the TNFa-IR group at Week 24, the ACR 50 response rate was higher in the ⩾90 kg weight group with the 300 mg dose, in line with the proposed posology. At Week 52 the ACR 50 responses with both 150 mg and 300 mg dose continued to be similar within each weight group. According to the MAH, the most clinically relevant factor for stratification was considered to be TNF-alpha response status and stratification by body weight was discounted due to the resulting very small sample sizes per subset. The MAH´s justifications were accepted by the CHMP as no consistent clinically meaningful benefit of the 300 mg dose over the 150 mg dose in heavier patients could be observed. The CHMP therefore concluded that no dose adjustment based on body weight would be needed. The higher efficacy observed with the 300 mg dose in the TNFα-IR patients >90kg was consistent with the proposed 300 mg dose for these patients.

Among PsA patients with psoriasis (BSA ≥3%), higher PASI75 and PASI90 rates were observed with secukinumab 300 mg dose compared to the 150 mg dose. This is consistent with the phase III psoriasis program. The difference was particularly evident in patients with moderate to severe psoriasis. Therefore the dosing proposed for patients with concomitant moderate to severe plaque psoriasis, *i.e.,* 300 mg secukinumab by sc injection, was considered justified.

2.4.1. Conclusions on the clinical efficacy

Both phase III studies met the primary endpoint as ACR20 response rates with all secukinumab doses tested were statistically significantly higher compared to placebo at Week 24. With the proposed sc

induction and maintenance regimen, the 150 mg dose provided clinically more relevant level of efficacy compared to the 75 mg dose, in particular in the long-term treatment up to Week 52. Based on subgroup analyses, the 300 mg dose was considered more appropriate for patients with concomitant moderate to severe plaque psoriasis and for TNFα-IR patients.

Other endpoints related to joint and skin disease, physical function, health-related quality of life and prevention of progression of structural damage consistently show clinically relevant efficacy of secukinumab in the treatment of PsA.

2.5. Clinical safety

Introduction

The secukinumab development program studied 7048 patients, including 6200 patients exposed to at least one dose of secukinumab in any indication, and 6267 patient-years of secukinumab exposure, are included in the safety pooling (**Table 18**). The safety data in the present submission provide an additional 2679 patient-years of secukinumab exposure (75% increase), including 955 patient-years of exposure in PsA patients and 691 patient-years of exposure in AS patients, beyond the 3588 patient-years of exposure reported previously for the psoriasis development program.

Patient exposure

Table 18. Exposure to secukinumab across Pools A, B1, B and C in the entire treatment period

	Pool A					Pool B1				Pool B			Pool C
	Any 75 mg N=391	Any 150 mg N=438	Any 300 mg N=145	Any AIN457 dose N=974		Any 150 mg N=681	Any 300 mg N=400	Any AIN457 dose N=1472		Any 150 mg N=1919	Any 300 mg N=1618	Any AIN457 dose N=3928	Any AIN457 dose N=6200
≥ 8 wk	382	431	140	953		671	394	1447		1888	1585	3855	6031
≥ 16 wk	373	410	128	911		581	323	1277		1572	1303	3248	5287
≥ 24 wk	367	388	110	865		556	298	1221		1521	1250	3138	4964
≥ 52 wk	225	226	2	453		317	101	643		869	667	1761	3671
Total pt-yrs	420.0	444.9	90.1	955.0		616.5	278.6	1315.1		1572.1	1232.3	3224.5	6266.6

Pool A consisted of 2 pivotal placebo-controlled Phase 3 trials (F2306 and F2312) in PsA with placebo and dose comparisons that allow risks to be evaluated in the PsA population during the first 16 weeks of treatment, which was the placebo-controlled phase, and during the entire treatment period (median 48 weeks of exposure to secukinumab, interim analyses on week 52 in study F2306 and on week 24 in study F2312).

Pool B1 included an expanded PsA population with PsA patients from the 2 Phase 3 PsA trials, F2306 and F2312, and psoriasis patients with concomitant PsA from 3 Phase 3 psoriasis trials, A2302, A2303, and A2304).

Pool B (a mixed population of PsA patients from the 2 Phase 3 PsA trials, F2306 and F2312, and psoriasis patients from the 5 Phase 3 psoriasis trials A2302, A2303, A2304, A2308, and A2309) increased the

probability of observing less common events over long-term treatment for the target doses of 150 mg sc and 300 mg sc.

Pool C, the largest data pool, includes all patients treated with secukinumab in 42 studies and maximised the probability of observing rare events in patients receiving secukinumab.

Induction and placebo-controlled study period of Pool A

The overall incidence of AEs during the loading period from Weeks 0 to 8 did not indicate differences in tolerability across the secukinumab 75 mg, 150 mg and 300 mg sc and pooled 10 mg/kg iv loading group or to placebo. A similar AE profile was observed for Weeks 0 to 16 (**Table 19**).

Table 19. Most frequent AEs by preferred term (≥ 2% in any group) – Short-term period (16 weeks) (Pool A: Phase 3 PsA trials - Safety set)

Preferred Term	AIN457 75mg N=99 n (%)	AIN457 150mg N=100 n (%)	AIN457 300mg N=100 n (%)	AIN457 10mg/kg -75mg N=202 n (%)	AIN457 10mg/kg -150mg N=202 n (%)	Any AIN457 N=703 n (%)	Placebo N=300 n (%)
- Any AE	48 (48.5)	57 (57.0)	56 (56.0)	122 (60.4)	131 (64.9)	414 (58.9)	175 (58.3)
Nasopharyngitis	6 (6.1)	4 (4.0)	6 (6.0)	14 (6.9)	19 (9.4)	49 (7.0)	17 (5.7)
Upper respiratory tract infection	10 (10.1)	8 (8.0)	4 (4.0)	9 (4.5)	13 (6.4)	44 (6.3)	17 (5.7)
Headache	2 (2.0)	4 (4.0)	7 (7.0)	11 (5.4)	11 (5.4)	35 (5.0)	10 (3.3)
Nausea	4 (4.0)	4 (4.0)	3 (3.0)	5 (2.5)	4 (2.0)	20 (2.8)	6 (2.0)
Diarrhoea	3 (3.0)	2 (2.0)	2 (2.0)	4 (2.0)	6 (3.0)	17 (2.4)	9 (3.0)
Hypercholesterolaemia	1 (1.0)	2 (2.0)	0	8 (4.0)	6 (3.0)	17 (2.4)	6 (2.0)
Hypertension	0	0	3 (3.0)	7 (3.5)	3 (1.5)	13 (1.8)	8 (2.7)
Urinary tract infection	1 (1.0)	4 (4.0)	2 (2.0)	2 (1.0)	4 (2.0)	13 (1.8)	6 (2.0)
Back pain	3 (3.0)	1 (1.0)	0	5 (2.5)	3 (1.5)	12 (1.7)	5 (1.7)
Pruritus	1 (1.0)	2 (2.0)	2 (2.0)	0	6 (3.0)	11 (1.6)	4 (1.3)
Fatigue	2 (2.0)	1 (1.0)	1 (1.0)	5 (2.5)	1 (0.5)	10 (1.4)	7 (2.3)
Oral herpes	1 (1.0)	0	4 (4.0)	0	5 (2.5)	10 (1.4)	3 (1.0)
Oropharyngeal pain	0	1 (1.0)	2 (2.0)	4 (2.0)	3 (1.5)	10 (1.4)	7 (2.3)
Cough	0	1 (1.0)	3 (3.0)	1 (0.5)	4 (2.0)	9 (1.3)	8 (2.7)
Dizziness	0	1 (1.0)	2 (2.0)	2 (1.0)	4 (2.0)	9 (1.3)	3 (1.0)
Dyslipidaemia	0	2 (2.0)	0	3 (1.5)	4 (2.0)	9 (1.3)	7 (2.3)
Gastroenteritis	2 (2.0)	1 (1.0)	1 (1.0)	2 (1.0)	3 (1.5)	9 (1.3)	3 (1.0)
Haematuria	1 (1.0)	3 (3.0)	2 (2.0)	3 (1.5)	0	9 (1.3)	1 (0.3)
Vomiting	2 (2.0)	2 (2.0)	2 (2.0)	3 (1.5)	0	9 (1.3)	2 (0.7)
Alanine aminotransferase increased	0	1 (1.0)	2 (2.0)	2 (1.0)	3 (1.5)	8 (1.1)	3 (1.0)
Arthralgia	1 (1.0)	0	2 (2.0)	3 (1.5)	2 (1.0)	8 (1.1)	4 (1.3)
Bronchitis	0	2 (2.0)	0	3 (1.5)	3 (1.5)	8 (1.1)	7 (2.3)
Oedema peripheral	3 (3.0)	2 (2.0)	0	1 (0.5)	2 (1.0)	8 (1.1)	0
Pain in extremity	3 (3.0)	1 (1.0)	0	3 (1.5)	1 (0.5)	8 (1.1)	5 (1.7)
Rhinitis	3 (3.0)	2 (2.0)	0	3 (1.5)	0	8 (1.1)	0
Depression	0	0	1 (1.0)	4 (2.0)	2 (1.0)	7 (1.0)	8 (2.7)
Dyspepsia	0	3 (3.0)	1 (1.0)	2 (1.0)	1 (0.5)	7 (1.0)	4 (1.3)
Excoriation	0	1 (1.0)	0	1 (0.5)	5 (2.5)	7 (1.0)	1 (0.3)
Gastrooesophageal reflux disease	0	0	1 (1.0)	5 (2.5)	1 (0.5)	7 (1.0)	2 (0.7)
Psoriasis	1 (1.0)	0	2 (2.0)	4 (2.0)	0	7 (1.0)	5 (1.7)
Rash	0	2 (2.0)	0	2 (1.0)	3 (1.5)	7 (1.0)	11 (3.7)
Sinusitis	0	2 (2.0)	1 (1.0)	2 (1.0)	2 (1.0)	7 (1.0)	5 (1.7)
Conjunctivitis	0	2 (2.0)	0	1 (0.5)	3 (1.5)	6 (0.9)	0
Mouth ulceration	0	1 (1.0)	2 (2.0)	1 (0.5)	2 (1.0)	6 (0.9)	0
Cellulitis	2 (2.0)	0	0	2 (1.0)	1 (0.5)	5 (0.7)	1 (0.3)
Insomnia	0	1 (1.0)	2 (2.0)	2 (1.0)	0	5 (0.7)	5 (1.7)
Lower respiratory tract infection	0	2 (2.0)	1 (1.0)	0	2 (1.0)	5 (0.7)	2 (0.7)

Migraine	0	2 (2.0)	1 (1.0)	1 (0.5)	1 (0.5)	5 (0.7)	1 (0.3)
Urticaria	1 (1.0)	0	2 (2.0)	1 (0.5)	1 (0.5)	5 (0.7)	0
Hyperlipidaemia	1 (1.0)	2 (2.0)	0	1 (0.5)	0	4 (0.6)	5 (1.7)
Muscle spasms	0	2 (2.0)	0	1 (0.5)	1 (0.5)	4 (0.6)	4 (1.3)
Psoriatic arthropathy	1 (1.0)	3 (3.0)	0	0	0	4 (0.6)	3 (1.0)
Abdominal pain upper	0	2 (2.0)	0	1 (0.5)	0	3 (0.4)	2 (0.7)
Contusion	0	3 (3.0)	0	0	0	3 (0.4)	2 (0.7)
Hypokalaemia	0	0	2 (2.0)	0	1 (0.5)	3 (0.4)	2 (0.7)
Pruritus generalised	0	0	2 (2.0)	1 (0.5)	0	3 (0.4)	1 (0.3)
Injection site erythema	2 (2.0)	0	0	0	0	2 (0.3)	0
Proteinuria	2 (2.0)	0	0	0	0	2 (0.3)	0
Respiratory tract infection	0	0	2 (2.0)	0	0	2 (0.3)	0
Wound	0	2 (2.0)	0	0	0	2 (0.3)	0
Anaemia	0	0	0	1 (0.5)	0	1 (0.1)	7 (2.3)
Viral upper respiratory tract infection	0	0	0	0	0	0	7 (2.3)

Preferred terms are sorted in descending order of frequency in the Any AIN457 column.

Entire studies

The overall exposure-adjusted incidence of AEs in the entire treatment period of Pool A was similar between the any 300 mg and any 150 mg secukinumab groups and lower in the any 75 mg group (**Table 20**). The exposure-adjusted AE rate for the placebo group was higher, reflecting the shorter duration of exposure for the placebo group in presence of decreasing reported rates over time. Taking account of the differences in duration of exposure over the entire treatment period, the general profile of AEs over the entire treatment period was similar to the initial 16-week treatment period, with no new involvement of SOCs over long-term treatment than was seen in the first 16 weeks of treatment. For many events, the rates for the any 300 mg group were comparable to or lower than for placebo, indicating no clinically meaningful increase in risk was observed for 300 mg over the entire treatment period.

Apparent small dose-related increases were seen for infections (URTI, bronchitis, sinusitis, pharyngitis, oral herpes, conjunctivitis), and ruritus, rash, increased ALT, gastroesophageal reflux disease, alopecia, palpitations, and epistaxis. In many cases rates for the 300 mg group were comparable to or lower than for placebo.

There were no meaningful differences between secukinumab groups in the distribution of AEs over time. AEs overall and most infection AEs and gastrointestinal AEs showed an overall trend of a decrease in the proportion of patients reporting AEs over time across treatment groups. This observation could be made both from Pool A and Pool B.

Table 20. Exposure-adjusted incidence of AEs by preferred term (≥2% in any group) – Entire treatment period (Pool A: Phase 3 PsA trials – Safety set)

Preferred Term	Any AIN457 75mg N=391 n/EX (IR)	Any AIN457 150mg N=438 n/EX (IR)	Any AIN457 300mg N=145 n/EX (IR)	Any AIN457 dose N=974 n/EX (IR)	Placebo N=300 n/EX (IR)
- Any AE	296/158.7 (186.5)	342/147.0 (232.6)	94/42.3 (222.3)	732/348.0 (210.3)	181/56.6 (319.6)
Upper respiratory tract infection	59/384.2 (15.4)	69/399.0 (17.3)	18/84.1 (21.4)	146/867.2 (16.8)	18/102.3 (17.6)
Nasopharyngitis	64/370.4 (17.3)	61/396.1 (15.4)	15/85.1 (17.6)	140/851.6 (16.4)	19/101.4 (18.7)

Preferred Term	Any AIN457 75mg N=391 n/EX (IR)	Any AIN457 150mg N=438 n/EX (IR)	Any AIN457 300mg N=145 n/EX (IR)	Any AIN457 dose N=974 n/EX (IR)	Placebo N=300 n/EX (IR)
Headache	30/394.3 (7.6)	29/421.2 (6.9)	8/84.9 (9.4)	67/900.5 (7.4)	12/102.7 (11.7)
Back pain	28/400.7 (7.0)	18/431.1 (4.2)	3/89.2 (3.4)	49/921.0 (5.3)	5/104.1 (4.8)
Diarrhoea	18/406.5 (4.4)	21/426.7 (4.9)	6/88.1 (6.8)	45/921.3 (4.9)	9/103.4 (8.7)
Bronchitis	11/411.8 (2.7)	22/430.1 (5.1)	5/88.1 (5.7)	38/930.0 (4.1)	8/103.7 (7.7)
Hypertension	21/405.4 (5.2)	13/435.7 (3.0)	4/87.6 (4.6)	38/928.7 (4.1)	8/103.5 (7.7)
Arthralgia	17/407.8 (4.2)	16/435.5 (3.7)	4/88.4 (4.5)	37/931.7 (4.0)	7/104.5 (6.7)
Psoriatic arthropathy	18/410.4 (4.4)	17/435.7 (3.9)	2/89.6 (2.2)	37/935.7 (4.0)	3/104.7 (2.9)
Nausea	18/407.3 (4.4)	12/435.7 (2.8)	5/87.2 (5.7)	35/930.2 (3.8)	6/103.9 (5.8)
Sinusitis	11/413.1 (2.7)	15/437.1 (3.4)	9/87.2 (10.3)	35/937.4 (3.7)	6/104.6 (5.7)
Urinary tract infection	10/413.8 (2.4)	21/427.2 (4.9)	3/88.6 (3.4)	34/929.6 (3.7)	6/104.1 (5.8)
Cough	10/412.5 (2.4)	20/429.3 (4.7)	3/88.0 (3.4)	33/929.8 (3.5)	8/103.7 (7.7)
Psoriasis	18/409.5 (4.4)	11/440.2 (2.5)	2/88.7 (2.3)	31/938.4 (3.3)	5/104.2 (4.8)
Gastroenteritis	9/413.9 (2.2)	17/432.5 (3.9)	3/88.8 (3.4)	29/935.1 (3.1)	3/105.1 (2.9)
Pharyngitis	10/413.2 (2.4)	13/433.8 (3.0)	5/88.9 (5.6)	28/935.9 (3.0)	0/105.6 (0.0)
Hypercholesterolaemia	13/406.8 (3.2)	12/432.2 (2.8)	2/89.2 (2.2)	27/928.2 (2.9)	6/104.0 (5.8)
Oropharyngeal pain	11/411.8 (2.7)	10/437.1 (2.3)	4/88.2 (4.5)	25/937.2 (2.7)	8/104.1 (7.7)
Oral herpes	7/415.5 (1.7)	12/434.2 (2.8)	5/87.4 (5.7)	24/937.2 (2.6)	4/104.4 (3.8)
Vomiting	15/409.0 (3.7)	7/441.0 (1.6)	2/88.4 (2.3)	24/938.5 (2.6)	3/104.8 (2.9)
Fatigue	11/409.0 (2.7)	10/439.4 (2.3)	2/89.5 (2.2)	23/937.9 (2.5)	7/103.8 (6.7)
Dyspepsia	6/416.3 (1.4)	14/434.3 (3.2)	1/89.5 (1.1)	21/940.0 (2.2)	4/105.0 (3.8)
Pruritus	8/415.1 (1.9)	10/435.3 (2.3)	3/88.5 (3.4)	21/938.9 (2.2)	4/104.9 (3.8)
Rash	7/413.9 (1.7)	9/438.0 (2.1)	5/88.9 (5.6)	21/940.9 (2.2)	11/103.3 (10.7)
ALT increased	5/414.5 (1.2)	12/436.8 (2.7)	3/88.1 (3.4)	20/939.4 (2.1)	4/105.0 (3.8)
Gastrooesophageal reflux disease	7/413.2 (1.7)	9/440.7 (2.0)	3/88.7 (3.4)	19/942.6 (2.0)	2/104.9 (1.9)
Dyslipidaemia	7/412.4 (1.7)	11/433.2 (2.5)	0/90.1 (0.0)	18/935.7 (1.9)	7/103.1 (6.8)
Influenza	8/413.5 (1.9)	8/440.1 (1.8)	2/89.9 (2.2)	18/943.6 (1.9)	2/105.1 (1.9)

Preferred Term	Any AIN457 75mg N=391 n/EX (IR)	Any AIN457 150mg N=438 n/EX (IR)	Any AIN457 300mg N=145 n/EX (IR)	Any AIN457 dose N=974 n/EX (IR)	Placebo N=300 n/EX (IR)
Pain in extremity	12/412.4 (2.9)	6/442.2 (1.4)	0/90.1 (0.0)	18/944.7 (1.9)	5/104.7 (4.8)
Laceration	8/415.4 (1.9)	9/440.9 (2.0)	0/90.1 (0.0)	17/946.3 (1.8)	3/104.9 (2.9)
Depression	10/413.6 (2.4)	4/441.0 (0.9)	2/89.2 (2.2)	16/943.8 (1.7)	8/103.1 (7.8)
Mouth ulceration	5/415.3 (1.2)	9/439.2 (2.0)	2/89.0 (2.2)	16/943.5 (1.7)	0/105.6 (0.0)
Insomnia	7/415.5 (1.7)	5/441.5 (1.1)	3/88.8 (3.4)	15/945.8 (1.6)	5/104.6 (4.8)
Viral upper respiratory tract infection	5/417.7 (1.2)	9/437.6 (2.1)	1/89.7 (1.1)	15/945.0 (1.6)	8/103.7 (7.7)
Tooth abscess	8/415.4 (1.9)	5/441.2 (1.1)	1/89.4 (1.1)	14/945.9 (1.5)	0/105.6 (0.0)
Abdominal pain upper	3/417.6 (0.7)	7/441.9 (1.6)	3/89.7 (3.3)	13/949.2 (1.4)	3/104.9 (2.9)
Excoriation	4/415.9 (1.0)	9/437.5 (2.1)	0/90.1 (0.0)	13/943.5 (1.4)	1/105.6 (0.9)
Fall	4/417.9 (1.0)	6/441.3 (1.4)	3/89.4 (3.4)	13/948.6 (1.4)	0/105.6 (0.0)
Toothache	6/416.5 (1.4)	4/443.4 (0.9)	3/88.9 (3.4)	13/948.9 (1.4)	2/105.3 (1.9)
Conjunctivitis	3/417.9 (0.7)	6/439.3 (1.4)	3/89.0 (3.4)	12/946.1 (1.3)	0/105.6 (0.0)
Alopecia	1/418.6 (0.2)	4/441.2 (0.9)	3/89.2 (3.4)	8/949.0 (0.8)	2/104.9 (1.9)
Palpitations	1/419.1 (0.2)	4/441.7 (0.9)	3/88.9 (3.4)	8/949.7 (0.8)	1/105.4 (0.9)

Preferred Term	Any AIN457 75mg N=391 n/EX (IR)	Any AIN457 150mg N=438 n/EX (IR)	Any AIN457 300mg N=145 n/EX (IR)	Any AIN457 dose N=974 n/EX (IR)	Placebo N=300 n/EX (IR)
Epistaxis	0/420.0 (0.0)	1/444.8 (0.2)	3/89.7 (3.3)	4/954.6 (0.4)	3/104.8 (2.9)

Preferred terms are sorted in descending order of frequency in the Any AIN457 column.
ALT=alanine aminotransferase; EX = exposure in patient years. Percentage cut-off refers to percentages for crude incidence rates. IR=incidence rate per 100 patient years.
For patients with event, exposure time is censored at time of first event

The exposure adjusted incidence rates of these AEs did not show dose-related differences for the 150 mg and 300 mg groups with sc-loading (in study F2312) with the exception of headache (IR=8.6 vs. 11.8), sinusitis (IR=5.6 vs. 8.4), oral herpes (IR=0 vs. 5.7), pharyngitis (IR=0 vs. 5.5), and epistaxis (IR=1.4 vs. 4.1).

In Pool B, the overall exposure-adjusted incidence of AEs were similar for the 150 mg and 300 mg groups (IR=247.1 and 250.4, respectively), suggesting the absence of a dose-response. AE rates were highest for the placebo group (IR=329.6), reflecting the lower exposure in this group. Exposure-adjusted incidence rates of AEs for most SOCs were similar for the 150 mg and 300 mg groups. A higher rate of respiratory, thoracic and mediastinal disorders for the Any 300 mg group compared to the Any 150 mg group (IR=21.0 vs. 13.9, respectively) reflected higher rates of cough (IR=6.7 vs. 4.3) and oropharyngeal pain (IR=5.8 vs. 3.5).

In Pool B the majority of AEs by preferred term were reported with comparable exposure-adjusted rates for the 150 mg and 300 mg secukinumab dose groups (**Table 21**).

Table 21. Exposure-adjusted incidence of the most frequent AEs by preferred term (≥2% in any group) – Entire treatment period (Pool B: Phase 3 PsA and psoriasis trials – Safety set)

Preferred Term	Any AIN457 150mg N=1919 n/EX (IR)	Any AIN457 300mg N=1618 n/EX (IR)	Any AIN457 N=3928 n/EX (IR)	Placebo N=994 n/EX (IR)
- Any preferred term	1438/581.9 (247.1)	1210/483.3 (250.4)	2944/1223.9 (240.5)	537/162.9 (329.6)
Nasopharyngitis	343/1368.6 (25.1)	301/1076.8 (28.0)	708/2815.7 (25.1)	80/272.3 (29.4)
Upper respiratory tract infection	173/1472.1 (11.8)	115/1180.1 (9.7)	347/3036.4 (11.4)	25/282.6 (8.8)
Headache	139/1481.2 (9.4)	129/1152.8 (11.2)	298/3028.4 (9.8)	53/277.1 (19.1)
Diarrhoea	86/1519.7 (5.7)	81/1184.5 (6.8)	185/3110.7 (5.9)	21/282.5 (7.4)
Arthralgia	83/1532.8 (5.4)	69/1202.3 (5.7)	169/3142.9 (5.4)	25/282.6 (8.8)
Hypertension	75/1526.4 (4.9)	71/1201.3 (5.9)	167/3133.0 (5.3)	20/284.0 (7.0)
Back pain	72/1532.4 (4.7)	62/1202.4 (5.2)	162/3135.5 (5.2)	15/284.5 (5.3)
Cough	66/1533.3 (4.3)	80/1192.7 (6.7)	156/3138.5 (5.0)	17/283.5 (6.0)
Pruritus	72/1528.0 (4.7)	58/1192.5 (4.9)	138/3135.5 (4.4)	23/283.3 (8.1)
Oropharyngeal pain	54/1542.7 (3.5)	69/1197.6 (5.8)	134/3152.1 (4.3)	20/284.3 (7.0)
Bronchitis	57/1541.8 (3.7)	56/1211.1 (4.6)	124/3164.7 (3.9)	15/284.3 (5.3)
Influenza	49/1546.4 (3.2)	46/1217.3 (3.8)	103/3177.2 (3.2)	9/285.8 (3.1)
Pharyngitis	46/1545.0 (3.0)	46/1211.8 (3.8)	102/3170.0 (3.2)	0/287.7 (0.0)
Gastroenteritis	51/1544.7 (3.3)	39/1213.6 (3.2)	99/3172.2 (3.1)	9/286.1 (3.1)
Nausea	42/1546.8 (2.7)	32/1211.9 (2.6)	92/3165.9 (2.9)	22/283.3 (7.8)
Fatigue	41/1549.5 (2.6)	32/1216.0 (2.6)	84/3174.5 (2.6)	14/284.4 (4.9)
Sinusitis	37/1557.3 (2.4)	35/1221.1 (2.9)	83/3191.5 (2.6)	9/286.3 (3.1)
Psoriasis	32/1559.7 (2.1)	29/1223.5 (2.4)	79/3192.7 (2.5)	25/283.1 (8.8)
Pain in extremity	34/1555.5 (2.2)	32/1215.7 (2.6)	78/3183.6 (2.5)	13/285.4 (4.6)
Folliculitis	36/1554.4 (2.3)	32/1218.4 (2.6)	72/3189.3 (2.3)	6/286.5 (2.1)
Urinary tract infection	37/1548.6 (2.4)	25/1223.1 (2.0)	72/3185.5 (2.3)	9/285.8 (3.1)
Rhinitis	31/1554.3 (2.0)	33/1215.7 (2.7)	71/3184.0 (2.2)	5/287.0 (1.7)
Hypercholesterolaemia	38/1544.4 (2.5)	17/1224.0 (1.4)	68/3175.1 (2.1)	15/283.3 (5.3)
Vomiting	23/1562.5 (1.5)	29/1212.8 (2.4)	67/3184.3 (2.1)	8/285.3 (2.8)
Eczema	26/1560.7 (1.7)	37/1217.5 (3.0)	66/3197.2 (2.1)	1/287.5 (0.3)
Psoriatic arthropathy	32/1559.4 (2.1)	15/1226.5 (1.2)	65/3196.3 (2.0)	8/285.8 (2.8)
Laceration	20/1565.4 (1.3)	12/1231.4 (1.0)	40/3212.2 (1.2)	5/286.9 (1.7)
Depression	18/1563.6 (1.2)	11/1229.4 (0.9)	39/3206.6 (1.2)	12/284.4 (4.2)
Tooth abscess	16/1566.1 (1.0)	10/1230.9 (0.8)	34/3212.4 (1.1)	2/287.3 (0.7)

Preferred terms are sorted in descending order of frequency in the Any AIN457 column.
EX = exposure in patient years. IR=incidence rate per 100 patient years. Percentage cut-off refers to percentages for crude incidence rates (preferred terms with >= 2% in Any AIN457 75mg (not shown), Any AIN457 150mg, or Any AIN457 300mg.
For patients with event, exposure time is censored at time of first event.

Adverse Drug Reactions

During the first 16 weeks (Pool A), the incidence of treatment related AEs in the 300 mg secukinumab dose group was higher compared to placebo (25.0%, 18.0%, and 21.2% for 300 mg, 150 mg and 75 mg, respectively, vs. 20.7% for placebo), due to a higher rate of infections and infestations (13.0%, 12.0%, and 11.1% for 300 mg, 150 mg and 75 mg, respectively, vs. 9.0% for placebo). This was driven by small differences between treatment groups for individual treatment-related infections, in particular respiratory tract infection (2.0% for 300 mg vs. 0% for 150 mg, 75 mg and placebo groups) and oral herpes (2.0% for 300 mg vs. 0% for 150 mg, 1.0% for 75 mg and 0% for placebo groups). A small increase in treatment-related AEs in the 300 mg secukinumab dose group was also seen for skin and subcutaneous

tissue disorders (5.0%, 1.0%, and 2.0% for 300 mg, 150 mg, and 75 mg, respectively, vs. 3.3% for placebo), although this was not driven by individual events.

During the entire treatment period for Pool A, there was a higher overall incidence of treatment-related AEs in the secukinumab dose groups compared to placebo (29.0%, 31.7% and 28.9% for Any 300 mg, Any 150 mg and 75 mg groups, respectively, vs. 21.3% for placebo), due to a higher rate of infections and infestations (16.6%, 20.8%, and 17.9% for 300 mg, 150 mg and 75 mg, respectively, vs. 9.7% for placebo). Upper respiratory tract infection and nasopharyngitis, the most common infections, as well as respiratory tract infections, urinary tract infections, sinusitis, oral herpes, bronchitis, and pharyngitis occurring at low rates, contributed to this imbalance. No dose response for secukinumab was seen in the total rate or in any event considered possibly related to study treatment.

AEs causing dose interruption or adjustment

As for Pool A, the overall incidence of patients with AEs causing dose interruption in Pool B did not show a dose increase across the secukinumab dose groups (5.3% and 6.0% for the Any 300 mg and Any 150 mg, respectively, and 3.3% for placebo). The most common AEs causing dose interruption were for infections and infestations and did not show a dose increase across the secukinumab dose groups (3.2% and 3.5%, respectively, for the Any 300 mg and Any 150 mg groups vs. 1.6% for placebo). Individual AEs causing dose interruption were reported for few patients and were comparable across treatment groups.

For the entire treatment period of Pool A, the overall incidence of AEs requiring concomitant medication was lowest for the secukinumab sc dose groups compared to the iv dose groups (57.0%, 62.0% and 47.5%, respectively, for the 300 mg, 150 mg and 75 mg sc groups vs. 74.3-76.7% for the iv loading groups, 45.3% for placebo). This difference was due to infections and infestations (38.0%, 42.0% and 29.3%, respectively, for the 300 mg, 150 mg and 75 mg vs. 51.0-54.5% for the iv loading groups, 20.7% for placebo), mainly as a result of a higher rate of upper respiratory tract infections.

Crohn´s disease

Of the 4 cases of IBD in pool A (**Table 22**), 2 cases were Crohn's disease (1 placebo patient – on baseline - and 1 patient on 75 mg).

Table 22. Exposure-adjusted incidence of inflammatory bowel disease – Entire treatment period (Pool A: Phase 3 PsA trials – Safety set)

Level 1 Preferred term	Any AIN457 75mg N=391 n/EX (IR)	Any AIN457 150mg N=438 n/EX (IR)	Any AIN457 300mg N=145 n/EX (IR)	Any AIN457 dose N=974 n/EX (IR)	Placebo N=300 n/EX (IR)
Based on all AEs					
Inflammatory bowel disease (narrow NMQ)	2/418.9 (0.5)	0/444.9 (0.0)	1/89.3 (1.1)	3/953.1 (0.3)	1/105.5 (0.9)
Diarrhea hemorrhagic (PT)	1/418.9 (0.2)	0/444.9 (0.0)	1/89.3 (1.1)	2/953.2 (0.2)	0/105.6 (0.0)
Crohn's disease (PT)	1/420.0 (0.2)	0/444.9 (0.0)	0/90.1 (0.0)	1/955.0 (0.1)	1/105.5 (0.9)
Based on SAEs					
Inflammatory bowel disease (narrow NMQ)	1/420.0 (0.2)	0/444.9 (0.0)	0/90.1 (0.0)	1/955.0 (0.1)	1/105.5 (0.9)
Crohn's disease (PT)	1/420.0 (0.2)	0/444.9 (0.0)	0/90.1 (0.0)	1/955.0 (0.1)	1/105.5 (0.9)

NMQ=Novartis MedDRA query; PT=preferred term
Preferred terms are sorted in descending order of frequency in the Any AIN457 dose column

Infections and infestations

Consistent with the psoriasis program, there was a small increase in the risk of localized (non-invasive) clinically manageable candidiasis, which was expected due to the role of IL-17A in immunity to fungal infections. A dose effect was apparent only in the entire treatment period (Pool A). Candida cases were all mild or moderate in severity, responsive to standard treatment and did not lead to discontinuation. Esophageal candidiasis was reported in 2 PsA patients, one in each of the 150 mg and 300 mg secukinumab dose groups. Both cases of esophageal candidiasis were mild or moderate in severity, non-

serious and resolved upon treatment with standard antifungal medication without requiring discontinuation of secukinumab.

In Pool A, herpes viral infections (HLT) occurred in a higher proportion of patients in the Any 300 mg group (4.8%) than in the other secukinumab dose groups (3.1% and 3.4% for Any 75 mg and Any 150 mg, respectively). Crude incidence of herpes viral infections (HLT) for the placebo group was 1.3%. The higher rate in the Any 300 mg group was due to oral herpes (3.4% for Any 300 mg vs. 1.8% and 2.7%, respectively, for Any 75 mg and Any 150 mg groups). All cases of oral herpes were of mild or moderate severity, were not SAEs and did not require study drug discontinuation. There was one case of herpes zoster cutaneous disseminated, also an event in the opportunistic infections NMQ, in a patient on iv-75 mg secukinumab.

There were no serious opportunistic infections, and no cases of reactivation of either tuberculosis or Hepatitis B.

The most common infections of skin structures reported in pool A are presented in **Table 23**.

Table 23. Exposure-adjusted incidence rate of adverse drug reactions (Pool A entire treatment period: Phase 3 PsA trials – Safety set)

High Level Term Preferred term	Any AIN457 75 mg N=391 n/EX (IR)	Any AIN457 150 mg N=438 n/EX (IR)	Any AIN457 300 mg N=145 n/EX (IR)	Any AIN457 dose N=974 n/EX (IR)	Placebo N=300 n/EX (IR)
Upper respiratory tract infections (HLT)	136/322.2 (42.2)	149/336.3 (44.3)	42/75.6 (55.6)	327/734.1 (44.5)	48/96.2 (49.9)
Upper respiratory tract infections (PT)	59/384.1 (15.4)	69/398.9 (17.3)	18/84.1 (21.4)	146/867.2 (16.8)	18/102.3 (17.6)
Nasopharyngitis (PT)	64/370.3 (17.3)	61/396.1 (15.4)	15/85.1 (17.6)	140/851.6 (16.4)	19/101.4 (18.7)
Pharyngitis (PT)	10/413.2 (2.4)	13/433.8 (3.0)	5/88.9 (5.6)	28/935.8 (3.0)	0/105.6 (0.0)
Rhinitis (PT)	7/413.9 (1.7)	7/441.0 (1.6)	1/89.8 (1.1)	15/944.8 (1.6)	0/105.6 (0.0)
Conjunctivitis (PT)	3/417.8 (0.7)	6/439.2 (1.4)	3/89.0 (3.4)	12/946.1 (1.3)	0/105.6 (0.0)
Oral herpes (PT)	7/415.5 (1.7)	12/434.2 (2.8)	5/87.4 (5.7)	24/937.2 (2.6)	4/104.4 (3.8)
Tinea pedis (PT)	4/415.4 (1.0)	2/442.2 (0.5)	2/89.3 (2.2)	8/946.9 (0.8)	0/105.6 (0.0)
Urticaria (PT)	2/419.4 (0.5)	1/444.8 (0.2)	2/89.3 (2.2)	5/953.5 (0.5)	0/105.6 (0.0)

Malignancies and skin tumours

Results from the PsA population continue to support the conclusion from the psoriasis program that secukinumab does not confer an increased risk for malignancy. The incidence of malignancies including skin tumours was low and comparable across the secukinumab dose groups and placebo.

Malignancy SAEs occurred at a low and comparable exposure-adjusted incidence rate in the Any secukinumab dose and placebo groups (IR: 0.3 vs. 0.9) (**Table 24**).

Table 24. Exposure-adjusted incidence rates for malignancies and skin tumors – Entire treatment period (Pool A: Phase 3 PsA trials – Safety set)

Level 1 Preferred term	Any AIN457 75 mg N=391 n/EX (IR)	Any AIN457 150 mg N=438 n/EX (IR)	Any AIN457 300 mg N=145 n/EX (IR)	Any AIN457 dose N=974 n/EX (IR)	Placebo N=300 n/EX (IR)
Based on all AEs					
Malignant or unspecified tumors (SMQ)	4/418.1 (1.0)	1/444.8 (0.2)	0/90.1 (0.0)	5/953.0 (0.5)	1/105.5 (0.9)
Skin tumors malignant and unspecified (broad NMQ)	4/418.1 (1.0)	0/444.9 (0.0)	0/90.1 (0.0)	4/953.1 (0.4)	0/105.6 (0.0)
Basal cell carcinoma (PT)	3/418.3 (0.7)	0/444.9 (0.0)	0/90.1 (0.0)	3/953.3 (0.3)	0/105.6 (0.0)
Squamous cell carcinoma (PT)	1/419.9 (0.2)	0/444.9 (0.0)	0/90.1 (0.0)	1/954.9 (0.1)	0/105.6 (0.0)
Based on all SAEs					
Malignant or unspecified tumors (SMQ)	2/419.4 (0.5)	1/444.8 (0.2)	0/90.1 (0.0)	3/954.3 (0.3)	1/105.5 (0.9)
Skin tumors malignant and unspecified (broad NMQ)	2/419.4 (0.5)	0/444.9 (0.0)	0/90.1 (0.0)	2/954.5 (0.2)	0/105.6 (0.0)
Basal cell carcinoma (PT)	1/419.6 (0.2)	0/444.9 (0.0)	0/90.1 (0.0)	1/954.6 (0.1)	0/105.6 (0.0)
Squamous cell carcinoma (PT)	1/419.9 (0.2)	0/444.9 (0.0)	0/90.1 (0.0)	1/954.9 (0.1)	0/105.6 (0.0)

EX=exposure in patient-years; IR=incidence rate per 100 patient-years; NMQ=Novartis MedDRA Query; PT=preferred term; SMQ=Standard MedDRA query

New malignancies from the psoriasis studies are from the ongoing studies A2308 and A2309, reported in the Week 52 study reports provided in the present submission, and include the following:

- Two uncomplicated cases of basal cell carcinoma
- One case of adenosquamous cell carcinoma, confounded by relevant medical history
- One case of B-cell lymphoma for which the investigator reported the event as suspected to be related to study treatment but also suspected to be related to past treatment of tofacitinib and ustekinumab.

Major adverse cardiovascular events (MACE)

Data from the Phase 3 program in PsA do not suggest an increased risk of MACE in PsA patients treated with secukinumab. In the psoriasis submission, secukinumab was comparable to placebo in the incidence of MACE in the first 12 weeks of treatment as well as over the entire treatment period. All MACE cases were associated with prior or active cardiovascular disease or risk factors at Baseline. There was no dose dependence for secukinumab.

Consistent with the psoriasis program, the Phase 3 studies in PsA did not exclude patients with stable cardiovascular risk factors from secukinumab treatment. A total of 7 (0.7%) adjudicated and confirmed MACE cases were reported in Pool A of PsA studies (6 cases for the 75 mg dose, and 1 case for the 150 mg dose) (**Table 25**). No MACE cases were reported for the 300 mg dose or for placebo.

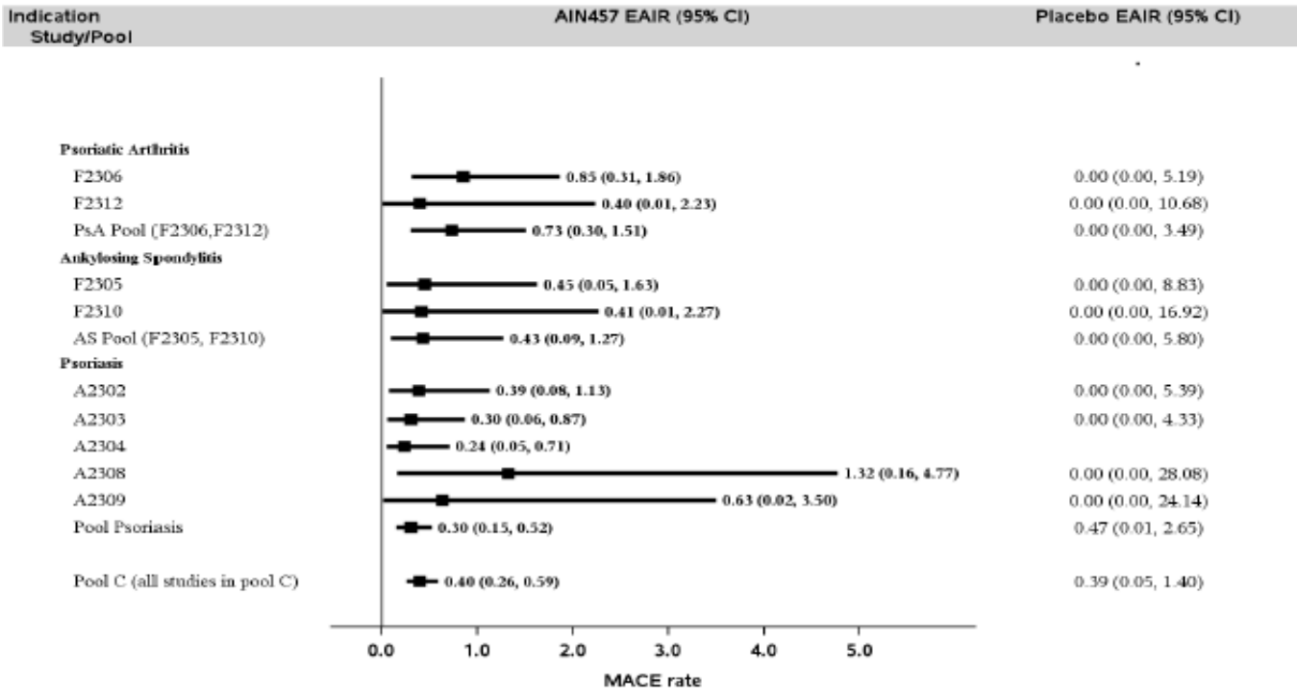
Table 25. MACE adjudication results in PsA patients – Entire treatment period (Pool A: Phase 3 PsA trials – Safety set)

MACE category Adjudication outcome	Any AIN457 75 mg N=391 n (%)	Any AIN457 150 mg N=438 n (%)	Any AIN457 300 mg N=145 n (%)	Any AIN457 dose N=974 n (%)	Placebo N=300 n (%)
Myocardial infarction					
Yes	2 (0.5)	1 (0.2)	0	3 (0.3)	0
Indeterminate	0	0	0	0	0
Stroke					
Yes	4 (1.0)	0	0	4 (0.4)	0
Indeterminate	0	0	0	0	0
Cardiovascular death					
Cardiovascular	0	0	0	0	0
Indeterminate	1 (0.3)	0	0	1 (0.1)	0
Total no. MACE (Yes)#	6 (1.5)	1 (0.2)	0	7 (0.7)	0

Only confirmed and indeterminate adjudicated MACE events were included.
Total MACE (Yes) is the sum of patients in the Myocardial infarction (Yes) and Stroke (Yes) rows; the indeterminate cardiovascular death is also counted in the Stroke (Yes) row.

In the present PsA submission, the rate of MACE on secukinumab across multiple indications was stable despite increased exposure in comparison to the psoriasis submission. Pooling across 42 studies including 8 new studies reported here for the first time, the exposure-adjusted incidence of potential MACE AEs over the entire treatment period of all secukinumab trials (Pool C) was 0.40 (n=30, CI: 0.26 - 0.59) for the Any secukinumab dose group and 0.39 (n=2, CI: 0.05 - 1.40) for placebo, **Figure 14**.

Figure 14. Exposure adjusted incidence rate for adjudicated and confirmed MACE by studies and data pools



Studies A2302 and A2303 include extension data.Pool Psoriasis include additional studies A2102, A2103, A2204 A2211, A2212, A2220, A2223, A2225, and A2307

Hepatotoxicity

Consistent with the conclusions from the psoriasis program, the safety data in the PsA population do not suggest an increased risk for drug-induced liver injury (DILI) from secukinumab treatment. Despite small imbalances in the incidence of mild hepatic transaminase elevations (CTCAE Grade 1) vs. placebo, secukinumab at any dose in the PsA program was not associated with any cases of combined elevations in hepatic transaminases and serum bilirubin. Discontinuations due to hepatotoxicity were rare in secukinumab treated patients and all cases were confounded by either a previously reported medical condition or concomitant treatment with isoniazid and methotrexate.

QTC-prolongation

A search for cases of QT prolongation yielded a total of 3 AEs in the PsA population, one case in each of the 75 mg, 150 mg, and placebo groups. No cases were reported for the 300 mg group. All 3 events were non-serious, mild or moderate in severity and considered unrelated to study medication. No patient discontinued study medication due to the event. There were no further events of QT prolongation in the expanded PsA population in Pool B1 or among the psoriasis patients included in Pool B. QT prolongation is being monitored as a routine risk.

Serious adverse events and deaths

Four deaths were reported across data pools A, B1 and B: one death was reported for the PsA trials (Pool A) due to an intracranial haemorrhage in a patient receiving iv-75 mg. One further death occurred in Pool B1 of unknown cause (300 mg secukinumab). Two additional deaths occurred in psoriasis patients contributing to Pool B as a result of cardiopulmonary arrest (150 mg secukinumab), and of alcohol poisoning (placebo-secukinumab 300 mg), respectively. None of these deaths was considered by the investigator to be related to study treatment.

For Pool A studies CAIN457F2306 and CAIN457F2312, one further death was reported between the data cut-off for Pool A (9-Oct-2013 for study F2306 and 12-May-2014 for study F2312) and the data cut-off used for the submission (10-Oct-2014).

In studies F2305 and F2310 on ankylosing spondylitis, there were three additional deaths (1 in the placebo group (suicide), 1 in the iv-75 mg group due to respiratory failure, and 1 in the 75 mg sc group due to an acute myocardial infarction). None of these deaths was considered by the respective investigators to be related to study treatment.

Overall exposure adjusted rates of SAEs (**Table 26**) were similar for the secukinumab dose groups and no higher than placebo. The exposure adjusted rates of infections and infestations were slightly higher for the “Any 300 mg group compared to the Any 150 mg and Any 75 mg groups (IR=4.5 vs. 2.5 and 2.2, respectively). This difference (based on few events) was also seen when comparing the two sc loading doses of 150 mg (n=1, IR=1.4) and 300 mg (n=3, IR=4.2).

Laboratory findings

Haematology

Most newly occurring or worsening haematology-related abnormalities observed for PsA patients were CTCAE Grade 1 or Grade 2 abnormalities and were consistent with findings from the initial psoriasis submission. The incidence of CTCAE Grade 2 and 3 laboratory abnormalities was higher in secukinumab-treated patients compared to placebo in the initial 16 weeks of treatment. A similar pattern was observed over the entire treatment period and no CTCAE Grade 4 abnormalities were observed as of 10-Oct-2014. In the current submission for PsA, no dose effect for secukinumab was observed in lab results or in AEs.

Table 26. Exposure-adjusted incidence of the most frequent SAEs by preferred term (>=0.5 per 100 patient-years in any group) – Entire treatment period (Pool A: Phase 3 PsA trials – Safety set)

Preferred Term	Any AIN457 75mg N=391 n/EX (IR)	Any AIN457 150mg N=438 n/EX (IR)	Any AIN457 300mg N=145 n/EX (IR)	Any AIN457 dose N=974 n/EX (IR)	Placebo N=300 n/EX (IR)
- Any SAE	34/406.7 (8.4)	41/420.3 (9.8)	7/86.6(8.1)	82/913.6 (9.0)	14/102.8 (13.6)
Erysipelas	1/419.8 (0.2)	2/443.5 (0.5)	1/89.6 (1.1)	4/953.0 (0.4)	1/105.4 (0.9)
Non-cardiac chest pain	0/420.0 (0.0)	2/444.7 (0.4)	1/89.6 (1.1)	3/954.4 (0.3)	1/105.4 (0.9)
Osteoarthritis	1/419.9 (0.2)	2/443.3 (0.5)	0/90.1 (0.0)	3/953.2 (0.3)	1/105.5 (0.9)
Sepsis	3/419.5 (0.7)	0/444.9 (0.0)	0/90.1 (0.0)	3/954.6 (0.3)	1/105.6 (0.9)
Atrial fibrillation	2/419.1 (0.5)	0/444.9 (0.0)	0/90.1 (0.0)	2/954.1 (0.2)	0/105.6 (0.0)
Cerebrovascular accident	2/419.2 (0.5)	0/444.9 (0.0)	0/90.1 (0.0)	2/954.2 (0.2)	0/105.6 (0.0)
Coronary artery disease	0/420.0 (0.0)	2/443.5 (0.5)	0/90.1 (0.0)	2/953.6 (0.2)	1/105.3 (0.9)
Deep vein thrombosis	0/420.0 (0.0)	2/444.1 (0.5)	0/90.1 (0.0)	2/954.2 (0.2)	0/105.6 (0.0)
Diverticulitis	0/420.0 (0.0)	2/444.0 (0.5)	0/90.1 (0.0)	2/954.1 (0.2)	0/105.6 (0.0)
Myocardial infarction	2/419.6 (0.5)	0/444.9 (0.0)	0/90.1 (0.0)	2/954.6 (0.2)	0/105.6 (0.0)
Pneumonia	2/419.7 (0.5)	0/444.9 (0.0)	0/90.1 (0.0)	2/ 954.7 (0.2)	0/105.6 (0.0)
Psoriatic arthropathy	0/420.0 (0.0)	2/443.5 (0.5)	0/90.1 (0.0)	2/953.6 (0.2)	0/105.6 (0.0)
Septic shock	2/419.8 (0.5)	0/444.9 (0.0)	0/90.1 (0.0)	2/954.8 (0.2)	1/105.6 (0.9)
Vertigo positional	2/417.8 (0.5)	0/444.9 (0.0)	0/90.1 (0.0)	2/952.9 (0.2)	0/ 105.6 (0.0)
Calculus urinary	0/420.0 (0.0)	0/444.9 (0.0)	1/90.1 (1.1)	1/955.0 (0.1)	0/105.6 (0.0)
Cervical radiculopathy	0/420.0 (0.0)	0/444.9 (0.0)	1/89.4 (1.1)	1/954.3 (0.1)	0/105.6 (0.0)
Crohn's disease	1/420.0 (0.2)	0/444.9 (0.0)	0/90.1 (0.0)	1/955.0 (0.1)	1/105.5 (0.9)
Dehydration	0/420.0 (0.0)	0/444.9 (0.0)	1/89.2 (1.1)	1/954.2 (0.1)	0/105.6 (0.0)
Intervertebral disc protrusion	0/420.0 (0.0)	0/444.9 (0.0)	1/89.4 (1.1)	1/954.3 (0.1)	0/105.6 (0.0)
Limb traumatic amputation	0/420.0 (0.0)	0/444.9 (0.0)	1/89.3 (1.1)	1/954.3 (0.1)	0/105.6 (0.0)
Migraine	0/420.0 (0.0)	0/444.9 (0.0)	1/89.4 (1.1)	1/954.4 (0.1)	0/105.6 (0.0)
Nephrolithiasis	0/420.0 (0.0)	1/444.8 (0.2)	0/90.1 (0.0)	1/954.9 (0.1)	1/105.3 (0.9)
Osteomyelitis	0/420.0 (0.0)	0/444.9 (0.0)	1/89.3 (1.1)	1/954.3 (0.1)	0/105.6 (0.0)
Sinusitis	0/420.0 (0.0)	0/444.9 (0.0)	1/89.8 (1.1)	1/954.7 (0.1)	1/105.4 (0.9)
Subcutaneous abscess	0/420.0 (0.0)	0/444.9 (0.0)	1/89.4 (1.1)	1/954.4 (0.1)	0/105.6 (0.0)
Cholecystitis acute	0/420.0 (0.0)	0/444.9 (0.0)	0/90.1 (0.0)	0/955.0 (0.0)	1/105.5 (0.9)
Depression	0/420.0 (0.0)	0/444.9 (0.0)	0/90.1 (0.0)	0/955.0 (0.0)	1/105.4 (0.9)
Haematoma infection	0/420.0 (0.0)	0/444.9 (0.0)	0/90.1 (0.0)	0/955.0 (0.0)	1/105.6 (0.9)
Hypertensive crisis	0/420.0 (0.0)	0/444.9 (0.0)	0/90.1 (0.0)	0/955.0 (0.0)	1/105.2 (1.0)
Inguinal hernia	0/420.0 (0.0)	0/444.9 (0.0)	0/90.1 (0.0)	0/955.0 (0.0)	1/105.4 (0.9)
Intraductal proliferative breast lesion	0/420.0 (0.0)	0/444.9 (0.0)	0/90.1 (0.0)	0/955.0 (0.0)	1/105.5 (0.9)
Pleural effusion	0/420.0 (0.0)	0/444.9 (0.0)	0/90.1 (0.0)	0/955.0 (0.0)	1/105.1 (1.0)
Rectal haemorrhage	0/420.0 (0.0)	0/444.9 (0.0)	0/90.1 (0.0)	0/955.0 (0.0)	1/105.6 (0.9)

Preferred terms are sorted in descending order of frequency in the Any AIN457 column.
EX = exposure in patient years. IR=incidence rate per 100 patient years.
For patients with event, exposure time is censored at time of first event

Among the 4 patients with CTCAE Grade 3 neutropenia, none experienced an infection any time during the reporting period. Further, neutropenia reported as AEs were transient (lasting only 1 visit and normalizing at the next subsequent visit) and did not result in permanent discontinuation of study drug.

These events are presented in **Table 27**. The overall incidence of neutropenia was similar between the different loading regimens.

Table 27. Neutropenia events – Entire treatment period (Pool A: Phase 3 PsA trials – Safety set)

Level 1 Preferred term	Any AIN457 75 mg N=391 n/EX (IR)	Any AIN457 150 mg N=438 n/EX (IR)	Any AIN457 300 mg N=145 n/EX (IR)	Any AIN457 dose N=974 n/EX (IR)	Placebo N=300 n/EX (IR)
Based on all AEs					
Neutropenia (narrow NMQ)	9/412.1 (2.2)	5/440.1 (1.1)	2/88.6 (2.3)	16/940.9 (1.7)	7/103.9 (6.7)
Leukopenia (PT)	6/415.5 (1.4)	3/443.4 (0.7)	0/90.1 (0.0)	9/949.0 (0.9)	3/105.0 (2.9)
Neutropenia (PT)	1/418.3 (0.2)	3/441.9 (0.7)	1/89.2 (1.1)	5/949.5 (0.5)	3/104.6 (2.9)
White blood cell count decreased (PT)	3/418.1 (0.7)	1/443.3 (0.2)	1/89.5 (1.1)	5/950.8 (0.5)	1/105.5 (0.9)
Neutrophil count decreased (PT)	1/419.3 (0.2)	0/444.9 (0.0)	0/90.1 (0.0)	1/954.3 (0.1)	0/105.6 (0.0)
Based on SAEs					
Neutropenia (narrow NMQ)	0	0	0	0	0

EX=exposure in patient-years; IR=incidence rate per 100 patient-years; PT=preferred term; NMQ=Novartis MedDRA query
Preferred terms are sorted in descending order of frequency in the Any AIN457 column
A patient with multiple occurrences of a level under one treatment is counted only once for the same risk for that treatment.
For patients with event, exposure time is censored at the time of the first event.

Clinical chemistry

Secukinumab at any dose showed a higher rate of Grade 1 ALT elevations and of Grade 1-2 abnormalities in cholesterol and triglycerides compared with placebo. Rates of Grade 1 or 2 elevations in ALT, alkaline phosphatase, bilirubin, creatinine and GGT for secukinumab were lower than or similar to placebo. Across the secukinumab dose groups, higher rates were not observed with the 300 mg dose, with the possible exception of Grade 1 values in bilirubin. The rates of Grade 1 or 2 elevations in the iv loading groups were comparable to or lower than the rates in the sc loading groups, suggesting no increase with higher exposure.

Grade 3 elevations in ALT, AST, GGT, increased fasting serum glucose and triglycerides were noted for a small number of patients in both secukinumab and placebo groups, with no meaningful difference between secukinumab and placebo treatments or across secukinumab doses. Grade 4 abnormalities in decreased fasting glucose were reported for 1 (1.0%) patients on 150 mg secukinumab and 1 (0.3%) patient on placebo. Grade 4 elevations in triglycerides were observed in 3 (0.4%) patients on secukinumab (all with iv loading) and none on placebo.

Grade 2 elevations in cholesterol were infrequent, but rates were slightly higher in the Any secukinumab dose group compared to placebo (1.6% vs. 0.3% respectively); the highest rate (4.0%) was reported in the iv-150 mg group. Grade 3 and 4 cholesterol abnormalities were not reported.

Safety in special populations

Baseline BSA

Rates of total AEs and most SOCs were higher in patients with <10% BSA than in those with ≥10% BSA in all treatment groups, including the placebo group (**Table 28**).

Table 28. Exposure-adjusted incidence of AEs by baseline BSA – Entire treatment period (Pool A: Phase 3 PsA trials – Safety set)

Primary SOC	Subgroup	Any AIN457 75mg n/EX (IR)	Any AIN457 150mg n/EX (IR)	Any AIN457 300mg n/EX (IR)	Any AIN457 dose n/EX (IR)	Placebo n/EX (IR)
Total of patients - N	BSA ≥ 10%	118	145	34	297	98
	BSA < 10%	265	288	106	659	198
Any AEs	BSA ≥ 10%	77/60.9 (126.5)	96/61.3 (156.5)	18/12.3 (146.1)	191/134.5 (142.0)	46/23.0 (200.4)
	BSA < 10%	213/ 95.6 (222.9)	241/85.1 (283.2)	71/29.0 (244.6)	525/209.7 (250.4)	133/33.1 (402.1)
Infections and infestations	BSA ≥ 10%	54/89.9 (60.1)	55/100.6 (54.7)	9/16.8 (53.4)	118/207.3 (56.9)	22/29.9 (73.5)
	BSA < 10%	140/180.9 (77.4)	175/160.1 (109.3)	47/44.3 (106.2)	362/385.3 (93.9)	59/56.0 (105.3)
Musculoskeletal and connective tissue disorders	BSA ≥ 10%	23/111.7 (20.6)	30/124.1 (24.2)	3/20.9 (14.4)	56/256.7 (21.8)	7/34.0 (20.6)
	BSA < 10%	80/233.4 (34.3)	61/252.5 (24.2)	16/58.3 (27.5)	157/544.2 (28.8)	37/ 61.1 (60.5)
Gastrointestinal disorders	BSA ≥ 10%	17/116.9 (14.5)	24/130.3 (18.4)	3/19.9 (15.1)	44/267.1 (16.5)	9/33.6 (26.8)
	BSA < 10%	70/231.6 (30.2)	75/237.8 (31.5)	24/54.4 (44.1)	169/523.9 (32.3)	29/61.7 (47.0)
Skin and subcutaneous tissue disorders	BSA ≥ 10%	13/119.9 (10.8)	18/135.9 (13.2)	2/21.5 (9.3)	33/277.3 (11.9)	5/34.1 (14.7)
	BSA < 10%	52/247.1 (21.0)	55/253.2 (21.7)	15/58.3 (25.7)	122/558.6 (21.8)	24/64.1 (37.4)
Nervous system disorders	BSA ≥ 10%	16/115.5 (13.9)	20/132.6 (15.1)	3/20.3 (14.8)	39/268.4 (14.5)	4/34.2 (11.7)
	BSA < 10%	43/249.5 (17.2)	48/255.1 (18.8)	14/56.9 (24.6)	105/561.5 (18.7)	24/ 63.4 (37.9)

Most frequently reported primary system organ classes (>15 per 100-patient-years in the Any AIN457 group in the overall population) are presented in descending order of IR in Any AIN457 group of Table 2-3
EX = exposure in patient-years, IR=incidence rate per 100 patient-years

Body weight

No specific weight-related trends in total AEs or in the most frequently affected SOC of infections and infestations were observed. There were no meaningful differences by weight observed in the incidence of cardiac disorders, skin and subcutaneous tissue disorders or gastrointestinal disorders or other SOCs compared to the overall population. The incidence of SAEs was low and no weight-related trends among the treatment groups were observed. Serious infections and infestations were reported in a slightly higher proportion of patients weighing < 90 kg (n=8, 1.8% in the Any secukinumab group vs. 0% in the placebo group), with no meaningful difference across dose groups, than in the patients weighing ≥ 90 kg (n=1, 0.4% in the Any secukinumab group vs. n=1, 1.1% in the placebo group).

10-year CHD risk category

The majority of patients across all treatment groups were in the low risk category for 10-year CHD risk (<10%). AEs by CHD risk category in the initial treatment period of Pool A were consistent with the profile observed in the overall population. There was no increase in the incidence of AEs in the SOCs of cardiac disorders, nervous system disorders and vascular disorders among patients in the high 10-year

CHD risk category (>20%) compared with patients in the medium (10-20%) or low (<10%) CHD risk category. There were no clinically meaningful differences across the treatment groups in any subgroups of CHD risk. Similar findings were observed for SAEs by CHD risk category, which showed no specific trends for any event and few SAEs among the small number of patients in the high risk category. The profile of AEs for Pool A over the entire treatment period by CHD risk category was consistent with those observed for the overall population. Similar results were seen for SAEs in Pool A over the entire treatment period.

Immunological events

In the PsA studies, the overall incidence of immune/administration reactions in the initial 16-week treatment period was comparable across the secukinumab and placebo groups. Some specific events were more common in placebo patients (mainly cough and rash), while other events (*e.g.,* peripheral edema, conjunctivitis, mouth ulceration, urticaria and injection site erythema) were reported with low rates in secukinumab patients only. There were no reports of anaphylactic reaction in a secukinumab treated patient. With longer exposure over the entire treatment period, the overall incidence was higher with the 300 mg dose compared with the 150 mg dose, mainly driven by rash, pruritus and conjunctivitis. Results from the expanded PsA population and from the pooled PsA and psoriasis population supported these findings.

One case of angioedema (PT) was reported. The event was non-serious, moderate in severity, lasted for 13 days and was considered related to study medication. The patient discontinued study medication and recovered from the event without requiring treatment. No systemic features of anaphylaxis were reported.

The exposure adjusted incidence of the most frequent immunological AEs over the entire treatment period, are presented in **Table 29**.

Table 29. Exposure-adjusted incidence rate of the most frequent AEs of immune/administration reactions (≥2% in any treatment group) – Entire treatment period (Pool A: Phase 3 PsA trials – Safety set)

Level 1 Preferred term	Any AIN457 75mg N=391 n/EX (IR)	Any AIN457 150mg N=438 n/EX (IR)	Any AIN457 300mg N=145 n/EX (IR)	Any AIN457 dose N=974 n/EX (IR)	Placebo N=300 n/EX (IR)
Based on all AEs					
Immune/administration reactions (NMQ)	98/354.8 (27.6)	117/354.7 (33.0)	30/76.4 (39.3)	245/785.8 (31.2)	43/95.4 (45.1)
Cough (PT)	10/412.5 (2.4)	20/429.3 (4.7)	3/88.0 (3.4)	33/929.7 (3.5)	8/103.7 (7.7)
Pruritus (PT)	8/415.0 (1.9)	10/435.3 (2.3)	3/88.5 (3.4)	21/938.9 (2.2)	4/104.9 (3.8)
Rash (PT)	7/413.9 (1.7)	9/438.0 (2.1)	5/88.9 (5.6)	21/940.9 (2.2)	11/103.2 (10.7)
Conjunctivitis (PT)	3/417.8 (0.7)	6/439.2 (1.4)	3/89.0 (3.4)	12/946.1 (1.3)	0/105.6 (0.0)
Mouth ulceration (PT)	5/415.3 (1.2)	9/439.2 (2.0)	2/89.0 (2.2)	16/943.4 (1.7)	0/105.6 (0.0)
Based on SAEs	2/419.8 (0.5)	3/443.4 (0.7)	0/90.1 (0.0)	5/953.2 (0.5)	1/105.5 (0.9)
Psoriatic arthropathy (PT)	0/420.0 (0.0)	2/443.5 (0.5)	0/90.1 (0.0)	2/953.6 (0.2)	0/105.6 (0.0)
Crohn's disease (PT)	1/420.0 (0.2)	0/444.9 (0.0)	0/90.1 (0.0)	1/955.0 (0.1)	1/105.5 (0.9)
Local swelling (PT)	0/420.0 (0.0)	1/444.8 (0.2)	0/90.1 (0.0)	1/954.9 (0.1)	0/105.6 (0.0)
Ocular myasthenia (PT)	1/419.8 (0.2)	0/444.9 (0.0)	0/90.1 (0.0)	1/954.8 (0.1)	0/105.6 (0.0)

EX=exposure in patient years; IR=incidence rate per 100 patient years; NMQ=Novartis MedDRA query; PT=preferred term;
Most frequently occurring preferred terms for AEs (>=2% in any treatment group) are presented and sorted in descending order of frequency in the Any AIN457 dose column

Exposure-adjusted incidence rates for hypersensitivity AEs were higher in the Any 300 mg group compared with the Any 150 mg and Any 75 mg groups (IR=14.0 vs. 9.6 and 7.7, respectively), but all secukinumab doses showed numerically lower rates than the placebo group (IR=21.7). The imbalance was mainly driven by the higher rate of rash and urticaria.

In the time interval of 0-8 weeks, the absolute incidence of immune/administration reactions was comparable between the sc loading (11.0%, 8.0% and 8.1% for 300 mg, 150 mg and 75 mg, respectively) and iv loading regimens (7.9% and 10.9% for iv-75 mg and iv-150 mg, respectively), and slightly lower for the no-load regimens (6.7%, 5.1% and 8.9% for 75 mg, 150 mg and 300 mg, respectively).

The profile of immune/administration reactions in the Phase 3 PsA and psoriasis studies (Pool B) was similar to that observed in PsA populations of Pools A and B1, also showing no new or unexpected reactions with secukinumab treatment.

Immunogenicity

Treatment-emergent ADA are defined as ADA that developed post-treatment in patients with negative ADA screens at Baseline (ie, seroconversion to ADA positivity from a seronegative state). Across both Phase 3 PsA trials, treatment-emergent ADA were detected in one patient only (1/996, 0.1%) who was receiving 75 mg secukinumab at the time of the positive result at Week 24. A subsequent sample collected at Week 52 was negative for ADA. There was no loss of efficacy, no immunogenicity-related AEs and no altered PK profile in this single case of treatment-emergent ADA.

Non-treatment emergent ADA were also observed in both Phase 3 PsA trials. A total of 16/996 (1.6%) patients were ADA positive at Baseline. This includes 10 patients who were ADA positive at Baseline only and reverted to a seronegative state while on secukinumab treatment, and 6 patients who had both baseline and post-baseline ADA positive samples. Overall, the non-treatment emergent positive ADA responses were mostly transient and of low titer. The MSD-based assay is highly sensitive and therefore capable of detecting very low levels of antibodies which can bind to secukinumab. Consequently, non-treatment related, naturally occurring ADA may lead to a confirmed positive response in this assay in either predose samples or samples derived from patients not exposed to secukinumab. These observations were not considered to be clinically relevant, as the ADA were not associated with secukinumab treatment. Of the 17 patients who tested positive for ADA at any time point in either Phase 3 PsA trials, 10 (58.8%) reverted to a seronegative state at a later time point with no detectable ADA while on secukinumab treatment. This total includes the single patient with treatment-emergent ADA who also reverted to a seronegative state while on treatment.

ADA were also not associated with altered PK profiles. Secukinumab concentrations in all patients with ADA and more than one evaluable PK sample fit into the observed range for all patients without ADA at Weeks 4, 16, 24 and 52. There was also no correlation between ADA titers and alteration in PK profile in Phase 2 or 3 patients.

Across all secukinumab-exposed patients evaluated for ADA in the 2 Phase 3 PsA trials, 8/996 (0.8%) patients tested positive for both ADA and neutralizing antibodies. PK profiles were normal and therapeutic efficacy was maintained in these patients with neutralizing antibodies, although one of these patients had only one PK sample available and another patient had too few evaluable visits while on active treatment to fully assess the impact on efficacy. The patient with possible loss of efficacy had no neutralizing antibodies associated with the positive ADA.

Drug interactions and other interactions

Prior anti-TNF-alpha exposure

The exposure-adjusted AE profile over the entire treatment period by prior anti-TNF-α exposure was similar to that observed in the overall population of Pool A. The incidence per 100 patient-years of total AEs and of the most frequently occurring SOCs including infections and infestations showed the same pattern as seen in the overall population, with numerically higher rates in the placebo group compared

with the Any secukinumab dose group. A dose dependency could be noted for infections and infestations as well as for gastrointestinal disorders, which appeared to be more pronounced and consistent in TNFa-IR patients.

Overall the incidence of exposure-adjusted incidence of total AEs was higher in TNFa-IR patient than in anti-TNFα naïve patients in all treatment groups).

The exposure-adjusted incidence rate of total SAEs was low and showed no trends by prior anti-TNF-α exposure (**Table 30**). Among the TNFa-IR patients, serious infections were more frequent with secukinumab vs. placebo (IR=2.9 for Any secukinumab dose vs. 0 for placebo), driven by a higher rate with the 300 mg dose (7.2 for Any 300 mg vs. 2.4 for Any 150 mg and 2.5 for Any 75 mg). However, similar to the overall population, the rate was higher with placebo vs. secukinumab among the anti-TNF-α naïve patients (IR=4.1 for placebo vs. 2.4 for Any secukinumab dose), with no meaningful dose effect across the secukinumab groups (IR=3.3, 2.6 and 2.0 for Any 300 mg, Any 150 mg and Any 75 mg, respectively).

Table 30. Exposure-adjusted incidence of AEs by previous TNF-alpha exposure – Entire treatment period (Pool A: Phase 3 PsA trials – Safety set)

Primary SOC	Subgroup	Any AIN457 75mg n/EX (IR)	Any AIN457 150mg n/EX (IR)	Any AIN457 300mg n/EX (IR)	Any AIN457 dose n/EX (IR)	Placebo n/EX (IR)
Total of patients - N	TNF-naive	273	302	96	671	206
	TNF-IR	118	136	49	303	94
Any AE	TNF-naive	204/111.2 (183.4)	234/107.1 (218.4)	59/29.8 (198.1)	497/248.2 (200.3)	121/40.1 (301.4)
	TNF-IR	92/47.5 (193.8)	108/39.9 (270.7)	35/12.5 (280.2)	235/99.8 (235.4)	60/16.5 (363.9)
Infections and infestations	TNF-naive	139/190.2 (73.1)	165/186.8 (88.3)	40/43.3 (92.3)	344/420.3 (81.8)	58/61.2 (94.8)
	TNF-IR	59/85.2 (69.2)	68/75.9 (89.6)	20/19.7 (101.3)	147/180.9 (81.3)	24/25.8 (93.0)
Musculoskeletal and connective tissue disorders	TNF-naive	68/247.5 (27.5)	55/276.6 (19.9)	10/57.4 (17.4)	133/581.5 (22.9)	29/67.9 (42.7)
	TNF-IR	37/102.9 (36.0)	38/103.9 (36.6)	10/25.6 (39.1)	85/232.4 (36.6)	16/27.9 (57.4)
Gastrointestinal disorders	TNF-naive	60/251.3 (23.9)	61/268.9 (22.7)	16/53.2 (30.1)	137/573.4 (23.9)	30/66.7 (45.0)
	TNF-IR	28/103.1 (27.2)	38/104.9 (36.2)	12/24.2 (49.7)	78/232.1 (33.6)	9/29.5 (30.5)
Skin and subcutaneous tissue disorders	TNF-naive	51/257.4 (19.8)	46/284.2 (16.2)	16/55.2 (29.0)	113/596.8 (18.9)	17/70.6 (24.1)
	TNF-IR	15/115.0 (13.0)	28/109.1 (25.7)	4/26.9 (14.9)	47/251.0 (18.7)	13/28.3 (45.9)
Nervous system disorders	TNF-naive	32/269.3 (11.9)	46/279.2 (16.5)	9/56.0 (16.1)	87/604.4 (14.4)	21/69.3 (30.3)
	TNF-IR	28/101.5 (27.6)	23/113.5 (20.3)	9/24.3 (37.1)	60/239.3 (25.1)	8/29.3 (27.3)

Most frequently reported primary system organ classes (>15 per 100-patient-years in the Any AIN457 group in the overall population) are presented in descending order of IR in Any AIN457 group of Table 2-3
EX = exposure in patient-years. IR=incidence rate per 100 patient-years; TNF-IR = anti-TNF-alpha incomplete responders

Concomitant methotrexate use

There were no additional trends in total AEs or in the most frequently affected SOC of infections and infestations compared to the overall population. No clinically meaningful differences were seen in the incidence of AEs in any SOC across subgroups of concomitant use of methotrexate.

Concomitant corticosteroid use

Exposure-adjusted incidence rates showed similar trends for total AEs and for the most frequently affected SOC of infections and infestations as compared to the overall population. No clinically meaningful

differences were seen in the incidence of safety risks based on SAEs between subgroups of concomitant use of corticosteroids

2.5.1. Discussion on clinical safety

The secukinumab development program studied 7048 patients, including 6200 patients exposed to at least one dose of secukinumab in any indication, and 6267 patient-years of secukinumab exposure, are included in the safety pooling. The safety data in the present submission provided an additional 2679 patient-years of secukinumab exposure (75% increase), including 955 patient-years of exposure in PsA patients, beyond the 3588 patient-years of exposure reported previously for the psoriasis development program.

Pool A consisted of 2 pivotal placebo-controlled Phase 3 trials (F2306 and F2312) in PsA with placebo and dose comparisons that allow risks to be evaluated in the PsA population during the first 16 weeks of treatment, which was the placebo-controlled phase, and during the entire treatment period (median 48 weeks of exposure to secukinumab, interim analyses on week 52 in study F2306 and on week 24 in study F2312).

Pool B1 (an expanded PsA population with PsA patients from the 2 Phase 3 PsA trials, F2306 and F2312, and psoriasis patients with concomitant PsA from 3 Phase 3 psoriasis trials, A2302, A2303, and A2304).

Pool B (a mixed population of PsA patients from the 2 Phase 3 PsA trials, F2306 and F2312, and psoriasis patients from the 5 Phase 3 psoriasis trials A2302, A2303, A2304, A2308, and A2309) increased the probability of observing less common events over long-term treatment for the target doses of 150 mg sc and 300 mg sc.

Pool C, the largest data pool, included all patients treated with secukinumab in 42 studies and maximized the probability of observing rare events in patients receiving secukinumab.

Deaths, overall AEs and SAEs were examined for Pools A, B1 and B. The severity of AEs, the relationship of AEs to study treatment, AEs causing permanent discontinuation of study treatment, laboratory parameters, vital signs, and electrocardiogram (ECG) data were examined for patients in PsA and psoriasis studies (Pools A and B). Risk categories (AEs of special interests, corresponding to potential and identified risks in the RMP) were examined for Pools A, B1 and B. Pool C was used to examine malignancies and major adverse cardiovascular events (MACE) only.

Pooling was done in a rational manner to 1) investigate the specific safety concerns during the induction period in the PsA studies (related to either iv or sc loading regimen), 2) to enable comparisons against placebo during the initial 16 weeks of PsA studies, 3) to find out about long term tolerability in psoriasis and PsA indications, and 4) to investigate the overall critical safety features of secukinumab pooled from all exposed patients (longest follow-up to date of reporting over 212 weeks in 1 subject and over 132 weeks in 108 subjects).

The AE profile of induction and placebo controlled study phases resembles closely the AE profile observed in the initial submission of psoriasis indication, where up to week 12, the most common AEs: were nasopharyngitis (placebo 8.6% vs. secukinumab 11.9%), headache (5.2% vs. 6.0%), diarrhoea (1.4% vs. 3.3%), pruritus (2.6% vs 3.2%), URTI (0.7% vs. 2.82%), oropharyngeal pain (1.7% vs. 2.3%), and arthralgia (2.4% vs. 2.1%).

In PsA patients it appeared that nasopharyngitis was slightly more common in patients receiving the iv-loading. Oral herpes was observed more in patients receiving 300 mg sc-doses (n=4) or iv-loading and 150 mg sc-doses (n=5). However, none of the herpes cases were severe or led to discontinuation from the study. Eight cases of rhinitis, 6 cases of conjunctivitis, and 6 cases of mouth ulcerations were

reported from patients receiving secukinumab, but not from patients who had received placebo. Mouth ulcerations were not associated with candidiasis. These observations supported the use of the sc-loading method and use of lower than 300 mg sc doses in maintenance, when possible, to ensure the greatest safety.

Similarly to weeks 0 to 16, in the entire study period the AE profile closely resembled that seen in the psoriasis studies, where nasopharyngitis, URTIs, arthralgia, hypertension, diarrhoea, back pain, pruritus, cough, psoriasis, and oropharyngeal pain were the top ten preferred terms for AEs.

There appeared to be no dose-dependence during maintenance treatment for most of the reported AEs. However, a trend for dose-dependence can be observed in the incidences of sinusitis (2.7%, 3.4%, 10.3% for 75 mg, 150 mg, and 300 mg sc doses, vs. 5.7% in the placebo patients), oral herpes (1.7%, 2.8%, 5.7% for 75 mg, 150 mg, and 300 mg sc doses, vs. 3.8% in the placebo patients) pharyngitis (2.4%, 3.0%, 5.6% for 75 mg, 150 mg, and 300 mg sc doses, vs. 0.0% in the placebo patients), and epistaxis (0%, 0,2%, 3.3% vs. 2.9% respectively) in the two PsA trials. In earlier psoriasis trials, headache was more common in patients receiving placebo, with no difference between 150 and 300 mg doses. Oral herpes affected 1.49% of patients receiving placebo, 1.50% of patients receiving 150 mg sc and 1.74% of patients receiving 300 mg sc. Therefore, escalation of the dose to 300 mg sc when needed in accordance with the PsA indication can be justified.

Upper respiratory tract infections, candida infections, and mainly oral herpes infections have been addressed in sufficient manner in the current Cosentyx-PI. There are no new findings in this respect from the PsA-studies. No cases of tuberculosis or viral hepatitis were reported.

Deaths in patients receiving secukinumab were all associated with severe cardiovascular risks and co-morbidity and do not seem to be related to the study medications in the PsA studies. The same conclusion could be made about deaths in the AS studies.

SAEs in Pool A first 16 weeks consisted of two occurrences of cerebrovascular accident in 10 mg/kg-75 mg sc group, and two occurrences of erysipelas in 150 mg sc and 300 mg sc groups. For rest of the studies, there was also one erysipelas case in the placebo group. Incidence rates of erysipelas, chest pain, osteoarthritis, sepsis, coronary artery disease, and septic shock were lower during secukinumab treatment compared to placebo treatment. Atrial fibrillation, cerebrovascular accident, deep vein thrombosis, diverticulitis, myocardial infarction, pneumonia, psoriatic arthropathy, septic shock, and positional vertigo were reported two times each during secukinumab treatment and never during placebo treatment. Most of these cases were reported from the 75 mg sc patients, thus no apparent dose-dependence could be observed. There were no significant findings in Pool B compared to pool A.

Two new diagnoses of Crohn's disease were made during or after secukinumab exposure in AS patients and one new diagnosis similarly in PsA patients. Crohn´s disease has already been addressed in sufficient manner in the product information of secukinumab and no further action was considered necessary in relation to the psoriatic arthritis indication.

Skin malignancies as well as other malignancies were rare, and not considered related to study medications in Pool A.

Three cases of lymphomas in psoriasis and ankylosing spondylitis studies were evaluated closely. While the 2 lymphoma cases observed on secukinumab occurred after many months of exposure to the IMP, they had quite different characteristics suggesting a different underlying etiopathogenesis. Some commonalities in these 2 lymphoma cases would have been expected if they were to be associated to neutralisation of IL-17A.

During the induction period in Pool B, there were 10 cardiac disorders reported as SAEs in the "Any secukinumab dose" group, compared to none in the placebo- and etanercept-groups. Number of patients

experiencing a serious cardiovascular adverse event (and the incidence rate per 100 patient years) for placebo 0 (0.00), secukinumab 150 mg 13 (1.14), secukinumab 300 mg 7 (0.60), and etanercept 3 (1.03) would suggest a slightly increased risk for users of secukinumab. However, taking into account the larger and - in particular - longer exposure to secukinumab and that most of the SAEs occurred weeks or months after continuous secukinumab use in patients with predisposing factors and cardiovascular morbidity, there was no implication that secukinumab would predispose patients to serious cardiovascular complications. The same conclusions can be drawn from the analyses of the PsA studies. The issue will remain under close review as it is included in the RMP as an important potential risk, but the CHMP considered that no updates to the SmPC would be warranted at this stage based on the available data.

There was a significant decrease in total leukocytes and neutrophils in the pooled secukinumab group during all pivotal studies in the psoriasis submission. This decrease was considered related to the pharmacodynamic effects of the drug (and it was somewhat more prominent in the etanercept group compared to secukinumab patients). In general, the neutropenia cases were not associated with SAEs or treatment discontinuation. There were no new findings in the PsA studies in this respect. There were no observed effects attributable to use of study medications in haemoglobin, lymphocyte, and platelet parameters. In the three cases of severe hepatobiliary AEs, there was concomitant morbidity at baseline or concomitant medications in use.

Mild elevations of ALT observed during induction period, with only slight differences between different induction regimens, appear not to be a relevant safety issue.

The mild elevations grade I elevation of total cholesterol and triglycerides appear in similar incidences irrespective of route of loading doses and clinically insignificant as well. Grade II elevations of cholesterol were observed in 2/293 (0.68%) in patients receiving sc loading and 9/390 (2.31%) in patients receiving iv loading (during the first 16 weeks). However, as iv loading is not foreseen in the clinical setting, the higher incidence in those patients is not considered a significant finding.

There were no clinically meaningful differences in the AE profile stratified by the baseline BSA (<10%, >10%), body weight (<90 kg, >90 kg), and gender.

AE profiles of patients having earlier taken biologicals and/or currently taking immunosuppressants appeared similar. Concomitant immunosuppression should warrant more careful follow up of the patient regarding severe infections and adequate warnings are contained in the SmPC. All immune reactions were non-serious. One case of angioedema was related to study medication and resolved in 13 days after discontinuation of study. One case of anaphylaxis was considered related to a concomitant antibiotic treatment.

Milder forms of hypersensitivity reactions were rare. Urticaria was seen here less frequently (0.5%) compared to the original psoriasis submission (1.85%). Rash was slightly less common here (2.2%) compared to the earlier submission (2.45%). Overall incidence of hypersensitivity reaction in here Pool A was 9.2% and 11.17% in the original submission in the secukinumab patients.

The presence of anti-secukinumab antibodies was scarce, suggesting that the potential risk of immunogenicity is low. Based on the clinical trial data, the immunogenicity to secukinumab did not appear to have a negative impact on the overall safety profile, efficacy, or pharmacokinetic parameters of secukinumab.

2.5.2. Conclusions on clinical safety

The safety profile of secukinumab in treatment of PsA in both the induction and maintenance phases of the studies resembled closely to the safety profile observed in the psoriasis indication of the initial submission. ADRs occurring more frequently in the secukinumab group included URTI, nasopharyngitis,

sinusitis, and diarrhoea. There were no new findings regarding Crohn´s disease or MACEs. There were no new concerns about malignancies. Hypersensitivity and immunological reactions remain rare and immunogenic potential of secukinumab appeared very low, with no clinical implications.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged. The PSUR cycle for the medicinal product should follow a half-yearly cycle until otherwise agreed by the CHMP.

The next data lock point will be 25 December 2015.

The annex II related to the PSUR refers to the EURD list which remains unchanged.

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 2.1 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 2.1 with the following content:

Safety concerns

Table 31. Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Infections and infestations Neutropenia Hypersensitivity
Important potential risks	Malignant or unspecified tumors Major Adverse Cardiovascular events (MACE) Immunogenicity Crohn's disease Hepatitis B reactivation Interaction with live vaccines
Missing information	Fetal exposure in utero Long-term safety data Long-term efficacy data Use in pediatric patients Patients with severe hepatic impairment Patients with severe renal impairment Patients with severe cardiac disease or uncontrolled hypertension

Pharmacovigilance plan

Table 32. Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Activity / Study Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports (planned or actual)**
Psoriasis Registry Category 3	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 tumours Long-term safety	Started	Progress reports including data presentation to be included in DSUR/PSUR according to the regulated timelines No additional Interim reports planned Final study report in Q2 2030.

The MAH proposed to update the RMP to change the due date of the Psoriasis registry (category 3 study). The revision in the final report date of the Psoriasis Registry resulted in an increase in the sample size from 2000 to 3000 secukinumab treated subjects and in the follow-up period from 5 to 8 years. These changes required a revision in the study duration and final report date which is now at Q2 2030.

Risk minimisation measures

Table 33. Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risks		
Infections and infestations	Labeling SmPC section 4.3 (Contraindications), SmPC section 4.4 (Special warnings and precautions for use), and section 4.8 (Undesirable effects-summary of the safety profile)	None
Neutropenia	Labeling SmPC section 4.8 (Undesirable effects-summary of the safety profile)	None
Hypersensitivity	Labeling SmPC section 4.3 (Contraindications), section 4.4 (Special warnings and precautions for use), and section 4.8 (Undesirable effects-summary of the safety profile)	None
Important Potential Risks		
Malignant or unspecified tumors	No specific measures are required for patients receiving secukinumab - standard of care is adequate	None
Major Adverse Cardiovascular Events (MACE)	No specific measures are required for patients receiving secukinumab - standard of care is adequate.	None
Immunogenicity	Labeling SmPC Section 4.8 (Undesirable effects-	None

	summary of the safety profile)	
Crohn's disease	Labeling SmPC section 4.4 (Special warnings and precautions for use)	None
Hepatitis B reactivation	No risk minimization measure is considered necessary at this time.	None
Interaction with live vaccines	Labeling SmPC section 4.4 (Special warnings and precautions for use) and section 4.5 (Interaction with other medicinal products and other forms of interaction)	None
Missing information		
Fetal exposure in utero	Labeling SmPC section 4.6 (Fertility, pregnancy and lactation)	None
Long-term safety data	No risk minimization measure is considered necessary at this time. Routine risk minimization (standard of care for the target population) is considered sufficient.	None
Long-term efficacy data	No risk minimization measure is considered necessary at this time. Routine risk minimization (standard of care for the target population) is considered sufficient.	None
Use in pediatric patients	Labeling SmPC section 4.1 (Therapeutic indications)	None
Patients with severe hepatic impairment	No risk minimization measure is considered necessary at this time.	None
Patients with severe renal impairment	No risk minimization measure is considered necessary at this time.	None
Patients with severe cardiac disease or uncontrolled hypertension	No risk minimization measure is considered necessary at this time.	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 and 5.2 of the SmPC have been updated as detailed in the appended product information. The package leaflet has been updated accordingly.

In addition, changes in relation to the study duration and the final report date of the study in the psoriasis registry which is included in the RMP were also made.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet for Cosentyx pre-filled syringe 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. No full user consultation with target patient groups on the package leaflet for Cosentyx pre-filled pen and Cosentyx powder for solution for injection has been performed on the basis of a bridging report making reference to Cosentyx pre-filled syringe. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Rapid and clinically meaningful efficacy of secukinumab in the treatment of PsA has been demonstrated. Both phase III studies met the primary endpoint of ACR20 response rates at Week 24. The response rates in Study F2306 were 50.5% for secukinumab 10 mg/kg-75 mg, 50.0% for 10 mg/kg-150 mg and 17.3% for placebo ($p<0.0001$ for each comparison vs. placebo). The response rates in Study F2312 were 29.3% for secukinumab 75 mg, 51.0% for secukinumab 150 mg, 54.0 for secukinumab 300 mg and 15.3% for placebo ($p<0.0001$ for secukinumab 150 mg and 300 mg vs. placebo, $p=0.0200$ for secukinumab 75 mg vs. placebo). The efficacy was also maintained up to Week 52.

Results of the secondary efficacy endpoints were in general consistent with those of the primary efficacy endpoint. Secondary efficacy endpoints related to signs and symptoms of PsA, such as DAS28-CRP change, ACR50 response, SF-36 PCS, HAQ-DI, and the presence of dactylitis and enthesitis, as well as those related to concomitant psoriasis such as PASI75 and PASI90 were generally met for secukinumab doses 150 mg and 300 mg. As an exception, HAQ-DI response at Week 24 was not statistically significantly different to placebo in Study F2312 in the secukinumab 150 mg dose group.

Overall, efficacy endpoints related to joint and skin disease, physical function, health-related quality of life consistently showed robust and clinically relevant efficacy of secukinumab in the treatment of PsA.

In Study F2306, statistically significant inhibition of progression of structural damage based on the vdH-mTSS at Week 24 was shown for both secukinumab doses. The lower dose of 10 mg/kg-75 mg demonstrated somewhat better efficacy vs. placebo compared to the higher dose of 10 mg/kg-150 mg (p-values 0.0132 and 0.0212, respectively).

The pivotal studies were stratified according to previous use of TNFα inhibitors. Based on results of Study F2312, in TNFα-IR patients at Week 24, ACR 20 response rates in the secukinumab 75 mg, 150 mg and 300 mg dose groups were 14.7%, 29.7% and 45.5%, respectively, compared with 14.3% in the placebo group. The difference vs. placebo was statistically significant for the 300 mg dose level ($p=0.0077$). Higher PASI75 and PASI90 rates were also observed with secukinumab 300 mg dose compared to the 150 mg dose, consistent with the phase III psoriasis program. Week 52 efficacy data was consistent with the results obtained at Week 24. Therefore, the recommended dose is 150 mg sc, while the 300 mg dose is more appropriate for TNFα-IR patients and for patients with concomitant moderate to severe plaque psoriasis. No dose adjustment based on body weight is needed.

Uncertainty in the knowledge about the beneficial effects

The data in Study F2306 was generated with an iv secukinumab loading regimen that resulted in greater initial exposure. The role of induction regimen appears however limited in the prevention of progression of structural damage. Nevertheless, Section 5.1 of the SmPC includes a statement that the inhibition of progression of structural damage in PsA has not yet been demonstrated using the subcutaneous loading regimen which is approved for clinical use.

Neither of the pivotal studies in PsA had an active control arm. The lack of active control is partly compensated by the etanercept-controlled psoriasis Study A2303 with a subset of PsA patients, as well as by the responses reported for other biologics studied in similar clinical study settings.

There is also a lack of dedicated assessment of axial inflammation, as recommended in the EMA PsA guideline. Considering the overall weight of evidence on the efficacy of secukinumab in both PsA and AS, extrapolation of the clinical benefit in axial involvement in AS to PsA is however considered meaningful.

Risks

Unfavourable effects

Infections were more commonly reported in secukinumab-treated patients compared to placebo. The imbalance with secukinumab vs. placebo was mainly due to upper respiratory tract infections. Also candida infections and oral herpes infections were more commonly reported compared to placebo. Infections are included in the RMP as an important identified risk with appropriate warnings also included in the SmPC.

The increased incidence of candida infections was mainly due to oral candidiasis and vulvovaginal candidiasis and consistent with the mechanism of action of secukinumab and knowledge on the IL-17 biology. All candida infections were mild to moderate in severity and none led to treatment discontinuation.

Neutropenia was more common in secukinumab-treated patients compare to placebo. In general, the neutropenia cases were not associated with SAEs or discontinuations. Majority of the neutropenia cases were associated with iv loading regimen, which will not be used in the clinical practice. Neutropenia is included in the RMP as an important identified risk with appropriate warnings in the SmPC.

Uncertainty in the knowledge about the unfavourable effects

Effects Table

Effects Table for Cosentyx in the treatment of psoriatic arthritis (data cut-off: 12 May 2014)

Effect	Short Description	Unit	Active 150mg	Active 300 mg	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects							
ACR 20[1]	% achieving response at Week 24 (primary endpoint) (sc loading regimen as proposed for clinical use)	%	51.0	54.0	15.3	Significant effect in the primary endpoint with all secukinumab doses compared to placebo after sc loading (p=0.0200 for 75 mg dose; p<0.0001 for 150/300 mg doses), 150/300 mg doses supported by the secondary endpoints. Study F2312 provides the most relevant efficacy data (posology as proposed for clinical use).	Study F2312
Unfavourable Effects							

Effect	Short Description	Unit	Active 150mg	Active 300 mg	Placebo	Uncertainties/ Strength of evidence	References
Infections	Overall rate of infections, SOC Infections and infestations	%[2)] IR[3)]	30.0 88.7	29.0 95.1	25.7 94.2	Increased incidence of infections during the first 16 weeks, mainly upper respiratory tract infections. No imbalance in the long-term using exposure-adjusted IR. No increased rate of mycobacterial or serious opportunistic infections.	Studies F2306 and F2312
	Candida infections (HLT)	%[2)] IR[3)]	1.0 1.6	1.0 3.4	0.0 0.0	Candida infections consisting mainly of oral candidiasis and vulvovaginal candidiasis. All cases mild/moderate in severity. None led to discontinuation.	Studies F2306 and F2312
	Oral herpes infections (PT)	%[2)] IR[3)]	0.0 2.8	4.0 5.7	1.0 3.8	Increased incidence of herpes viral infections. No cases of disseminated or CNS herpes.	Studies F2306 and F2312
Neutro-penia	Neutropenia (PT)	%[2)] IR[3)]	0 0.7	1.0 1.1	1.0 2.9	Cases of grade 2, and 3 (n=5) neutropenia were not associated with severe/serious infections.	Studies F2306 and F2312

[1)] ≥20% improvement in the American College of Rheumatology criteria (ACR)
[2)] % rate (first 16 weeks, only patients with sc loading in study F2312, placebo patients from both studies)
[3)] IR = exposure adjusted incidence rate (entire treatment period, from both studies F2306 and F2312), expressed as number of subjects with event per 100 patient-years
SOC = System Organ Class
HLT = High Level Term
PT = Preferred Term

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Statistically significant efficacy of secukinumab in the treatment of PsA has been shown with respect to joint and skin disease, physical function, health-related quality of life and prevention of progression of structural damage. These results are considered robust and clinically relevant.

Secukinumab provides a novel treatment option for PsA, including the hard-to-treat patients, *i.e.,* TNFα-IR population.

The most relevant safety concerns of secukinumab identified so far are related to mild infections. Appropriate measures to minimise this risk are included in the SmPC and further information on this issue will be collected as described in the RMP.

Benefit-risk balance

Efficacy of secukinumab in the treatment of PsA has been demonstrated. The safety profile is favourable based on the data currently available.

Discussion on the Benefit-Risk Balance

Clinically relevant efficacy has been shown for secukinumab in the treatment of PsA. These results are considered robust. The overall safety profile of secukinumab appears favourable. Unfavourable effects typical for biologic therapies have been observed, including infections and mild neutropenia, but no increase was observed in the rate of mycobacterial or serious opportunistic infections.

Based on the data available, secukinumab alone or in combination with methotrexate (MTX) is approvable for the treatment of active psoriatic arthritis in adult patients when the response to previous disease modifying anti rheumatic drug (DMARD) therapy has been inadequate is approvable.

4. Recommendations

Outcome

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

Variations 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 and IIIB
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None

Extension of Indication to include new indication for Cosentyx in the treatment alone or in combination with methotrexate (MTX) of active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 of the SmPC are updated in order to update the safety and efficacy information. The Package Leaflet and RMP have been updated accordingly. Furthermore, the due of the final report for the psoriasis registry in the RMP has been amended and minor editorial changes have been introduced throughout the PI.

The group of variations leads to amendments to the Summary of Product Characteristics, Package Leaflet and the Risk Management Plan (RMP).

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include new indication for Cosentyx in the treatment alone or in combination with methotrexate (MTX) of active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 of the SmPC are updated in order to update the safety and

efficacy information. The Package Leaflet and RMP have been updated accordingly. Furthermore, the due of the final report for the psoriasis registry in the RMP has been amended and minor editorial changes have been introduced throughout the PI.

Summary

Please refer to the Scientific Discussion Cosentyx-H-C-3729-II-01 G

Attachments

1. SmPC, Package Leaflet (changes highlighted) as adopted by the CHMP on 22 October 2015.
2. Rapporteurs initial Assessment Report dated 26 May 2015.
3. Co - Rapporteurs initial Assessment Report dated 26 May 2015.
4. PRAC Assessment Report as endorsed by PRAC on 11 June 2015.
5. CHMP Request for supplementary information as agreed by the CHMP on 25 June 2015.
6. Rapporteur's response Assessment Report dated 28 September 2015.
7. PRAC Assessment Report as endorsed by PRAC on 8 October 2015.
8. Joint Rapporteur/Co-Rapporteur Assessment Report on the responses provided by the applicant, dated 16 October 2015.