22 October 2015
EMA/CHMP/665405/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cosentyx

International non-proprietary name: SECUKINUMAB

Procedure No. EMEA/H/C/003729/II/0002

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
ADR	Adverse drug reaction
AE	Adverse event
AI	Autoinjector /pen
AIN457	Secukinumab
ANCOVA	Analysis of co-variance
AS	Ankylosing spondylitis
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASAS	Assessment of spondyloarthritis international society
ASQoL	Ankylosing spondylitis quality of life
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
BASDAI	Bath ankylosing spondylitis disease activity index
BASFI	Bath ankylosing spondylitis functional index
BASMI	Bath ankylosing spondylitis metrology index
BSA	body surface area
C_{avg}	Average concentration
CHMP	Committee for human medicinal products
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
COX	Cyclo-oxygenase
CSR	Clinical study report
CV	Coefficient of variation
CYP	Cytochrome
DMARD	Disease modifying anti rheumatic drug
EAIR	Exposure adjusted incidence rate
EC	European Commission
EMA	European Medicines Agency
EQ-5D	Euro quality of life 5
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
EU	European Union
FACIT-fatigue	Functional assessment of chronic illness therapy-fatigue
Fimea	Finnish medicines agency
GCP	Good clinical practice
HAQ	Health assessment questionnaire
hCG	Human chorionic gonadotropin
HLT	High level term
hsCRP	High-sensitivity C-reactive protein
IL-17A	Interleukin 17A
IR	Incidence rate
IUD	Intrauterine (contraceptive) device
IUS	Intrauterine (contraceptive) system
iv	Intravenous
LEI	Leeds enthesitis index
loess	Locally weighted scatterplot smoothing
LLOQ	Low limit of quantification
LOCF	Last observation carried forward
LoQ	List of questions
LYO	Lyophilisate
MAA	Marketing authorisation application
MACE	Major adverse cardiovascular event

MAH	Marketing authorisation holder
MAR	Missing at random
MASES	Maastricht ankylosing spondylitis enthesitis score
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed model repeated measures
MPA	Medicinal product agency (Sweden)
MRI	Magnetic resonance imaging
mSASS	Modified Stoke ankylosing spondylitis spinal score
MTX	Methotrexate
NMQ	Novartis MedDRA Query
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York heart association
OFV	Objection function value
q4w	Once every 4 weeks
PD	Pharmacodynamic
PDCO	Paediatric committee
PIP	Paediatric investigation plan
PK	Pharmacokinetic
PPK	Population pharmacokinetic
PL	Package leaflet
PFS	Pre-filled syringe
PsA	Psoriatic arthritis
PT	Preferred term
RA	Rheumatoid arthritis
RF	Rheumatoid factor
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 PCS	Short form 36 health survey physical component summary
SmPC	Summary of product characteristics
SMQ	Standardized MedDRA query
SOC	System organ class
SpA	Spondylarthropathy/-pathies
t_{max}	Time to maximum concentration
$t_{1/2}$	Terminal half-life
TNFαi	Tumour necrosis factor alpha inhibitor
TNF-IR	TNF alpha inhibitor incomplete responder
ULN	Upper limit of normal
US	United States
VAS	Visual analog scale
WFI	Water for injections
WPAI-GH	Work productivity and activity impairment – general health

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 9 March 2015 an application for a variation.

The following variation was requested:

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

Extension of indication to add new indication for Cosentyx in the 'treatment of severe active ankylosing spondylitis in adults who have responded inadequately to conventional therapy'; consequently, SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 have been revised to include new efficacy and safety information. The Package Leaflet and RMP have been updated accordingly.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision 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

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of marketing protection for a new indication.

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	9 March 2015
Start of procedure:	28 March 2015
CHMP Rapporteur Assessment Report	26 May 2015
CHMP Co-Rapporteur Assessment Report	28 May 2015
PRAC Rapporteur Assessment Report	26 May 2015
PRAC members comments	4 June 2015
PRAC Outcome	11 June 2015
CHMP members comments	15 June 2015
Updated CHMP Rapporteur Assessment Report	16 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

The concept of spondyloarthropathies (SpA) comprises a group of diseases which share common clinical and genetic features. These clinical features include inflammation of the axial skeleton (spine and sacroiliac joints), peripheral arthritis, enthesitis, dactylitis, uveitis, psoriatic arthritis, arthritis associated with inflammatory bowel disease and reactive arthritis. The most common genetic feature is the presence of HLA-B27 antigen.

SpA can be classified as axial SpA or peripheral SpA, depending on the predominant clinical manifestations. The typical clinical symptom for axial SpA is chronic inflammatory back pain.

Ankylosing spondylitis (AS) is the prototype of axial SpA. The estimated prevalence of AS in the Caucasian population is 0.5%. AS is more common in males (male to female ratio 2-3:1). Clinical manifestations of AS usually begin in late adolescence or early childhood, rarely after the age of 45 years. Classical symptoms of AS include lower back or gluteal pain and stiffness which are worse in the morning or after long period of inactivity. The symptoms are eased by exercise. Functional limitations in the early

phase of the AS are mostly related to inflammation, but may be also related to structural changes in bone during the later course of the disease. The most widely used diagnosis criteria for AS are the modified New York Classification criteria which have also been used in most of the registration studies for medicinal product indicated for AS. According to these criteria, the definite AS is diagnosed if in addition to the radiologic criteria (bilateral sacroilitis grade > II or unilateral sacroilitis grade III to IV) at least two of the three clinical criteria (low back pain and stiffness of at least 3 months duration improved by exercise and not relieved by rest; limitation of motion of lumbar spine in both the sagittal and the frontal planes; limitation of chest expansion relative to value normal for age and sex) are present.

As suggested by Assessment of SpondyloArthritis International Society (ASAS) in 2009, the term axial SpA includes the patients with at least 3 months of back pain (onset > 45 years) and either 1) sacroilitis on imaging (radiographs or magnetic resonance imaging (MRI)) and at least one clinical feature of SpA or 2) the presence of HLA-B27-antigen and at least two clinical features of AS ("non-radiological axial SpA"). These ASAS classification criteria presenting expanding the criteria for axial SpA have also changed the regulatory situation of the medicinal products intended for axial SpA.

According to the clinical guidelines, physical therapy and non-steroidal anti-inflammatory drugs (NSAID) (intermittent or continuous use) comprise the first-line treatment in AS. In contrast, clinical guidelines do not support the use of traditional non-biological disease-modifying antirheumatic drug in the treatment of AS, with the exception of consideration of sulphasalazine in AS with peripheral arthritis. The treatment with tumour necrosis factor alpha inhibitors (TNFαi) is recommended for the patients with persistently high disease activity despite conventional treatment with nonsteroidal anti-inflammatory drug (NSAID) and physiotherapy.

To date, there are five TNFαis which have been approved for treatment of AS in Europe. Two of these (infliximab and golimumab) are indicated for the treatment of severe active ankylosing spondylitis in adults who have responded inadequately to conventional therapy. In contrast, etanercept, adalimumab, and certolizumab-pegol are indicated also for non-radiographic axial SpA.

Secukinumab is a first-in-class selective high-affinity human monoclonal anti-human interleukin-17A (IL-17A) antibody of the IgG1/k isotype, designed to bind to and neutralize the activity of human IL-17A, a pro-inflammatory cytokine, leading to abrogation of IL-17A pathway-related inflammatory cascade. This cascade promoted by the IL-17A result in the activation of neutrophils and macrophages, as well as epithelial cells and fibroblasts, and is believed to play an important role in the pathophysiology ofautoimmune diseases, including psoriasis and AS. Cosentyx was authorised for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy in the European Union on 15 January 2015. The same indication has also to date been approved in the United States, Chile, Australia and in Japan (psoriasis vulgaris). This medicinal product is currently approved in Japan also for treatment of psoriatic arthritis.

The development of new products for treatment of AS is covered in the Guideline on clinical investigation of medicinal product for the treatment of ankylosing spondylitis (CPMP/EWP/4891/03). Recommendations of this guideline were taken into account in the clinical development programme (selection of patients, efficacy endpoints). A paediatric investigation plan (PIP) in the treatment of chronic idiopathic arthritis has been accepted by the paediatric committee (PDCO, EMEA-000380-PIP01-09-M02). All measures have been deferred and the agreed date of completion of the PIP is by December 2018, i.e., after the submission date.

CHMP scientific advice or protocol assistance was not sought in the current indication.

2.1. Non-clinical aspects

Comparative pharmacokinetic analyses as well as comparative systemic exposure in cynomolgus monkeys and AS patients were provided in support of the use of secukinumab in ankylosing spondylitis.

2.1.1. Introduction

Secukinumab is a high-affinity monoclonal antibody targeting specifically IL-17A cytokine. It also binds the IL-17AF heterodimer and to a lesser extent the IL-17F homodimer. The binding data showed that secukinumab had high affinity to the intended target in the cynomolgus monkey.

A comprehensive non-clinical data package was submitted with the initial marketing authorisation application which adequately provides evidence on target specificity and mode of action i.e. neutralising the IL-17A related cellular events.

Secukinumab was well tolerated in a full set of toxicology studies. The main findings from the toxicity studies were slight decreases in lymphocyte subsets and neutrophils which are likely related to the pharmacological activity of secukinumab. T cell dependent antibody response was slightly reduced which may have an impact on the vaccination. Exposure multiples for safety in humans at dose levels that produce maximal neutralising effect of IL-17A were significant; for the AUC 48-108 fold and for the Cmax 53-100 fold.

No signs of teratogenicity, embryo toxicity, or effects on fertility were observed in the reproductive toxicology studies.

IL-17A neutralization may impair host resistance to certain infectious agents, and therefore, there may be an increased risk of infection to patients treated with secukinumab.

Based on literature evidence IL-17A has both pro-tumour and antitumor activity in animal models. The available data do not give a clear answer on the effects of neutralizing IL-17A or other IL-17 family members on tumour growth in humans. Therefore, secukinumab may carry a potential risk for cancer.

The risks of infection and tumour promotion for patients treated with secukinumab are addressed in the Risk Management Plan (RMP).

2.1.2. Pharmacology

No new pharmacology data were included with this application.

2.1.3. 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).

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.)	84 [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: [Summary of Clinical Pharmacology – section 1.2.1]

n.a.: not available

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**.

The average serum concentrations at steady-state observed in monkeys after 13 weekly s.c. doses are 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. In AS patients very similar mean Cav,ss, Cmax,ind and Cmax,ss values at the 150 mg dose level, 25.8, 64.3, and 34.1 µg/mL, respectively were observed. Thus, for AS, human exposure multiples were very similar to the values calculated in PsA patients.

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 in this respect.

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

2.1.4. Toxicology

No new toxicity data were included with this application.

2.1.5. 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.

2.1.6. Discussion on non-clinical aspects

Comparison of PK characteristics and systemic exposure to humans demonstrated significant exposure margin to AS patients and that the nonclinical safety data generated to support the initial marketing authorisation of secukinumab treatment in patients with psoriasis patients were adequate and sufficient to support the application in AS.

2.1.7. Conclusion on the non-clinical aspects

The data submitted in this application support the use of secukinumab in ankylosing spondylitis.

2.2. Clinical aspects

2.2.1. Introduction

GCP

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

The MAH 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.

2.2.2. Pharmacokinetics

Secukinumab (AIN457) is a high-affinity, fully human monoclonal anti-human IL-17 antibody of the immunoglobulin G (IgG1)/k isotype. It 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.

This dossier contained one phase II and two phase III clinical studies, which included pharmacokinetic (PK) data (**Table 3**). The administration routes in the clinical studies of secukinumab were iv (CAIN457A2209) or sc (CAIN457F2305 & CAIN457F2310). An intravenous (iv) loading dose was used in one phase II (CAIN457A2209) and in one phase III (CAIN457F2305) study. In study CAIN457F2310 a sc loading dose was used.

Table 3. Summary of clinical studies contributing to the PK of secukinumab

Study	Description	Regimens	Note
A2209	PoC PD study of efficacy of AIN457	• 2 x 0.1 mg/kg i.v. q3w • 2 x 1 mg/kg i.v. q3w • 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 , 12, 16, 20, 24 and 28/end of study
F2305*	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 pre-dose samples in weeks 0, 4, 16, 24 and 52. For premature discontinuation, samples at 4 weeks after last dose.
F2310**	Phase III efficacy, safety and tolerability	• 4 x 150 mg s.c. q1w + 150 mg s.c. q4w from week 4 • 4 x 75 mg s.c. q1w + 75 mg s.c. q4w from week 4 • placebo + 150 mg s.c. q4w from week 16 • placebo + 75 mg s.c. q4w from week 16 • placebo	PK pre-dose samples in weeks 0, 4, 16

* F2305: Week 52 interim lock
** F2310: Week 16 interim lock

Study number	Phase	Population / N of subjects enrolled	Treatments	PK sampling	PK parameters

CAIN457A2209	II	ankylosing spondylitis patients	Part 1 (n=30) Two doses of 10 mg/kg iv secukinumab or placebo spaced 3 weeks apart Part 2 (n=30) Two doses of 0.1 mg/kg, 1.0 mg/kg or 10 mg/kg iv secukinumab or placebo spaced 3 weeks apart	pre-dose, 2, 3, 4, and 24 hours after initiation of the infusion (Days 1 and 22) and weeks 1, 2, 4, 6, 8, 12, 16, 20, 24, and at the end of the study/Week 28	Steady state concentrations (data used in PPK model and PK/PD model)
CAIN457F2305	III	ankylosing spondylitis patients	Secukinumab iv loading dose 10 mg/kg or placebo weeks 0, 2, 4 followed by 75 mg sc, 150 mg sc or placebo every 4 weeks	pre-dose, weeks 4, 16, 24, and 52	Steady state concentrations (data used in PPK model and PK/PD model)
CAIN457F2310	III	ankylosing spondylitis patients	Secukinumab sc loading dose 75 mg, 150 mg or placebo weeks 0, 1, 2, 3 and 4 followed by 75 mg sc, 150 mg sc or placebo every 4 weeks	pre-dose, weeks 4, 16, 24, and 52	Steady state concentrations (data used in PPK model and PK/PD model)

In addition, a population PK modeling report has been submitted for the following studies: CAIN457A2209, CAIN457F2305, CAIN457F2310.

The analytical method used for the measurement of secukinumab concentrations was an enzyme-linked immunosorbent assay (ELISA) with a lower limit of quantification (LLOQ) of 80 ng/ml in all clinical studies. The descriptive statistics for PK parameters included mean, standard deviation (SD) and coefficient of variation (CV). When geometric mean was presented it was stated as such.

Pharmacokinetic studies of secukinumab in ankylosing spondylitis

Study CAIN457A2209

The study was a randomised, placebo controlled double blind, multi-centre, phase II, proof-of-concept study. The secondary objective was to assess the pharmacokinetics of secukinumab.

The study consisted of two parts. In part 1 of the study 30 patients were recruited and the patients were randomized to either secukinumab or placebo in ratio 4:1. The patients received two doses of either 10 mg/kg of secukinumab or placebo (2 iv infusions 3 weeks apart). All subjects were analysed for PK and safety although for pharmacodynamics (PD) analysis one patient was excluded due to protocol violation.

In part 2 also 30 patients were recruited. The patients were randomized to receive either secukinumab 0.1 mg/kg or 1.0 mg/kg or 10 mg/kg of secukinumab as iv in ratio 2:2:1. Part 2 of the study included two doses of secukinumab 3 weeks apart. All subjects were analysed for PK and safety. One patient was excluded from PD analysis due to non-availability of the PD measurements post baseline.

Blood samples (2 ml) for determination of secukinumab concentrations in serum were taken pre-dose, 2, 3, 4, and 24 hours after initiation of the infusion (Days 1 and 22), Weeks 1, 2, 4, 6, 8, 12, 16, 20, 24, and end of the study/Week 28. PK parameters of secukinumab were determined using non-

compartmental methods with WinNonlin, version 5.2. The calculated parameters were AUC_{inf}, AUC_{last}, $T_{1/2}$, λ_z, C_{max}, T_{max}, CL and V_z. Descriptive statistics of plasma concentrations and PK parameters were presented.

Main findings related to the PK of secukinumab

The pK parameters of secukinumab after two infusions of 10 mg/kg with a three-week dosing interval are shown in **Table 4**. Due to several discontinuations, the full set of pK parameters could not be obtained in all treated patients.

Table 4. pK parameters of secukinumab in Part 1 after 10 mg/kg of secukinumab

	Cmax (µg/mL)	Tmax * (day)	AUCinf (day*µg/mL)	AUClast (day*µg/mL)	Cl (L/day)	Vz (L)	T1/2 (day)
n	23	23	20	20	20	20	20
Mean (SD)	357.7 (87.74)	21.07 (0.083 - 21.9)	10510 (3036)	10310 (2869)	0.1594 (0.04998)	6.121 (0:999)	27.95 (5.624)
CV% mean	24.5	-	28.9	27.8	31.4	16.3	20.1

*Median (range) is given for T_{max}

The pK of secukinumab after two infusions of 10 mg/kg, two infusions of 1 mg/kg and two infusions of 0.1 mg/ml with a three week dosing interval are summarized in **Table 5**.

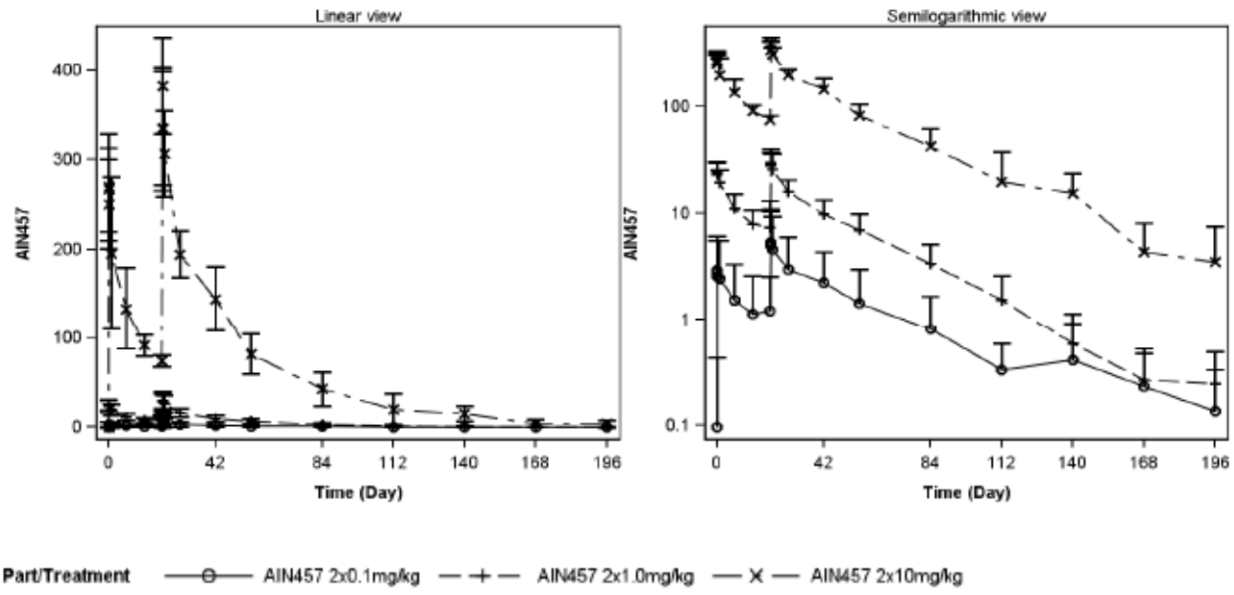
Table 5. Summary table of PK parameters of secukinumab from Part 1 and 2 combined

	Cmax (µg/mL)	Tmax * (day)	AUCinf (day*µg/mL)	AUClast (day*µg/mL)	Cl (L/day)	Vz (L)	T1/2 (day)
2 x 10 mg/kg							
n	28	28	25	25	25	25	25
Mean (SD)	363.9 (82.30)	21.08 (0.083 - 22.2)	10880 (2983)	10630 (2818)	0.1571 (0.04734)	6.055 (0.943)	28.09 (5.994)
CV%	22.6		27.4	26.5	30.1	15.6	21.3
2 x 1 mg/kg							
n	12	12	11	11	11	11	11
Mean (SD)	33.13 (9.828)	21.08 (0.125 - 23.0)	1025 (276.0)	993.0 (279.5)	0.1718 (0.04942)	6.481 (1.701)	27.32 (7.234)
CV%	29.7		26.9	28.1	28.8	26.2	26.5
2 x 0.1 mg/kg							
n	12	12	11	11	11	11	11
Mean (SD)	5.509 (5.418)	21.12 (19.1 - 22.1)	198.0 (195.5)	187.7 (190.7)	0.1182 (0.05474)	5.827 (2.887)	34.31 (6.656)
CV%	98.3		98.8	101.6	46.3	49.5	19.4

With secukinumab 10 mg/kg infusions, the mean clearance (CL) was 0.157 L/day. The mean apparent distribution volume (V_z) was 6.06 L, which is close to the blood volume. The mean apparent elimination half-life was 28.1± 6.0 days.

Mean arithmetic concentration-time profiles on a linear and semi-logarithmic concentration scale over the complete sampling time period are seen in **Figure 1**.

Figure 1. Arithmetic mean (SD) serum concentration-time profile of secukinumab



Study CAIN457F2305

A randomised, double-blind, parallel-group, placebo-controlled, multi-centre, phase III study of secukinumab was performed to demonstrate the efficacy of secukinumab at 16 weeks and to assess the long term safety, tolerability and efficacy up to 2 years in patients with active AS. One of the exploratory objectives was to explore the pharmacokinetic/pharmacodynamic (pK/PD) relationship of secukinumab.

A screening period running 4 weeks before randomization was used to assess eligibility, followed by a treatment period of 2 years.

- At baseline, patients whose eligibility was confirmed were randomized by the Interactive Response Technology to one of three treatment groups:
- Group 1 (iv-75 mg): Secukinumab 10 mg/kg iv at baseline, Week 2 and Week 4, and then secukinumab 75 mg sc starting at Week 8 and injected every 4 weeks (124 patients)
- Group 2 (iv-150 mg): Secukinumab 10 mg/kg iv at baseline, Week 2 and Week 4, and then secukinumab 150 mg sc starting at Week 8 and injected every 4 weeks (125 patients)
- Group 3 (Placebo): Placebo iv at baseline, Week 2 and Week 4, and then placebo sc at Week 8 and Week 12 (122 patients)

Patients were stratified according to being TNFαi inadequate responders (TNF-IR) or TNFαi naïve patients.

At Week 16, the efficacy of secukinumab treatment was assessed based on ASAS 20 improvement criteria and all patients were classified as responders or non-responders. Patients initially randomized to placebo (Group 3) at baseline were re-randomized to receive double-blind treatment up to 2 years, as follows:

- Placebo non-responders were re-randomized to receive secukinumab 75 mg or 150 mg sc (1:1) injected every 4 weeks.
- Placebo responders remained on placebo sc at Weeks 16 and 20. At Week 24, these patients received secukinumab 75 mg sc or 150 mg sc (1:1) injected every 4 weeks, regardless of responder status, as dictated by the re-randomization.

Venous blood samples were collected pre-dose at baseline, Weeks 4, 16, 24, and 52 for p analyses.

Main findings related to the pK of secukinumab

Serum secukinumab concentrations were in the expected ranges over the iv and sc treatment courses. Patients initially treated with placebo and then re-randomized to sc secukinumab attained a similar steady-state mean concentration as patients who received secukinumab from the beginning of the study. There was evidence of dose-proportionality in exposure between the two dose levels during sc treatment.

Secukinumab concentrations in Group 1 and 2

At Week 4, mean concentrations were similar in the two groups (132 and 131 µg/mL, respectively), reflecting the rise in concentrations during the iv dosing phase which used identical doses in both treatment groups. At Weeks 16, 24, and 52, concentrations diverged and serially declined as steady state was approached during every-4-week administration at the two sc dose levels. The lower mean concentrations at these visits compared with the values at Week 4 were due to the lower milligram doses and the less frequent administration during sc dosing. At Week 52, inter-subject variability was 44.6% in the iv-75 mg group and 39.7% in the iv-150 mg group. One patient in both groups had a quantifiable secukinumab serum concentration before randomization.

Secukinumab concentrations in placebo non-responders starting at week 16

Two patients in the 150 mg group had quantifiable serum concentrations before randomization. The first s.c dose in these groups was at Week 16. Mean concentrations at the two pharmacokinetic visits in Weeks 24 and 52 increased over time as exposure approached steady-state. By Week 52 after 9 months of every-4-week dosing, the mean concentrations were 11.4 µg/mL (75 mg) and 17.2 µg/mL (150 mg) yielding a 150 mg / 75 mg concentration ratio of 1.51, less than the expected ratio of 2.0 for dose-proportionality, perhaps due to the small sample size of these treatment groups. At Week 52, the inter-subject variability was 43.9% in the placebo non-responder 75 mg group and 38.6% in the placebo non-responder 150 mg group. The Week 52 mean concentrations in the placebo non-responder 75 mg and 150 mg groups were similar to those in the iv-75 mg and iv-150 mg groups (10.9 and 20.0 µg/mL, respectively).

Secukinumab concentrations in placebo-responders starting at week 16

Before re-randomization, three patients had quantifiable secukinumab concentrations in their serum sample. The first sc dose in these groups was at Week 24. By Week 52 after 7 months of every-4-week dosing, the mean concentration was at steady-state with values of 11.7 µg/mL (75 mg) and 18.2 µg/mL (150 mg). The 150 mg / 75 mg concentration ratio was 1.56, less than the expected ratio of 2.0 for dose-proportionality perhaps due to the small sample size. At Week 52, the inter-subject variability was 44.7% in the placebo responder 75 mg group and 34.1% in the placebo responder 150 mg group.

These results are summarised in **Table 6**.

Table 6. Secukinumab concentrations by treatment and visit

Visit	10 mg/kg-75 mg		Placebo non-responders 75 mg		Placebo responders 75 mg	
	n	Conc (µg/mL)	n	Conc (µg/mL)	n	Conc (µg/mL)
Week 4	116	132 ± 37.9	--	--	--	--
Week 16	112	37.1 ± 17.6	--	First dose	--	--
Week 24	110	17.2 ± 9.06	35	8.92 ± 4.25	--	First dose
Week 52	93	10.9 ± 4.88	28	11.4 ± 5.03	14	11.7 ± 5.25
Visit	10 mg/kg-150 mg		Placebo non-responders 150 mg		Placebo responders 150 mg	
	n	Conc (µg/mL)	n	Conc (µg/mL)	n	Conc (µg/mL)
Week 4	111	131 ± 38.5	--	--	--	--
Week 16	117	43.6 ± 18.8	--	First dose	--	--
Week 24	112	25.5 ± 11.7	35	13.7 ± 5.57	--	First dose
Week 52	96	20.0 ± 7.92	28	17.2 ± 6.65	17	18.2 ± 6.19

Conc = secukinumab concentration

Study CAIN457F2310

A randomised, double-blind, double-dummy, parallel-group, placebo-controlled phase III multicentre study was performed to evaluate the efficacy of secukinumab in pre-filled syringes at 16 weeks and to evaluate the long-term efficacy, safety and tolerability up to 5 years in patients with AS.

The primary objective of this study was to demonstrate that the efficacy of secukinumab 75 mg sc or 150 mg sc at Week 16 was superior to placebo in subjects with active AS based on the proportion of subjects achieving an ASAS 20 response. One of the exploratory objectives was assessment of pK/PD relationship of secukinumab.

A screening period running 4-10 weeks before randomization was used to assess eligibility, followed by a treatment period of 52 weeks of blinded treatment. At BSL, patients whose eligibility was confirmed were randomized by the Interactive Response Technology (IRT) to one of three treatment groups:

- Group 1: secukinumab 75 mg plus placebo 150 mg sc once weekly at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4 (n=73)
- Group 2: secukinumab 150 mg plus placebo 75 mg sc once weekly at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4 (n=72)
- Group 3: placebo 75 mg and placebo 150 mg sc once weekly at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4 (n=74)

Patients were stratified according to being TNFα inhibitor inadequate responders (TNF-IR) or TNFα inhibitor naïve patients.

At Week 16, subjects who had been randomized to placebo at baseline were re-randomized by the IRT to receive secukinumab 75 mg plus placebo 150 mg sc or secukinumab 150 mg plus placebo 75 mg sc (1:1) every 4 weeks up to 256 weeks. The study is ongoing.

Venous blood samples were collected pre-dose at baseline, Weeks 4, 16, 24, and 52 for PK analyses.

Main findings related to the PK of secukinumab

Secukinumab 75 mg and 150 mg groups

In the 75 mg sc group (before randomisation) 2 patients had a quantifiable secukinumab concentration. As these concentrations were near the analytical limit of quantification, they may represent analytical noise. At Week 4 near the end of the weekly dose administration phase, the mean concentration was

approximately 2-fold higher in the 150 sc mg arm (52.9 µg/mL) compared to the 75 mg sc arm (25.4 µg/mL) consistent with dose-proportionality. At Weeks 16 to 52, concentrations approached and attained steady-state during every-4-week administration. The lower mean concentrations at these visits compared with the values at Week 4 were due to the less frequent administration during the maintenance phase.

Placebo group patients re-randomized to secukinumab starting at Week 16

Three patients had quantifiable serum concentrations before the first secukinumab administration. Two concentrations may have been analytical noise as they were close to the assay quantification limit and one concentration may have been from a blood sample taken post-dose although not documented as such.

The first dose in these arms was at Week 16 followed by every-4-week dosing. In placebo group mean concentrations at Weeks 24 and 52 (that is, 8 and 36 weeks after starting treatment) increased as drug accumulated to steady-state. At the Week 52 visit when exposure was at steady state, mean concentrations were consistent with dose-proportionality. These concentrations were similar to those in the respective 75 mg sc and 150 mg sc regimen arms at Week 52.

The results from this study are summarised in **Table 7**.

Table 7. Secukinumab concentrations by treatment and visit

Visit	75 mg		150 mg		Placebo → 75 mg		Placebo → 150 mg	
	N	Conc (ug/mL)	N	Conc (ug/mL)	N	Conc (ug/mL)	N	Conc (ug/mL)
Week 4	56	25.4 ± 9.42	63	52.9 ± 17.9	--	Placebo	--	Placebo
Week 16	52	13.0 ± 5.35	56	23.0 ± 10.8	--	First dose	--	First dose
Week 24	50	11.3 ± 4.63	55	20.3 ± 9.98	18	8.37 ± 3.38	25	15.5 ± 4.79
Week 52	47	10.8 ± 5.15	48	20.7 ± 8.63	15	11.0 ± 6.70	17	18.8 ± 5.70

Conc = secukinumab concentration.

Secukinumab population pK modelling report

Population pharmacokinetic (PPK) analysis of secukinumab in patients with AS was performed using pooled concentration data from studies CAIN457A2209, CAIN457F2305 and CAIN457F2310. The effects of potentially important covariates such as bodyweight, gender, race (non-Asian vs. Asian and disease characteristics assessed by the BASDAI 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 ankylosing spondylitis were estimated. The studies covered a mix of dosing regimens with either iv (2 x 0.1 mg/kg to 2 x 10 mg/kg iv) or sc (75 mg to 150 mg sc) administration. The population model was built based on 2138 secukinumab concentrations from 484 patients.

A linear two-compartmental distribution model with first-order absorption (for sc) administration and first-order elimination was used as basis. The disposition kinetics were modeled using a parameterization involving clearance (CL), central volume (Vc), inter-compartmental clearance (Q1), and peripheral volume (Vp1). A first-order absorption rate constant (ka) and bioavailability term (Fabs1) were used to characterize the rate and extent of the absorption process of the sc administration.

Covariates included in the PK analysis are summarised in **Tables 8** and **9**.

Table 8. Summary table of the continuous covariates

	N	missing	mean	std	min	q05	median	q95	max
Bodyweight [kg]	484	-	78.3	17.3	40	66	77	88	142
Age [years]	484	-	41.8	12.4	18	32	41	51	77
Height [cm]	484	-	170	9.76	138	164	170	178	196
BMI [kg/m^2]	484	-	26.9	5.39	15.9	22.9	26.4	30.1	46.1
BASDAI score at baseline (BASDAI0)	484	1	6.41	1.51	0.73	5.44	6.56	7.4	9.98
CRP at baseline (CRP0) [mg/L]	484	-	18.3	28.7	0.2	2.6	7.38	22.4	237
Time since first diagnosis of AS (TDIAG) [years]	484	4	7.18	8.48	0.003	1.19	3.98	10.7	56.8

(N = number of subjects; std = standard deviation; q05 = the 5th percentile; q95 = the 95th percentile)

Table 9. Summary table of the categorical covariates

	N	Frequency (%of the population)
Gender (SEX)	484	1:323 (67%), 2:161 (%)
Race (RACE)	484	1:341 (70%), 2:1 (0.2%), 3:55 (11%), 7:10 (2%), 88:77 (16%)
Ethnicity (ETHN)	484	1:85 (17%), 20:312 (64%), 88:87 (18%)
Asian (ASIAN)	484	0:429 (89%), 1:55 (11%)
Number of previously used biologics (PREBIO)	484	0:335 (69%), 1:129 (27%), 2:20 (4%)
Response status for anti-TNFα therapy (TNF)	484	0:334 (69%), 1:150 (31%)
Concomitant use of methotrexate (MTX)	484	0:468 (97%), 1:16 (3%)
Concomitant use of glucocorticoids	484	0:465 (96%), 1:19 (4%)

Gender: 1=male, 2=female (used synonymously with sex)

Race: 1=Caucasian; 2=Black; 3=Asian; 7=Native American; 88=Other/unknown

Ethnicity: 1=Hispanic/Latino; 20=not Hispanic/Latino; 88=Other/unknown/not reported

Asian: as defined by Race=3

Anti-TNFα history: 0=TNF-naïve, 1=TNF-inadequate responders (TNF-IR)

Methotrexate use: 0=no; 1=yes

Corticosteroids use: 0=no; 1=yes

There were no relevant correlations between bodyweight, age, or BASDAI at baseline, but there was a correlation between AGE at baseline and TDIAG (time since first diagnosis of AS). Female and Asian patients had lower bodyweight. Asian patient subpopulation was slightly younger than non-Asian, and females were slightly older than males.

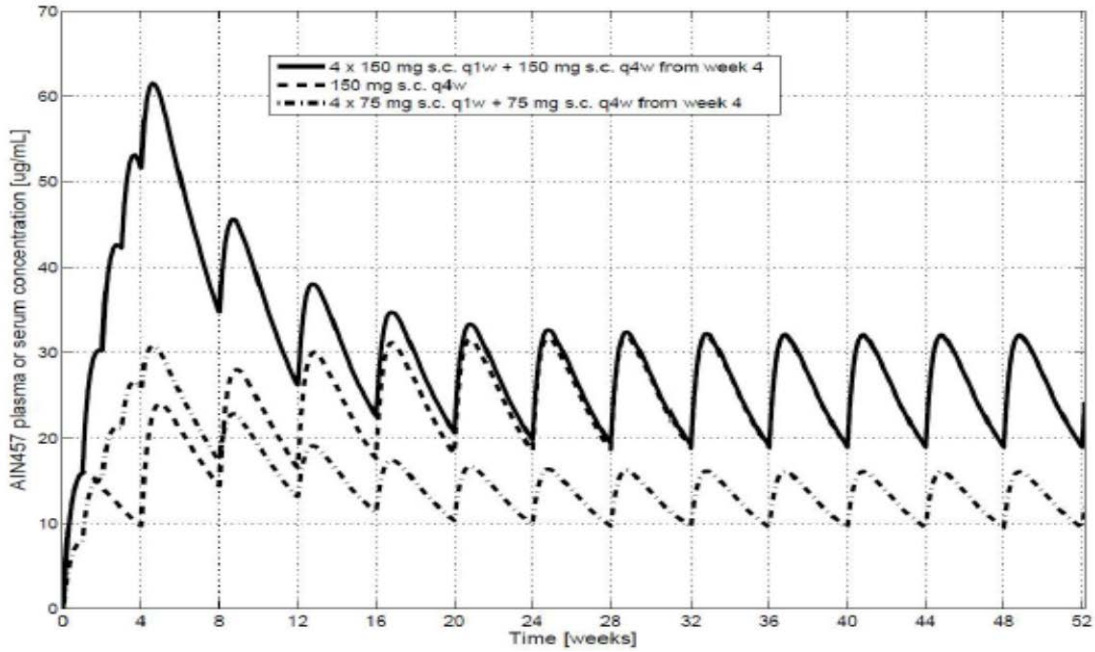
The effect of different covariates on clearance (CL) was estimated (**Table 10**). Changes to typical subject parameter of more than 20 % are considered potentially of clinical relevance. Therefore only body weight was retained in the PPK model as potentially relevant covariate and it was included in the PPK.

Table 10. Effect of key covariates on CL

	Estimated clearance [L/day]	%Change from "typical"
"Typical" clearance	*0.15*	*0*
Bodyweight = 53 kg	0.11	-25
Bodyweight = 112 kg	0.21	35
Baseline CRP = 0.7 mg/L	0.13	-18
Baseline CRP = 64 mg/L	0.18	20
TNF-IR	0.16	8

Simulated secukinumab exposure for sc loading + sc maintenance 75 mg and 150 mg regimen with regular q4w dosing without loading dose was presented (**Figure 2**).

Figure 2. Simulated concentration profiles of the sc loading + s.c maintenance phase III regimends compared to regular q4wdosing. The 150 mg dose sc yielded twice the exposure level of the 75 mg sc dose



Simulated PK parameters for the sc-loading and sc-maintenance phase III dose are shown in **Table 11**.

Table 11. Simulated PK metric for 150 mg sc phase III regimen

	Mean	std	%CV	Range (90%)
C_{min} at week 16 [µg/mL]	24.7	11	44.5	[10.9 – 46.2]
C_{min} at steady state [µg/mL]	20.8	9.1	43.8	[9.7 – 39]
C_{avg} at steady state [µg/mL]	25.8	8.1	31.4	[14.7 – 48.5]
AUC at steady state [day·µg/mL]	722.9	227.2	31.4	[410.7 – 1359.3]
C_{max} at steady state [µg/mL]	34.1	12.1	35.5	[18.7 – 57.5]
T_{max} at steady state [day]	6	0.7	11.7	[5 – 7]
C_{max} overall [µg/mL]	64.3	19	29.6	[38.5 – 99.8]
T_{max} overall [day]	32.3	0.64	1.98	[32 – 33]
C_{max} after first dose [µg/mL]	16.1	4.57	28.4	[9.65 – 24.2]
T_{max} after first dose [day]	5.98	0.14	2.34	[6 – 6]
Terminal half-life [day]	25.7	6.93	27	[17.3 – 39.4]

Absorption

Pharmacokinetics of secukinumab was described by first order absorption and linear pharmacokinetics. Based on two compartment PK model of secukinumab in AS patients using data from studies CAIN457A2209, CAIN457F2305 and CAIN457F2310 minimum concentration of secukinumab at steady-state ($C_{min,ss}$) was estimated to be 20.8 µg/mL after s.c loading and s.c maintenance dose of 150 mg of secukinumab. The average concentration at steady state ($C_{av,ss}$) was estimated to be 25.8 µg/mL and the mean peak concentration at steady state (C_{max}) to be 34.1 µg/mL and to occur approximately 6 days after dosing. C_{max} after the first dose was estimated to be 16.1 µg/mL, which is about a half of the C_{max} at steady-state.

Based on the PPK modeling report bioavailability secukinumab was estimated to be 79 % in patients with AS which is similar to the absolute availability in plaque psoriasis patients.

Distribution

Based on PPK analysis the volume of distribution was low being 3.09 L (CV% 30.7) for central compartment volume and 2.38 L (CV% 30.7) for peripheral compartment volume in typical AS patient weighting 77 kg. The estimated values for volume of distribution are low and similar to the value in patients with plaque psoriasis patients.

Metabolism

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

Elimination

Based on PPK analysis terminal half-life ($t_{1/2}$) of secukinumab is estimated to be 25.7 days in patients with AS with inter-patient variability 27 %. Serum CL is estimated to be low (CL=0.16 L/day with 32.8 % CV inter-patient variability in an allometric relationship). For CL and central volume of distribution (V_c) the allometric exponents were estimated to be 0.83 and 1.24, respectively. CRP at baseline and anti-TNFα response status did not have a clinically relevant influence on clearance (after adjusting for bodyweight).

Excretion

Since secukinumab is a human IgG1 immunoglobulin with large molecular size (about 150 kDa) little intact immunoglobulin can be filtered by the kidneys. Secukinumab is not expected to be excreted in urine or secreted into the bile.

Dose proportionality and time dependencies

Approximately 2-fold higher secukinumab concentrations were observed with the 150 mg dosing regimen compared to values with the 75 mg sc dosing regimen (Study CAIN457F2310). PPK analysis revealed no time-dependent or dose-dependence change in CL indicating that the PK of secukinumab is linear.

The exploratory E-R evaluation suggested a significant association between secukinumab exposure and clinical end-points. While the median patient treated with the proposed 150 mg dose (including loading regimen) appeared to have an adequate Cmin to attain Emax, patients with an increased body weight might have a significantly lower exposure. Therefore the CHMP requested the MAH to discuss the potential clinical benefit of a weight based dosing of secukinumab. From the simulation of expected efficacy outcomes based on study [CAIN457F2310] and the observed clinical data from the pivotal trial [CAIN457F2305] with higher initial (weight-adjusted) exposures due to intravenous loading there is insufficient evidence to recommend a weight-based posology for secukinumab in patients with AS. A dose

of 300 mg for heavier patients is unlikely to result in consistent clinically meaningful advantage over the 150 mg dose.

Special populations

No paediatric studies were conducted.

No formal PK studies have been performed in patients with impaired hepatic or renal function. As majority of IgG elimination occurs via intracellular catabolism following fluid-phase or receptor-mediated endocytosis, impaired renal or hepatic function is not expected to influence neither metabolism nor excretion of secukinumab.

Based on PPK analysis gender or race has no effect on clearance of secukinumab in patients with AS.

Pharmacokinetic interaction studies

Drug-drug interactions between monoclonal antibodies and low molecular weight drugs were not investigated *in vitro* or in formal interaction clinical studies. The CHMP noted that methotrexate and corticosteroids were used as categorical covariates in the PPK analysis. However, data and conclusions of the concomitant use of methotrexate and corticosteroids with secukinumab were lacking from the PPK report. The MAH was therefore requested to perform additional analyses to that effect. These analyses showed that secukinumab concentration profiles in two Phase III studies [studies CAIN457F2305 and CAIN457F2310] in patients with and without concomitant methotrexate were similar at weeks 16 and 52. There were also no systematic trends either downward or upward in secukinumab concentrations from patients using concomitant glucocorticoids compared to those who did no at weeks 16 and 52.

2.2.3. Pharmacodynamics

Mechanism of action

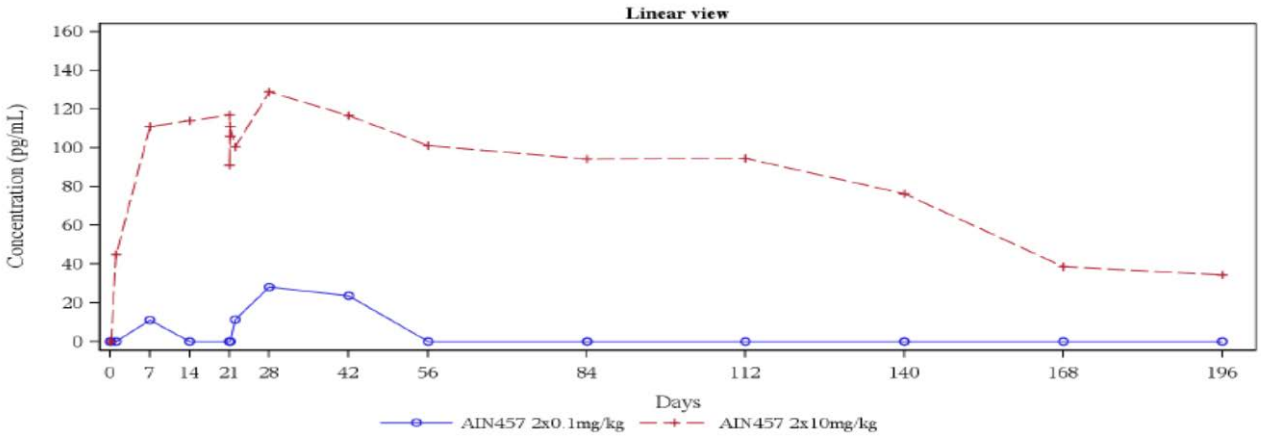
The pharmacodynamic effect of secukinumab in binding to IL-17A, and therefore inhibiting IL-17A signalling, is in the reduction of the inflammatory processes of AS. Based on the data provided within the initial marketing authorisation application, the engagement of IL-17A was seen as an increase in serum 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 (report date: 06-Feb-2015) was provided. The scope of the report was 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 clinical study reports (CSR, Studies A1101, A2206, A2209, A2212, A2220, A2309, F2201 and F2208).
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 electrochemoluminescence assay was used.

The median total IL-17A concentration-time profiles after doses of 0.1 mg/kg iv and 10 mg/kg iv on Days 0 and 22 from Study A2209, is shown in **Figure 3**. The highest median concentrations were observed a week after the second dose, followed by slowly declining concentrations.

Figure 3. Median total IL-17A concentration – time profiles in AS patients (Study A2209)



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

The following observations were made:

During a time span of one to two weeks after the first dose of secukinumab, total IL-17A levels raised until a plateau was reached in both healthy subjects and patient populations, indicating fast target engagement (IL-17A) of secukinumab in all studies analysed.

Plateau levels of median total IL-17A were approximately 100 pg/mL with a high inter-subject variability. This was confirmed in the phase III regimen in Pso in which after the initial 4 once-weekly injections, median concentrations at Week 4 were about 130 pg/mL in both secukinumab groups.

Median C_{max} levels of total IL-17A were higher with secukinumab doses of 3 x 10 mg/kg iv in psoriasis patients and single 10 mg/kg iv in Japanese healthy subjects, compared to single 3 mg/kg iv in psoriasis, 2 x 10 mg/kg iv in psoriatic arthritis and ankylosing spondylitis patients and single 150 mg sc in Japanese healthy subjects.

With increasing doses of secukinumab or multiple doses, total IL-17A concentrations were sustained for a longer duration.

In the elimination phase, the total IL-17A concentration-time profiles showed similarity to the elimination behaviour of secukinumab itself (similar half-lives for bound IL-17A and secukinumab). This indicated a joint clearance of secukinumab with (bound) IL-17A.

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

2.2.1. PK/PD modeling

A graphical exploratory analysis of secukinumab exposure-response (E-R) relationships for efficacy and adverse events in study CAIN457F2310 was performed. The focus was on describing E-R trend at a fixed time point, rather than through longitudinal PKPD modeling.

The following efficacy endpoints, evaluated at Week 16, were considered: ASAS (20/40/5-6) response, BASDAI, and SF36-PCS. Full analysis sets were used. Crude incidence rates for the following treatment emergent adverse events (up to Week 16) were considered: “Any adverse event” (AE), “Any serious

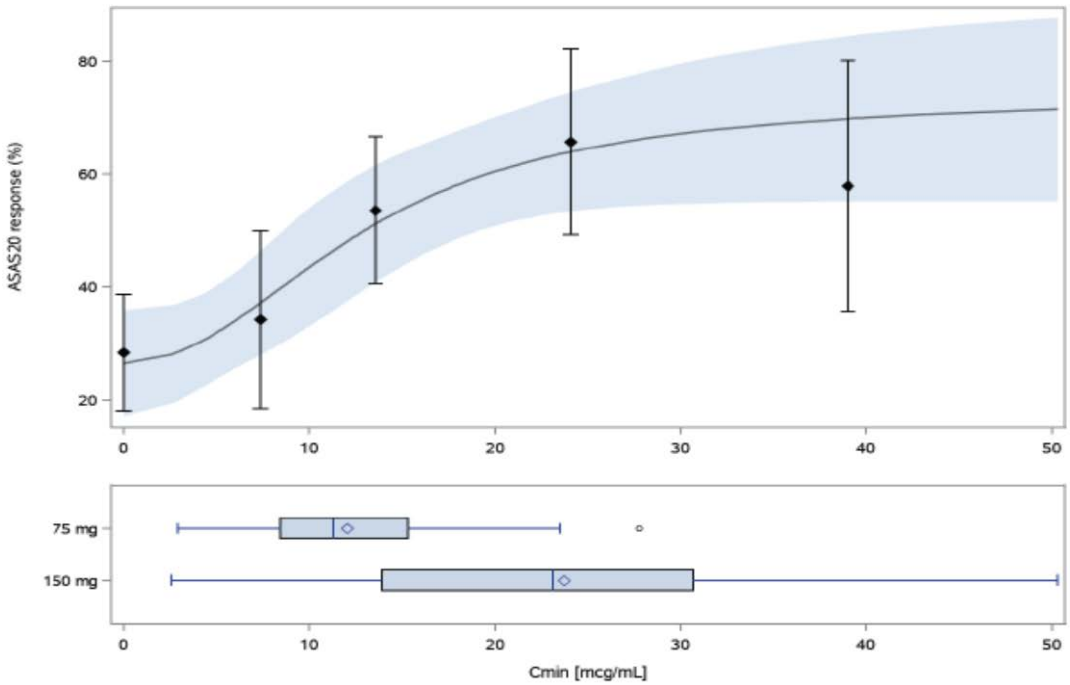
adverse event" (SAE), "Any infections and infestations" (primary system organ class), "Upper respiratory tract infections" (preferred term), "Nasopharyngitis" (preferred term) and "Oral Herpes" (preferred term).

The secukinumab exposure metric was trough concentration (Cmin) at Week 16. Concentrations were set to zero for all patients randomised to the placebo group. All concentrations reported in the database were used in the analysis, including those flagged for being out of sampling window. A total of 216 patients contributed to the exposure-response analyses.

ASAS20 response rate

Figure 4 illustrates the E-R relationship for ASAS20 response rates at Week 16. The E-R correlation appeared similar across ASAS response. The black line and the blue shaded area represent the mean and 95 % (pointwise) confidence limits from the logistic regression model. The black diamonds and the whiskers represent the mean and 95% confidence interval of the observed response rates for the exposure subgroups. The model fit showed a trend for an increased probability of achieving ASAS response with higher Cmin levels. The exposure response curve flattens at Cmin levels that are higher than ca. 25 mcg/mL. This approximately corresponds to the mean concentration achieved with the 150 mg dosing regimen tested in the study, as illustrated by the boxplots of observed Cmin concentrations at Week 16 in the different arms.

Figure 4. ASAS20 response rate versus Cmin at week 16.



Similar conclusions were reached for BASDAI and SF36-PCS.

An increasing trend with exposure was seen for infections and infestations, nasopharyngitis and oral herpes.

The results of this exploratory analysis are limited to the subcutaneous loading regimen tested in study CAIN457F2310 (loading dose on weeks 0, 1, 2, 3, 4, followed by Q4W dosing). It was not possible to infer from this analysis the exposure-response relationship following a subcutaneous no-load regiment or other loading regimen (such as iv loading). In consequence, results presented here are only indicative of potential trends in the data.

Exposure-response relationships were observed in all efficacy parameters (ASAS, BASDAI, and SF36-PCS), with a trend for increased response with higher C_{min} concentrations. The exposure-response appeared to flattenen at C_{min} levels higher than ca. 25 mcg/mL. This was approximately the mean concentration of the studied regimen of 150 mg, suggesting a small benefit from further increasing the dose. However, in some of the patients receiving a 150 mg dose, C_{min} will be below 25 mcg/mL. These patients, with lower exposure, may experience a decreased clinical response.

It can be noted that the value of 25 mcg/mL is slightly higher than the value referenced in the corresponding analyses in psoriatic arthritis (PsA) patients, i.e. 20 mcg/mL; this is because the effect of loading is more prominent at Week 16, resulting in higher trough concentrations than at Week 24 (reference visit in PsA).

No evidence of an effect of C_{min} was observed on AE rates for the following categories: any AE, any SAE, and upper respiratory tract infections. A trend for increased rates of for infections and infestations, nasopharyngitis and oral herpes with higher C_{min} was observed. However, uncertainty around the predicted curves is considerably greater as C_{min} increases. These results could be suggestive of possible signals and infections are included in the RMP as an important identified risk which will be closely monitored in PSURs.

2.2.1. Discussion on clinical pharmacology

Secukinumab PK in AS patients after sc administration was studied in three clinical studies in patients. 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 clinical study A2209, the studied secukinumab dose in Part 1 was 10 mg/kg as an iv infusion administered twice by 3 weeks interval (also placebo group). In Part 2 two doses of 0.1 mg/kg, 1.0 mg/kg and 10 mg/kg or placebo 3 weeks apart were administered. The reported PK parameters for secukinumab were quite similar as earlier seen in the study with similar dosing regimen and route with psoriasis patients. The low CL and Vz and quite long t1/2 are typical for secukinumab.

In study CAIN457F2305, the studied loading dose of secukinumab was 10 mg/kg iv at baseline, at weeks 2 and 4 and thereafter the studied secukinumab doses were 75 mg and 150 mg sc monthly (starting at week 8). 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 17.2 µg/ml and 10.9 µg/ml at weeks 24 and 52 and with 150 mg sc dose 25.5 µg/ml and 20.0 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. Patients initially treated with placebo and re-randomized to sc secukinumab attained similar steady state concentrations at week 52 as patients who received secukinumab from the beginning of the study.

In clinical study CAIN457F2310 the studied secukinumab doses were 75 mg or 150 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 F2305. The dose-proportionality in the secukinumab concentrations was found at week 4 and also at steady-state (weeks 16 and 24 and 52). The mean secukinumab concentrations were in the expected range.

Based on PPK analysis, gender, age, race, concomitant use of methotrexate, baseline BASDAI score and time since first diagnosis of AS were not identified as covariates with a nominal p-value of <0.05. An allometric relationship between bodyweight and clearance and volume has been observed in the PPK.

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, and the bioavailability after sc administration was 79% in AS patients being slightly higher than in psoriasis patients (66-77%).

On the basis of the PPK model and graphical analysis increased body weight correlated with lower Cmin concentrations. There was also a trend that the higher Cmin concentrations, the better response in efficacy. Nevertheless, the available data suggest that the 150 mg dose appears to be effective even in patients with an increased body weight. 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 sc. The 75 mg sc was demonstrated to be not sufficiently effective.

The CHMP considered that the PPK model was able to predict the observed data sufficiently. The estimated PK parameters (e.g., Cmin,ss, AUCss, Cmax,ss, tmax and t1/2) for secukinumab 150 mg obtained with the PPK model were in line with the PK parameters obtained in the clinical studies with secukinumab.

In all clinical studies with AS 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.

In conclusion, the PK data of secukinumab in AS patients was very similar to the PK data obtained in psoriasis patients. This was reflected in Section 5.2 of the SmPC, which also contains a statement that secukinumab clearance and volume of distribution increase as body weight increases.

2.2.2. Conclusions on clinical pharmacology

The results indicate that the PK of secukinumab in AS patients is similar to other indications both after iv and after sc administration and blood serum concentrations increased dose-proportionally between doses of 75 mg to 150 mg sc in patients with AS.

2.3. Clinical efficacy

2.3.1. Dose response studies

Study A2209

This was a randomized, placebo controlled double blind, multi-centre phase II proof-of-concept study to assess the efficacy of AIN457 in patients with moderate to severe ankylosing spondylitis (Report date 28 February 2012). Secukinumab was administered iv from 50 mg/ml LYO formulation. A total of 60 participants were randomized.

The primary objective of the first part of the study was to evaluate the efficacy of secukinumab at 6 weeks based on the proportion of patients achieving ASAS20 response. The subjects were randomized to either secukinumab 10 mg/kg iv or placebo in a ratio of 4:1. Each patient received the study drug dose on Day 1 and Day 22.

Conversely, the primary objective of second part to evaluate the efficacy of three different doses of secukinumab at 6 weeks based on the change in Bath Ankylosing spondylitis disease activity index (BASDAI) score. The subjects were randomized to either secukinumab 0.1 mg/kg iv, secukinumab 1 mg/kg iv or secukinumab 10 mg/kg iv in a ratio of 2:2:1. Each patient received the study drug dose on Day 1 and Day 22.

In the first part of the Study, the proportion of ASAS20 responders at week 6 was 59.2% in the secukinumab group versus 24.5% of the placebo group (95% CI for the difference 11.5% to 56.4%). There were no significant differences in ASAS20 response between the randomized groups in patients with previous TNFαi use.

In the second part of the Study, the differences in change of BASDAI score at week 6 from baseline between the secukinumab groups were not statistically significant. The numerical reductions in BASDAI score were of equal magnitude in the secukinumab 1.0 mg/kg and 10 mg/kg groups: -2.02 versus -1.87, respectively (95% CI: -1.85, 1.56; p=0.57). The reductions in BASDAI score in the 0.1 mg/Kg group was -1.20 versus -1.87 of the 10 mg/kg group (95% CI: -1.09, 2.43; p=0.22).

Study A2209E1

This was an open label non-randomized extension study to evaluate the safety and tolerability of AIN457 (secukinumab) in patients with moderate to severe ankylosing spondylitis (Report date 2 July 2013). From the core study A2209, 39 patients were recruited to the extension study. Secukinumab LYO formulation 3 mg/kg iv was administered to all participants every 4 weeks up to 6 months (7 doses, part I of the study) with a possible extension of further 7 doses, one very 4 weeks up to 6 months (part II of the study). The first dose of the study drug was given within 3 weeks after completion visit of the core study A2209 (Visit 17 at Week 28).

ASAS20 response had been maintained by 23% of the participants of the core study A2209 at the screening visit of this extension study. The proportion of patients with the ASAS20 response increased to 50-59% during the whole 56-week period of study drug administration. This increased response was achieved already from Week 4 onwards. Similar improvements were also detected in terms of responses for ASAS40 (26-49%) and ASAS 5/6 (28-50%). The mean BASDAI decreased from 6.1 to 3.9 during the whole treatment period. Conversely, the median CRP levels decreased from 8.0 mg/l to around 3.0 mg/l during the follow-up indicating the effect of treatment on chronic inflammation. These positive effects of on efficacy outcomes were reversed at post-treatment study visits.

Study F2201

This was a 16-week multicentre, 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 (Report date 23 May 2012).

The primary objective of the study was to assess the efficacy and safety of various doses of secukinumab compared to placebo as add-on therapy at Week 16. 237 patients were randomized with 1:1:1:1:1 ratio to 1 of 5 treatment groups: secukinumab 300 mg sc q4wk, 150mg sc q4wk, 75 mg sc q4wk, 25mg sc q4wk, or placebo sc q4wk for 48 weeks. At Week 20, patients who were randomized to placebo at Week 0 or to secukinumab but did not achieve an ACR20 response at Week 16 were re-assigned by the IVRS to receive double-blind treatment (150 mg or 300 mg sc q4w) up to Week 48. American college for rheumatology (ACR)20/50/70 score and disease activity score (DAS)28 response/remission were used as efficacy criteria.

Higher proportions of patients treated with 75 mg, 150 mg or 300 mg sc q4wk achieved ACR20, ACR50 or ACR70 response compared with patients treated with placebo sc q4wk, as early as Week 2 and up to Week 16. However, the placebo group had an unexplained increase in the proportion of patients with an ACR20 response from 24% at Week 12 to 36% at Week 16. Consequently, none of the differences reached statistical significance and therefore the primary efficacy endpoint was not achieved (see **Table 12** and **Figure 5**). Nonetheless, the 75-300 mg dose groups showed consistently greater improvements

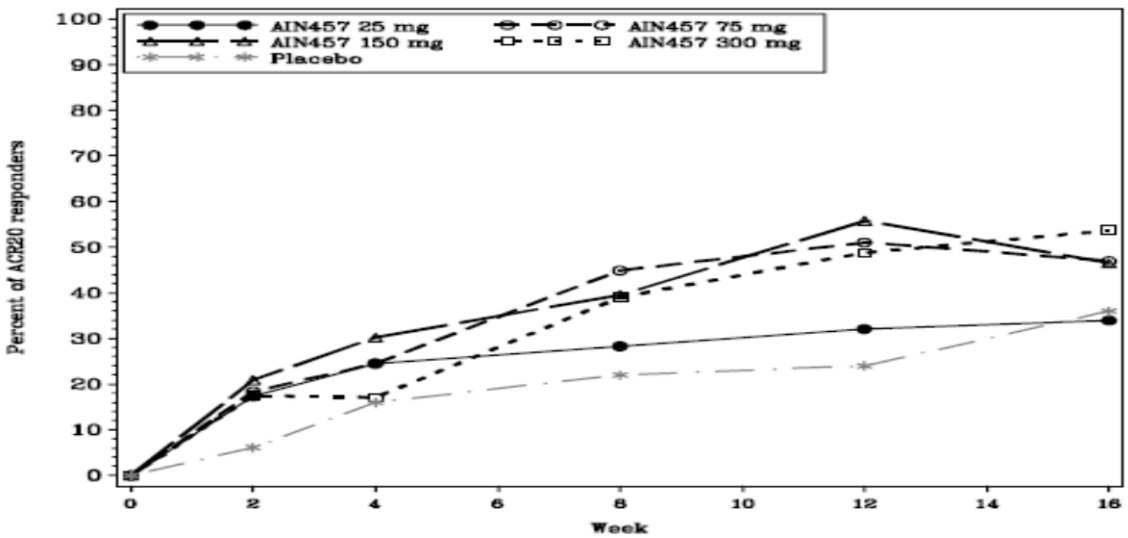
in secondary efficacy variables including ACR50 response, ACR70 response, DAS28 scores and individual ACR components over the 16 weeks. In contrast, the 25 mg dose provided a non-effective or minimal therapeutic benefit over placebo. Efficacy responses from Week 20 reaffirmed the efficacy observed for secukinumab 75-300 mg.

Table 12. Primary Endpoint - ACR20 responders: comparison between secukinumab groups and placebo at Week 16, LOCF (Full analysis set, Study F2201)

Treatment group	n / N' (%)	Comparison	Odds ratio	95% Confidence Interval	p-value
AIN457 25 mg (N=53)	18 / 53 (34.0)	vs. Placebo	0.75	(0.32, 1.78)	0.5188
AIN457 75 mg (N=49)	23 / 49 (46.9)	vs. Placebo	1.44	(0.62, 3.36)	0.3988
AIN457 150 mg (N=43)	20 / 43 (46.5)	vs. Placebo	1.30	(0.54, 3.15)	0.5598
AIN457 300 mg (N=41)	22 / 41 (53.7)	vs. Placebo	1.99	(0.81, 4.87)	0.1324
Placebo (N=50)	18 / 50 (36.0)				

Logistic regression model is used, odds ratio is used for test statistics and corresponding 95% confidence intervals, and p-values test for odds ratio equal to 1. Odds ratio >1 favors AIN457.
Logistic regression is adjusted by the following covariates: center, baseline weight, baseline DAS28-CRP.
n: The number of subjects who are ACR20 responders.
N': The total number of subjects in the treatment group with ACR20 evaluation.
* indicates statistical significance (two-sided) at 0.05 level.

Figure 5. ACR20 response over time through Week 16, LOCF (Full analysis set, Study F2201)



2.3.2. Main studies

Study F2305

Study F2305 was a randomized, double-blind, placebo-controlled, multi-centre study of secukinumab to demonstrate the efficacy at 16 weeks and to assess the long-term safety, tolerability and efficacy up to 2 years in patients with active ankylosing spondylitis (Report date 15 October 2014).

Methods

Study participants

Inclusion criteria

The main inclusion criteria were:

1. Male or non-pregnant, non-lactating female patients at least 18 years of age.
2. Diagnosis of moderate to severe AS with prior documented radiologic evidence (X-ray) fulfilling the Modified New York criteria for AS with active AS and a BASDAI ≥4 (0-10) and spinal pain as measured by visual analog scale (VAS) ≥ 4 cm at baseline.
3. Patient had to be on NSAIDs at the highest recommended dose for at least 3 months with an inadequate response or failure to respond, or less than 3 months if therapy had to be withdrawn due to intolerance, toxicity or contraindications.
4. Patient who are regularly taking NSAIDs (cyclo-oxygenase (COX)-1 or COX-2 inhibitors) as part of their AS therapy are required to be on a stable dose for at least 2 weeks before randomization.
5. Patients who have been on an TNF-αi agent (not more than one) must have experienced an inadequate response to previous or current treatment given at an approved dose for at least 3 months or have been intolerant to at least one administration of an TNF-αi agent.
6. Patients who have previously been on a TNF-αi were allowed entry into study after appropriate wash-out period prior to randomization:
    - 4 weeks for Enbrel® (etanercept) – with a terminal half-life of 102 ± 30 hours (SC route).
    - 8 weeks for Remicade® (infliximab) – with a terminal half-life of 8.0-9.5 days (IV infusion).
    - 10 weeks for Humira® (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) (SC route).
    - 10 weeks for Simponi® (golimumab) – with a terminal half-life of 11-14 days.
    - 10 weeks for Cimzia® (certolizumab) – with a terminal half-life of 14 days.
7. Patients taking methotrexate (MTX ,7.5 to 25 mg/week) or Sulfasalazine (≤ 3 g/day) must have taken it for at least 3 months and have to be on a stable dose for at least 4 weeks before randomization.

Exclusion criteria

The main exclusion criteria are listed below:

1. Chest X-ray with evidence of ongoing infectious or malignant process, obtained within 3 months of screening and evaluated by a qualified physician.
2. Patients with total ankylosis of the spine.
3. Patients taking high potency opioid analgesics (*e.g.*, methadone, hydromorphone, or morphine).
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 a period of 5 half-lives of the investigational drug, whichever is longer.
6. History of hypersensitivity to the study drug or its excipients or to drugs of similar chemical classes.

7. Any therapy by intra-articular injections (*e.g.*, corticosteroid) within 4 weeks before randomization.
8. Any intramuscular corticosteroid injection within 2 weeks before randomization.
9. Patients previously treated with any biological immunomodulating agents except for those targeting TNFα.
10. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20, investigational agents (*e.g.*, alemtuzumab, anti-CD4, anti-CD5, anti-CD3, anti-CD19).
11. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human choriontic gonadotropin (hCG) laboratory test.

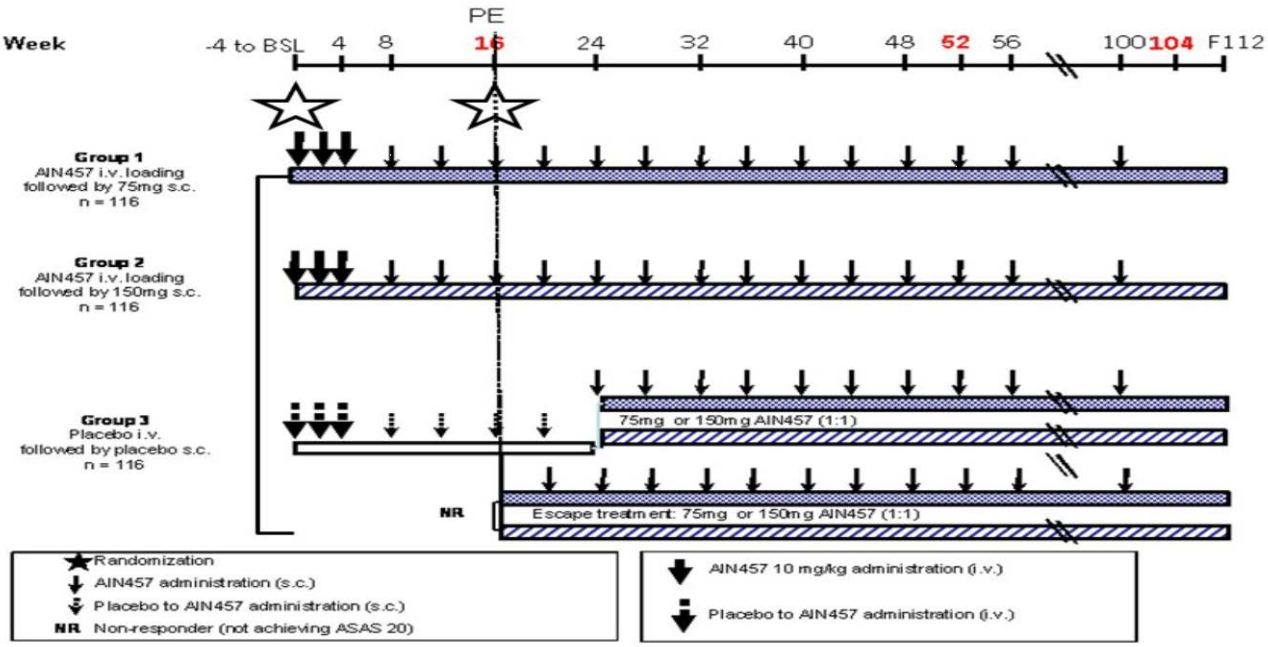
Treatment

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

A 4-week screening period before randomization was followed by a treatment period of two years. At baseline, patients were randomized (1:1:1) to one of the three treatment groups:

- Group 1: Secukinumab iv (10 mg/kg) at baseline, Weeks 2 and 4, then secukinumab 75 mg sc starting at Week 8 and injected every 4 weeks
- Group 2: Secukinumab iv (10 mg/kg) at baseline, Weeks 2 and 4, then secukinumab 150 mg sc starting at Week 8 and injected every 4 weeks
- Group 3: Placebo iv at baseline, Weeks 2 and 4, then placebo sc at Week 8 and Week 12.
- At Week 16 (Visit 8), all patients were classified as ASAS20 responders ($\geq$20% improvement from baseline in main ASAS response measures) or non-responders. Placebo non-responders were re-randomized to receive secukinumab 75 mg sc or 150 mg sc. The placebo responders remained at placebo until Week 24, when also these patients were randomized to either of the sc-doses.
- Rescue treatment was not allowed until Week 16. Patients who completed the 2 year study might be eligible to enter a planned extension trial.

Figure 6. Study design (Study F2305)



Objectives

The primary objective was to demonstrate the efficacy of at least one dose of secukinumab (IV-75 mg or IV-150 mg) at Week 16 was superior compared to placebo in patients with active AS based on the proportion of patients achieving an ASAS 20 response.

The secondary objectives were:

- To demonstrate that the efficacy of at least one dose of secukinumab (IV-75 mg or IV-150 mg) at Week 16 was superior to placebo in patients with active AS based on the proportion of patients achieving an ASAS 40 response.
- To demonstrate that the efficacy of at least one dose of secukinumab (IV-75 mg or IV-150 mg) at Week 16 was superior to placebo in patients with active AS based on the change from baseline of hsCRP.
- To demonstrate that the efficacy of at least one dose of secukinumab (IV-75 mg or IV-150 mg) at Week 16 was superior to placebo in patients with active AS based on the proportion of patients achieving an ASAS 5/6 response.
- To demonstrate that the efficacy of at least one dose of secukinumab (IV-75 mg or IV-150 mg) at Week 16 was superior to placebo in patients with active AS based on the change from baseline in total BASDAI.
- To demonstrate that the efficacy of at least one dose of secukinumab (IV-75 mg or IV-150 mg) at Week 16 was superior to placebo in patients with active AS based on the change from baseline in SF-36 physical component summary (PCS)
- To demonstrate that the efficacy of at least one dose of secukinumab (IV-75 mg or IV-150 mg) at Week 16 was superior to placebo in patients with active AS based on the change from baseline in ankylosing spondylitis quality of Life (ASQoL)

- To demonstrate that the efficacy of at least one dose of secukinumab (IV-75 mg or IV-150 mg) at Week 16 was superior to placebo in patients with active AS based on the proportion of patients achieving an ASAS partial remission
- To evaluate the overall safety and tolerability of secukinumab (IV-75 mg or IV-150 mg) compared to placebo as assessed by vital signs, clinical laboratory values, and adverse events monitoring

The exploratory objectives of the study were to evaluate the above-mentioned outcomes of treatment in other time points than Week 16. In addition, the efficacy was evaluated by assessing the change from baseline in other outcomes than mentioned above, *e.g.*, different ASAS components, BASFI, BASMI, bone oedema measured by MRI in patients with active AS.

Outcomes / endpoints

The primary efficacy endpoint was ASAS 20 at week 16, defined as an improvement of ⩾20% and ⩾1 unit on a scale of 0-10 in at least three of the four main domains and no worsening of ⩾20% and ⩾1 unit on a scale of 10 in the remaining domain. The ASAS (Assessment of SpondyloArthritis International Society Criteria) response measures consist of the following core assessment domains:

1. Patient's global assessment of disease activity measured on a VAS scale (0-100 mm)
2. Patient's assessment of spinal pain, represented by either total or nocturnal back pain scores, both measured on a VAS scale (0-100 mm)
3. Function represented by the Bath Ankylosing Spondylitis Functional Index (BASFI), the average of 10 questions regarding ability to perform specific tasks as measured by VAS scale (0-10 cm)
4. Inflammation represented by mean duration and severity of morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI as measured by VAS scale (0-10 cm)

Secondary efficacy endpoints included ASAS40 (defined as an improvement of ⩾40% and ⩾2 units on a scale of 10 in at least three of the four main domains and no worsening at all in the remaining domain), ASAS 5/6 (improvement of ⩾ 20% in at least five domains), ASAS partial remission (defined as a value of ⩽ 2 units in each of the 4 core domains on a scale of 10), BASDAI (0 through 10 scale pertaining to the 5 major symptoms of AS: Fatigue, Spinal pain, Joint pain/ swelling, enthesitis, Morning stiffness duration and severity), hsCRP (change from baseline in high-sensitivity C-reactive protein), ASQoL (change from baseline in Ankylosing Spondylitis Quality of Life) and SF-36 version 2 (Medical Outcome Short Form Health Survey: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health). The exploratory endpoints included BASFI (Bath Ankylosing Spondylitis Functional Index), BASMI (spinal mobility evaluation), 44-tender and swollen joint count assessment, ESR (Erythrocyte sedimentation rate), MASES (Maastricht Ankylosing Spondylitis Enthesitis Score), X-Ray of the cervical, thoracic and lumbar spine assessed by modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) at 2 years, MRI of spine and sacroiliac joints in a subgroup of TNF-αi naïve patients at selected clinical sites only (Berlin total sacroiliac joint oedema score, total Ankylosing Spondylitis spinal MRI-active score, and Berlin spine score), DXA of the lumbar spine, total hip and femoral neck, FACIT-Fatigue, EuroQol 5D (EQ-5D) and Work Productivity and Activity Impairment - General Health (WPAI-GH).

Sample size

An overall type I error (2-sided) 5% was used to control type I error. Since two secukinumab doses were tested versus placebo with respect to the primary endpoint (ASAS 20 response at Week 16), the type-I-error was split to 2.5% two-sided for each comparison. For 90% power and assuming a response rate of 20% in the placebo group, at least 39 patients per group would be needed to show a response rate of 60% in the secukinumab groups based on Fisher's exact test. In this study population, a placebo response rate of about 20% after 14 weeks has been reported.

In order to collect additional safety information on the use of secukinumab in this population, 348 patients were planned to be equally allocated to 3 treatment groups (116 patients in each treatment group), stratifying for prior treatment or not with TNF-αi. The study was planned to have at least 70% TNF-αi naïve patients.

Randomisation

At baseline (Visit 2), all eligible patients were randomized to one of the treatment arms (ratio 1:1:1). The patients were stratified according to being either TNF-IR or TNF-αi naïve status. Approximately 30% of the patients had to be TNF-IR to ensure a representative patient population for the assessment of efficacy and safety.

Blinding (masking)

This was a double-blind study.

Statistical methods

The analysis of the primary variable was based on the "full analysis set" (FAS). The statistical null hypotheses for ASAS 20 (primary endpoint) being tested was that there was no difference in the proportion of patients fulfilling the ASAS 20 criteria at Week 16 in any of the secukinumab regimens versus placebo regimen.

The primary analysis was conducted via logistic regression with treatment and TNFαi status as factors and weight as a covariate. Odds ratios and 95% CI were presented comparing each secukinumab regimen to placebo.

Sensitivity analyses and supportive analyses were conducted in order to provide evidence that the results seen from the primary analysis are robust.

Interactions between treatment and selected baseline demographics and disease characteristics were explored for ASAS 20 response at Week 16.

In order to determine the robustness of the logistic regression model used for the primary analysis, ASAS 20 response at Week 16 was also evaluated using a non-parametric analysis of covariance (ANCOVA) model) with the same independent variables as the logistic regression model.

The impact of missing data on the analysis results of ASAS 20 response was assessed as well by repeating the logistic regression model using different ways to handle missing data, including, but not limited to, multiple imputation or observed data analysis.

Missing data for ASAS20/40 response and other binary efficacy variables (*e.g.*, ASAS5/6, etc.) for data up to 1-year (Week 52) were handled as follows: patients who drop out of the trial for any reason were considered non-responders from the time they drop out through Week 52; patients who do not have the

required data to compute response (*e.g.*, ASAS components) at baseline and at the specific time point were classified as non-responders.

Patients who were un-blinded prior to the scheduled time point were considered non-responders from the time of un-blinding up to placebo-controlled period (Week 24). The primary analysis used the non-responder imputation.

Continuous variables (*e.g.*, ASAS components) were analysed using a mixed effect model repeat measurement (MMRM) which is valid under the missing at random (MAR) assumption. As such, single-point imputation of missing data was not performed (*e.g.*, last observation carried forward, LOCF). For analyses of these parameters, if all post-baseline values were missing then these missing values were not imputed and this patient was removed from the analysis of the corresponding variable, i.e., it might be that the number of patients providing data to an analysis is smaller than the number of patients in the FAS.

In general, the handling of data for patients who were rescued at Week 16 were handled in the following fashion (up to Week 24): for binary endpoints, patients were considered non-responders. This was done for all treatment regimens in order to minimize bias.

The family-wise error was set to α=5% and it was controlled with the proposed hierarchical testing strategy. Each of the hypotheses (H1 and H2) for the primary objective (ASAS 20 at Week 16) for each secukinumab regimen versus placebo was tested simultaneously at $\alpha/2$.

Then based on the rejection of one or both (of H1 and H2), the ASAS 40 at Week 16 endpoint was tested hierarchically for each dose (through H3 and/or H4). This procedure was continued (pending rejection of the null hypotheses) until H15 and/or H16 were/was rejected, then the respective $\alpha/2$ could be passed on to the other secukinumab regimen's hierarchy of hypotheses, if they were not already rejected at $\alpha/2$.

Results

Participant flow

A total of 448 patients were screened, and 371 of these patients completed the screening phase and were randomized to study treatment. The most common reasons for not completing the screening phase were screen failure (13.6%) and subject/guardian decision (2.0%). All other reasons were reported for 0.2% to 0.4% (1-2 patients) each.

There were 371 patients randomized equally to one of three treatment groups, patient disposition is shown in **Table 13**.

Of the 122 patients in the original placebo group, 11 discontinued while on placebo (10 before Week 16 and 1 at Week 20) and 9 non-responders discontinued after switching to secukinumab treatment.

Of a total of 112 placebo patients who were re-randomized to secukinumab treatment, 77 were placebo non-responders and 35 were placebo responders. Amongst placebo non-responders, discontinuation rates were 12.8% (5 patients) for the 75 mg and 10.5% (4 patients) for the 150 mg group. For the placebo responders, one patient discontinued and did so while on placebo at Week 20 due to lack of efficacy as per eCRF reported by the patient and/or investigator.

Table 13. Patient disposition up to Week 52 (Study F2305)

Disposition /Reason	AIN457 10mg/kg - 75 mg N = 124 n (%)	AIN457 10mg/kg - 150 mg N = 125 n (%)	Placebo N = 122 n (%)	Placebo Non-Resp AIN457 75 mg N = 39 n (%)	Placebo Non-Resp AIN457 150 mg N = 38 n (%)	Placebo Resp AIN457 75 mg N = 17 n (%)	Placebo Resp AIN457 150 mg N = 18 n (%)
Randomized	124	125	122	39	38	17	18
Completed Week 1-52	111 (89.5)	106 (84.8)	102 (83.6)	34 (87.2)	34 (89.5)	16 (94.1)	18 (100.0)
Discontinued Week 1-52	13 (10.5)	19 (15.2)	20 (16.4)	5 (12.8)	4 (10.5)	1 (5.9)[a]	0 (0.0)
Adverse event	6 (4.8)	7 (5.6)	7 (5.7)	0 (0.0)	2 (5.3)	0 (0.0)	0 (0.0)
Lack of efficacy	2 (1.6)	6 (4.8)	5 (4.1)	3 (7.7)	1 (2.6)	1 (5.9)[a]	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-compliance with study treatment	0 (0.0)	1 (0.8)	1 (0.8)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Physician decision	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No longer requires treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Technical problems	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject/guardian decision	4 (3.2)	3 (2.4)	5 (4.1)	1 (2.6)	1 (2.6)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Non-Resp=Non-responders; Resp=responders
[a] This patient discontinued while on placebo (before Week 24)

Recruitment

Study initiation date: 19 October 2011 (first patient, first visit).

Study completion date: Not applicable. All patients had completed the Visit 17 on Week 52 before the conduct of the current interim analysis (data cut-off date 10 December 2013).

There were 65 study centres in 14 countries: Belgium (4 centres), Bulgaria (5), Canada (3), France (3), Germany (9), Italy (6), Mexico (4), the Netherlands (2), Peru (5), Russian Federation (6), Taiwan (2), Turkey (3), United Kingdom (4) and United States (9).

Conduct of the study

The study protocol was amended 3 times (04 August 2011, 10 December 2012 and 22 November 2013).

The following changes were made to the planned analysis:

- The update of handling of missing values
- To expand the statistical hierarchy (primary plus ranked secondary variables) to include more endpoints which are relevant to determining the overall therapeutic value of a therapy for AS
- To align the primary and secondary assessments with the ASAS Handbook

Comparable proportions of patients across the secukinumab and placebo groups had at least one protocol deviation up to Week 16 (27.4% vs. 22.4% vs. 21.3% in the secukinumab 10 mg/kg-75 mg, secukinumab 10 mg/kg-150 mg and placebo groups, respectively) or up to Week 52 (32.3% vs. 25.6% vs. 25.4% in the secukinumab 10 mg/kg-75 mg, secukinumab 10 mg/kg-150 mg and placebo groups, respectively). The most common categories of protocol deviations in both analysis periods were 'Selection criteria not met' and "Key procedures not performed as per protocol". There were no meaningful differences in the categories of protocol deviations among the treatment groups.

Approximately half (24/42) of the protocol deviations in the category of “Selection criteria not met” were reported in patients who were randomized despite not meeting inclusion criteria with respect to either a baseline BASDAI score ≥ 4 or spinal pain ≥ 4 cm (moderate to severe AS) as measured by VAS according to BASDAI question 2. These deviations were distributed equally across the 3 treatment groups. Of the 24 patients who did not meet the BASDAI entry criteria, 10 had a baseline total back pain score ≥ 40.0 based on two ASAS core set questions on back pain. Prohibited concomitant medications were taken by 17 patients across the 3 treatment groups, with no clinically meaningful differences among the groups.

Baseline data

The majority of the patients (95.4%) were < 65 years of age, with a median ranging from 39.0 years (secukinumab 10 mg/kg-150 mg group) to 41.0 years (both other treatment groups. More than two thirds (69.3%) of the patients were male. Most of the patients (60.9%) were of Caucasian origin and 17.0% of Asian origin, respectively. The prevalence of current smokers was 23.7% and the mean BMI 26.5 kg/m2, with no significant differences between the randomised groups. The prevalence of HLA-B27 positivity varied between 68.8% and 79.8% in the study groups.

Baseline disease characteristics are reported in **Table 14**.

Table 14. Disease history and baseline characteristics by randomized treatment (Randomized set, Study F2305)

Background Characteristics	AIN457 10mg/kg - 75 mg N=124	AIN457 10mg/kg - 150 mg N=125	Placebo N=122	Total N=371
Patient's global assessment of disease activity (0-100 mm)				
n	124	125	122	371
Mean	60.5	64.0	66.3	63.6
SD	18.29	19.42	18.59	18.87
Median	62.5	66.0	68.5	65.0
Min – Max	0 - 100	3 - 96	17 - 100	0 - 100
Total back pain (0-100 mm)				
n	124	125	122	371
Mean	61.7	64.0	66.7	64.1
SD	18.87	18.56	16.45	18.07
Median	65.0	65.0	69.0	67.0
Min – Max	3 - 93	2 - 98	18 - 100	2 - 100

Background Characteristics	AIN457 10mg/kg - 75 mg N=124	AIN457 10mg/kg - 150 mg N=125	Placebo N=122	Total N=371

Nocturnal back pain (0-100 mm)				
n	124	125	122	371
Mean	58.3	60.8	65.3	61.4
SD	20.22	20.04	18.30	19.71
Median	62.5	63.0	69.0	64.0
Min – Max	0 - 92	1 - 100	10 - 100	0 - 100
BASFI				
n	124	125	122	371
Mean	5.39	5.64	5.82	5.61
SD	2.157	2.211	2.034	2.138
Median	5.59	5.81	6.11	5.80
Min – Max	0.4 - 9.4	0.8 - 9.8	0.4 - 9.7	0.4 - 9.8
BASDAI				
n	124	125	122	371
Mean	6.05	6.35	6.51	6.30
SD	1.415	1.576	1.533	1.518
Median	6.20	6.44	6.70	6.44
Min – Max	1.4 - 9.1	1.7 - 9.4	0.7 - 9.4	0.7 - 9.4
BASMI (linear)				
n	120	120	119	359
Mean	4.21	3.91	4.07	4.06
SD	1.756	1.785	1.579	1.709
Median	4.38	3.85	4.03	4.05
Min - Max	0.4 - 7.8	0.2 - 9.2	0.5 - 8.4	0.2 - 9.2
BASMI - lateral spinal flexion (cm)				
n	122	123	120	365
Mean	10.79	10.93	10.15	10.63
SD	7.456	6.113	5.149	6.308
Median	9.95	10.00	10.50	10.00
Min - Max	0.5 - 63.2	0.0 - 34.7	1.8 - 25.0	0.0 - 63.2
BASMI - tragus to wall distance (cm)				
n	123	124	122	369
Mean	15.24	13.99	14.76	14.66
SD	5.664	5.136	5.163	5.337
Median	14.00	12.00	12.50	13.00
Min - Max	8.0 - 40.0	7.5 - 38.0	6.5 - 33.0	6.5 - 40.0

Background Characteristics	AIN457 10mg/kg - 75 mg N=124	AIN457 10mg/kg - 150 mg N=125	Placebo N=122	Total N=371
BASMI - lumbar flexion (modified Schober, cm)				
n	120	121	120	361
Mean	3.52	4.00	3.84	3.79
SD	2.075	2.404	2.283	2.261
Median	3.50	4.00	3.50	3.80
Min - Max	0.0 - 8.0	0.0 - 12.5	0.0 - 14.0	0.0 - 14.0
BASMI - maximal intermalleolar distance (cm)				
n	123	124	122	369
Mean	95.90	94.28	96.91	95.69
SD	26.469	22.485	20.109	23.139
Median	98.00	97.50	100.00	98.30
Min - Max	4.0 - 160.0	26.0 - 136.0	40.0 - 137.0	4.0 - 160.0
BASMI - cervical rotation angle (degrees)				
n	123	123	122	368
Mean	47.18	49.25	49.12	48.51
SD	21.044	22.494	21.512	21.654
Median	47.50	50.00	50.00	49.00
Min - Max	2.5 - 90.0	0.0 - 92.5	3.9 - 90.0	0.0 - 92.5
BASMI - chest expansion (cm)				
n	123	123	121	367
Mean	3.67	3.46	3.44	3.52
SD	2.072	1.928	1.747	1.919
Median	3.50	3.20	3.00	3.20
Min - Max	0.6 - 14.0	0.0 - 10.0	1.0 - 9.2	0.0 - 14.0
BASMI - occiput-to-wall distance (cm)				
n	123	123	121	367
Mean	5.18	5.36	4.84	5.13
SD	5.791	7.496	6.176	6.516
Median	3.00	2.00	2.50	3.00
Min - Max	0.0 - 23.0	0.0 - 33.1	0.0 - 29.0	0.0 - 33.1
MASES				
n	124	125	122	371
Mean	3.89	4.02	4.17	4.03
SD	3.770	4.029	4.109	3.963
Median	3.00	3.00	3.00	3.00
Min - Max	0.0 - 13.0	0.0 - 13.0	0.0 - 13.0	0.0 - 13.0
hs C-reactive protein (mg/L)				
n	124	125	121	370
Mean	17.63	17.04	16.91	17.19
SD	23.822	22.246	22.305	22.745
Median	9.20	7.40	7.90	8.10
Min - Max	0.4 - 139.7	0.2 - 147.7	0.2 - 146.8	0.2 - 147.7

Background Characteristics	AIN457 10mg/kg - 75 mg N=124	AIN457 10mg/kg - 150 mg N=125	Placebo N=122	Total N=371
Erythrocyte sedimentation rate (mm/h)				
N	122	124	121	367
Mean	35.3	33.7	31.2	33.4
SD	26.60	26.02	24.25	25.63
Median	28.0	29.0	24.0	26.0
Min - Max	1 - 130	0 - 137	0 - 110	0 - 137
HLA-B27				
Negative	19 (15.3)	32 (25.6)	21 (17.2)	72 (19.4)
Positive	99 (79.8)	86 (68.8)	90 (73.8)	275 (74.1)
Indeterminate	1 (0.8)	2 (1.6)	0 (0.0)	3 (0.8)
Missing	5 (4.0)	5 (4.0)	11 (9.0)	21 (5.7)
Naive to TNF-α inhibitors				
No	34 (27.4)	33 (26.4)	33 (27.0)	100 (27.0)
Yes	90 (72.6)	92 (73.6)	89 (73.0)	271 (73.0)
Number of prior TNF-α inhibitors*				
=0	90 (72.6)	92 (73.6)	89 (73.0)	271 (73.0)
=1	33 (26.6)	30 (24.0)	33 (27.0)	96 (25.9)
≥2	1 (0.8)	3 (2.4)	0 (0.0)	4 (1.1)
Time since first diagnosis of AS (years)				
N	123	125	122	370
Mean	7.938	6.538	8.339	7.597
SD	9.7301	6.9313	8.8589	8.5896
Median	4.988	4.090	5.844	5.039
Min - Max	0.00 - 56.82	0.00 - 32.65	0.00 - 47.18	0.00 - 56.82
Methotrexate use at randomization				
No	102 (82.3)	108 (86.4)	106 (86.9)	316 (85.2)
Yes	22 (17.7)	17 (13.6)	16 (13.1)	55 (14.8)
Dose of methotrexate at randomization (mg/week)				
n	22	15	16	53
Mean	13.64	14.08	12.63	13.46
SD	5.160	6.382	3.594	5.078
Median	11.25	10.00	13.75	12.50
Min - Max	7.5 - 25.0	3.8 - 25.0	7.5 - 20.0	3.8 - 25.0
Sulfasalazine use at randomization				
No	84 (67.7)	83 (66.4)	80 (65.6)	247 (66.6)
Yes	40 (32.3)	42 (33.6)	42 (34.4)	124 (33.4)
Dose of sulfasalazine at randomization (g/day)				
n	36	42	40	118
Mean	1.51	1.81	1.69	1.68
SD	0.514	0.584	0.814	0.659
Median	1.75	2.00	2.00	2.00
Min - Max	0.5 - 2.0	1.0 - 3.0	0.0 - 3.0	0.0 - 3.0

Background Characteristics	AIN457 10mg/kg - 75 mg N=124	AIN457 10mg/kg - 150 mg N=125	Placebo N=122	Total N=371
Corticosteroid use at randomization				
No	109 (87.9)	106 (84.8)	106 (86.9)	321 (86.5)
Yes	15 (12.1)	19 (15.2)	16 (13.1)	50 (13.5)
Dose of corticosteroid at randomization (mg/day)				
n	12	15	13	40
Mean	7.88	6.77	7.19	7.24
SD	3.248	2.321	2.411	2.629
Median	10.00	5.00	6.00	5.50
Min - Max	2.0 - 12.5	5.0 - 10.0	5.0 - 10.0	2.0 - 12.5
MNYC1: Low back pain for at least 3 months duration improved by exercise and not relieved by rest				
No	1 (0.8)	1 (0.8)	0 (0.0)	2 (0.5)
Yes	122 (98.4)	124 (99.2)	122 (100.0)	368 (99.2)
Missing	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)
MNYC2: Limitation of lumbar spine motion in sagittal and frontal planes				
No	10 (8.1)	16 (12.8)	13 (10.7)	39 (10.5)
Yes	113 (91.1)	109 (87.2)	109 (89.3)	331 (89.2)
Missing	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)
MNYC3: Chest expansion decreased relative to normal values for age and sex				
No	36 (29.0)	40 (32.0)	38 (31.1)	114 (30.7)
Yes	87 (70.2)	84 (67.2)	84 (68.9)	255 (68.7)
Missing	1 (0.8)	1 (0.8)	0 (0.0)	2 (0.5)
MNYC4: Unilateral sacroiliitis grade 3-4 on x-ray				
No	100 (80.6)	97 (77.6)	98 (80.3)	295 (79.5)
Yes	23 (18.5)	28 (22.4)	24 (19.7)	75 (20.2)
Missing	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)
MNYC5: Bilateral sacroiliitis grade 2-4 on x-ray				
No	10 (8.1)	17 (13.6)	10 (8.2)	37 (10.0)
Yes	113 (91.1)	108 (86.4)	112 (91.8)	333 (89.8)
Missing	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)

* Started before first dose of study treatment

Numbers analysed

The analysis sets were defined as follows:

- Randomized set comprised randomized patients
- FAS comprised all patients who were randomized and to whom study treatment had been assigned. The efficacy analyses are based on the FAS.
- Safety set comprised all patients who received at least one dose of study treatment during the treatment period. The safety analyses are based on the Safety set.
- Per-protocol set included all patients who completed the study without a major protocol deviation leading to exclusion from the Per-protocol set.

The analysis sets by treatment sequence are presented in **Table 15**.

Table 15. Analysis sets by treatment sequence (Randomized set, Study F2305)

Analysis Set	AIN457 10 mg/kg - 75 mg	AIN457 10 mg/kg - 150 mg	Placebo	Placebo Non-Resp - AIN457 75 mg	Placebo Non-Resp - AIN457 150 mg	Placebo Resp - AIN457 75 mg	Placebo Resp - AIN457 150 mg
Randomized set	124	125	122	39	38	17	18
Full analysis set	124	125	122	39	38	17	18
Per protocol set	105	105	105	34	31	15	16
Safety set	124	125	122	39	38	17	18
Treated with AIN457 after re-randomization			111	39	38	16	18

Placebo column includes patients randomized to placebo at baseline 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

Primary endpoint

The results of the primary efficacy variable ASAS20 response using non-responder imputation for the FAS at Week 16 are shown in **Table 16**.

Table 16. ASAS 20 response using non-responder imputation – up to Week 24 (Full analysis set, Study F2305)

Analysis visit	Treatment Group	n/M (%)	Comparison	Odds ratio	95% Confidence Interval	p-value
Week 1	AIN457 10 mg/kg - 75 mg (N = 124)	45/124 (36.3)	vs. Placebo	3.13	(1.69, 5.78)	0.0003
	AIN457 10 mg/kg - 150 mg (N = 125)	39/125 (31.2)	vs. Placebo	2.45	(1.32, 4.56)	0.0047
	Placebo (N = 122)	19/122 (15.6)				
Week 2	AIN457 10 mg/kg - 75 mg (N = 124)	51/124 (41.1)	vs. Placebo	2.76	(1.56, 4.88)	0.0005
	AIN457 10 mg/kg - 150 mg (N = 125)	48/125 (38.4)	vs. Placebo	2.44	(1.38, 4.33)	0.0023
	Placebo (N = 122)	25/122 (20.5)				
Week 4	AIN457 10 mg/kg - 75 mg (N = 124)	65/124 (52.4)	vs. Placebo	2.89	(1.69, 4.93)	<0.0001
	AIN457 10 mg/kg - 150 mg (N = 125)	60/125 (48.0)	vs. Placebo	2.42	(1.42, 4.13)	0.0012
	Placebo (N = 122)	34/122 (27.9)				
Week 8	AIN457 10 mg/kg - 75 mg (N = 124)	76/124 (61.3)	vs. Placebo	3.40	(1.99, 5.79)	<0.0001
	AIN457 10 mg/kg - 150 mg (N = 125)	67/125 (53.6)	vs. Placebo	2.41	(1.42, 4.07)	0.0010
	Placebo (N = 122)	40/122 (32.8)				
Week 12	AIN457 10 mg/kg - 75 mg (N = 124)	70/124 (56.5)	vs. Placebo	2.72	(1.61, 4.59)	0.0002
	AIN457 10 mg/kg - 150 mg (N = 125)	70/125 (56.0)	vs. Placebo	2.66	(1.57, 4.49)	0.0003
	Placebo (N = 122)	40/122 (32.8)				
Week 16	AIN457 10 mg/kg - 75 mg (N = 124)	74/124 (59.7)	vs. Placebo	3.76	(2.20, 6.42)	<0.0001
	AIN457 10 mg/kg - 150 mg (N = 125)	76/125 (60.8)	vs. Placebo	3.89	(2.28, 6.65)	<0.0001
	Placebo (N = 122)	35/122 (28.7)				
Week 20	AIN457 10 mg/kg - 75 mg (N = 124)	70/124 (56.5)	vs. Placebo	5.26	(2.96, 9.34)	<0.0001
	AIN457 10 mg/kg - 150 mg (N = 125)	71/125 (56.8)	vs. Placebo	5.33	(3.00, 9.47)	<0.0001
	Placebo (N = 122)	25/122 (20.5)				
Week 24	AIN457 10 mg/kg - 75 mg (N = 124)	64/124 (51.6)	vs. Placebo	4.84	(2.70, 8.69)	<0.0001
	AIN457 10 mg/kg - 150 mg (N = 125)	69/125 (55.2)	vs. Placebo	5.52	(3.07, 9.90)	<0.0001
	Placebo (N = 122)	23/122 (18.9)				

Odds ratio, 95% CI and p-value are from a logistic regression model with treatment and TNF-α inhibitor status as factors and baseline weight as a covariate.
M: The total number of patients in the treatment group.
n: The number of patients who were ASAS20 responders with corresponding imputation approach

Secukinumab at both doses (10 mg/kg-75 mg and 10 mg/kg-150 mg) was statistically significantly superior to placebo for ASAS20 response at Week 16 ($p<0.0001$) regardless of TNFαi status: the ASAS20

response rate was 59.7% for secukinumab 10 mg/kg-75 mg, 60.8% for secukinumab 10 mg/kg-150 mg and 28.7% for placebo.

The ASAS 20 response at Week 16 in the per-protocol analysis set was consistent with that observed in the FAS, with the response rate of 61.9% for secukinumab 10 mg/kg-75 mg, 64.8% for secukinumab 10 mg/kg-150 mg and 30.5% for placebo, respectively (both comparisons, p<0.0001).

Interactions between treatment and selected baseline demographic and disease characteristics were explored for ASAS 20 response at Week 16. Of the baseline covariates tested, only body weight showed a significant interaction with treatment on the ASAS 20 response at Week 16 (p=0.0122). Randomization was not stratified by body weight. The difference in ASAS 20 response in favour of IV-75 mg vs. placebo was consistent across the weight groups (<70 kg, 70-90 kg, >90 kg), but the efficacy of IV-150 mg vs. placebo decreased with increasing body weight.

TNFαi naïve patients showed numerically higher ASAS 20 response rates at Week 16 (60.0% for IV-75 mg and 66.3% for IV-150 mg vs. 32.6% for placebo) compared with the patients with previous insufficient response for TNFαi (TNF-IR) (58.8% for IV-75 mg and 45.5% for IV-150 mg vs. 18.2% for placebo). Consistent with the differences seen in the overall response rates, treatment differences for each secukinumab dose vs. placebo were also statistically significant (p<0.05) for both TNFαi naïve and TNF-IR patients.

Secondary endpoints

Results in terms of secondary efficacy endpoints at week 16 are reported in **Table 17**.

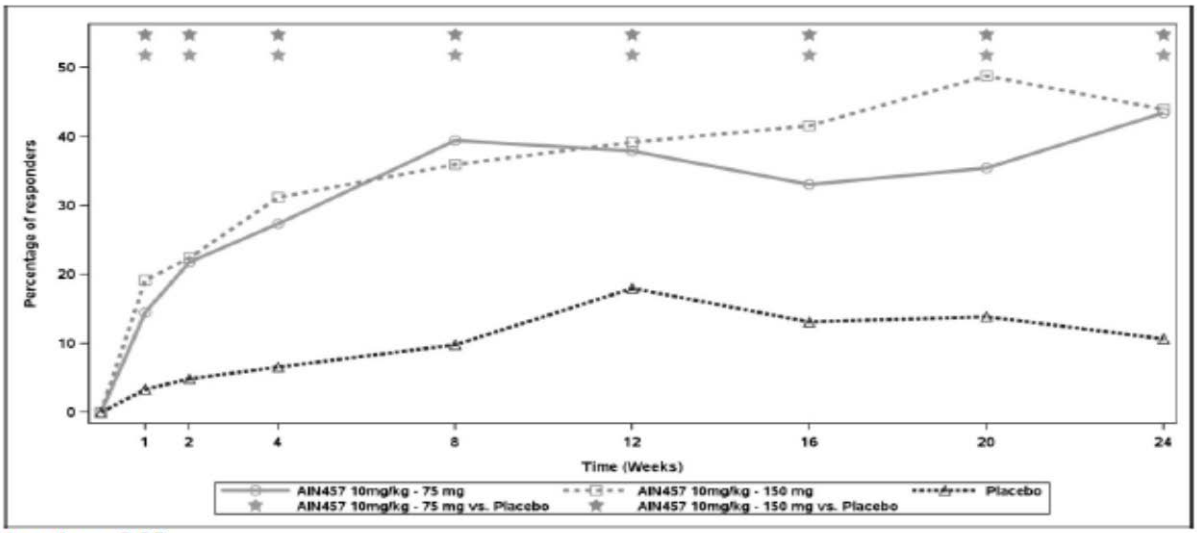
Table 17. Estimates for the primary and secondary efficacy endpoints at Week 16 (Full analysis set, Study F2305)

Variable	AIN457 10mg/kg - 75 mg N=124	AIN457 10mg/kg - 150 mg N=125	Placebo N=122
Primary endpoint: ASAS 20 response	59.7% (p<0.0001)	60.8% (p<0.0001)	28.7%
ASAS 40 response	33.1% (p=0.0003)	41.6% (p<0.0001)	13.1%
hsCRP (ratio: post-BSL/BSL)	0.45 (p<0.0001)	0.40 (p<0.0001)	0.97
ASAS 5/6 response	45.2% (p<0.0001)	48.8% (p<0.0001)	13.1%
BASDAI change from baseline	−2.34 (p<0.0001)	−2.32 (p<0.0001)	−0.59
SF-36 PCS change from baseline	5.64 (p<0.0001)	5.57 (p<0.0001)	0.96
ASQoL change from baseline	−3.61 (p<0.0001)	−3.58 (p<0.0001)	−1.04
ASAS partial remission	16.1% (p=0.0020)	15.2% (p=0.0033)	3.3%

BSL = baseline

ASAS 40 responses up to week 24 are presented in **Figure 7**.

Figure 7. ASAS 40 response using non-responder imputation – up to Week 24 (Full analysis set, Study F2305)



*p-value < 0.05

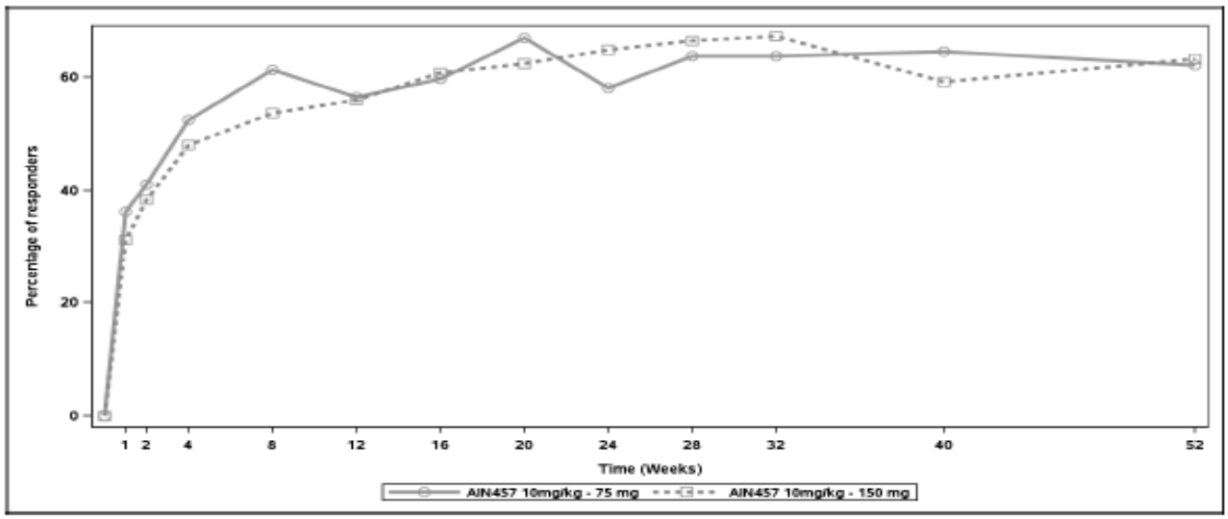
The ASAS 40 response varied over time among the TNF-IR patients: both doses were associated with higher rates than placebo at Weeks 8 and 20 (both time-points, $p<0.05$), while only the IV-75 mg dose was higher than placebo at Weeks 12 and 16 (both time-points, $p<0.05$).

Similar results favouring secukinumab vs. placebo were observed up to Week 24 for the secondary endpoints.

Selected exploratory efficacy analyses

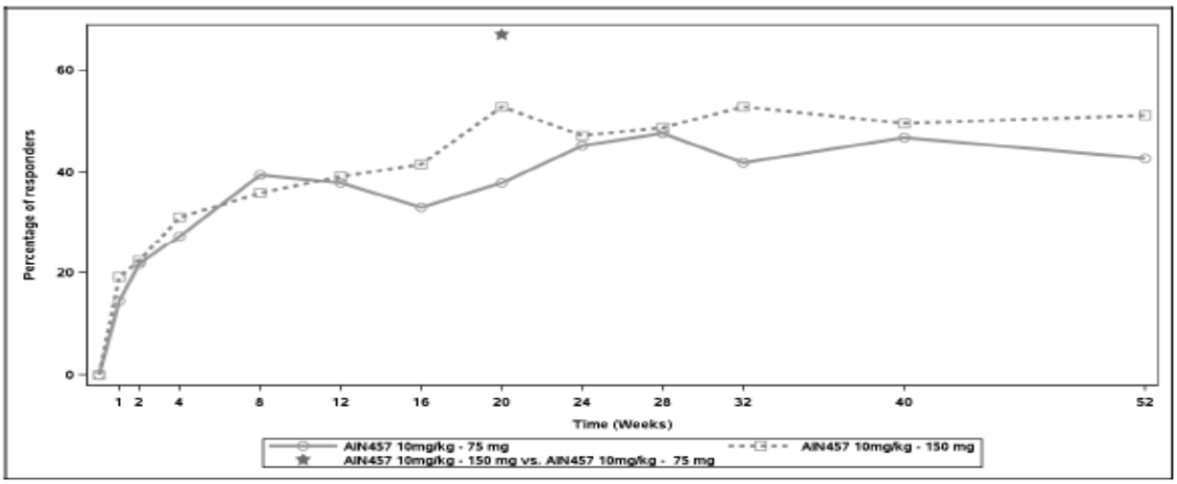
The rates of ASAS 20 response observed for both secukinumab dose groups at the Week 16 primary endpoint analysis visit were sustained through Week 52 and ASAS 20 responses were comparable between the two secukinumab dose groups at all analysis visits through Week 52 (**Figure 8**).

Figure 8. AS 20 response using non-responder imputation – up to Week 52 (Full analysis set, Study F2305)



The ASAS 40 response rates achieved in both secukinumab dose groups at the Week 16 primary endpoint analysis visit were sustained through Week 52 (see **Figure 9**) and the two secukinumab dose groups showed comparable ASAS 40 response rates at all time-points through Week 52.

Figure 9. ASAS 40 response using non-responder imputation – up to Week 52 (Full analysis set, Study F2305)



Among the placebo non-responders, the ASAS 20 and ASAS 40 responses increased after switch to active treatment at Week 16: at Week 32 the ASAS 20 response rates were 56.4% for the placebo non-responders on 75 mg secukinumab and 50.0% for the placebo non-responders on 150 mg secukinumab, respectively. At Week 52, the corresponding response rates were 61.5% (24/39) and 47.4% (18/38).

There were no treatment differences between the secukinumab dose groups through Week 52 in other secondary efficacy variables, including ASAS 5/6 response, ASAS partial remission, and changes from baseline in hsCRP, total BASDAI, SF-36 PCS and ASQoL. Comparable levels of response were sustained from Weeks 24 to 52 in both secukinumab groups.

Secukinumab was superior to placebo in the change from baseline in BASMI linear score at most time-points up to Week 24. At Week 16, the LS mean change from baseline was −0.34 for IV-75 mg (p=0.0502) and −0.40 for IV-150 mg (p=0.0114) vs. −0.12 for placebo.

At Week 16, the change from baseline in lateral spinal flexion component (score), one of the six ASAS domains used to determine the ASAS 5/6 response, was −0.529 for IV-75 mg and −0.462 for IV-150 mg vs. −0.312 for placebo. MRI of the spine and sacroiliac joints was performed on a subset of TNF-αi naïve patients at selected study sites (34 patients in the IV-75 mg group; 38 patients in the IV-150 mg group; and 33 patients in the placebo group), with analysis of the following 3 MRI variables: Berlin sacroiliac joint total edema score, total ASspi-MRI-a score, and Berlin spine score. The change from baseline at Week 16 is reported in **Table 18**.

Table 18. MRI measurements at baseline, Week 16 and change from baseline (MRI subset of TNF-alpha inhibitor naïve patients, Study F2305)

MRI variable	n	Baseline (mean ± SD)	Week 16 (mean ± SD)	Change from baseline (mean ± SD)	p-value for comparison vs. placebo
Berlin sacroiliac joint total edema score					
10 mg/kg – 75 mg (N=34)	30	1.67 ± 2.551	0.62 ± 0.971	−1.05 ± 2.090	0.0024
10 mg/kg – 150 mg (N=38)	32	2.22 ± 3.377	0.92 ± 1.783	−1.30 ± 2.170	0.0013
Placebo (N=33)	26	2.40 ± 3.240	2.23 ± 3.238	−0.17 ± 1.232	
Total ASspi-MRI-a score					
10 mg/kg – 75 mg (N=34)	30	6.37 ± 10.757	2.93 ± 6.403	−3.43 ± 6.315	0.0027
10 mg/kg – 150 mg (N=38)	32	2.70 ± 3.801	1.58 ± 3.869	−1.13 ± 1.675	0.0790
Placebo (N=33)	28	5.73 ± 9.748	5.07 ± 8.600	−0.66 ± 2.553	
Berlin spine score					
10 mg/kg – 75 mg (N=34)	30	5.02 ± 7.580	2.48 ± 5.410	−2.53 ± 4.096	0.0063
10 mg/kg – 150 mg (N=38)	32	2.23 ± 2.826	1.16 ± 2.474	−1.08 ± 1.403	0.0570
Placebo (N=33)	28	4.50 ± 7.617	3.95 ± 6.820	−0.55 ± 2.447	

MRI Subset: a subgroup of patients who have MRI performed at selected centers.
TNF-IR patients who had MRI performed at baseline and post-baseline are not included in this table

Study F2310

Study F2310 was a randomized, double-blind, placebo-controlled phase III multicentre study of subcutaneous secukinumab in prefilled syringes to demonstrate the efficacy at 16 weeks and to assess the long-term efficacy, safety and tolerability up to 5 years in patients with active ankylosing spondylitis (Report date 26 November 2014)

Methods

Study participants

The inclusion and exclusion criteria were identical to Study F2305.

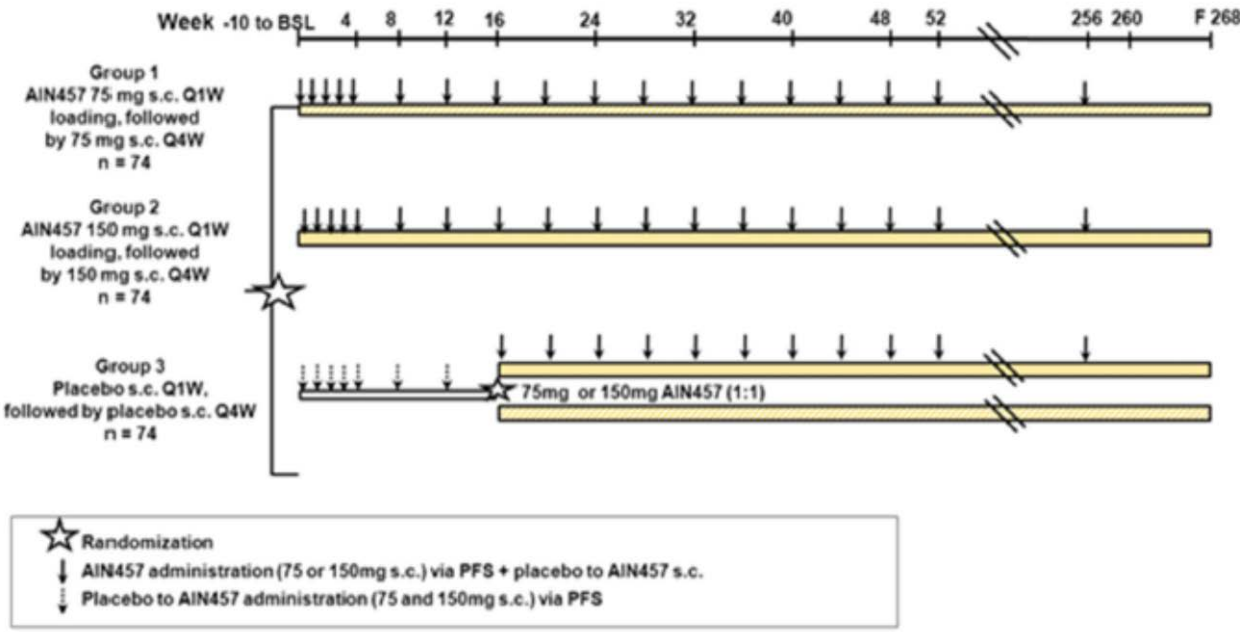
Treatment

The study design is presented in **Figure 10**.

A screening period of 4-10 weeks before randomization was followed by a blinded treatment period of 52 weeks and an additional long-term treatment of 4 years. At baseline, patients were randomized (1:1:1) to one of the three treatment groups:

- Group 1: secukinumab 75 mg plus placebo 150 mg once weekly at baseline, Weeks 1, 2, 3 and 4, followed by dosing every four weeks starting at Week 4.
- Group 2: secukinumab 150 mg plus placebo 75 mg once weekly at BSL, Weeks 1, 2, 3 and 4, followed by dosing every four weeks starting at Week 4.
- Group 3: placebo 75 mg and placebo 150 mg once weekly at BSL, Weeks 1, 2, 3 and 4, followed by dosing every four weeks starting at Week 4.

Figure 10. Design of Study F2310



At Week 16 (Visit 8), all patients on placebo were re-randomized to receive secukinumab 75 mg plus placebo 150 mg sc or 150 mg secukinumab plus 75 mg placebo sc. After Week 52 analyses were conducted, the study personnel and patients were un-blinded to treatment, i.e., the placebo injections were discontinued. Rescue treatment was not allowed until Week 20.

Objectives

The primary, secondary, and exploratory objectives were identical with those of Study F2305, with exception of the assessment of treatment on radiographic findings and bone mineral density, not investigated in Study F2310.

Outcomes / endpoints

The primary and the secondary efficacy variables as well as safety and other assessments were identical to those of Study F2305, except that assessment of joint/bone structural damage was not performed.

Sample size

An overall type I error (2-sided) 5% was used to control type I error. Since two secukinumab doses were tested versus placebo with respect to the primary endpoint (ASAS20 response at Week 16), the type-I-error was split to 2.5% two-sided for each comparison. For 90% power and assuming a response rate of 20% in the placebo group, at least 39 subjects per group were needed to show a response rate of 60% in the secukinumab groups based on Fisher's exact test. In this study population, a placebo response rate of about 20% after 14 weeks has been reported.

In order to collect additional safety information on the use of secukinumab in this population, 222 subjects were equally allocated to three treatment groups (74 subjects in each treatment group), stratifying for prior treatment or not with TNFai treatment. The study had at least 60% TNFai treatment naive subjects. The power of the test for the primary endpoint based on 74 subjects per group was over 99%.

Randomisation

At baseline (Visit 2), all eligible patients were randomized in a ratio to 1:1:1 to one of the treatment arms. The patients were stratified according to being either TNF-IR or TNF-αi naïve status. Approximately 40% of the patients had to be TNF-IR to ensure a representative patient population for the assessment of efficacy and safety.

Blinding (masking)

This was a double-blind study.

Statistical methods

Refer to evaluation of study F2305.

Results

Participant flow

A total of 253 patients were screened, and 219 of these patients completed the screening phase and were randomized to study treatment. The most common reasons for not completing the screening phase were screen failure (10.3%) and subject/guardian decision (2.4%).

The patient disposition up to Week 16 and Week 52 is reported in **Table 19** and **Table 20**, respectively.

Table 19. Patient disposition – up to Week 16 (Randomized set, Study F2310)

Disposition /Reason	AIN457 75 mg N = 73 n (%)	AIN457 150 mg N = 72 n (%)	Any AIN457 N = 145 n (%)	Placebo N = 74 n (%)
Randomized	73	72	145	74
Completed week 1-16	68 (93.2)	66 (91.7)	134 (92.4)	66 (89.2)
Discontinued week 1-16	5 (6.8)	6 (8.3)	11 (7.6)	8 (10.8)
Adverse event	2 (2.7)	5 (6.9)	7 (4.8)	4 (5.4)
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-compliance with study treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Physician decision	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No longer requires treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Technical problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject/guardian decision	2 (2.7)	1 (1.4)	3 (2.1)	2 (2.7)
Death	1 (1.4)	0 (0.0)	1 (0.7)	0 (0.0)

Table 20. Patient disposition – up to Week 52 (Randomized set, Study F2310)

Disposition /Reason	AIN457 75 mg N = 73 n (%)	AIN457 150 mg N = 72 n (%)	Placebo total N = 74 n (%)	Placebo - AIN457 75 mg N = 32 n (%)	Placebo - AIN457 150 mg N = 34 n (%)
Randomized	73	72	74	32	34
Completed week 1-52	60 (82.2)	61 (84.7)	60 (81.1)	28 (87.5)	32 (94.1)
Discontinued week 1-52	13 (17.8)	11 (15.3)	14 (18.9)	4 (12.5)	2 (5.9)
Adverse event	3 (4.1)	6 (8.3)	4 (5.4)	0 (0.0)	0 (0.0)
Lack of efficacy	4 (5.5)	3 (4.2)	6 (8.1)	4 (12.5)	1 (2.9)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-compliance with study treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Physician decision	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No longer requires treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Technical problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject/guardian decision	5 (6.8)	2 (2.8)	3 (4.1)	0 (0.0)	1 (2.9)
Death	1 (1.4)	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: 18 October 2012 (first patient first visit).

Study completion date: Not applicable. All patients had completed the Visit 17 on Week 52 before the conduct of the current interim analysis (data cut-off date 4 August 2014).

There were 54 study centres in 13 countries: Austria (2), Canada (4), Czech Rep (4), Finland (5), Germany (3), Italy (3), Netherlands (2), Russian Federation (7), Singapore (2), Spain (4), Switzerland (3), United Kingdom (4) and United States (11).

Conduct of the study

The study protocol was amended once (22 November 2013).

The following changes were made to the planned analysis:

- To limit the blinded period of study medication for patients to 52 weeks.
- To expand the statistical hierarchy (primary plus ranked secondary variables) to include more endpoints which are relevant to determining the overall therapeutic value of a therapy for AS and to include also the TNF-IR patients in the FAS population.
- To align the primary and secondary assessments with the ASAS Handbook.
- To limit the blinding for study medication for sponsor to 16 weeks (the time point for assessment of primary efficacy endpoint).

Comparable proportions of patients across the secukinumab and placebo groups had at least one protocol deviation up to Week 16 (28.8% vs. 26.4% vs. 29.7% in the secukinumab 75 mg, secukinumab 150 mg and placebo groups, respectively) or up to Week 52 (34.2% vs. 29.2% vs. 33.8% in the secukinumab 75 mg, secukinumab 150 mg and placebo groups, respectively). The most common category of protocol deviations in both analysis periods (n=40 and n=45, respectively) with no difference in the occurrence between the groups was “Treatment deviation”. Vast majority of these cases were related with premature

administration of study during the first 4 weeks of the Study i.e., less than 7 days after the previous administration. No patient had a protocol deviation that led to exclusion from the FAS or Safety set. A small proportion of patients in all treatment groups had a protocol deviation that led to exclusion from the Per-protocol set, most of these protocol deviations were in the categories of 'Selection criteria not met' (n=6)(i.e.,, patient did not meet BASDAI criteria at baseline) and "Treatment deviation" (n=4) (I.e., incorrect study medication given).

Baseline data

The majority of the patients (96.8%) were < 65 years of age, with a median ranging from 41.0 years (secukinumab 150 mg group) to 46.0 years (secukinumab 75 mg group). Approximately two thirds (69.9%) of the patients were male. The vast majority of the patients (95.4%) were of Caucasian origin. The prevalence of current smoking was 32.9% and the mean BMI 27.5 kg/m^2, with no significant differences between the randomized groups. The prevalence of verified HLA-B27 positivity varied between 72.6% and 79.2% in the randomized groups.

Disease history and baseline characteristics are reported in **Table 21**.

Table 21. Disease history and baseline characteristics by randomized treatment (Randomized set, Study F2310)

Background Characteristics	AIN457 75 mg N=73	AIN457 150 mg N=72	Placebo N=74	Total N=219
Patient's global assessment of disease activity (0-100 mm)				
N	73	72	74	219
Mean	64.6	67.5	70.5	67.5
SD	17.88	16.84	15.75	16.94
Median	64.0	68.0	72.0	67.0
Min – Max	1 - 99	31 - 99	28 - 100	1 - 100
Total back pain (0-100 mm)				
N	73	72	74	219
Mean	65.1	66.2	69.2	66.8
SD	17.65	16.67	18.83	17.75
Median	66.0	68.0	70.0	68.0
Min – Max	22 - 97	22 - 99	0 - 100	0 - 100

Background Characteristics	AIN457 75 mg N=73	AIN457 150 mg N=72	Placebo N=74	Total N=219
Nocturnal back pain (0-100 mm)				
N	73	72	74	219
Mean	61.8	65.9	64.0	63.9
SD	20.75	17.15	21.76	19.98
Median	65.0	68.0	68.0	66.0
Min – Max	4 - 97	0 - 99	0 - 100	0 - 100
BASFI				
N	73	72	73	218
Mean	5.98	6.22	6.10	6.10

SD	2.132	2.133	2.007	2.084
Median	6.27	6.74	6.34	6.40
Min – Max	1.0 - 9.7	1.4 - 9.9	0.1 - 9.5	0.1 - 9.9
BASDAI				
N	73	72	74	219
Mean	6.57	6.59	6.78	6.65
SD	1.272	1.471	1.280	1.341
Median	6.50	6.83	6.93	6.74
Min – Max	2.4 - 9.6	3.2 - 10.0	4.0 - 9.5	2.4 - 10.0
BASMI (linear)				
N	71	71	70	212
Mean	3.92	3.61	3.91	3.81
SD	1.689	1.937	1.622	1.753
Median	3.89	3.61	4.17	3.90
Min – Max	0.3 - 7.8	0.2 - 7.8	0.4 - 7.2	0.2 - 7.8
BASMI - lateral spinal flexion (cm)				
N	72	71	72	215
Mean	10.88	12.28	11.29	11.48
SD	6.848	5.721	6.988	6.543
Median	9.78	11.40	10.65	10.50
Min – Max	2.0 - 48.0	2.5 - 26.0	0.0 - 47.5	0.0 - 48.0
BASMI - tragus to wall distance (cm)				
N	72	72	73	217
Mean	14.81	13.73	14.82	14.45
SD	5.347	4.873	5.277	5.172
Median	12.55	12.00	13.50	12.50
Min - Max	9.0 - 30.0	6.0 - 28.0	7.0 - 33.0	6.0 - 33.0
BASMI - lumbar flexion (modified Schober, cm)				
N	72	72	72	216
Mean	4.14	4.26	3.79	4.06
SD	2.072	2.328	1.931	2.116
Median	4.00	4.10	3.65	4.00
Min - Max	0.0 - 10.0	0.0 - 10.0	0.4 - 8.1	0.0 - 10.0

Background Characteristics	AIN457 75 mg N=73	AIN457 150 mg N=72	Placebo N=74	Total N=219
BASMI - maximal intermalleolar distance (cm)				
N	73	72	74	219
Mean	95.37	95.87	96.52	95.93
SD	26.418	30.008	25.481	27.229
Median	96.00	97.50	97.50	97.00
Min - Max	36.0 - 158.5	11.6 - 153.0	25.0 - 149.0	11.6 - 158.5
BASMI - cervical rotation angle (degrees)				
N	73	72	74	219
Mean	51.62	53.28	54.11	53.01
SD	20.997	22.872	18.684	20.832
Median	52.50	52.00	53.50	52.50
Min - Max	7.0 - 90.0	7.0 - 90.0	6.0 - 90.0	6.0 - 90.0
BASMI - chest expansion (cm)				
N	73	72	74	219
Mean	3.24	3.62	3.87	3.58
SD	1.548	1.961	1.891	1.819
Median	3.00	3.40	4.00	3.50
Min - Max	0.0 - 7.0	0.0 - 8.5	0.2 - 10.0	0.0 - 10.0
BASMI - occiput-to-wall distance (cm)				
N	73	72	74	219
Mean	4.95	3.38	4.65	4.33
SD	5.520	5.078	6.295	5.674
Median	4.00	0.00	3.00	2.00
Min - Max	0.0 - 21.0	0.0 - 20.0	0.0 - 30.0	0.0 - 30.0
MASES				
N	73	72	74	219
Mean	3.40	4.04	3.70	3.71
SD	3.192	4.085	3.659	3.654
Median	3.00	3.00	2.00	3.00
Min - Max	0.0 - 11.0	0.0 - 13.0	0.0 - 13.0	0.0 - 13.0

hs C-reactive protein (mg/L)				
N	73	72	74	219
Mean	15.33	25.80	15.71	18.90
SD	19.813	50.088	18.498	32.936
Median	5.70	7.50	8.30	7.30
Min - Max	0.5 - 86.2	0.4 - 237.0	0.5 - 84.6	0.4 - 237.0

Background Characteristics	AIN457 75 mg N=73	AIN457 150 mg N=72	Placebo N=74	Total N=219
Erythrocyte sedimentation rate (mm/h)				
N	73	72	74	219
Mean	28.6	33.9	29.5	30.7
SD	20.61	24.76	17.76	21.24
Median	24.0	29.0	28.0	28.0
Min - Max	0 - 78	0 - 125	2 - 80	0 - 125
HLA-B27				
Negative	15 (20.5)	12 (16.7)	11 (14.9)	38 (17.4)
Positive	53 (72.6)	57 (79.2)	58 (78.4)	168 (76.7)
Missing	5 (6.8)	3 (4.2)	5 (6.8)	13 (5.9)
Naive to TNF alpha inhibitors				
No	28 (38.4)	28 (38.9)	29 (39.2)	85 (38.8)
Yes	45 (61.6)	44 (61.1)	45 (60.8)	134 (61.2)
Number of prior TNF alpha inhibitors				
=0	45 (61.6)	44 (61.1)	45 (60.8)	134 (61.2)
=1	28 (38.4)	27 (37.5)	29 (39.2)	84 (38.4)
>=2	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.5)
Time since first diagnosis of AS (years)				
N	72	70	73	215
Mean	5.273	6.978	6.371	6.201
SD	7.3664	8.2307	8.9380	8.1989
Median	2.747	3.781	2.779	2.894
Min - Max	0.00 - 28.59	0.00 - 32.70	0.00 - 37.89	0.00 - 37.89
Methotrexate use at randomization				
No	64 (87.7)	64 (88.9)	65 (87.8)	193 (88.1)
Yes	9 (12.3)	8 (11.1)	9 (12.2)	26 (11.9)
Dose of methotrexate at randomization (mg/week)				
N	9	7	9	25
Mean	13.33	15.00	13.61	13.90
SD	2.500	2.887	4.167	3.234
Median	15.00	15.00	12.50	15.00
Min - Max	10.0 - 15.0	10.0 - 20.0	10.0 - 20.0	10.0 - 20.0
Sulfasalazine use at randomization				

No	61 (83.6)	62 (86.1)	65 (87.8)	188 (85.8)
Yes	12 (16.4)	10 (13.9)	9 (12.2)	31 (14.2)
Dose of sulfasalazine at randomization (g/day)				
N	12	9	9	30
Mean	2.13	2.11	2.33	2.18
SD	0.433	1.054	1.000	0.815
Median	2.00	2.00	2.00	2.00
Min - Max	1.5 - 3.0	1.0 - 4.0	1.0 - 4.0	1.0 - 4.0

Background Characteristics	AIN457 75 mg N=73	AIN457 150 mg N=72	Placebo N=74	Total N=219
Corticosteroid use at randomization				
No	66 (90.4)	68 (94.4)	67 (90.5)	201 (91.8)
Yes	7 (9.6)	4 (5.6)	7 (9.5)	18 (8.2)
Dose of corticosteroid at randomization (mg/day)				
N	5	4	6	15
Mean	6.50	3.75	9.17	6.83
SD	2.236	1.443	2.041	2.907
Median	5.00	3.75	10.00	5.00
Min - Max	5.0 - 10.0	2.5 - 5.0	5.0 - 10.0	2.5 - 10.0
MNYC1: Low back pain for at least 3 months duration improved by exercise and not relieved by rest				
No	1 (1.4)	0 (0.0)	2 (2.7)	3 (1.4)
Yes	72 (98.6)	72 (100.0)	72 (97.3)	216 (98.6)
MNYC2: Limitation of lumbar spine motion in sagittal and frontal planes				
No	7 (9.6)	10 (13.9)	8 (10.8)	25 (11.4)
Yes	66 (90.4)	62 (86.1)	66 (89.2)	194 (88.6)
MNYC3: Chest expansion decreased relative to normal values for age and sex				
No	21 (28.8)	25 (34.7)	29 (39.2)	75 (34.2)
Yes	52 (71.2)	46 (63.9)	45 (60.8)	143 (65.3)
Missing	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.5)
MNYC4: Unilateral sacroiliitis grade 3-4 on x-ray				
No	64 (87.7)	59 (81.9)	66 (89.2)	189 (86.3)
Yes	9 (12.3)	13 (18.1)	8 (10.8)	30 (13.7)
MNYC5: Bilateral sacroiliitis grade 2-4 on x-ray				
No	5 (6.8)	5 (6.9)	7 (9.5)	17 (7.8)
Yes	68 (93.2)	67 (93.1)	67 (90.5)	202 (92.2)

Numbers analysed

The analysis sets were defined as follows:

- Randomised set comprised randomized patients
- FAS comprised all patients who were randomized and to whom study treatment had been assigned. The efficacy analyses are based on the FAS.
- Safety set comprised all patients who received at least one dose of study treatment during the treatment period. The safety analyses are based on the Safety set.
- Per-protocol set included all patients who completed the study without a major protocol deviation leading to exclusion from the FAS.

The analysis sets by treatment sequence are presented in **Table 22**.

Table 22. Analysis sets by treatment sequence (Randomised set, Study F2310)

Analysis Set	AIN457 75 mg	AIN457 150 mg	Placebo	Placebo - AIN457 75 mg	Placebo - AIN457 150 mg
Randomized set	73	72	74	32	34
Full analysis set	73	72	74	32	34
Per protocol set	71	67	71	31	32
Safety set	73	72	74	32	34
Treated with AIN457 after re-randomization			66	32	34

Placebo column includes 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 column only.

Outcomes and estimation

Primary endpoint

The results of the primary efficacy variable ASAS20 response using non-responder imputation for the FAS at Week 16 are shown in **Table 23**.

Table 23. ASAS 20 response using non-responder imputation – up to Week 16 (Full analysis set, Study F2310)

Analysis visit	Treatment Group	n/M (%)	Comparison	Odds ratio	95% Confidence Interval	p-value, unadjusted
Week 1	AIN457 75 mg (N = 73)	19/73 (26.0)	vs. Placebo	4.04	(1.51, 10.85)	0.0056
	AIN457 150 mg (N = 72)	15/72 (20.8)	vs. Placebo	3.05	(1.11, 8.39)	0.0312
	Placebo (N = 74)	6/74 (8.1)				
Week 2	AIN457 75 mg (N = 73)	25/73 (34.2)	vs. Placebo	4.32	(1.79, 10.41)	0.0011
	AIN457 150 mg (N = 72)	28/72 (38.9)	vs. Placebo	5.31	(2.21, 12.74)	0.0002
	Placebo (N = 74)	8/74 (10.8)				
Week 3	AIN457 75 mg (N = 73)	23/73 (31.5)	vs. Placebo	1.54	(0.74, 3.23)	0.2486
	AIN457 150 mg (N = 72)	37/72 (51.4)	vs. Placebo	3.61	(1.76, 7.40)	0.0005
	Placebo (N = 74)	17/74 (23.0)				
Week 4	AIN457 75 mg (N = 73)	28/73 (38.4)	vs. Placebo	1.93	(0.95, 3.93)	0.0701
	AIN457 150 mg (N = 72)	38/72 (52.8)	vs. Placebo	3.47	(1.71, 7.03)	0.0006
	Placebo (N = 74)	18/74 (24.3)				
Week 8	AIN457 75 mg (N = 73)	38/73 (52.1)	vs. Placebo	5.63	(2.60, 12.17)	<.0001
	AIN457 150 mg (N = 72)	42/72 (58.3)	vs. Placebo	7.28	(3.34, 15.84)	<.0001
	Placebo (N = 74)	12/74 (16.2)				
Week 12	AIN457 75 mg (N = 73)	32/73 (43.8)	vs. Placebo	2.14	(1.07, 4.30)	0.0323
	AIN457 150 mg (N = 72)	41/72 (56.9)	vs. Placebo	3.71	(1.84, 7.48)	0.0003
	Placebo (N = 74)	20/74 (27.0)				
Week 16	AIN457 75 mg (N = 73)	30/73 (41.1)	vs. Placebo	1.82	(0.90, 3.67)	0.0967
	AIN457 150 mg (N = 72)	44/72 (61.1)	vs. Placebo	4.38	(2.14, 8.96)	<.0001
	Placebo (N = 74)	21/74 (28.4)				

Odds ratio, 95% CI and p-value are from a logistic regression model with treatment and TNF-α inhibitor status as factors and baseline weight as a covariate.
n = number of patients who were ASAS20 responders
M = total number of patients in the treatment group with ASAS20 evaluation.
Missing ASAS responders are considered as non-responders

The ASAS 20 response at Week 16 in the Per-protocol Set analysis was consistent with that observed in the FAS, with the response rates of 40.8%, 61.2% and 26.8% for secukinumab 75 mg, secukinumab 150 mg and placebo groups, respectively (for comparison between secukinumab 150 mg and placebo, p<0.0001).

TNFαi naïve patients showed numerically higher ASAS 20 response rates at Week 16 (51.1% for secukinumab 75 mg, 68.2% for secukinumab 150 mg and 31.1% for placebo, respectively) compared with the TNF-IR patients (25.0% for secukinumab 75 mg, 50.0% for secukinumab 150 mg and 24.1% for placebo, respectively).

Secondary endpoints

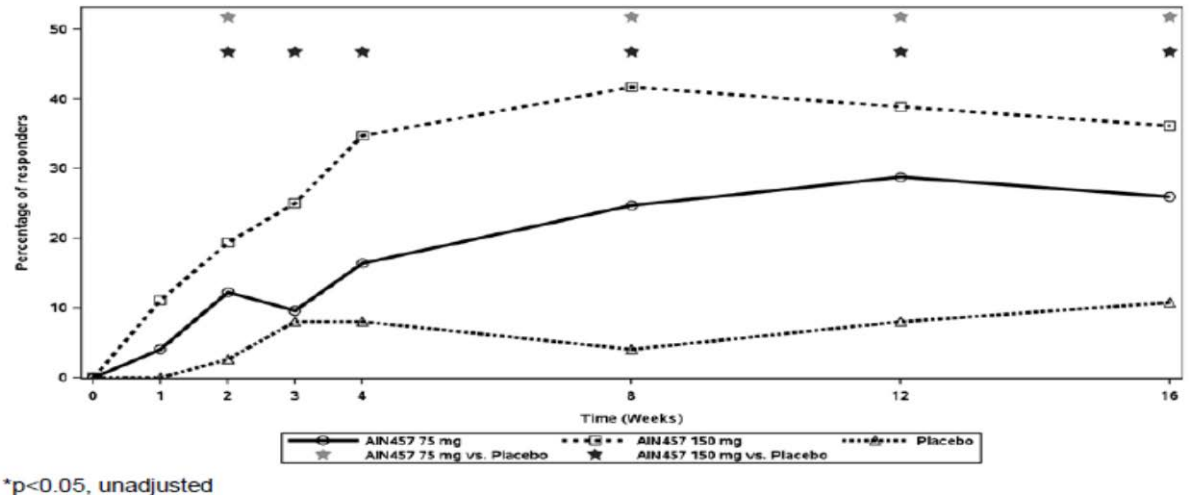
Results in terms of secondary efficacy endpoints are shown in **Table 24** and **Figure 11**.

Table 24. Estimates for the primary and secondary efficacy endpoints at Week 16 (Full analysis set, Study F2310)

Variable	AIN457 75 mg N=73	AIN457 150 mg N=72	Placebo N=74
Primary endpoint: ASAS 20	41.1% (p=0.0967)	61.1% (p=0.0001)*	28.4%
ASAS 40	26.0% (p=0.0967)	36.1% (p=0.0008)*	10.8%
hsCRP (ratio: post-BSL/BSL)	0.61 (p=0.0967)	0.55 (p=0.0008)*	1.13
ASAS 5/6	34.2% (p=0.0967)	43.1% (p=0.0008)*	8.1%
BASDAI change from baseline	−1.92 (p=0.0967)	−2.19 (p=0.0008)*	−0.85
SF-36 PCS change from baseline	4.77 (p=0.0967)	6.06 (p=0.0008)*	1.92
ASQoL change from baseline	−3.33 (p=0.0967)	−4.00 (p=0.001)*	−1.37
ASAS partial remission	15.1% (p=0.0967)	13.9% (p=0.0941)	4.1%

BSL = baseline
* statistically significant adjusted p-values

Figure 11. ASAS 40 response using non-responder imputation – up to Week 16 (Full analysis set, Study F2310)



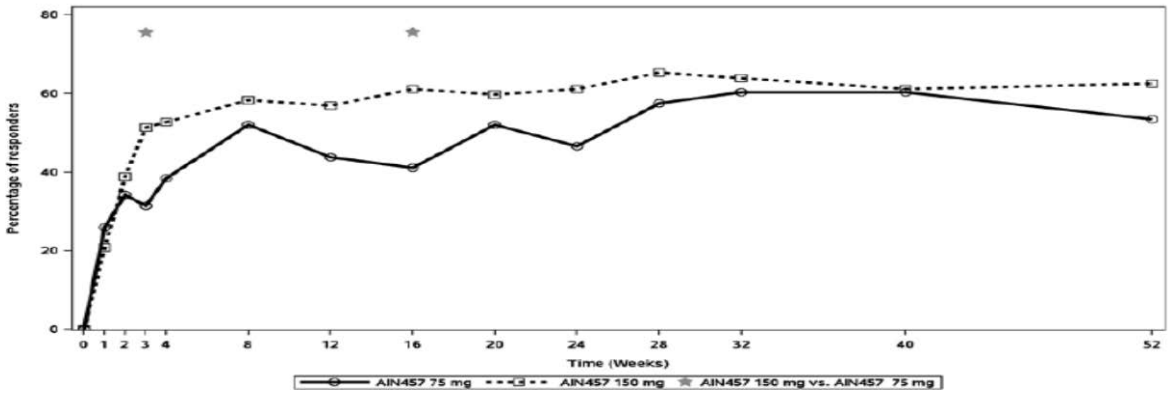
*p<0.05, unadjusted

The profile of ASAS 40 response over the 16 weeks for the TNFαi naïve patients was similar to the overall population: both secukinumab dose groups achieved at least numerically higher response rates than placebo at all analysis visits, but the difference in response rate at Week 16 was statistically significant only with the secukinumab 150 mg group (odds ratio 3.46, 95% CI 1.22 to 10.67). The response varied over time among the TNF-IR patients (n=85). Both doses of secukinumab were however associated with higher response rates than placebo at Week 16 (p=0.0469 and p=0.009 for secukinumab 75 mg and secukinumab 150 mg group, respectively).

Selected exploratory efficacy analyses

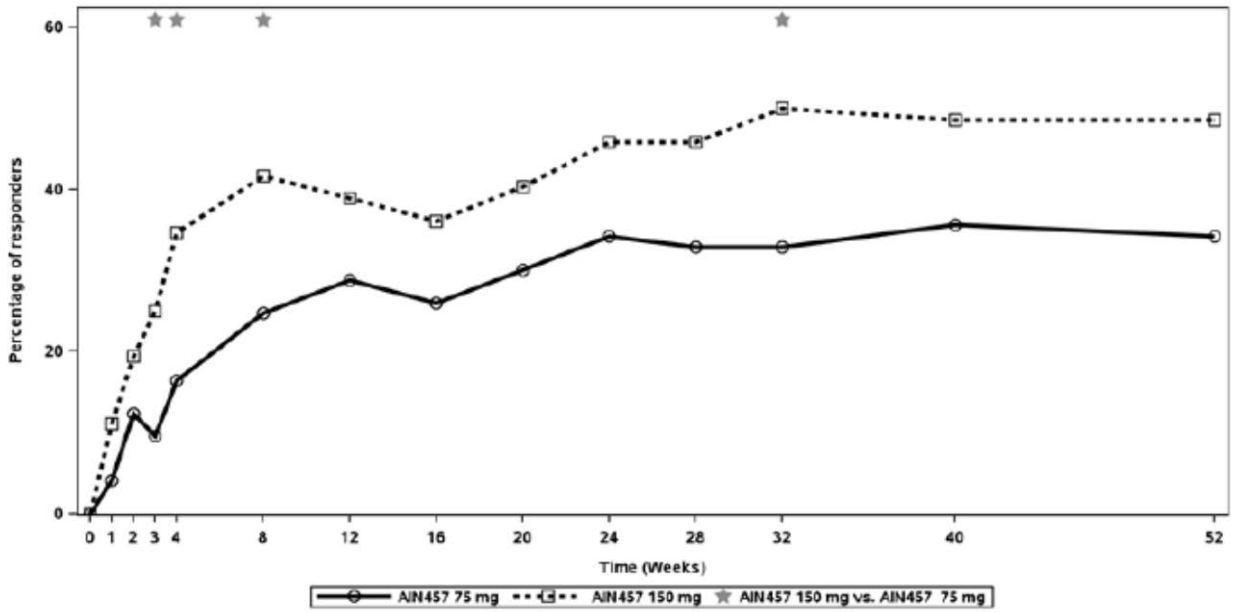
The rates of ASAS 20 and ASAS 40 response up to Week 52 are presented in **Figure 12** and **Figure 13**, respectively.

Figure 12. ASAS 20 response using non-responder imputation – up to Week 52 (Full analysis set, Study F2310)



*p<0.05, unadjusted

Figure 13. ASAS 40 response using non-responder imputation – up to Week 52 (Full analysis set, Study F2310)



*p<0.05, unadjusted

There were no treatment differences between the secukinumab dose groups through Week 52 in other secondary efficacy variables, including ASAS 5/6 response, ASAS partial remission, and changes from baseline in hsCRP, total BASDAI, SF-36 PCS and ASQoL. Comparable levels of response were sustained from Weeks 24 to 52 in both secukinumab groups. Both secukinumab dose groups had numerically greater improvements from baseline compared with the placebo group in the patient's global assessment of disease activity (VAS), total spinal pain, inflammation assessed by BASDAI questions 5 and 6, BASFI, BASDAI 50 and in nocturnal back pain at Week 16. These differences were statistically significant compared to placebo with all above-mentioned variables, with the exception of secukinumab 75 mg group in the patient's global assessment of disease activity (VAS) variable (p=0.0506). The improvements observed in all of these variables with both secukinumab groups were sustained up to Week 52.

The change in BASMI linear score was numerically greater in the secukinumab 150 mg group (the LS mean change -0.51) compared to secukinumab 75 mg (-0.29) and placebo groups (-0.22), with no statistical difference compared to placebo (p=0.0533). At Week 16, the change from baseline in lateral spinal flexion component (score), one of the six ASAS domains used to determine the ASAS 5/6 response, was −0.617 for secukinumab 75 mg, −0.344 for secukinumab 150 mg and −0.334 for placebo, respectively.

Summary of main studies

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

Table 25. Summary of Efficacy for trial F2305

Title: MEASURE 1 (A randomized, double-blind, placebo-controlled, multicentre study of secukinumab to demonstrate the efficacy at 16 weeks and to assess the long term safety, tolerability and efficacy up to 2 years in patients with active ankylosing spondylitis)			
Study identifier	CAIN457F2305		
Design	A randomized, double-blind, placebo-controlled, multicentre trial		
	Duration of main phase: Duration of Extension phase:		16 weeks (timepoint of primary and secondary efficacy analyses) 96 weeks (interim analyses at Week 52)
Hypothesis	Superiority to placebo		
Treatments groups	Secukinumab 10 mg/kg-75 mg		Secukinumab 10 mg/kg iv at baseline, Week 2, Week 4, and then secukinumab 75 mg sc every 4 weeks; N=124
	Secukinumab 10 mg/kg-150 mg		Secukinumab 10 mg/kg iv at baseline, Week 2, Week 4, and then secukinumab 150 mg sc every 4 weeks: N=125
	Placebo		Placebo(sham injections) iv at baseline, Week 2, Week 4, and then placebo sc at Week 8 and 12; N=122
Endpoints and definitions	Primary endpoint	ASAS 20 response at Week 16	improvement of ⩾20% and ⩾1 unit on a scale of 0-10 in at least three of the four main domains and no worsening of ⩾20% and ⩾1 unit on a scale of 10 in the remaining domain, at week 16
	Secondary endpoint	ASAS 40 response at Week 16	improvement of ⩾40% and ⩾2 units on a scale of 10 in at least three of the four main domains and no worsening at all in the remaining domain, at week 16
	Secondary endpoint	The change in hsCRP from baseline at Week 16	change from baseline in high-sensitivity C-reactive protein, at week 16
	Secondary endpoint	ASAS 5/6 response at Week 16	improvement ≥20% in at least five domains, at week 16
	Secondary endpoint	The change in BASDAI from baseline at Week 16	0 through 10 scale pertaining to the 5 major symptoms of AS (Fatigue, Spinal pain, Joint pain/ swelling, enthesitis, Morning stiffness duration and severity), at week 16

	Secondary endpoint	The change in SF-36 PCS from baseline at Week 16	Medical Outcome Short Form Health Survey: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health, at week 16
	Secondary endpoint	The change in ASQoL from baseline at Week 16	change from baseline in Ankylosing Spondylitis Quality of Life, at week 16
	Secondary endpoint	ASAS partial remission at Week 16	value not above 2 units in each of the domains 1 to 4 on a scale of 10, at week 16.
Database lock	10 December 2013 (last patient visit for Week 52)		

Results and Analysis

Analysis description	**Primary Analysis: ASAS 20 response at Week 16**			
Analysis population and time point description	Full Analysis Set 16 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 10 mg/kg – 75 mg	Secukinumab 10 mg/kg – 150 mg	Placebo
	Number of subjects	124	125	122
	ASAS 20	74/124 (59.7%)	76/125 (60.8%)	35/122 (28.7%)

Effect estimate per comparison	ASAS 20	Comparison groups	Secukinumab 10 mg/kg – 75 mg vs. Placebo
		Logistic regression, odds ratio	3.76
		95% CI	2.20, 6.42
		P-value	p<0.0001 (unadjusted and adjusted)
	ASAS 20	Comparison groups	Secukinumab 10 mg/kg – 150 mg vs. Placebo
		Logistic regression, odds ratio	3.89
		95% CI	2.28, 6.65
		P-value	p<0.0001 (unadjusted and adjusted)

Analysis description	**Secondary analysis: ASAS 40 response at Week 16**			
Analysis population and time point description	Full Analysis Set 16 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 10 mg/kg – 75 mg	Secukinumab 10 mg/kg – 150 mg	Placebo
	Number of subjects	124	125	122
	ASAS 40	41/124 (33.1%)	52/125 (41.6%)	16/122 (13.1%)

Effect estimate per comparison	ASAS 40	Comparison groups	Secukinumab 10 mg/kg – 75 mg vs. Placebo
		Logistic regression, odds ratio	3.35
		95% CI	1.75, 6.41
		P-value	p=0.0003 (unadjusted) p=0.0006 (adjusted)
	ASAS 40	Comparison groups	Secukinumab 10 mg/kg – 150 mg vs. Placebo
		Logistic regression, odds ratio	4.87
		95% CI	2.56, 9.25
		P-value	p<0.0001 (unadjusted and adjusted)

Analysis description	**Secondary analysis: The change in hsCRP at Week 16**			
Analysis population and time point description	Full Analysis Set 16 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 10 mg/kg – 75 mg	Secukinumab 10 mg/kg – 150 mg	Placebo
	Number of evaluable subjects	115	121	107
	Ratio of the Week 16 hsCRP value to the baseline value (SE)	0.45 (1.092)	0.40 (1.090)	0.97 (1.095)

Effect estimate per comparison	Ratio of the Week 16 hsCRP value to the baseline value (SE)	Comparison groups	Secukinumab 10 mg/kg – 75 mg vs. Placebo
		Treatment contrast in LS mean change	0.46
		95% CI	0.36, 0.59
		P-value	p<0.0001 (unadjusted) p=0.0006 (adjusted)
	Ratio of the Week 16 hsCRP value to the baseline value (SE)	Comparison groups	Secukinumab 10 mg/kg – 150 mg vs. Placebo
		Treatment contrast in LS mean change	0.41
		95% CI	0.32, 0.52
		P-value	p<0.0001 (unadjusted and adjusted)

Analysis description	**Secondary analysis: ASAS 5/6 response at Week 16**

Analysis population and time point description	Full Analysis Set 16 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 10 mg/kg – 75 mg	Secukinumab 10 mg/kg – 150 mg	Placebo
	Number of subjects	124	125	122
	ASAS 5/6	56/124 (45.2%)	61/125 (48.8%)	16/122 (13.1%)
Effect estimate per comparison	ASAS 5/6	Comparison groups	Secukinumab 10 mg/kg – 75 mg vs. Placebo	
		Logistic regression, odds ratio	5.61	
		95% CI	2.96, 10.62	
		P-value	p<0.0001 (unadjusted) p=0.0006 (adjusted)	
	ASAS 5/6	Comparison groups	Secukinumab 10 mg/kg – 150 mg vs. Placebo	
		Logistic regression, odds ratio	6.54	
		95% CI	3.46, 12.40	
		P-value	p<0.0001 (unadjusted and adjusted)	
Analysis description	**Secondary analysis: The change in BASDAI at Week 16**			
Analysis population and time point description	Full Analysis Set 16 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 10 mg/kg – 75 mg	Secukinumab 10 mg/kg – 150 mg	Placebo
	Number of evaluable subjects	116	121	108
	Change in LS mean BASDAI from baseline (SE)	-2.34 (0.175)	-2.32 (0.172)	-0.59 (0.180)
Effect estimate per comparison	Change in LS mean BASDAI from baseline (SE)	Comparison groups	Secukinumab 10 mg/kg – 75 mg vs. Placebo	
		Treatment contrast in LS mean change (SE)	-1.75 (0.245)	
		95% CI	-2.23, -1.27	
		P-value	p<0.0001 (unadjusted) p=0.0006 (adjusted)	
	Change in LS mean BASDAI from baseline	Comparison groups	Secukinumab 10 mg/kg – 150 mg vs. Placebo	

	(SE)	Treatment contrast in LS mean change (SE)		-1.74 (0.242)
		95% CI		-2.22, -1.26
		P-value		p<0.0001 (unadjusted and adjusted)
Analysis description	**Secondary analysis: The change in SF-36 PCS score at Week 16**			
Analysis population and time point description	Full Analysis Set 16 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 10 mg/kg – 75 mg	Secukinumab 10 mg/kg – 150 mg	Placebo
	Number of evaluable subjects	118	122	111
	Change in LS mean SF-36 PCS score from baseline (SE)	5.64 (0.595)	5.57 (0.586)	0.96 (0.612)
Effect estimate per comparison	Change in LS mean SF-36 PCS score from baseline (SE)	Comparison groups		Secukinumab 10 mg/kg – 75 mg vs. Placebo
		Treatment contrast in LS mean change (SE)		4.68 (0.828)
		95% CI		3.05, 6.30
		P-value		p<0.0001 (unadjusted) p=0.0006 (adjusted)
	Change in LS mean SF-36 PCS score from baseline (SE)	Comparison groups		Secukinumab 10 mg/kg – 150 mg vs. Placebo
		Treatment contrast in LS mean change (SE)		4.61 (0.822)
		95% CI		2.99, 6.22
		P-value		p<0.0001 (unadjusted and adjusted)
Analysis description	**Secondary analysis: The change in ASQoL at Week 16**			
Analysis population and time point description	Full Analysis Set 16 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 10 mg/kg – 75 mg	Secukinumab 10 mg/kg – 150 mg	Placebo
	Number of evaluable subjects	118	121	111

	Change in mean ASQoL from baseline (SE)	-3.61 (0.424)	-3.58 (0.420)	-1.04 (0.437)

Effect estimate per comparison	Change in LS mean ASQoL from baseline (SE)	Comparison groups	Secukinumab 10 mg/kg – 75 mg vs. Placebo
		Treatment contrast in LS mean change (SE)	-2.57 (0.592)
		95% CI	-3.74, -1.41
		P-value	p<0.0001 (unadjusted) p=0.0006 (adjusted)
	Change in LS mean ASQoL from baseline (SE)	Comparison groups	Secukinumab 10 mg/kg – 150 mg vs. Placebo
		Treatment contrast in LS mean change (SE)	-2.54 (0.591)
		95% CI	-3.70, -1.38
		P-value	p<0.0001 (unadjusted and adjusted)

Analysis description	**Secondary analysis: ASAS partial remission at Week 16**			
Analysis population and time point description	Full Analysis Set 16 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 10 mg/kg – 75 mg	Secukinumab 10 mg/kg – 150 mg	Placebo
	Number of subjects	124	125	122
	ASAS partial remission	20/124 (16.1%)	19/125 (15.2%)	4/122 (3.3%)

Effect estimate per comparison	ASAS partial remission	Comparison groups	Secukinumab 10 mg/kg – 75 mg vs. Placebo
		Logistic regression, odds ratio	5.77
		95% CI	1.90, 17.48
		P-value	p=0.002 (unadjusted) p=0.0039 (adjusted)
	ASAS partial remission	Comparison groups	Secukinumab 10 mg/kg – 150 mg vs. Placebo
		Logistic regression, odds ratio	5.30
		95% CI	1.74, 16.14
		P-value	p=0.0033 (unadjusted) p=0.0039 (adjusted)
Notes	The patients were stratified according to being either TNF-IR or TNF-ai naïve status		

Table 26. Summary of Efficacy for trial F2310

Title: MEASURE 2 (A randomized, double-blind, placebo-controlled Phase III multicentre study of subcutaneous secukinumab in prefilled syringes to demonstrate the efficacy at 16 weeks and to assess the long-term efficacy, safety and tolerability up to 5 years in patients with active Ankylosing Spondylitis)			
Study identifier	CAIN457F2310		
Design	A randomized, double-blind, placebo-controlled, multicentre trial		
	Duration of main phase: Duration of Extension phase:		16 weeks (timepoint of primary and secondary efficacy analyses) 244 weeks (interim analyses at Week 52)
Hypothesis	Superiority to placebo		
Treatments groups	Secukinumab 75 mg		Secukinumab 75 mg sc at baseline, Weeks 1, 2, 3, 4 and then every 4 weeks; N=73
	Secukinumab 150 mg		Secukinumab 150 mg sc at baseline, Weeks 1, 2, 3, 4 and then every 4 weeks; N=72
	Placebo		Placebo(sham injections) sc at baseline, Weeks 1, 2, 3, 4, and then placebo sc every 4 weeks; N=74
Endpoints and definitions	Primary endpoint	ASAS 20 response at Week 16	To demonstrate that the efficacy of at least one dose of secukinumab at Week 16 is superior to placebo in patients with active AS based on the proportion of patients achieving an ASAS 20 response
	Secondary endpoint	ASAS 40 response at Week 16	To demonstrate that the efficacy of at least one dose of secukinumab at Week 16 is superior to placebo in patients with active AS based on the proportion of patients achieving an ASAS 40 response
	Secondary endpoint	The change in hsCRP from baseline at Week 16	To demonstrate that the efficacy of at least one dose of secukinumab at Week 16 is superior to placebo in patients with active AS based on the change in hsCRP from baseline
	Secondary endpoint	ASAS 5/6 response at Week 16	To demonstrate that the efficacy of at least one dose of secukinumab at Week 16 is superior to placebo in patients with active AS based on the proportion of patients achieving an ASAS 5/6 response
	Secondary endpoint	The change in BASDAI from baseline at Week 16	To demonstrate that the efficacy of at least one dose of secukinumab at Week 16 is superior to placebo in patients with active AS based on the change in BASDAI from baseline
	Secondary endpoint	The change in SF-36 PCS from baseline at Week 16	To demonstrate that the efficacy of at least one dose of secukinumab at Week 16 is superior to placebo in patients with active AS based on the change in SF-36 PCS from baseline
	Secondary endpoint	The change in ASQoL from baseline at Week 16	To demonstrate that the efficacy of at least one dose of secukinumab at Week 16 is superior to placebo in patients with active AS based on the change in ASQoL from baseline
	Secondary endpoint	ASAS partial remission at Week 16	To demonstrate that the efficacy of at least one dose of secukinumab at Week 16 is superior to placebo in patients with active AS based on the proportion of patients achieving ASAS partial remission
Database lock	4 August 2014 (last patient visit for Week 52)		

Results and Analysis				
Analysis description	**Primary Analysis: ASAS 20 response at Week 16**			
Analysis population and time point description	Full Analysis Set 16 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 75 mg	Secukinumab 150 mg	Placebo
	Number of subjects	73	72	74
	ASAS 20	30/73 (41.1%)	44/72 (61.1%)	21/74 (28.4%)
Effect estimate per comparison	ASAS 20	Comparison groups	Secukinumab 75 mg vs. Placebo	
		Logistic regression, odds ratio	1.82	
		95% CI	0.90, 3.67	
		P-value	p=0.0967 (unadjusted and adjusted)	
	ASAS 20	Comparison groups	Secukinumab 150 mg vs. Placebo	
		Logistic regression, odds ratio	4.38	
		95% CI	2.14, 8.96	
		P-value	p<0.0001 (unadjusted) p=0.0001 (adjusted)	
Analysis description	**Secondary analysis: ASAS 40 response at Week 16**			
Analysis population and time point description	Full Analysis Set 16 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 75 mg	Secukinumab 150 mg	Placebo
	Number of subjects	73	72	74
	ASAS 40	19/73 (26.0%)	26/72 (36.1%)	8/74 (10.8%)
Effect estimate per comparison	ASAS 40	Comparison groups	Secukinumab 75 mg vs. Placebo	
		Logistic regression, odds ratio	2.99	
		95% CI	1.19, 7.48	
		P-value	p=0.0194 (unadjusted) p=0.0967 (adjusted)	
	ASAS 40	Comparison groups	Secukinumab 150 mg vs. Placebo	
		Logistic regression, odds ratio	5.07	
		95% CI	2.06, 12.44	
		P-value	p=0.0004 (unadjusted) p=0.0008 (adjusted)	

Analysis description	**Secondary analysis: The change in hsCRP at Week 16**			
Analysis population and time point description	Full Analysis Set 16 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 75 mg	Secukinumab 150 mg	Placebo
	Number of evaluable subjects	69	68	66
	Ratio of the Week 16 hsCRP value to the baseline value (SE)	0.61 (1.103)	0.55 (1.104)	1.13 (1.105)
Effect estimate per comparison	Ratio of the Week 16 hsCRP value to the baseline value (SE)	Comparison groups	Secukinumab 75 mg vs. Placebo	
		Treatment contrast in LS mean change	0.54	
		95% CI	0.41, 0.71	
		P-value	p<0.0001 (unadjusted) p=0.0967 (adjusted)	
	Ratio of the Week 16 hsCRP value to the baseline value (SE)	Comparison groups	Secukinumab 150 mg vs. Placebo	
		Treatment contrast in LS mean change	0.49	
		95% CI	0.37, 0.64	
		P-value	p<0.0001 (unadjusted) p=0.0008 (adjusted)	

Analysis description	**Secondary analysis: ASAS 5/6 response at Week 16**			
Analysis population and time point description	Full Analysis Set 16 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 75 mg	Secukinumab 150 mg	Placebo
	Number of subjects	73	72	74
	ASAS 5/6	25/73 (34.2%)	31/72 (43.1%)	6/74 (8.1%)
Effect estimate per comparison	ASAS 5/6	Comparison groups	Secukinumab 75 mg vs. Placebo	
		Logistic regression, odds ratio	6.13	
		95% CI	2.31, 16.26	
		P-value	p=0.0003 (unadjusted) p=0.0967 (adjusted)	
	ASAS 5/6	Comparison groups	Secukinumab 150 mg vs. Placebo	
		Logistic regression, odds ratio	9.15	

		95% CI		3.47, 24.12
		P-value		p<0.0001 (unadjusted) p=0.0008 (adjusted)
Analysis description	**Secondary analysis: The change in BASDAI at Week 16**			
Analysis population and time point description	Full Analysis Set 16 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 75 mg	Secukinumab 150 mg	Placebo
	Number of evaluable subjects	73	72	74
	Change in mean BASDAI from baseline (SE)	-1.92 (0.249)	-2.19 (0.248)	-0.85 (0.252)
Effect estimate per comparison	Change in mean BASDAI from baseline (SE)	Comparison groups		Secukinumab 75 mg vs. Placebo
		Treatment contrast in LS mean change (SE)		-1.07 (0.353)
		95% CI		-1.77, -0.37
		P-value		p=0.0028 (unadjusted) p=0.0967 (adjusted)
	Change in mean BASDAI from baseline (SE)	Comparison groups		Secukinumab 150 mg vs. Placebo
		Treatment contrast in LS mean change (SE)		-1.34 (0.353)
		95% CI		-2.04, -0.65
		P-value		p=0.0002 (unadjusted) p=0.0008 (adjusted)
Analysis description	**Secondary analysis: The change in SF-36 PCS score at Week 16**			
Analysis population and time point description	Full Analysis Set 16 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 75 mg	Secukinumab 150 mg	Placebo
	Number of evaluable subjects	66	67	66
	Change in mean SF-36 PCS score from baseline (SE)	4.77 (0.798)	6.06 (0.784)	1.92 (0.786)
Effect estimate per comparison	Change in mean SF-36 PCS score from baseline (SE)	Comparison groups		Secukinumab 75 mg vs. Placebo
		Treatment contrast in LS mean change (SE)		2.84 (1.108)
		95% CI		0.66, 5.03

		P-value	p=0.011 (unadjusted) p=0.0967 (adjusted)
	Change in mean SF-36 PCS score from baseline (SE)	Comparison groups	Secukinumab 150 mg vs. Placebo
		Treatment contrast in LS mean change (SE)	4.14 (1.105)
		95% CI	1.96, 6.32
		P-value	p=0.0002 (unadjusted) p=0.0008 (adjusted)

Analysis description	**Secondary analysis: The change in ASQoL at Week 16**			
Analysis population and time point description	Full Analysis Set 16 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 75 mg	Secukinumab 150 mg	Placebo
	Number of subjects	66	66	66
	Change in mean ASQoL from baseline (SE)	-3.33 (0.537)	-4.00 (0.528)	-1.37 (0.530)

Effect estimate per comparison	Change in mean ASQoL from baseline (SE)	Comparison groups	Secukinumab 75 mg vs. Placebo
		Treatment contrast in LS mean change (SE)	-1.96 (0.748)
		95% CI	-3.43, -0.48
		P-value	p=0.0096 (unadjusted) p=0.0967 (adjusted)
	Change in mean ASQoL from baseline (SE)	Comparison groups	Secukinumab 150 mg vs. Placebo
		Treatment contrast in LS mean change (SE)	-2.63 (0.743)
		95% CI	-4.09, -1.16
		P-value	p=0.0005 (unadjusted) p=0.001 (adjusted)

Analysis description	**Secondary analysis: ASAS partial remission at Week 16**			
Analysis population and time point description	Full Analysis Set 16 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 75 mg	Secukinumab 150 mg	Placebo
	Number of subjects	73	72	74
	ASAS partial remission	11/73 (15.1%)	10/72 (13.9%)	3/74 (4.1%)

Effect estimate per comparison	ASAS partial remission	Comparison groups	Secukinumab 75 mg vs. Placebo

		Logistic regression, odds ratio	4.28
		95% CI	1.13, 16.21
		P-value	p=0.0325 (unadjusted) p=0.0967 (adjusted)
	ASAS partial remission	Comparison groups	Secukinumab 150 mg vs. Placebo
		Logistic regression, odds ratio	3.91
		95% CI	1.02, 15.01
		P-value	p=0.0471 (unadjusted) p=0.0941 (adjusted)

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

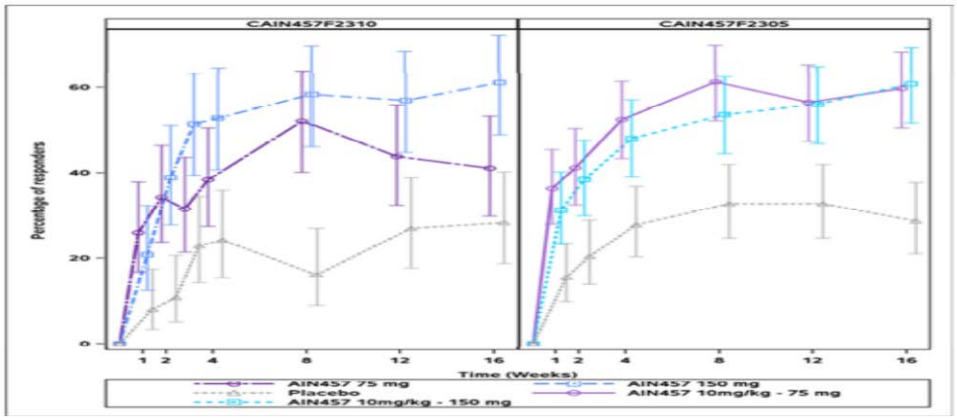
The pooled efficacy analyses are based on FAS of the pivotal studies F2305 and F2310. The total number of randomized AS patients was altogether 590. The patient population analysed for combined efficacy data consisted only of patients on secukinumab with a dose having shown efficacy in the pivotal studies (secukinumab 10 mg/kg-75 mg, secukinumab 10 mg/kg-150 mg and secukinumab 150 mg sc; n=321).

Demographics of the patients in the Studies F2305 and F2310 were broadly similar, with the exception of slightly heavier patients in the Study F2310 (median weight 80 kg vs. 74 kg). The median time since the diagnosis of AS was somewhat longer in the patients of Study F2305 (5.0 years vs. 2.9 years). 27.0% and 38.8% of the patients had a history of previous use of TNFαi in the Studies F2305 and F2310, respectively. The variables reflecting activity of AS (*e.g.*, BASDAI, hCRP) were very similar between the Studies.

The vast majority of patients in both studies completed Week 52 (pooled secukinumab group: 86.6%). In both studies, the most common reason for premature discontinuation was the occurrence of AEs, which was reported with similar frequency in pooled placebo (5.6%) and pooled secukinumab (5.9%) groups. Discontinuations due to the lack of efficacy also occurred at comparable rates between pooled secukinumab (3.4%) and pooled placebo groups (5.6%).

The primary efficacy endpoint of superiority compared to placebo in ASAS 20 response rate at Week 16 was reached with comparable rates in secukinumab 10 mg/kg-75 mg, secukinumab 10 mg/kg-150 mg and secukinumab 150 mg sc groups (59.7%, 60.8% and 61.1%, respectively vs. 28.4-28.7% in placebo groups). The ASAS 20 responses were achieved rapidly from Week 1 onwards (**Figure 14**).

Figure 14. Time course of ASAS 20 response (estimate and 95% CI) using non-responder imputation by study and treatment up to Week 16 for Studies F2310 and F2305 (based on individual study results, FAS)



Both secukinumab groups showed better efficacy in all secondary endpoints compared to placebo at Week 16 in Study F2305. In Study F2310, the secukinumab 150 mg s.c was superior to placebo with all secondary efficacy endpoints except with ASAS partial remission. Of note, although not reaching statistical significance the secukinumab 75 mg sc group showed also numerically greater response compared to placebo in all primary and secondary endpoints, including the changes in hCRP and in total BASDAI (see **Figure 15**). The proportion of patients reaching ASAS partial remission was numerically very similar in all secukinumab groups of both studies, although these changes were statistically significant only in the larger Study F2305 (see **Figure 16**).

Numerically (not statistically tested) somewhat greater improvements were reported for both secukinumab groups in Study F2305, but not for secukinumab 150 mg sc group in Study F2310 compared to placebo in lateral lumbar flexion score of the BASMI components at Week 16.

Figure 15. Mean change from baseline in total BASDAI (estimate +/- SE) using MMRM by study and treatment up to Week 16 for Studies F2310 and F2305 (based on individual study results, FAS)

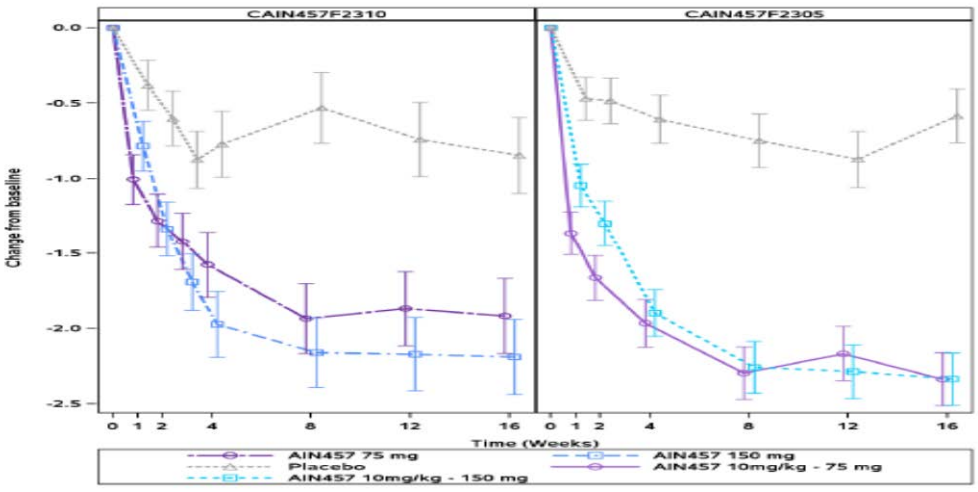
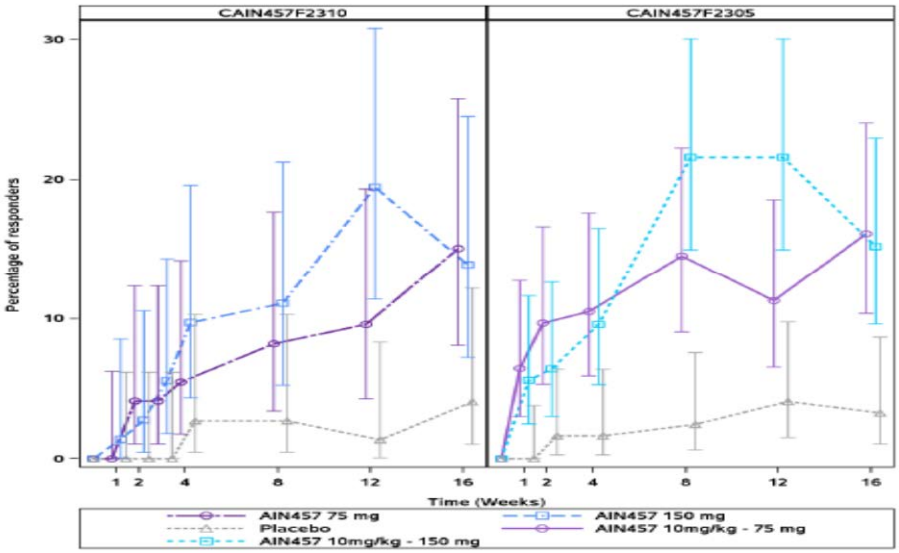


Figure 16. Time course of ASAS partial remission (estimate and 95% CI) using non-responder imputation by study and treatment up to Week 16 for Studies F2310 and F2305 (based on individual study results, FAS)



The ASAS 20 and ASAS 40 response rates achieved in all secukinumab groups of both studies at Week 16 were sustained through Week 52 (see **Figures 17** and **18**). Interestingly, the ASAS 20 and ASAS 40 response rates at Week 52 were very similar between the secukinumab groups in the Study F2305. The corresponding response rates in Study F2310 were somewhat greater in the secukinumab 150 mg sc group compared to the secukinumab 75 mg sc group in the Study F2310 (73.8% vs. 63.9% and 57.4% vs. 41.0%, respectively). Among the patients randomized from placebo to secukinumab at Week 16 in Study F2310, the ASAS 20 response rates at Week 52 were somewhat greater in patients randomized to secukinumab 150 mg than in the lower dose group (75.0% vs. 59.3%). Correspondingly, the ASAS 20 response rates at Week 52 in the patients randomized to placebo at baseline in Study F2305 were 61.5% and 47.4% in the patients receiving 75 mg and 150 mg secukinumab sc, respectively.

In both studies, the improvements achieved at Week 16 in all secondary efficacy endpoints were sustained through Week 52. There were no statistically significant differences in the treatment responses in respect of these variables between the secukinumab groups in either of the pivotal studies.

In pre-specified sub-group analysis, the effect of secukinumab on ASAS 20 response at Week 16 was not dependent of baseline age, gender, race or region of the patients (see **Figure 19**). In subgroup analysis stratified by body weight (<70 kg, 70-90 kg, >90 kg), the response rates with secukinumab were numerically declining along with the increasing weight. The treatment response in favour of pooled secukinumab group was significant in all weight groups. However, the difference in treatment response between secukinumab 150 mg sc and placebo was not statistically significant in patients weighing>90 kg. The effect of secukinumab on primary efficacy outcome did not significantly vary according to disease activity (*e.g.*, hCRP, BASDAI) at baseline.

The analysis of ASAS 20 response at Week 16 stratified by the baseline TNFαi status and the reason for stopping previous TNFαi treatment is presented in **Figure 20**. According to this analysis, the treatment response with secukinumab was irrespective of the TNFαi status (TNFαi naïve or TNF-IR), but the treatment benefit was not statistically significant in patients who had stopped previous TNFαi treatment due to tolerability problems. However, the latter analysis is restricted by a limited number of patients in this TNF-IR subgroup.

Figure 17. Time course of ASAS 20 response (estimate and 95% CI) using non-responder imputation by study and treatment up to Week 52 for Studies F2310 and F2305 (based on individual study results, FAS)

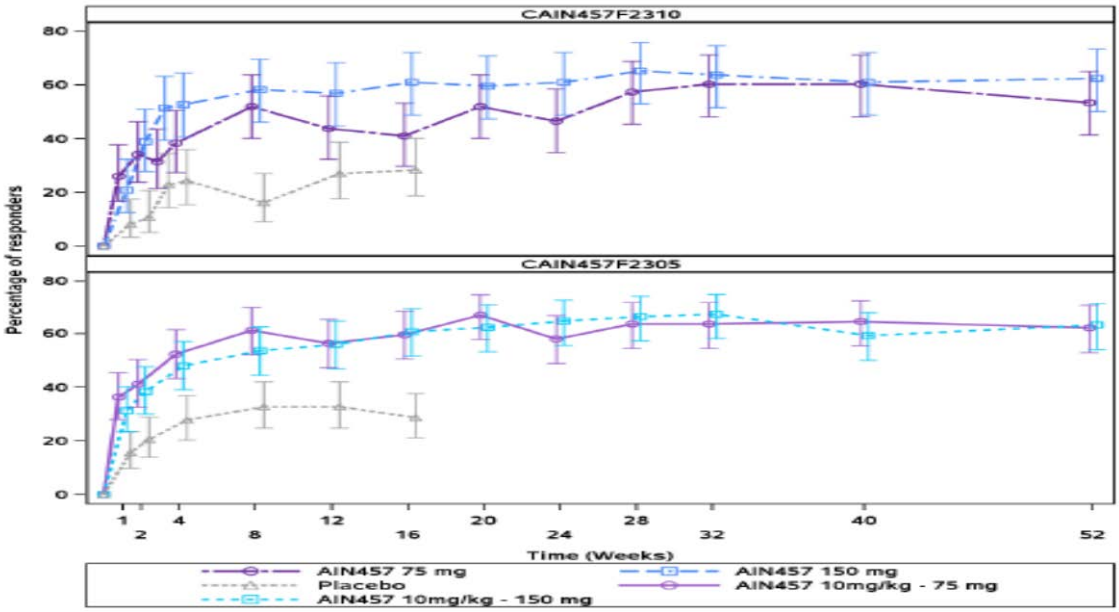


Figure 18. Time course of ASAS 40 response (estimate and 95% CI) using non-responder imputation by study and treatment up to Week 52 for Studies F2310 and F2305 (based on individual study results, FAS)

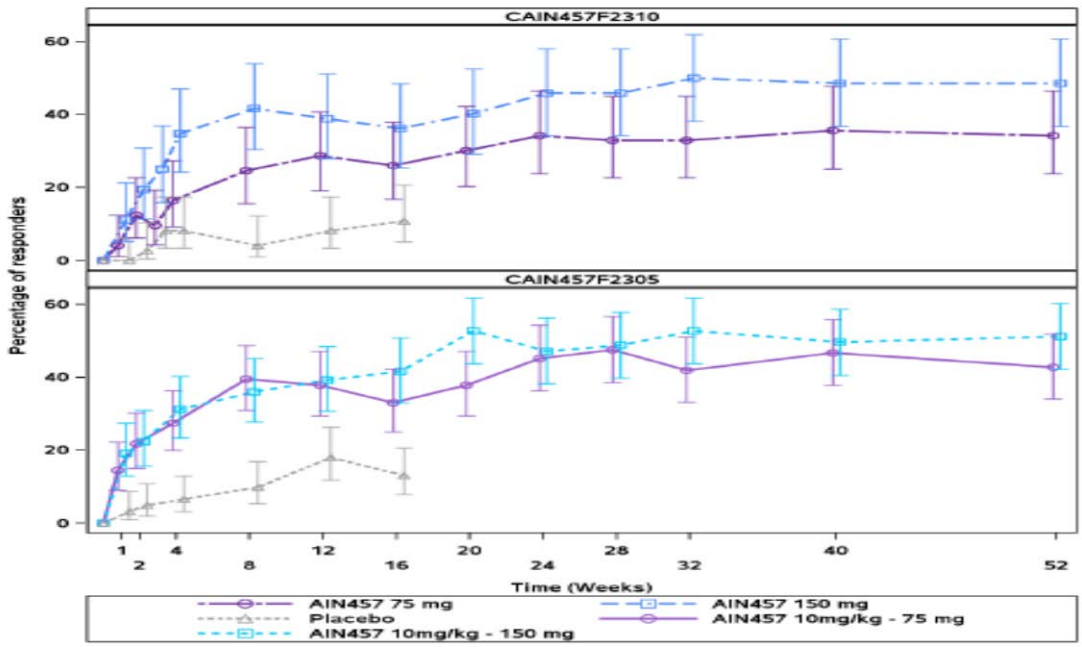
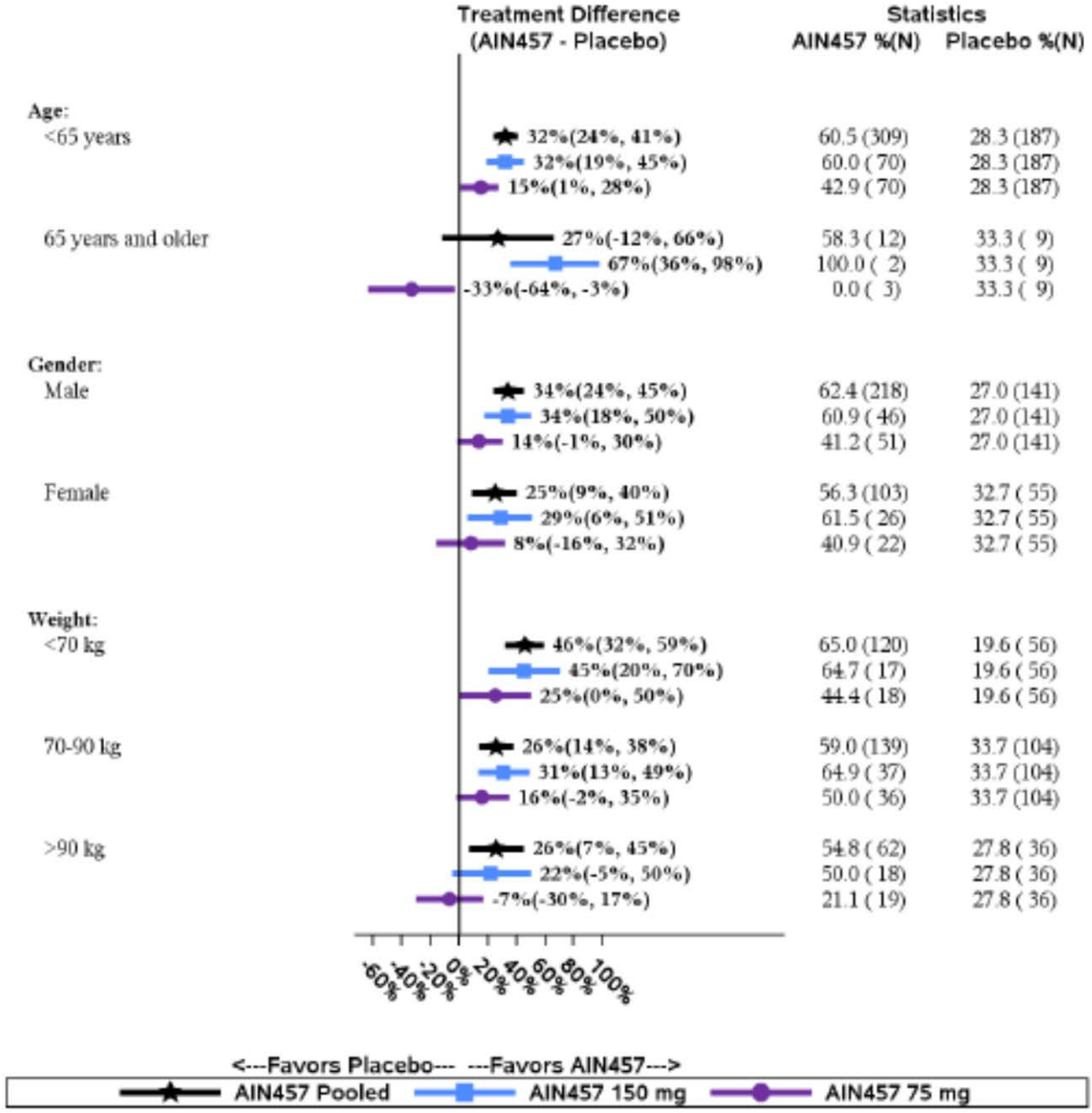
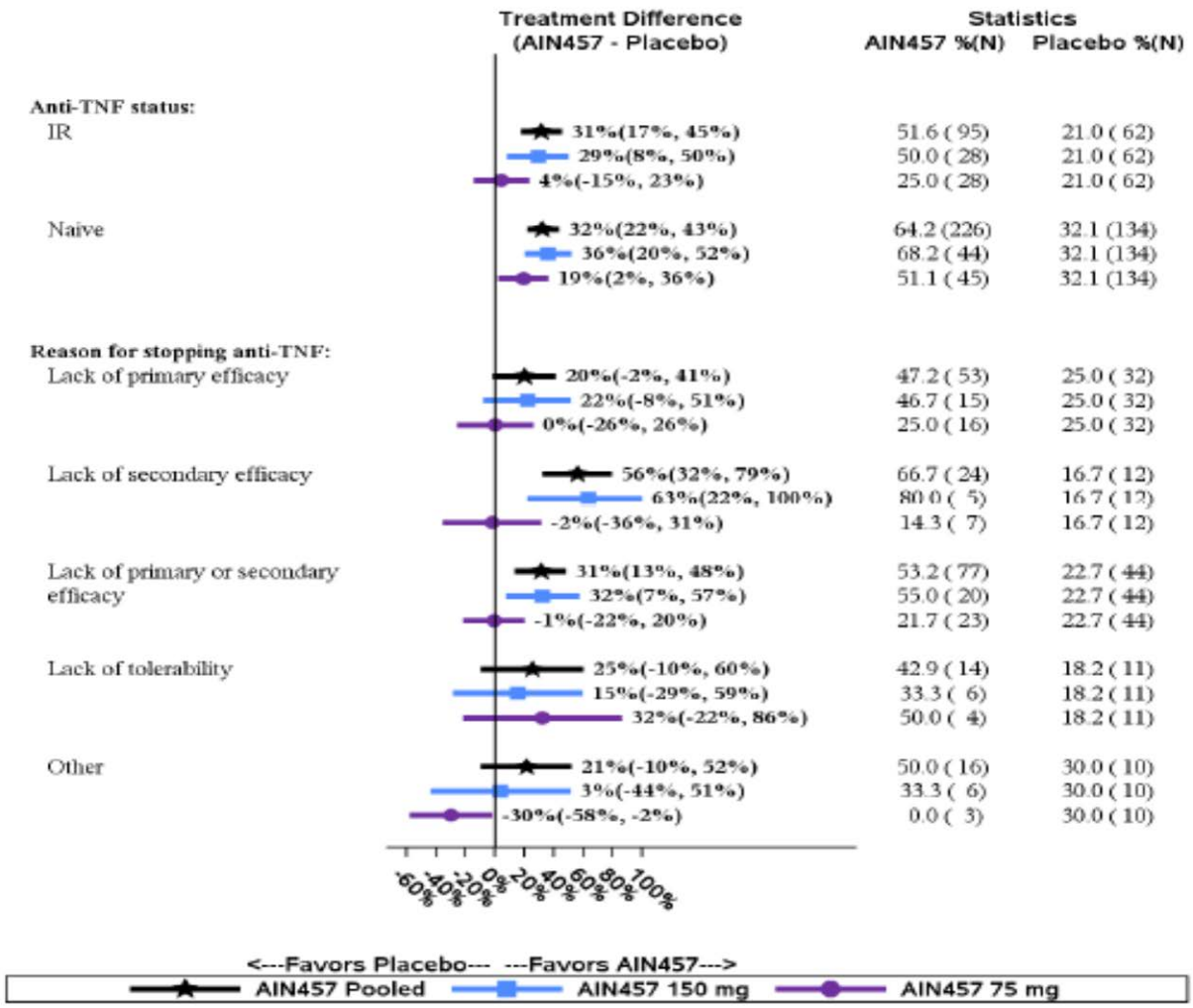


Figure 19. Forest plot of treatment difference between pooled secukinumab and placebo for ASAS20 response at Week 16 stratified by age, gender and weight (Full analysis set)



AIN457 Pooled includes AIN457 150 mg, AIN457 10mg/kg - 75 mg and AIN457 10mg/kg - 150 mg only.

Figure 20. Forest plot of treatment difference between pooled secukinumab and placebo for ASAS20 response at Week 16 stratified by TNF alpha inhibitor status and reasons for stopping TNF alpha inhibitors (Full analysis set)



AIN457 Pooled includes AIN457 150 mg, AIN457 10mg/kg - 75 mg and AIN457 10mg/kg - 150 mg only.

2.3.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The AS clinical development program included two phase II studies (A2209 in AS patients and F2201 in a related arthritic indication with RA patients) and two pivotal phase III studies in AS (F2305 and F2310). Efficacy data up to Week 52 in both pivotal studies were provided.

Recommendations of the EMA clinical guidance for AS (Guideline on clinical investigation of medicinal product for the treatment of ankylosing spondylitis, CPMP/EWP/4891/03) were mostly taken into account in the clinical development programme. Missing elements included the lack of active comparator and the lack of dedicated assessment of spinal mobility as a secondary endpoint. The lack of these elements was adequately justified by the MAH and considered acceptable by the CHMP. No CHMP Scientific advice had been sought in the current indication. All studies were conducted in compliance with GCP.

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 and pharmacokinetic modeling from the psoriasis studies. The two phase II studies A2209 and F2201 provided preliminary evidence of efficacy in two arthritic disease models, AS and RA. The posology carried forward to the phase III studies was mainly based on PK/PD modeling 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 AS. They fulfilled the modified New York criteria for diagnosis of AS. The disease activity was based on measurements of BASDAI (≥ 4) and spinal pain VAS (≥ 4 cm). The CHMP noted however that given the characteristics of the patients studied in the pivotal studies (with respect to BASDAI score and degree of spinal pain) "active AS" may be a more relevant definition comparted to "active, severe AS" as was initially proposed by the MAH.

Study F2305 was a double-blind, randomized, parallel-group, placebo-controlled study. 52-week interim analyses of the 2-year study were provided, with the assessment of the primary efficacy variable of ASAS 20 response at Week 16. 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 spinal mobility. MRI of spine and sacroiliac joints was assessed only in a subgroup of TNFαi naïve patients at selected study sites. BMD of the lumbar spine, total hip and femoral neck was assessed in all patients. With regard to statistical methods, the missing at random (MAR) assumption for missing data in MMRM analyses without any sensitive analyses for continuous endpoints is questionable. However, appropriate sensitivity analyses were provided by the Applicant afterwards.

The design of Study F2310 was otherwise identical to that of Study F2305, but the iv loading regimen was replaced by sc loading regimen that is similar to that approved for the treatment of psoriasis (sc dosing at baseline, Weeks 1, 2, 3 and 4 and then q4w). No assessment of progression of structural damage was performed in this study.

The percentage of subjects with treatment deviation in study F2310 was around one third, which was considered high. The MAH was asked to display what types of errors occurred, and the possible impact on the study results and clarified what types of treatment deviations occurred. The CHMP agreed that it would have been unlikely that, the by far, most common deviation, short visit window during sc loading period, would have had a significant impact on the result. In study F2305 there was a remarkably high number of selection criteria not met, and key procedures not performed as per protocol. The MAH provided acceptable explanations on how the most frequent deviations, (low VAS pain at BL and study treatment administered by unblinded personnel) occurred, and what corrective action was taken. A sensitivity analysis was performed and the results were consistent with the full analysis set.

Efficacy data and additional analyses

In Study F2305, 371 patients were randomized to each of the 3 treatment groups (secukinumab 10 mg/kg-75 mg, secukinumab 10 mg/kg-150 mg group and the placebo group. Demographics and baseline disease activity were generally comparable across the treatment groups. The placebo patients were randomized either at Week 16 (placebo non-responders) or at Week 24 (placebo responders) to secukinumab 75 mg or 150 mg.

The primary efficacy endpoint of ASAS 20 response was achieved as secukinumab at both 10 mg/kg-75 mg and 10 mg/kg-150 mg doses was statistically significantly superior to placebo at Week 16 ($p<0.0001$). The ASAS 20 response rates at Week 16 were 59.7% for secukinumab 10 mg/kg-75 mg, 60.8% for secukinumab 10 mg/kg-150 mg and 28.7% for placebo. Superior response rates compared to placebo were seen as early as from Week 1 onwards.

Secondary efficacy endpoints (responses of ASAS 40, ASAS 5/6 and ASAS partial remission; changes in BASDAI, hCRP, SF-36 and ASQoL) were met for both secukinumab doses without any apparent dose-response.

For Study F2310, a total of 219 patients were randomized to 3 treatment groups: secukinumab 75 mg, 150 mg and placebo. The primary efficacy endpoint was achieved with secukinumab dose 150 mg, which

was statistically significantly superior to placebo for ASAS20 response at Week 16 ($p<0.0001$). The difference in response rate between secukinumab 75 mg dose and placebo was not statistically significant ($p=0.0967$). The ASAS 20 response rates at Week 16 were 41.1% for secukinumab 75 mg, 61.1% for secukinumab 150 mg and 28.4% for placebo. For the 150 mg dose, statistically superior response rates compared to placebo were seen already from Week 1 onwards.

All secondary endpoints except for ASAS partial remission at Week 16 were met with the 150 mg dose group compared with placebo.

Within analyses performed across trials, similar efficacy at Week 16 based on assessment of primary and secondary outcomes was seen for both secukinumab dose groups in Study F2305 and for the secukinumab 150 mg dose group in Study F2310. According to the results of the both pivotal studies, the loading regimen is an efficient method to achieve rapid relief of AS symptoms.

Although the ASAS 20 response at Week 16 was numerically somewhat more pronounced in TNFαi naïve patients, a significant treatment effect was seen also with TNF-IR patients as early as Week 1. The small number of patients in the TNF-IR subgroups (reason for stopping TNFαi) limited the conclusions of the further analyses in this subgroup.

The improvements in ASAS 20 response, ASAS 40 response and also in other secondary efficacy endpoints achieved in all secukinumab groups of both studies at Week 16 were sustained through Week 52. Interestingly, the ASAS 20 and ASAS 40 response rates between the secukinumab groups at Week 52 were very similar in the Study F2305. The corresponding response rates at Week 52 in Study F2310 were numerically somewhat greater in the secukinumab 150 mg sc group compared to the secukinumab 75 mg sc group in the Study F2310, but with no statistical significance. Among the patients randomized from placebo to secukinumab at Week 16 in Study F2310, the ASAS 20 response rates at Week 52 were somewhat greater in patients randomized to secukinumab 150 mg than in the 75 mg dose group, but in Study F2305 the patients re-randomized to secukinumab 75 mg showed numerically greater ASAS response compared to secukinumab 150 mg group. In addition, there were no statistically significant differences in the treatment responses in respect of all secondary endpoints between the secukinumab groups in either of the pivotal studies.

Data from Study F2305 and Study F2310 were pooled for subgroup analyses. ”AIN457 pooled” consisted of the regimens that demonstrated statistical significance across the primary and key secondary endpoints from Study F2310 (150 mg sc only) and Study F2305 (both iv-75 mg and iv- 150 mg regimens) and were evaluated by subgroup in comparison to a pooled placebo (F2310 and F2305) group. Considering however the use of different induction regimens in the two studies, the same subgroup analyses which were performed on the pooled dataset, was requested for each study separately and was provided by the MAH. Although small subgroups limited conclusions, compared to the outcomes in primary analyses of ASAS 20 and ASAS 40, similar trends were shown supporting consistent outcomes across subgroups also within each study respectively.

2.3.4. Conclusions on the clinical efficacy

Both phase III studies met the primary endpoint of superiority over placebo in ASAS 20 response rate at Week 16. Three induction + maintenance dose regimens were shown to induce a clinically significant and durable response. Based on subgroup analyses, secukinumab was considered as an efficacious treatment alternative for AS patients with previous use of TNFαi.

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

2.4. 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. 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 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 27. Exposure to secukinumab across Pools A and C in the entire treatment period

	Pool A			Pool C
	Any AIN457 75 mg N=284	Any AIN457 150 mg N=287	Any AIN457 dose N=571	Any AIN457 dose N=6200
≥ 8 wks	279	284	563	6031
≥ 16 wks	269	276	545	5287
≥ 24 wks	266	269	535	4964
≥ 52 wks	223	221	444	3671
Total exposure (pt-yrs)	344.6	346.5	691.1	6266.6

Duration of exposure to study treatment is defined as end of treatment period – start date of study treatment + 1. Subject-time in subject years is calculated as a sum of individual subject durations in days divided by 365.25.

The first data pool (A) consisted of the 2 pivotal placebo-controlled Phase 3 trials in AS (CAIN457F2305 and CAIN457F2310) that allowed risks to be evaluated in the AS population during the first 16 weeks of treatment and during the entire treatment period (median 66 weeks of exposure to secukinumab). The baseline characteristics of the patients included in this pool are summarised in **Table 28**.

In order to keep a consistent naming convention across indications within the secukinumab program, the naming convention of Pool A, Pool B (where required) and Pool C was maintained in the analysis provided by the MAH. However, as there were no additional studies in AS evaluating the same treatment regimen as in the pivotal Phase 3 AS studies, there was no designated Pool B data pool for AS.

The largest data pool (C), which includes all patients treated with secukinumab in 42 studies for which an interim or final CSR is currently available, maximized the chances of observing rare events of MACE (major adverse cardiovascular events) and malignancy in patients receiving secukinumab. Excluded from Pool C were very small studies enrolling primarily healthy volunteers. The current submission added 8 additional studies to Pool C reported as part of the psoriasis application: 2 in the target AS indication Study CAIN457F2305 and Study CAIN457F2310 and 6 in other indications, Study CAIN457A2302E1 and Study CAIN457A2304E1 in psoriasis; Study CAIN457F2306 and Study CAIN457F2312 in psoriatic arthritis, Study CAIN457B2203 in multiple sclerosis; and Study CPJMR0012201 in polymyalgia rheumatica. This provided an additional 1702 secukinumab-treated patients with 2679 patient-years of exposure compared to the psoriasis program.

Table 28. Demographics and other baseline characteristics – Short-term period (16 weeks) (Pool A: Phase 3 AS trials - Safety set)

Demographic variable	AIN457 75mg N=73 n (%)	AIN457 150mg N=72 n (%)	AIN457 10mg/kg -75mg N=124 n (%)	AIN457 10mg/kg -150mg N=125 n (%)	Any AIN457 N=394 n (%)	Placebo N=196 n (%)
Age group in years, n (%)						
<65	70 (95.9)	70 (97.2)	117 (94.4)	122 (97.6)	379 (96.2)	187 (95.4)
>=65	3 (4.1)	2 (2.8)	7 (5.6)	3 (2.4)	15 (3.8)	9 (4.6)
>=75	1 (1.4)	0	1 (0.8)	0	2 (0.5)	1 (0.5)
Age (Years)						
n	73	72	124	125	394	196
Mean	44.4	41.9	42.3	40.1	41.9	43.3
SD	13.06	12.48	13.24	11.61	12.61	12.69
Median	46.0	41.0	41.0	39.0	41.0	42.5
Min - Max	19 - 77	20 - 66	18 - 76	19 - 67	18 - 77	18 - 77
Sex, n (%)						
Female	22 (30.1)	26 (36.1)	36 (29.0)	41 (32.8)	125 (31.7)	55 (28.1)
Male	51 (69.9)	46 (63.9)	88 (71.0)	84 (67.2)	269 (68.3)	141 (71.9)
Race, n (%)						
White	70 (95.9)	69 (95.8)	76 (61.3)	69 (55.2)	284 (72.1)	151 (77.0)
Black or African American	0	0	0	0	0	1 (0.5)
Asian	3 (4.1)	2 (2.8)	23 (18.5)	21 (16.8)	49 (12.4)	23 (11.7)
American Indian or Alaska Native	0	1 (1.4)	3 (2.4)	8 (6.4)	12 (3.0)	3 (1.5)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	1 (0.5)
Other*	0	0	22 (17.7)	27 (21.6)	49 (12.4)	17 (8.7)
Ethnicity, n (%)						
Hispanic or Latino	6 (8.2)	5 (6.9)	27 (21.8)	39 (31.2)	77 (19.5)	28 (14.3)
Not Hispanic or Latino	59 (80.8)	59 (81.9)	91 (73.4)	78 (62.4)	287 (72.8)	153 (78.1)
Unknown	7 (9.6)	8 (11.1)	3 (2.4)	6 (4.8)	24 (6.1)	12 (6.1)
Not reported	1 (1.4)	0	3 (2.4)	2 (1.6)	6 (1.5)	3 (1.5)
Height (cm)						
n	73	72	124	125	394	195
Mean	170.6	173.4	170.3	168.1	170.2	170.9
SD	9.04	8.84	10.96	9.58	9.94	9.02
Median	172.0	172.3	170.0	168.0	170.0	171.5
Min - Max	153 -193	151 - 189	138 - 196	146 - 192	138 - 196	150 - 192
Weight (kg)						
n	73	72	124	125	394	196
Mean	81.4	82.3	77.7	74.7	78.3	78.0
SD	17.39	17.96	19.62	16.16	18.05	14.79
Median	80.0	79.8	73.6	73.4	76.7	77.2
Min - Max	51 - 123	50 - 134	41 - 142	40 - 112	40 - 142	48 - 134
BMI (kg/m^2)						
n	73	72	124	125	394	195
Mean	28.01	27.42	26.68	26.36	26.96	26.72
SD	5.858	5.802	5.618	5.076	5.546	5.111
Median	27.64	26.59	25.80	25.91	26.23	25.88
Min - Max	17.2 - 44.5	17.7 - 44.1	14.7 - 46.1	15.9 - 40.3	14.7 - 46.1	17.5 - 54.8
Current smoker at baseline, n (%)						
Yes	21 (28.8)	21 (29.2)	22 (17.7)	35 (28.0)	99 (25.1)	61 (31.1)
No	52 (71.2)	51 (70.8)	102 (82.3)	90 (72.0)	295 (74.9)	135 (68.9)

Adverse events

Induction and placebo controlled study period of Pool A

During the short-term (16-week) period of the pivotal, placebo-controlled AS studies in Pool A, the most frequently reported treatment-emergent adverse events (AEs) in the "Any secukinumab dose group" were nasopharyngitis, dyslipidemia, headache, nausea, and oropharyngeal pain. The absolute incidence of AEs was slightly higher in the "Any secukinumab group" compared with placebo, mainly due to increased rates of nasopharyngitis and dyslipidemia in the secukinumab-treated group. During the first 16 weeks, infections occurred more frequently in the "Any secukinumab group" compared with the placebo group, mainly due to increased rates of mild to moderate upper respiratory tract infections (high level term, HLT) such as nasopharyngitis and upper respiratory tract infection (preferred terms, PTs). No case of upper respiratory tract infection was serious or led to study drug discontinuation.

The most frequent AEs in this data set are presented in **Table 29**.

Table 29. Most frequent AEs by preferred term (>=2.0% in any group) – Short term period (16 weeks) (Pool A: Phase 3 AS trials - Safety set)

Preferred Term	AIN457 75mg N=73 n (%)	AIN457 150mg N=72 n (%)	AIN457 10mg/kg -75mg N=124 n (%)	AIN457 10mg/kg -150mg N=125 n (%)	Any AIN457 N=394 n (%)	Placebo N=196 n (%)
- Any preferred term	42 (57.5)	47 (65.3)	83 (66.9)	87 (69.6)	259 (65.7)	115 (58.7)
Nasopharyngitis	6 (8.2)	8 (11.1)	13 (10.5)	17 (13.6)	44 (11.2)	12 (6.1)
Dyslipidaemia	1 (1.4)	1 (1.4)	15 (12.1)	9 (7.2)	26 (6.6)	7 (3.6)
Headache	3 (4.1)	3 (4.2)	6 (4.8)	14 (11.2)	26 (6.6)	13 (6.6)
Nausea	1 (1.4)	3 (4.2)	5 (4.0)	6 (4.8)	15 (3.8)	5 (2.6)
Oropharyngeal pain	3 (4.1)	2 (2.8)	4 (3.2)	6 (4.8)	15 (3.8)	8 (4.1)
Diarrhoea	1 (1.4)	2 (2.8)	5 (4.0)	4 (3.2)	12 (3.0)	7 (3.6)
Fatigue	2 (2.7)	1 (1.4)	4 (3.2)	3 (2.4)	10 (2.5)	7 (3.6)
Leukopenia	0	0	6 (4.8)	4 (3.2)	10 (2.5)	1 (0.5)
Mouth ulceration	0	1 (1.4)	4 (3.2)	5 (4.0)	10 (2.5)	3 (1.5)
Upper respiratory tract infection	4 (5.5)	1 (1.4)	4 (3.2)	1 (0.8)	10 (2.5)	4 (2.0)
Gastroenteritis	3 (4.1)	1 (1.4)	2 (1.6)	3 (2.4)	9 (2.3)	2 (1.0)
Abdominal pain upper	0	0	5 (4.0)	3 (2.4)	8 (2.0)	1 (0.5)
Hypertension	1 (1.4)	2 (2.8)	2 (1.6)	3 (2.4)	8 (2.0)	0
Influenza	3 (4.1)	3 (4.2)	0	2 (1.6)	8 (2.0)	1 (0.5)
Arthralgia	0	1 (1.4)	3 (2.4)	3 (2.4)	7 (1.8)	6 (3.1)
Cough	0	1 (1.4)	3 (2.4)	3 (2.4)	7 (1.8)	3 (1.5)
Hypercholesterolaemia	2 (2.7)	2 (2.8)	1 (0.8)	2 (1.6)	7 (1.8)	5 (2.6)
Rash	2 (2.7)	0	1 (0.8)	3 (2.4)	6 (1.5)	1 (0.5)
Anaemia	0	0	2 (1.6)	3 (2.4)	5 (1.3)	1 (0.5)
Back pain	1 (1.4)	0	4 (3.2)	0	5 (1.3)	1 (0.5)
Bronchitis	1 (1.4)	2 (2.8)	0	2 (1.6)	5 (1.3)	2 (1.0)
Hepatic enzyme increased	1 (1.4)	2 (2.8)	2 (1.6)	0	5 (1.3)	1 (0.5)
Oral herpes	0	2 (2.8)	2 (1.6)	1 (0.8)	5 (1.3)	0
Pain in extremity	0	3 (4.2)	1 (0.8)	1 (0.8)	5 (1.3)	3 (1.5)
Pharyngitis	0	0	2 (1.6)	3 (2.4)	5 (1.3)	1 (0.5)
Viral infection	2 (2.7)	3 (4.2)	0	0	5 (1.3)	2 (1.0)
Ankylosing spondylitis	0	1 (1.4)	1 (0.8)	2 (1.6)	4 (1.0)	5 (2.6)
Dizziness	0	0	0	4 (3.2)	4 (1.0)	8 (4.1)
Dyspepsia	1 (1.4)	2 (2.8)	1 (0.8)	0	4 (1.0)	2 (1.0)
Haematuria	0	0	1 (0.8)	3 (2.4)	4 (1.0)	1 (0.5)
Hyperlipidaemia	0	1 (1.4)	1 (0.8)	2 (1.6)	4 (1.0)	4 (2.0)
Injection site pain	0	4 (5.6)	0	0	4 (1.0)	1 (0.5)
Musculoskeletal pain	2 (2.7)	0	2 (1.6)	0	4 (1.0)	0
Paraesthesia	1 (1.4)	0	0	3 (2.4)	4 (1.0)	0
Urinary tract infection	0	0	1 (0.8)	3 (2.4)	4 (1.0)	2 (1.0)
Cystitis	0	2 (2.8)	1 (0.8)	0	3 (0.8)	0
Nasal congestion	0	2 (2.8)	1 (0.8)	0	3 (0.8)	1 (0.5)
Costochondritis	0	2 (2.8)	0	0	2 (0.5)	0
Sinusitis	0	0	1 (0.8)	0	1 (0.3)	4 (2.0)
Leukocytosis	0	0	0	0	0	4 (2.0)

Most dyslipidemia events occurred in the iv loading dose groups. When compared to the individual laboratory values over time, these dyslipidemia AEs as reported by the investigators were not indicative of clinically meaningful changes in cholesterol since in the Any secukinumab group, the majority of shifts in cholesterol that occurred were from normal range to Grade 1, and the incidence of these shifts was comparable to that observed in the placebo group.

Entire studies

Over the entire treatment period, the most frequently affected SOCs in the "Any secukinumab group" were infections and infestations (mainly nasopharyngitis and upper respiratory tract infection), gastrointestinal disorders (mainly diarrhea), musculoskeletal and connective tissue disorders (mainly arthralgia, back pain, and musculoskeletal pain), and nervous system disorders (mainly headache).

The incidence of treatment-emergent AEs was comparable between the "Any 150 mg group"(84.0%) and the "Any 75 mg group (79.2%). SOCs that had a ≥ 3% higher incidence in the "Any 150 mg group" vs. the "Any 75 mg group were skin and subcutaneous tissue disorders and investigations. The PTs within the skin and subcutaneous tissue disorders SOC that had a ≥ 1% higher incidence in the "Any 150 mg group" vs the "Any 75 mg group" were pruritis (2.4% vs 1.4%, respectively), dermatitis (1.7% vs 0.7%, respectively), and dermatosis (1.0% vs 0.0%, respectively). The PTs within the investigations SOC that had a ≥ 1% higher incidence in the "Any 150 mg group" vs. the "Any 75 mg group" were osteoprotegerin decreased (2.4% vs 0.4%, respectively) and blood cholesterol increased (1.7% vs 0.7%, respectively). Osteoprotegerin is a bone biomarker whose levels were assessed in patients in Study CAIN457F2305.

Clinically meaningful differences where the absolute incidence of individual PTs was > 2% higher in the "Any 150 mg group" vs the "Any 75 mg group" were not observed (**Table 30**). PTs that were reported in ≥ 5 additional patients in the "Any 150 mg group" vs. the "Any 75 mg group" were nasopharyngitis, headache, influenza, back pain, pain in extremity, dizziness, spinal pain, osteoprotegerin decreased, tonsillitis, non-cardiac chest pain, and osteoporosis. None of these PTs showed a dose-dependent difference in frequency during the short-term 16-week period and none of these differences were considered to be clinically meaningful.

Adverse drug reactions

Up to Week 16 (Pool A), the overall profile of AEs related to study treatment was similar to that observed for all treatment-emergent AEs (**Tables 31** and **32**). AEs related to study treatment were comparable between the "Any secukinumab group" (25.9%) and the placebo group (26.5%). Patients in the 150 mg sc group reported AEs related to study treatment more frequently than the 75 mg sc group (26.4% vs 17.8%, respectively). This difference was driven mainly by the AEs injection site pain (5.6% vs 0%, respectively), nasopharyngitis (4.2% vs. 1.4%, respectively), headache (4.2% vs 1.4%, respectively), oral herpes (2.8% vs 0%, respectively) and pain in extremity (2.8% vs 0%, respectively). Overall, the frequency of AEs related to study treatment was higher in the iv loading groups (secukinumab iv-75 mg and iv-150 mg) compared with the sc loading groups (secukinumab 75 mg and 150 mg). The largest differences between the iv loading groups and the sc loading groups were in the incidences of the PTs leukopenia, fatigue, dyslipidaemia, and headache. Infections and infestations (mainly nasopharyngitis and upper respiratory tract infection) were the AEs that most frequently required concomitant medication (39.8%) in the "Any secukinumab group". The crude incidence of AEs requiring concomitant medication was 71.2% for the 75 mg sc group, 68.1% for the 150 mg 150 mg sc group, 62.9% for the iv-75 mg group, 71.2% for the iv-150 mg group, 56.3% for the 75 mg no-load group, and 57.8% for the 150 mg no-load group. In general, the profile of AEs requiring concomitant medication was similar to that for all treatment-emergent AEs across all treatment groups.

Median follow up in Pool A was 66 weeks. Similarly to weeks 0 to 16, in the entire study period the AE profile closely resembles 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.

Exposure adjusted incidences for dyslipidaemia were 4.8% in any secukinumab group vs 11.4% in placebo patients. Hypercholesterolemia 1.8% vs 8.1%, and hyperlipidaemia 1.3% vs 6.4% respectively. Leukopenia was observed in 3.6% in any 75 mg secukinumab group 3.0% in 150 mg group and 1.6% in placebo group, notably the most cases were evident in the iv-loaded patients..

Treatment emergent adverse events (TAEs) from study F2305 occurring more frequently in the secukinumab group were nasopharyngitis, diarrhoea, URTI, dyslipidaemia, pharyngitis, influenza, leukopenia, back pain, nausea, and neutropenia. And similarly from study F2310, nasopharyngitis, URTI, hypertension, influenza, bronchitis, oral herpes, pharyngitis and tonsillitis.

Table 30. Exposure-adjusted incidence of AEs by preferred term (>=2.0% in any group) – Entire treatment period (Pool A: Phase 3 AS trials – Safety set)

Preferred Term	Any AIN457 75mg N=284 n/EX (IR)	Any AIN457 150mg N=287 n/EX (IR)	Any AIN457 N=571 n/EX (IR)	Placebo N=196 n/EX (IR)
- Any preferred term	225/ 120.6 (186.6)	241/ 104.8 (229.9)	466/ 225.4 (206.8)	118/ 32.8 (359.5)
Nasopharyngitis	51/ 299.9 (17.0)	56/ 297.7 (18.8)	107/ 597.6 (17.9)	12/ 61.4 (19.5)
Diarrhoea	27/ 324.0 (8.3)	26/ 329.5 (7.9)	53/ 653.5 (8.1)	8/ 61.8 (13.0)
Headache	24/ 325.4 (7.4)	29/ 313.4 (9.3)	53/ 638.8 (8.3)	13/ 60.6 (21.5)
Upper respiratory tract infection	30/ 318.8 (9.4)	22/ 330.3 (6.7)	52/ 649.1 (8.0)	4/ 62.8 (6.4)
Oropharyngeal pain	17/ 329.9 (5.2)	17/ 331.8 (5.1)	34/ 661.6 (5.1)	8/ 62.0 (12.9)
Influenza	14/ 335.2 (4.2)	19/ 333.9 (5.7)	33/ 669.1 (4.9)	2/ 63.3 (3.2)
Dyslipidaemia	19/ 320.9 (5.9)	12/ 330.4 (3.6)	31/ 651.2 (4.8)	7/ 61.5 (11.4)
Pharyngitis	14/ 334.2 (4.2)	17/ 336.9 (5.0)	31/ 671.1 (4.6)	1/ 63.4 (1.6)
Arthralgia	14/ 335.1 (4.2)	12/ 336.3 (3.6)	26/ 671.4 (3.9)	6/ 62.5 (9.6)
Hypertension	12/ 337.1 (3.6)	14/ 334.6 (4.2)	26/ 671.8 (3.9)	0/ 63.6 (0.0)
Nausea	10/ 337.1 (3.0)	13/ 332.3 (3.9)	23/ 669.4 (3.4)	5/ 62.2 (8.0)
Gastroenteritis	11/ 335.2 (3.3)	11/ 338.1 (3.3)	22/ 673.3 (3.3)	2/ 63.3 (3.2)
Leukopenia	12/ 330.5 (3.6)	10/ 336.7 (3.0)	22/ 667.2 (3.3)	1/ 63.4 (1.6)
Back pain	8/ 338.1 (2.4)	13/ 340.4 (3.8)	21/ 678.5 (3.1)	1/ 63.5 (1.6)
Cough	12/ 334.9 (3.6)	9/ 337.4 (2.7)	21/ 672.3 (3.1)	3/ 62.8 (4.8)
Mouth ulceration	11/ 333.8 (3.3)	9/ 336.8 (2.7)	20/ 670.6 (3.0)	3/ 62.6 (4.8)
Bronchitis	8/ 339.8 (2.4)	10/ 340.6 (2.9)	18/ 680.4 (2.6)	3/ 63.1 (4.8)
Rhinitis	7/ 339.8 (2.1)	11/ 338.4 (3.3)	18/ 678.2 (2.7)	1/ 63.4 (1.6)
Abdominal pain upper	9/ 335.6 (2.7)	8/ 339.9 (2.4)	17/ 675.5 (2.5)	1/ 63.3 (1.6)
Fatigue	9/ 334.3 (2.7)	8/ 339.7 (2.4)	17/ 674.0 (2.5)	7/ 61.8 (11.3)
Oral herpes	6/ 339.7 (1.8)	9/ 340.1 (2.6)	15/ 679.8 (2.2)	0/ 63.6 (0.0)
Musculoskeletal pain	8/ 337.0 (2.4)	6/ 342.6 (1.8)	14/ 679.6 (2.1)	0/ 63.6 (0.0)
Urinary tract infection	6/ 340.0 (1.8)	8/ 340.7 (2.3)	14/ 680.7 (2.1)	2/ 63.1 (3.2)
Insomnia	6/ 342.7 (1.8)	7/ 343.7 (2.0)	13/ 686.4 (1.9)	2/ 63.5 (3.1)
Pain in extremity	4/ 341.9 (1.2)	9/ 339.0 (2.7)	13/ 680.9 (1.9)	3/ 63.0 (4.8)
Paraesthesia	5/ 341.5 (1.5)	8/ 339.8 (2.4)	13/ 681.3 (1.9)	0/ 63.6 (0.0)
Ankylosing spondylitis	4/ 343.6 (1.2)	8/ 341.3 (2.3)	12/ 684.9 (1.8)	5/ 62.5 (8.0)
Dizziness	3/ 342.6 (0.9)	9/ 339.6 (2.6)	12/ 682.2 (1.8)	8/ 61.1 (13.1)
Dyspepsia	6/ 339.6 (1.8)	6/ 341.2 (1.8)	12/ 680.9 (1.8)	2/ 63.3 (3.2)
Fall	7/ 340.2 (2.1)	5/ 343.5 (1.5)	12/ 683.7 (1.8)	1/ 63.5 (1.6)
Hypercholesterolaemia	4/ 340.6 (1.2)	8/ 337.8 (2.4)	12/ 678.3 (1.8)	5/ 62.1 (8.1)
Neutropenia	7/ 337.6 (2.1)	5/ 341.6 (1.5)	12/ 679.2 (1.8)	0/ 63.6 (0.0)
Sinusitis	5/ 340.8 (1.5)	7/ 341.8 (2.0)	12/ 682.6 (1.8)	4/ 62.9 (6.4)
Abdominal pain	4/ 340.5 (1.2)	7/ 342.0 (2.0)	11/ 682.6 (1.6)	0/ 63.6 (0.0)
Acute tonsillitis	6/ 341.0 (1.8)	5/ 342.9 (1.5)	11/ 684.0 (1.6)	0/ 63.6 (0.0)
Pruritus	4/ 340.5 (1.2)	7/ 339.4 (2.1)	11/ 679.9 (1.6)	3/ 62.9 (4.8)
Alanine aminotransferase increased	4/ 341.3 (1.2)	6/ 341.8 (1.8)	10/ 683.1 (1.5)	1/ 63.3 (1.6)
Hyperlipidaemia	3/ 340.9 (0.9)	6/ 339.6 (1.8)	9/ 680.5 (1.3)	4/ 62.2 (6.4)
Lymphadenopathy	6/ 339.9 (1.8)	3/ 344.3 (0.9)	9/ 684.3 (1.3)	0/ 63.6 (0.0)
Spinal pain	2/ 343.4 (0.6)	7/ 341.8 (2.0)	9/ 685.2 (1.3)	0/ 63.6 (0.0)
Osteoprotegerin decreased	1/ 343.5 (0.3)	7/ 339.2 (2.1)	8/ 682.7 (1.2)	1/ 63.1 (1.6)
Tendonitis	6/ 340.7 (1.8)	2/ 344.6 (0.6)	8/ 685.3 (1.2)	3/ 63.2 (4.7)
Tonsillitis	1/ 343.4 (0.3)	7/ 340.6 (2.1)	8/ 684.0 (1.2)	1/ 63.3 (1.6)
Anxiety	6/ 342.0 (1.8)	1/ 346.4 (0.3)	7/ 688.4 (1.0)	0/ 63.6 (0.0)
Non-cardiac chest pain	1/ 344.5 (0.3)	6/ 342.6 (1.8)	7/ 687.1 (1.0)	0/ 63.6 (0.0)
Osteoporosis	1/ 344.1 (0.3)	6/ 343.4 (1.7)	7/ 687.5 (1.0)	1/ 63.1 (1.6)

Table 31. Most frequent treatment emergent adverse events (at least 2% in the Any AIN457 group) by preferred term up to Week 16 (Safety set of study F2305)

Preferred Term	AIN457 10mg/kg - 75 mg N = 124 n (%)	AIN457 10mg/kg - 150 mg N = 125 n (%)	Any AIN457 N = 249 n (%)	Placebo N = 122 n (%)
-Any preferred term	83 (66.9)	87 (69.6)	170 (68.3)	68 (55.7)
Nasopharyngitis	13 (10.5)	17 (13.6)	30 (12.0)	9 (7.4)
Dyslipidemia	15 (12.1)	9 (7.2)	24 (9.6)	6 (4.9)
Headache	6 (4.8)	14 (11.2)	20 (8.0)	7 (5.7)
Nausea	5 (4.0)	6 (4.8)	11 (4.4)	2 (1.6)
Leukopenia	6 (4.8)	4 (3.2)	10 (4.0)	1 (0.8)
Oropharyngeal pain	4 (3.2)	6 (4.8)	10 (4.0)	6 (4.9)
Diarrhea	5 (4.0)	4 (3.2)	9 (3.6)	6 (4.9)
Mouth ulceration	4 (3.2)	5 (4.0)	9 (3.6)	3 (2.5)
Abdominal pain upper	5 (4.0)	3 (2.4)	8 (3.2)	0 (0.0)
Fatigue	4 (3.2)	3 (2.4)	7 (2.8)	2 (1.6)
Arthralgia	3 (2.4)	3 (2.4)	6 (2.4)	4 (3.3)
Cough	3 (2.4)	3 (2.4)	6 (2.4)	2 (1.6)
Anemia	2 (1.6)	3 (2.4)	5 (2.0)	1 (0.8)
Gastroenteritis	2 (1.6)	3 (2.4)	5 (2.0)	1 (0.8)
Hypertension	2 (1.6)	3 (2.4)	5 (2.0)	0 (0.0)
Pharyngitis	2 (1.6)	3 (2.4)	5 (2.0)	1 (0.8)
Upper respiratory tract infection	4 (3.2)	1 (0.8)	5 (2.0)	2 (1.6)

Table 32. Most frequent treatment emergent adverse events (at least 2% in the Any AIN457 group) by preferred term up to Week 16 (Safety set of study F2310)

Preferred Term	AIN457 75 mg N = 73 n (%)	AIN457 150 mg N = 72 n (%)	Any AIN457 N = 145 n (%)	Placebo N = 74 n (%)
-Any preferred term	42 (57.5)	47 (65.3)	89 (61.4)	47 (63.5)
Nasopharyngitis	6 (8.2)	8 (11.1)	14 (9.7)	3 (4.1)
Headache	3 (4.1)	3 (4.2)	6 (4.1)	6 (8.1)
Influenza	3 (4.1)	3 (4.2)	6 (4.1)	0 (0.0)
Oropharyngeal pain	3 (4.1)	2 (2.8)	5 (3.4)	2 (2.7)
Upper respiratory tract infection	4 (5.5)	1 (1.4)	5 (3.4)	2 (2.7)
Viral infection	2 (2.7)	3 (4.2)	5 (3.4)	2 (2.7)
Gastroenteritis	3 (4.1)	1 (1.4)	4 (2.8)	1 (1.4)
Hypercholesterolaemia	2 (2.7)	2 (2.8)	4 (2.8)	3 (4.1)
Injection site pain	0 (0.0)	4 (5.6)	4 (2.8)	1 (1.4)
Nausea	1 (1.4)	3 (4.2)	4 (2.8)	3 (4.1)
Bronchitis	1 (1.4)	2 (2.8)	3 (2.1)	1 (1.4)
Diarrhoea	1 (1.4)	2 (2.8)	3 (2.1)	1 (1.4)
Dyspepsia	1 (1.4)	2 (2.8)	3 (2.1)	1 (1.4)
Fatigue	2 (2.7)	1 (1.4)	3 (2.1)	5 (6.8)
Hepatic enzyme increased	1 (1.4)	2 (2.8)	3 (2.1)	0 (0.0)
Hypertension	1 (1.4)	2 (2.8)	3 (2.1)	0 (0.0)
Pain in extremity	0 (0.0)	3 (4.2)	3 (2.1)	1 (1.4)

The overall profile of AEs related to study treatment during the entire treatment period was comparable to that observed up to Week 16. A higher rate of AEs related to study treatment was observed in the "Any 150 mg group" (44.9%) vs the "Any 75 mg group" (34.9%). The AEs that showed an increased incidence of ≥ 2% in the "Any 150 mg group" vs the "Any 75 mg group" were nausea (2.4% vs 0.4%, respectively), nasopharyngitis (7.3% vs 3.5%, respectively), pharyngitis (3.8% vs 0.7%, respectively), headache (5.2% vs 1.8%, respectively) and oral herpes (2.8% vs. 0.7%, respectively). The crude incidence of AEs possibly related to study treatment was 31.5% in the 75 mg sc group, 41.7% in the 150 mg sc group, 38.7% in the iv-75 mg group, 52.0% in the iv-150 mg group, 32.2% in the 75 mg no-load group, and 37.8% in the 150 mg no-load group.

AEs causing dose interruption or adjustment

In study F2305 and F2310, study treatment dose adjustments were not permitted. Study treatment interruption was permitted only if, in the opinion of the investigator, a patient's safety was deemed to be at risk unless dosing was interrupted.

The incidence of AEs causing dose interruption in the "Any secukinumab group" was 13.3%. Overall, the rate of AEs was comparable between the Any 75 mg and Any 150 mg groups (12.3% and 14.3%, respectively). The most common AEs causing dose interruption were infections and infestations (7.7% in the "Any 75 mg group" and 9.8% in the "Any 150 mg group"). The most common infections and infestations in the "Any secukinumab group" were upper respiratory tract infection (1.6%), bronchitis (0.9%), and influenza, nasopharyngitis, and urinary tract infection (each 0.7%). The crude incidence of AEs causing dose interruption was 17.8% for the 75 mg sc group, 18.1% for the 150 mg sc group, 10.5% for the iv-75 mg group, 10.4% for the iv-150 mg group, 10.3% for the 75 mg no-load group, and 16.7% for the 150 mg no-load group.

Crohn´s disease

Over the entire treatment period, 5 cases of Crohn's disease were reported in the "Any secukinumab group" (**Table 33**), 4 of which occurred in patients with a prior history or suspected history of Crohn's disease. The remaining case had a prior history of intestine polyps/adenoma, was treated with infliximab for over 2 years which was stopped 6 months prior to the event. No cases of Crohn's disease were reported in the placebo group. Of note, when comparing secukinumab-treated AS patients with placebo-treated AS patients, the number of patients being treated and patient-years of exposure are 2.9-fold and 10.9-fold higher, respectively, in the secukinumab-treated group, which may have led to the observed differences in the number of reported AEs of IBD or Crohn's disease.

Table 33. Exposure-adjusted incidence of inflammatory bowel disease – Entire treatment period (Pool A: Phase 3 AS trials – Safety set)

Level 1 Preferred term	Any AIN457 75 mg N=284 n/EX (IR)	Any AIN457 150 mg N=287 n/EX (IR)	Any AIN457 dose N=571 n/EX (IR)	Placebo N=196 n/EX (IR)
Based on all AEs				
Inflammatory bowel disease (narrow NMQ)	5/342.3 (1.5)	3/344.3 (0.9)	8/686.6 (1.2)	0/63.6 (0.0)
Colitis ulcerative (PT)	1/344.5 (0.3)	2/344.7 (0.6)	3/689.2 (0.4)	0/63.6 (0.0)
Crohn's disease (PT)	4/342.5 (1.2)	1/346.1 (0.3)	5/688.6 (0.7)	0/63.6 (0.0)
Inflammatory bowel disease (PT)	1/344.6 (0.3)	0/346.5 (0.0)	1/691.1 (0.1)	0/63.6 (0.0)
Based on all SAEs				
Inflammatory bowel disease (narrow NMQ)	2/344.4 (0.6)	1/345.6 (0.3)	3/690.0 (0.4)	0/63.6 (0.0)
Colitis ulcerative (PT)	1/344.5 (0.3)	1/345.6 (0.3)	2/690.0 (0.3)	0/63.6 (0.0)
Crohn's disease (PT)	1/344.6 (0.3)	0/346.5 (0.0)	1/691.1 (0.1)	0/63.6 (0.0)

In total, the search yielded 4 events of IBD in 3 patients during the first 16-week period, with 1 SAE of Crohn's disease (PT) in the 75 mg group and 1 SAE of colitis ulcerative in the 75 mg group. The patient in

the 75 mg sc group who experienced the SAE of Crohn's disease on Day 45 had experienced rectal bleeding prior to randomization. The investigator therefore considered the patient to have had an exacerbation of a pre-existing condition of Crohn's disease. In addition, the patient was treated with adalimumab for 8 months which was stopped 4 months prior to the event. A second patient with a 6-year history of Crohn's disease and a colectomy in the iv-75 mg group reported a flare on Days 42 and 89.

The SAE of ulcerative colitis that occurred in the first 16 weeks was reported in a patient in the 75 mg sc group, did not lead to study treatment discontinuation, and was not suspected by the investigator to be related to study medication.

For the cases of Crohn's disease after 16 weeks in study, 2 occurred in patients in the iv-75 mg group. One was an exacerbation in a patient with a 7-year history of Crohn's disease, which was ongoing at baseline. This exacerbation was reported on Day 162, was moderate in severity, not a SAE, was suspected to be related to study medication, and led to the discontinuation of study treatment. The outcome of the event was unknown at the time of reporting. The other case occurred in a patient with a history of large intestinal polyps and colon adenoma who developed Crohn's disease on Day 141. The patient was treated with infliximab for over 2 years which was stopped 8 months prior to the event. This event was moderate in severity, not a SAE, considered unrelated to study treatment, and did not lead to discontinuation.

The third case of Crohn's disease (exacerbation of Crohn's disease) occurred on Day 428 in a patient in the 150 mg no-load group who had no reported pre-existing gastrointestinal disorders prior to the study. The event occurred after the patient had stopped study treatment, was a serious adverse event (SAE), and was not considered to be related to study treatment. Prior to the SAE, on Day 263, the patient was diagnosed with Crohn's disease (non-serious) and was treated with prednisone, pinaverium and proctosedyl. The patient was treated with methylprednisolone sodium succinate and the event resolved.

For the 2 additional cases of colitis ulcerative that occurred in the entire treatment period, one was an SAE that was an exacerbation of pre-existing disease in a patient in the 150 mg sc group reported as a complete recovery. This patient had a 1-year history of ulcerative colitis, was taking concomitant NSAIDs, and was treated with mesalazine at baseline. The other case occurred in a patient in the 150 mg sc group with no history of IBD. This patient had a 3-year history of chronic diarrhoea. Prior medications include adalimumab (for 2 years) and NSAIDs (long term), and the patient was a current smoker. The event of colitis ulcerative was not a SAE, did not lead to study treatment discontinuation, and resolved with mesalazine treatment.

Infections and infestations

The profile of infections and infestations among AS patients was consistent with that observed in the extensive psoriasis safety database. The rate of non-serious infections, mainly of the upper respiratory tract, was higher than placebo in the short-term period (16 weeks) and similar across secukinumab doses. During the entire treatment period, exposure adjusted incidence rates (EAIRs) for infections across all secukinumab dose groups were comparable to placebo with no evidence of a dose effect (**Table 34**).

A total of 6 cases of Candida infections were reported for secukinumab patients, with 2 cases occurring in the first 16 weeks and the remaining 4 thereafter. No cases were reported for placebo patients in the entire treatment period. The absolute incidence of Candida infections was comparable between the secukinumab dose groups (1.4% and 0.7%, respectively, for the Any 75 mg group and the Any 150 mg group). The most common event was oral candidiasis with 3 (0.5%) total cases. All Candida cases were mild in severity, non-serious, resolved with standard treatment when provided, and did not necessitate treatment discontinuation.

Herpes viral infections (HLT) occurred in a higher proportion of patients in the Any secukinumab group compared with placebo (2.0% vs 0%). Oral herpes comprised the majority of events (1.3%). No herpes

viral infection was a SAE or led to permanent discontinuation. No cases of herpes viral infections were seen in the 75 mg group.

A search for opportunistic infections by NMQ was performed and yielded 1 case of herpes zoster cutaneous disseminated in patient. This event occurred in a patient in the iv-75 mg group, was considered moderate in severity and limited only to the skin, was non-serious, and did not lead to study treatment interruption or discontinuation.

There were no serious opportunistic infections, and no cases of reactivation of tuberculosis. There was 1 event of hepatitis viral (PT) (verbatim term: probably viral hepatitis) reported in a patient in the iv-75 mg group that was moderate in severity, non-serious, and did not lead to study treatment interruption or discontinuation. This patient did not have a history of hepatitis; this event was therefore not considered to be hepatitis reactivation.

The proportion of patients with infections of skin structures (NMQ) was comparable between the secukinumab dose groups (9.2% and 10.8%, respectively, for "Any 75 mg" and "Any 150 mg"). Overall, the rate of skin structure infections was higher in the "Any secukinumab group" (10.0%) compared with the placebo group (1.5%). The most common infections of skin structures in the "Any secukinumab group" were folliculitis and tinea pedis (each occurring in 4 patients, 0.7%) with similar rates between the dose groups.

Table 34. Exposure-adjusted incidence rates for infections and opportunistic infections – Entire treatment period (Pool A: Phase 3 AS trials – Safety set)

Level 1 Level 2 Level 3	Any AIN457 75 mg N=284 n/EX (IR)	Any AIN457 150 mg N=287 n/EX (IR)	Any AIN457 dose N=571 n/EX (IR)	Placebo N=196 n/EX (IR)
Based on all AEs				
Infections and infestations (SOC)*	150/217.7 (68.9)	148/215.7 (68.6)	298/433.3 (68.8)	36/56.4 (63.8)
Upper respiratory tract infections (HLT)	100/258.7 (38.7)	102/260.8 (39.1)	202/519.5 (38.9)	21/59.5 (35.3)
Candida infections (HLT)	4/340.7 (1.2)	2/345.7 (0.6)	6/686.5 (0.9)	0/63.6 (0.0)
Opportunistic infections (NMQ) §	1/343.5 (0.3)	0/346.5 (0.0)	1/690.0 (0.1)	0/63.6 (0.0)
Based on all SAEs				
Infections and infestations (SOC)*	3/342.3 (0.9)	3/343.9 (0.9)	6/686.2 (0.9)	0/63.6 (0.0)
Upper respiratory tract infections (HLT)	1/344.0 (0.3)	1/345.7 (0.3)	2/689.7 (0.3)	0/63.6 (0.0)
Candida infections (HLT)	0/344.6 (0.0)	0/346.5 (0.0)	0/691.1 (0.0)	0/63.6 (0.0)
Opportunistic infections (NMQ)	0/343.5 (0.0)	0/346.5 (0.0)	0/690.0 (0.0)	0/63.6 (0.0)

Malignancies and skin tumours

Over the entire treatment period in the AS Phase 3 studies, the incidence of malignancies was low, with an exposure-adjusted incidence rate per 100 patient-years of 0.6 in the "Any secukinumab group" and comparable across the secukinumab dose groups and placebo (**Table 35**). There was no imbalance in malignancy AEs between secukinumab and placebo in Pool C of all secukinumab studies across multiple indications.

One case of malignant melanoma (PT) was reported in a patient in the 150 mg secukinumab group. This event was a SAE and led to study treatment discontinuation. One case of lymphoma (PT) was reported in a patient in the placebo group. This event was a SAE and led to study treatment discontinuation. In addition to the malignancies that occurred during the first 16 weeks, there was a case of B-cell lymphoma in the iv-75 mg group, a case of breast cancer in the iv-150 mg group and a case of bladder transitional cell carcinoma in the iv-150 mg group. Each of these events was a SAE that led to study treatment discontinuation. During the follow-up period, a case of malignant melanoma was reported in a placebo patient.

Table 35. Exposure-adjusted incidence rates for malignancies and skin tumors – Entire treatment period (Pool A: Phase 3 AS trials – Safety set)

Level 1 Preferred term	Any AIN457 75 mg N=284 n/EX (IR)	Any AIN457 150 mg N=287 n/EX (IR)	Any AIN457 dose N=571 n/EX (IR)	Placebo N=196 n/EX (IR)
Based on all AEs				
Malignant or unspecified tumors (SMQ)	1/344.5 (0.3)	3/346.0 (0.9)	4/690.4 (0.6)	1/63.6 (1.6)
B-cell lymphoma (PT)	1/344.5 (0.3)	0/346.5 (0.0)	1/691.0 (0.1)	0/63.6 (0.0)
Bladder transitional cell carcinoma (PT)	0/344.6 (0.0)	1/346.1 (0.3)	1/690.7 (0.1)	0/63.6 (0.0)
Breast cancer (PT)	0/344.6 (0.0)	1/346.4 (0.3)	1/691.1 (0.1)	0/63.6 (0.0)
Lymphoma (PT)	0/344.6 (0.0)	0/346.5 (0.0)	0/ 691.1 (0.0)	1/63.6 (1.6)
Malignant melanoma (PT)	0/344.6 (0.0)	1/346.5 (0.3)	1/ 691.1 (0.1)	0/63.6 (0.0)
Based on all SAEs				
Malignant or unspecified tumors (SMQ)	1/344.5 (0.3)	3/346.0 (0.9)	4/690.4 (0.6)	1/63.6 (1.6)
B-cell lymphoma (PT)	1/344.5 (0.3)	0/346.5 (0.0)	1/ 691.0 (0.1)	0/63.6 (0.0)
Bladder transitional cell carcinoma (PT)	0/344.6 (0.0)	1/346.1 (0.3)	1/ 690.7 (0.1)	0/63.6 (0.0)
Breast cancer (PT)	0/344.6 (0.0)	1/346.4 (0.3)	1/ 691.1 (0.1)	0/63.6 (0.0)
Lymphoma (PT)	0/344.6 (0.0)	0/346.5 (0.0)	0/ 691.1 (0.0)	1/63.6 (1.6)
Malignant melanoma (PT)	0/344.6 (0.0)	1/346.5 (0.3)	1/691.1 (0.1)	0/63.3 (0.0)

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 (in the upper lip taken care by an excision, not related to study medication according to investigator) and (with a history of actinic keratosis, 3 incidents in different body parts earlier and one more during 300 mg sc secukinumab treatment on day 280).
- One case of adenosquamous cell carcinoma (in the lung in a patient with COPD and after 23 pack years of smoking during 150 mg sc secukinumab treatment on day 81.
- One case of B-cell lymphoma in a patient which was originally randomized to receive placebo and was then re-randomized to receive Placebo-300 mg secukinumab. Patient medical history included left shoulder lipoma, periodontal disease and genital herpes. Past medications taken prior to study entry included calcipotriene, cyclosporine, ustekinumab (Jul 2006 to Sep 2006) and tofacitinib (Feb 2012 to May 2012). All past medications were taken for psoriasis. The patient started receiving study medication on 12-Jul-2012. On 23-Dec-2013, the patient presented with abnormal laboratory tests and differential pathology showed atypical haematopoietic forms. The last dose of study medication was taken on 23-Dec-2013 and study treatment was officially discontinued on 11-Jan-2014. Bone marrow biopsy on 13-Feb-2014 revealed the final diagnosis of low grade B-cell lymphoproliferative disorder in line with marginal zone lymphoma. The investigator reported the event as suspected to be related to study treatment and also suspected to be related to past treatment of tofacitinib and ustekinumab.

There was no imbalance in malignancy AEs between secukinumab and placebo over the entire treatment period in Pool C of all secukinumab studies across multiple indications. The exposure-adjusted incidence per 100 patient-years of malignant or unspecified tumours (SMQ) based on all AEs was comparable between the “Any secukinumab dose” group and placebo over the entire treatment period of all secukinumab trials (IR=0.95 for “Any secukinumab dose” vs. 1.55 for placebo). For malignant or unspecific skin tumours (broad NMQ), the incidence per 100 patient-years was also comparable between the “Any secukinumab dose” group and placebo (0.59 vs. 0.97). For malignant or unspecific tumours reported as SAEs, the exposure-adjusted rate was nearly identical between the “Any secukinumab dose” group vs. placebo (IR=0.54 vs. 0.58)

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

Major adverse cardiovascular events

Eligibility criteria permitted patients with stable cardiovascular risk factors or a history of cardiovascular disease to enrol in the Phase 3 studies in AS. All confirmed MACE cases (n=3) had prior cardiovascular disease or pre-existing risk factors at baseline. No cases of MACE were reported in the placebo group. There was no evidence of a dose-dependency with 2 of 3 cases reported at a dose of 75 mg. Despite all 3 confirmed MACE cases occurring on secukinumab, a comparison of crude incidence rates between secukinumab and placebo is complicated by significant differences in the average length of follow-up which for patients in the secukinumab treatment groups was 10 times that of patients in the placebo group (Table 36).

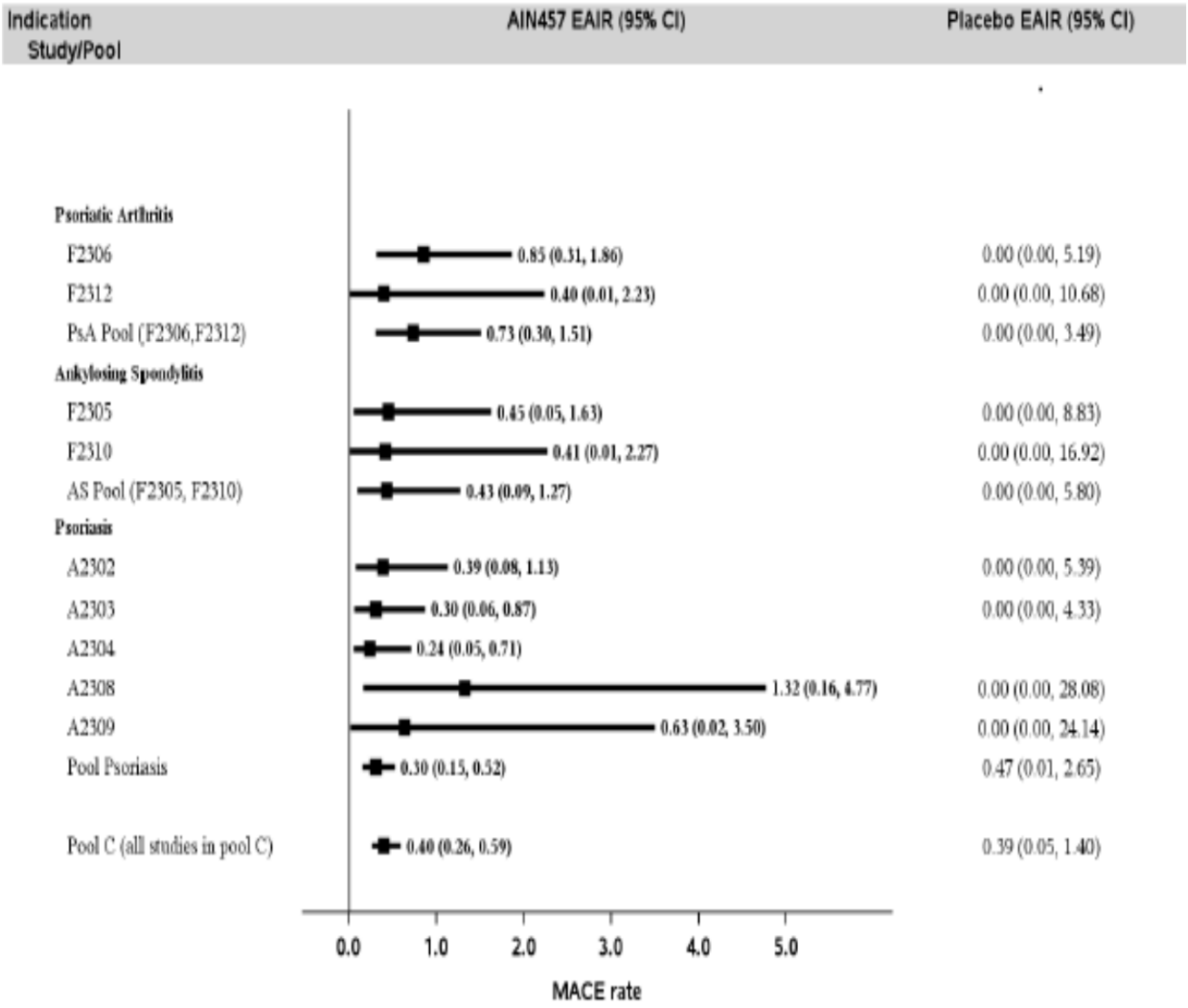
There was no evidence of an increased risk of MACE relative to the expected rate in AS patients. Further, there was no direct evidence of a causal relationship between the incidence of MACE and the loading period. The overall EAIR of adjudicated and confirmed MACE over the entire treatment period in the Phase 3 AS studies was 0.43 per 100 patient-years (95% CI: 0.09-1.27) (**Table 36**). The point estimates in the two AS studies ranged between 0.41 (95% CI=0.01 to 2.27) for F2310 and 0.45 (95% CI=0.05 to 1.63) for F2305 with overlapping 95% CIs.

Table 36. MACE adjudication results in AS patients – Entire treatment period (Pool A: Phase 3 AS trials – Safety set)

MACE category Adjudication outcome	Any AIN457 75 mg N=284 n (%)	Any AIN457 150 mg N=287 n (%)	Any AIN457 dose N=571 n (%)	Placebo N=196 n (%)
Myocardial infarction				
Yes	2 (0.7)	0	2 (0.4)	0
No	0	1 (0.3)*	1 (0.2)	0
Stroke				
Yes	0	1 (0.3)	1 (0.2)	0
Cardiovascular death				
Cardiovascular	1 (0.4)**	0	0	0
Total no. MACE (Yes)#	2 (0.7)	1 (0.3)	3 (0.6)	0

In the present submission, the rate of MACE on secukinumab across multiple indications was stable with increased exposure. 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, 95% CI: 0.26 - 0.59) for the Any secukinumab dose group and 0.39 (n=2, 95% CI: 0.05 - 1.40) for placebo, **Figure 21**.

Figure 21. 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 AS population did not suggest an increased risk for drug-induced liver injury (DILI) from secukinumab treatment. Despite small imbalances in the incidence of mild transaminase elevations versus placebo, the overall incidence was low and comparable across the secukinumab treatment groups showing no dose-response relationships. Discontinuations due to hepatotoxicity were rare in secukinumab treated patients and 4 of 5 cases (liver function analysis HLT) were confounded by either a previously reported medical condition or concomitant treatment with isoniazid or methotrexate.

A case of severe hepatic enzyme increased in a patient in the 150 mg sc group, which was reported as a SAE also led to treatment discontinuation. The patient had normal baseline hepatic enzyme levels. On Day 57, ALT was >5×ULN, and AST was >6×ULN; both remained elevated at these levels for >2 wks. The patient's GGT and ALP levels were also elevated starting on the same day. An SAE of hepatic enzyme increased was reported. The event was suspected to be related to the study medication.

One patient in the iv-75 mg group had a history of hyperbilirubinemia and normal liver function tests at baseline. From Day 366, the ALT began to rise and the patient was diagnosed with increased alanine aminotransferase. The patient developed elevated ALT >8-10×ULN (424 U/L), AST >3-5×ULN (194 U/L) and TBL >2-3×ULN (44 µmol/L) at Day 440 (Week 60). Prior to this event, ALT elevations were also reported at Day 373 (180 U/L) and Day 394 (161 U/L). A non-serious AE of alanine aminotransferase increased was reported earlier at Day 366 which did not lead to discontinuation.

One patient in the iv-75 mg group with baseline normal AST (19 U/L) developed AST >8-10×ULN (338 U/L) at Day 169 (Week 24) with elevations in ALT to >3-5×ULN (146 U/L) and ALP to >2-3 ×ULN (282 U/L). A non-serious AE of viral hepatitis with an onset at Day 165 was reported at the time of these elevations.

One patient in the iv-150 mg group, with active medical conditions of hypertension and hepatic steatosis reported increased ALT levels (non-serious event) on Day 15 and was treated with ademetionine. The event (ALT increased) was considered resolved on Day 31. On Day 123, the patient's hepatic enzymes were reported to be increased (moderate severity) (laboratory values not reported). Treatment for increased hepatic enzymes included ademetionine and ursodeoxycholic acid. Treatment with the study medication was permanently discontinued due to increased hepatic enzymes. The event (hepatic enzyme increased) was ongoing at the time of last reporting. The event was not suspected to be related the study medication.

One patient in the iv-75 mg group entered the study with normal hepatic enzymes at screening. At the time of study entry, the patient was receiving etoricoxib for AS and isoniazid (Day -24 to Day 9) for positive PPD test. Laboratory tests showed increased transaminase levels on Day 8. At baseline (Day 1), the patient's ALT and AST levels were elevated (79 U/L [RR: 0 to 45 U/L] and 58 U/L [RR: 0 to 41 U/L], respectively). No treatment was reported for this event. Treatment with the study medication was permanently discontinued due to this event. The event was suspected to be related to the study medication.

One patient in the iv-150 mg group, with baseline elevated ALT of 77 U/L (RR: 0 to 45 U/L) and AST of 58 U/L (RR: 0 to 41 U/L), reported increased transaminases (moderate severity) on Day 114. ALT was 157 U/L and AST was 71 U/L. Treatment with the study medication was permanently discontinued due to increased transaminases. The event was suspected to be related to the study medication.

One patient on placebo discontinued due to an AE of "toxic hepatitis".

QTC-prolongation

A search for cases of QT prolongation yielded 1 AE of QTcB prolonged (>480 msec) in the AS population in the Any 150 mg group. The event was non-serious, mild in severity and considered unrelated to the study medication. This patient did not discontinue study medication due to this event. There were no patients in the secukinumab treatment groups with QTcB and QTcF changes from baseline >60 msec. Two patients on placebo were noted with QTcB changes from baseline >60 msec, while only 1 patient on placebo had this change based on the Fridericia correction (QTcF).

Serious adverse event / deaths / other significant events

Deaths

A total of 3 deaths,1 in the placebo group (suicide) on Day 80, 1 in the iv-75 mg group due to respiratory failure on Day 706, and 1 in the 75 mg sc group due to an acute myocardial infarction on Day 29 occurred in the 2 AS studies. None of these deaths were considered to be related to study treatment. The case of fatal respiratory failure was attributed to a relevant medical history of pulmonary fibrosis and

cardiac failure. This patient had multiple cardiopulmonary risk factors at baseline. The case of fatal myocardial infarction also occurred in a patient with multiple baseline cardiovascular risk factors.

Four deaths were reported across data pools A, B1 and B in studies F2306, A2302 and A2308 (psoriatic arthritis, psoriasis): one death was reported for the PsA trials 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 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).

Serious adverse events

The overall rate of SAEs in the first 16 weeks was low (≤ 5.6% of patients in any treatment group) and comparable for the "Any secukinumab" group" and the placebo group. While the incidence of serious gastrointestinal disorders was higher in the "Any secukinumab" group compared to the placebo group, this was based on a small number of patients affected (n = 4, 1.0% vs n = 0). No dose-dependent increase in SAEs was observed across the studies in comparing between the 75 mg sc and 150 mg sc (5.5% and 5.6%, respectively) groups and further supported by the numerically lower SAE rate observed in the iv dose groups (iv-75 mg: 1.6% and iv-150 mg: 2.4%).

Over the entire treatment period, the incidence of SAEs within any SOC was low and no individual SAE occurred in > 2 patients (0.4%) in the "Any secukinumab group". The most frequently affected SOCs in the "Any secukinumab group" were gastrointestinal disorders and injury, poisoning, and procedural complications. The incidence of serious infections in the "Any secukinumab group" (0.9%) was low and no dose response was observed. Comparable frequencies of SAEs were reported in the "Any 75 mg group" (9.5%) and the "Any 150 mg group" (8.7%). No dose effect was apparent in any individual SOC or preferred term.

Four Phase 3 studies in AS (F2305, F2305E1, F2310, F2314) were ongoing at time of review. For Pool A, treatment blinded SAEs reported between the data cut-off dates for Pool A studies (F2305: 10-Dec-2013 and F2310: 04-Aug-2014, respectively) and 10-Oct-2014 included:

- 15 SAEs for 14 patients in Study F2305. Notable events included 2 cases of myocardial infarction: (myocardial infarction in a patient with medical history of angioplasty, stent placement and current tobacco use and concomitant etoricoxib use and myocardial infarction in a patient with current conditions of obesity, metabolic syndrome, Type 2 diabetes mellitus and medical history of coronary angioplasty and stent placement), and 1 case of bilateral pulmonary fibrosis leading to death.
- 3 SAEs in 3 patients in Study F2310. These included a case each of pneumonia, nephrotic syndrome and acute coronary syndrome (unstable angina, ischemic cardiopathy,Non ST elevation) in a patient with current conditions of hypertension, dyslipidemia, diabetes mellitus and history of myocardial infarction.

Other significant events

The AEs leading to discontinuation that occurred more than once in the "Any secukinumab group" were Crohn's disease, dyspnoea, hemoglobin decreased, hepatic enzyme increased, pregnancy, and

transaminases increased (**Table 37**). Of two patients who discontinued due to hepatic enzyme increased, one patient was in the 150 mg secukinumab group and one patient was in the iv-150 mg group. Additional information regarding the two patients who discontinued due to transaminases increased is described above. The crude incidence of AEs leading to study treatment discontinuation at any time during the entire treatment period was 5.5% for the 75 mg sc group, 8.3% for the 150 mg sc group, 4.8% for the iv-75 mg group, 9.6% for the iv-150 mg group, 1.1% for the 75 mg no-load group, and 2.2% for the 150 mg no-load group.

Table 37.AEs leading to discontinuation by preferred term – Entire treatment period (Pool A: Phase 3 AS trials - Safety set)

Preferred Term	Any AIN457 75mg N=284 n (%)	Any AIN457 150mg N=287 n (%)	Any AIN457 N=571 n (%)
- Any preferred term	11 (3.9)	20 (7.0)	31 (5.4)
Crohn's disease	2 (0.7)	0	2 (0.4)
Dyspnoea	1 (0.4)	1 (0.3)	2 (0.4)
Haemoglobin decreased	1 (0.4)	1 (0.3)	2 (0.4)
Hepatic enzyme increased	0	2 (0.7)	2 (0.4)
Pregnancy	0	2 (0.7)	2 (0.4)
Transaminases increased	1 (0.4)	1 (0.3)	2 (0.4)
Alanine aminotransferase increased	0	1 (0.3)	1 (0.2)
Anaemia	0	1 (0.3)	1 (0.2)
Ankylosing spondylitis	0	1 (0.3)	1 (0.2)
Arthralgia	1 (0.4)	0	1 (0.2)
B-cell lymphoma	1 (0.4)	0	1 (0.2)
Bladder transitional cell carcinoma	0	1 (0.3)	1 (0.2)
Blood pressure increased	1 (0.4)	0	1 (0.2)
Breast cancer	0	1 (0.3)	1 (0.2)
Colitis	0	1 (0.3)	1 (0.2)
Headache	1 (0.4)	0	1 (0.2)
Herpes zoster	0	1 (0.3)	1 (0.2)
Hyperhidrosis	0	1 (0.3)	1 (0.2)
Malignant melanoma	0	1 (0.3)	1 (0.2)
Myocardial infarction	1 (0.4)	0	1 (0.2)
Nuclear magnetic resonance imaging brain abnormal	0	1 (0.3)	1 (0.2)
Polyneuropathy	0	1 (0.3)	1 (0.2)
Pulmonary cavitation	0	1 (0.3)	1 (0.2)
Skin ulcer	1 (0.4)	0	1 (0.2)
Small intestinal obstruction	0	1 (0.3)	1 (0.2)

Laboratory findings

Haematology

Although a higher incidence of neutropenia was observed in secukinumab-treated AS patients vs placebo-treated AS patients, no secukinumab dose-relationship was observed (**Table 38**). A small proportion of patients across the secukinumab treatment groups reported neutrophil abnormalities. No CTCAE Grade 3 (n=4) or Grade 4 (n=1) neutropenia events were associated with a serious infection. Neutropenia related AEs were non-serious in nature and the majority of these (21 out of 27) were reported in the iv loading groups.

Among the 4 patients overall with CTCAE Grade 3 neutropenia, 1 patient experienced a non-serious mild upper respiratory tract infection at the time of the neutrophil abnormality. Rates of AEs in the

neutropenia narrow NMQ (absolute and exposure-adjusted) showed an increased rate with secukinumab relative to placebo but none of the events were reported as SAEs or led to discontinuation.

In the submission for psoriasis, the incidence of neutropenia for secukinumab was higher than placebo. No dose effect for secukinumab was observed in laboratory results or in AEs. As of 10-Oct-2014 (data cut-off for the submission), no Grade 4 neutropenia event was reported.

Table 38. Neutropenia events – Entire treatment period (Pool A: Phase 3 AS trials – Safety set)

Level 1 Preferred term	Any AIN457 75 mg N=284 n/EX (IR)	Any AIN457 150 mg N=287 n/EX (IR)	Any AIN457 dose N=571 n/EX (IR)	Placebo N=196 n/EX (IR)
Based on all AEs				
Neutropenia (narrow NMQ)	15/327.8 (4.6)	12/334.9 (3.6)	27/662.8 (4.1)	1/63.4 (1.6)
Based on all SAEs				
Neutropenia (narrow NMQ)	0	0	0	0

Clinical chemistry

Shifts in CTCAE grades for clinical chemistry parameters during the first 16 weeks: The majority of patients had values within the normal range at baseline and continued to show normal values post-baseline during the initial treatment period. A proportion of patients in all treatment groups shifted from normal range to Grades 1-2 for most clinical chemistry parameters, but there were no clinically meaningful differences across the treatment groups.

Shifts from normal values or Grade 1 to Grade 3 were noted for ALT, AST, fasting glucose, increased fasting glucose, and triglycerides in a small number of patients, with the ALT and fasting glucose shifts reported in the “Any secukinumab dose group” only. A shift from normal range to Grade 4 in ALT was observed in 1 patient on placebo.

Similar to the initial 16-week treatment period, the majority of patients had values within the normal range at baseline and post-baseline for the entire treatment period. Two patients experienced a shift from normal values at baseline to abnormal values of Grade 4 over the entire treatment period: 1 patient in the “Any AIN457 75 mg group” for neutrophils and 1 patient in the placebo group for ALT values. For the Grade 4 values in cholesterol and triglycerides, all affected secukinumab patients had abnormal values at baseline.

Safety in special populations

10-year CHD risk category

The incidence rates of AEs by SOC in each CHD risk category were similar to that of the overall population of Pool A over the entire treatment period. The EAIR for cardiac disorders increased with increasing CHD risk in the Any secukinumab group (3.8 in the low risk group, 6.8 in the medium risk group) and in the placebo group (7.9 in the low risk group, 9.8 in the medium risk group). There were too few patients to draw meaningful conclusions in the high CHD risk group (N = 18 in the Any secukinumab group and N = 3 in the placebo group).

The incidence of SAEs in the overall population was low, and the trends in the concomitant CHD use subgroups were similar to those in the overall population of Pool A.

Safety related to drug-drug interactions and other interactions

Prior TNF-ai exposure

AS patients enrolled in the Phase 3 Pool A studies were categorized as either TNFai naïve (no prior TNFαi treatment) or TNF-IR (prior TNFαi treatment). Most patients in Pool A were naïve to TNFai (68.8% in the Any secukinumab group) and the AE profiles by SOC and PT by prior TNFai exposure were generally similar to that seen in the overall population of Pool A over the first 16 weeks. In the Any secukinumab group, the absolute AE incidence was 65.0% in TNF-IR patients and 66.1% in TNFai-naïve patients. In TNF-IR patients, the incidence of infections and infestations was 28.5% and the incidence of gastrointestinal disorders was 23.6% in the Any secukinumab group. In TNFai-naïve patients, the incidence of infections and infestations was 31.4% and the incidence of gastrointestinal disorders was 14.0% in the Any secukinumab group. A similar difference between TNF-IR and TNFai-naïve patients in the incidence of gastrointestinal disorders was observed in the placebo group.

The profiles of EAIRs of AEs by SOC in TNF-IR and TNFai-naïve patients were similar to that of the overall population of Pool A over the entire treatment period. The EAIR for any SOC was higher in TNF-IR patients vs TNFai-naïve patients in the Any 75 mg group, the Any 150 mg group, the Any secukinumab group, and the placebo group

The incidence of SAEs in the overall population was low and the trends in the TNFai subgroups were similar to those in the overall Pool A population. The EAIR for infections and infestations was not higher in patients taking concomitant methotrexate.

Concomitant methotrexate use

Few patients in Pool A were taking concomitant corticosteroids (11.4% in the Any secukinumab group), and the AE profiles by SOC and PT grouped by concomitant corticosteroid use (yes/no) was generally similar to that seen in the overall population of Pool A over the first 16 weeks. In the Any secukinumab group, the absolute AE incidence was 66.7% in patients taking concomitant corticosteroids and 65.6% in patients not taking concomitant corticosteroids. The incidence of infections and infestations in the Any secukinumab group was similar between patients taking concomitant corticosteroids (31.1%) and those not taking concomitant corticosteroids (30.4%).

The EAIRs of AEs by SOC in each MTX use category were similar to that of the overall population of Pool A over the entire treatment period.

The incidence of SAEs in the overall population was low, and the trends in the MTX use subgroups were similar to those in the overall Pool A population.

Concomitant corticosteroid use

Few patients in Pool A were taking concomitant corticosteroids (11.4% in the Any secukinumab group, and the AE profiles by SOC and PT grouped by concomitant corticosteroid use (yes/no) was generally similar to that seen in the overall population of Pool A over the first 16 weeks. In the Any secukinumab group, the absolute AE incidence was 66.7% in patients taking concomitant corticosteroids and 65.6% in patients not taking concomitant corticosteroids. The incidence of infections and infestations in the Any secukinumab group was similar between patients taking concomitant corticosteroids (31.1%) and those not taking concomitant corticosteroids (30.4%).

The incidence rates of AEs by SOC in each corticosteroid use category were similar to that of the overall population of Pool A over the entire treatment period.

The incidence of SAEs in the overall population was low, and the trends in the corticosteroid use subgroups were similar to those in the overall Pool A population.

Immunological events

Over the first 16 weeks, the crude IR of immune/administration reactions was 18.9% for the placebo group, 6.8% and 16.7% for 75 mg sc and 150 mg sc, respectively, and 10.5% for iv- 75 mg and 15.2% for iv-150 mg, respectively. Mouth ulceration (2.5%), cough (1.8%), rash (1.5%), pruritus (1.0%), injection site pain (1.0%), and worsening ankylosing spondylitis (1.0%) were the most frequently reported preferred terms in the "Any secukinumab group". Mouth ulceration was reported with a higher incidence compared to placebo (2.5% and 1.5%, respectively) but was not considered to be clinically significant as all cases were mild in severity, did not lead to discontinuation and resolved without treatment. The majority of AEs for immune/administration reactions were of mild or moderate severity. The severe immune/administration reactions were Crohn's disease (1 patient in the 75 mg group), dyspnoea (1 patient in the 150 mg group), and iritis (1 patient in the placebo group).

The exposure adjusted incidence of the most frequent immunological AEs over the entire treatment period, are presented in **Table 39**.

Table 39. Exposure-adjusted incidence of most frequent AEs (>= 1.0% crude incidence in Any secukinumab dose group) of immune/administration reactions – Entire treatment period (Pool A: Phase 3 AS trials – Safety set)

Level 1 Preferred term	Any AIN457 75 mg N=284 n/EX (IR)	Any AIN457 150 mg N=287 n/EX (IR)	Any AIN457 dose N=571 n/EX (IR)	Placebo N=196 n/EX (IR)
Based on all AEs				
Immune/administration reactions (NMQ)	63/297.4 (21.2)	68/286.0 (23.8)	131/583.3 (22.5)	37/54.7 (67.6)
Cough (PT)	12/334.9 (3.6)	9/337.4 (2.7)	21/672.3 (3.1)	3/62.8 (4.8)
Mouth ulceration (PT)	11/333.8 (3.3)	9/336.8 (2.7)	20/670.6 (3.0)	3/62.6 (4.8)
Ankylosing spondylitis (PT)	4/343.6 (1.2)	8/341.3 (2.3)	12/684.9 (1.8)	5/62.5 (8.0)
Pruritus (PT)	4/340.5 (1.2)	7/339.4 (2.1)	11/679.9 (1.6)	3/62.9 (4.8)
Dyspnea (PT)	4/342.1 (1.2)	3/344.5 (0.9)	7/686.6 (1.0)	2/63.1 (3.2)
Rash (PT)	5/339.7 (1.5)	5/340.9 (1.5)	10/680.6 (1.5)	1/63.3 (1.6)
Seasonal allergy (PT)	3/342.8 (0.9)	3/345.5 (0.9)	6/688.3 (0.9)	1/63.4 (1.6)
Conjunctivitis (PT)	5/341.6 (1.5)	4/344.0 (1.2)	9/685.5 (1.3)	2/63.0 (3.2)
Based on all SAEs				
Immune/administration	5/341.9 (1.5)	4/342.2 (1.2)	9/684.1 (1.3)	0/63.6 (0.0)

The incidence of hypersensitivity events was higher in the "Any secukinumab group" (7.5%) compared with placebo (4.1%), in contrast to what was observed in the 16-week period, where secukinumab and placebo rates were comparable. The most common hypersensitivity events in the "Any secukinumab group" were rash (1.8%), eczema (1.4%) and dermatitis (1.2%).

No cases of angioedema or anaphylactic reaction were reported during the entire treatment period. All hypersensitivity events were mild or moderate in severity. There were no SAEs or events that required study treatment discontinuation/interruption in the hypersensitivity narrow SMQ during the entire treatment period.

There was no apparent difference between iv and sc load on hypersensitivity events. In the first 8 weeks, the absolute incidence of hypersensitivity AEs was low and generally comparable for the sc loading regimens (4.1% for 75 mg sc and 2.8% for 150 mg sc) and the iv loading regimens (1.6% for iv-75 mg and 3.2% for iv-150 mg). Hypersensitivity AEs did not occur more frequently in the Any secukinumab group (1.9%) compared with the placebo group (3.1%). In the first 16 weeks, the hypersensitivity AE rates showed a similar profile as that observed for the first 8 weeks.

Immunogenicity

Treatment-emergent ADAs are defined as ADAs that developed post-treatment in patients with negative ADA screens at baseline (i.e., seroconversion to ADA positivity from a seronegative state). Across both Phase 3 AS trials, treatment-emergent ADAs were detected in 2 patients (2/584, 0.3%) from study F2305, both of whom were receiving 150 mg secukinumab at the time of ADA detection at Week 52. Neutralizing antibodies to secukinumab were detected in one of these patients. There was no loss of efficacy, no IG-related AEs and no altered PK profile in both cases of treatment-emergent ADAs.

Non-treatment emergent ADA were observed in both Phase 3 AS trials. A total of 8/584 (1.4%) patients were ADA positive at baseline. These included 7 patients who were ADA positive at baseline only and reverted to a seronegative state while on secukinumab treatment, and 1 patient who had both baseline and post-baseline ADA positive samples. Of the 7 patients who were ADA positive at baseline only one patient reported an AE (seasonal allergy) which could be possibly IG-related. PK normality for this patient could not be established as only one PK result was available. Neutralizing antibodies were detected in 4 out of these 7 patients. Neutralizing antibodies were also detected in the 1 patient with both baseline and post-baseline ADA positive samples: a placebo non-responder patient with ADAs detected prior to receiving secukinumab at Week 16. No explanation can be provided for the presence of ADAs at baseline or while on placebo treatment. Non-specific binding to pre-existing antibodies may have occurred in some 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 ADAs may lead to a confirmed positive response in this assay in either pre-dose samples or samples derived from patients not exposed to secukinumab. These observations were not considered to be clinically relevant, as the ADAs were not associated with secukinumab treatment.

ADAs were not associated with injection site reactions or serious or severe AEs mapping to the hypersensitivity SMQ. Across the 2 AS Phase 3 studies, 1 patient with baseline ADAs also experienced a mild non-serious AE of seasonal allergy which did not lead to discontinuation.

Loss of efficacy was defined as failure to achieve ASAS 20 while on treatment after previously achieving ASAS 20 for at least 2 consecutive visits at any time prior to first detection of ADA. Loss of efficacy was not detected in either of the 2 patients who developed treatment emergent ADAs or the 1 patient with baseline and post baseline ADA. There were no discontinuations due to ADAs.

ADAs were also not associated with altered PK profiles. Secukinumab concentrations in all patients with ADAs 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 3 patients.

Across all patients (584 patients) evaluated for ADAs in the Phase 3 trials, 6/584 (1%) patients tested positive for both ADAs 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 time point during treatment to assess.

2.4.1. 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 provide 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.

The first data pool (A) consisted of 2 pivotal placebo-controlled Phase 3 trials in AS (CAIN457F2305 and CAIN457F2310) with placebo and dose comparisons that allow risks to be evaluated in the AS population during the first 16 weeks of treatment and during the entire treatment period (median 66 weeks of exposure to secukinumab).

The largest data pool (C), which includes all patients treated with secukinumab in 42 studies for which an interim or final CSR is currently available, maximized the chances of observing rare events of MACE and malignancy in patients receiving secukinumab.

Pooling was conducted in a rational manner in order to 1) investigate the specific safety concerns during the induction period in the AS studies (related to either iv or sc loading regimen), 2) enable comparisons against placebo during the initial 16 weeks of AS studies, 3) find out about long term tolerability in AS indication, and 4) 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 in AS patients resembles closely the AE profile observed in the initial submission of psoriasis-indication, where up to week 12, the most common AE:s 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%). There appeared to be no differences or dose-dependence in the AE profiles between patients receiving 75 mg and 150 mg sc loading doses.

Similarly to weeks 0 to 16, in the entire study period the AE profile closely resembles 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, some trends of dose-dependence can be observed in the incidences of influenza, pharyngitis, hypertension, oral herpes, paraesthesia, and neutropenia – more strongly associated with iv-loading.

Treatment emergent adverse events from study F2305 with iv loading occurring more frequently in the secukinumab group were nasopharyngitis, diarrhoea, URTI, dyslipidaemia, pharyngitis, influenza, leukopenia, back pain, nausea, and neutropenia. And from study F2310 with sc loading, nasopharyngitis, URTI, hypertension, influenza, bronchitis, oral herpes, pharyngitis and tonsillitis.

Regarding current Pool A, it appeared that nasopharyngitis was slightly more common in patients receiving the iv-loading. Oral herpes was observed more in patients receiving 150 mg sc-doses (n=2) or iv-loading (n=3). However, none of the herpes cases were severe or led to discontinuation from the study. Headache, nausea, and diarrhoea were also more common in iv-loaded patients. 10 cases of mild leukopenia were reported in iv-loaded patients and only 1 in placebo group. Also dyslipidaemias were reported more from secukinumab patients and especially those receiving iv loading. These observations gave support to use of the sc-loading method.

Upper respiratory tract infections, candida infections, and mainly oral herpes infections are adequately addressed in the current Cosentyx product information. With regards to opportunistic infections, no cases of tuberculosis and only one case of suspected viral hepatitis were reported. One case of herpes zoster activation was reported. Therefore the CHMP considered that there were no new findings regarding the risk of infections from the AS studies.

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

SAEs of interest in Pool A first 16 weeks consisted of one occurrence each of ischaemic colitis, "microscopic" colitis, ulcerative colitis, Crohn´s disease, increased hepatic enzymes, malignant melanoma, and myocardial infarction. There was also one lymphoma reported in patient receiving placebo. However, as these are all single cases of SAEs occurring to patients receiving either secukinumab or placebo, they do not raise concerns about the safety profile of secukinumab.

It appeared that Crohn´s disease at baseline was more common in AS patients than in PsA patients addressed in another extension of indication (3/752 vs 1/1274, respectively). Only two new diagnoses were made during or after secukinumab exposure in AS patients and one new diagnosis similarly in PsA patients. Following a request from the CHMP the MAH discussed the possibility of adding Crohn´s disease or exacerbation of Crohn´s disease to section 4.8 of the SmPC. Three out of five cases of Crohn in AS-studies reported a medical history including Crohn´s disease. One of the cases lacked information on medical history, and one reported history of polyps. The MAH therefore concluded, that an update of section 4.8 was currently not warranted, and this was considered acceptable by the CHMP. The current warnings in the SmPC include a warning in section 4.4 that caution should be exercised when prescribing secukinumab to patients with Crohn's disease, as exacerbations of Crohn's disease, in some cases serious, were observed in clinical studies and this was considered sufficient to minimise this risk. In addition Crohn's disease is included in the RMP as an important potential risk.

Skin malignancies as well as other malignancies were reported rarely and not regarded related to study medications in Pool A. Three cases of lymphomas in psoriasis and ankylosing spondylitis studies were observed and were evaluated more closely. In two of the cases, lymphoma was observed after many months of exposure to the IMP. The two cases had quite different characteristics suggesting a different underlying etiopathogenesis. Some common features in these 2 lymphoma cases might have been expected if they were related to the mechanism of action of secukinumab. Finally, in the last case, which was reported as marginal cell lymphoma, previous exposure to cyclosporine, ustekinumab and tofacitinib may have contributed to the event. Malignancies are included in the RMP as an important potential risk.

In the original psoriasis submission, the cardiovascular co-morbidity was over-presented at baseline in the secukinumab groups. 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 AS studies.

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 probably due 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 are no new findings in the AS studies in this respect. There were no observed effects attributable to use of study medications in haemoglobin, lymphocyte, and platelet parameters. Neutropenia is included in the RMP as an important identified risk with appropriate warnings in the SmPC.

Mild elevations of ALT observed during induction period, with only slight differences between different induction regimens, appear not to be a relevant safety issue. Increased incidence of ALT elevations during iv-loading will not be an issue in the clinical use with sc-loading. Similarly, the mild grade I elevations of total cholesterol and triglycerides appear more commonly in iv-loaded patients. Grade II elevations of

cholesterol were scarce (only 1 case during iv-loading). Grade II elevation on triglycerides were observed in 3/139 (2.16%) in patients receiving sc loading and 7/231 (3.03%) in patients receiving iv loading (during the first 16 weeks). However the incidence of the events observed with the iv loading will not apply in the clinical setting.

Two patients experienced significant hepatic enzyme elevations without any baseline morbidity or concomitant medication, cases that could be attributed to use of secukinumab. Three further hepatic enzyme elevations were observed in patients with previous hyperbilirubinemia or hepatic steatosis, and in conjunction with viral hepatitis. Hepatitis B reactivation is included in the RMP as an important potential risk.

There did not appear to be any other clinically meaningful differences evident in either haematology or blood chemistry parameters attributable to use of secukinumab in the AS studies.

There were no clinically meaningful differences in the AE profile stratified by the body weight (<90 kg, >90 kg) or gender. The incidence of SAEs in the overall population was low and the trends in the TNFai subgroups were similar to those in the overall Pool A population. The EAIR for infections and infestations was not higher in patients taking concomitant methotrexate.

All immune reactions were non-serious. No cases of angioedema or anaphylaxis were reported.

Milder forms of hypersensitivity reactions were rare. Urticaria was seen here less frequently (<1.0%) compared to original psoriasis-submission (1.85%). Rash was slightly less common here (1.5%) compared to earlier submission (2.45%). Overall incidence of hypersensitivity reaction in Pool A was 6.5% 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. This did not change in the current AS submission either.

2.4.2. Conclusions on clinical safety

The safety profile of secukinumab in treatment of AS in both the induction and maintenance phases of the studies resembles closely the safety profile observed in the psoriasis-indication of the initial submission. Treatment emergent adverse event occurring more frequently in the secukinumab group included nasopharyngitis, URTI, hypertension, influenza, bronchitis, oral herpes, pharyngitis and tonsillitis. And mainly observed in patients receiving iv loading, also mild manifestations dyslipidaemia, leukopenia, and neutropenia. Some trends of dose dependence during maintenance treatment could be seen in the incidences of influenza, pharyngitis, hypertension, oral herpes, paraesthesia, and neutropenia. There were no new findings regarding Crohn´s disease or MACEs. Otherwise 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.

2.4.3. 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.

2.5. 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 40. 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 41. 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.

Risk minimisation measures

Table 42. 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-summary of the safety profile)	None
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

2.6. 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.

2.6.1. User consultation

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

3. Benefit-Risk Balance

Benefits

Beneficial effects

Short-term and long-term efficacy of secukinumab has been robustly shown in comparison to placebo. In the pivotal study F2305 secukinumab 150 mg administered subcutaneously after an initial one-month intravenous loading period was superior to placebo with respect to the primary endpoint of ASAS 20 and also with respect of all secondary endpoints (ASAS 40, hsCRP, ASAS 5/6, BASDAI, SF-36, ASQoL and ASAS partial remission) at Week 16. Conversely, in Study F2310 the subcutaneous secukinumab dose of 150 mg, used both during the loading and maintenance periods was superior to placebo in ASAS 20 response and also with all other secondary endpoints except for ASAS partial remission at Week 16. In the analysis across the studies, the magnitude of ASAS 20 response was not dependent on the method of administration (iv or sc). Despite the numerically greater improvements in TNFαi naïve subjects, the ASAS 20 response was significantly superior to placebo also in TNF-IR patients. The onset of efficacy of secukinumab was rapid as the difference in ASAS 20 response rate over placebo was evident already from Week 1 onwards. In both studies, the response rates in primary and secondary endpoints achieved at Week 16 were sustained through Week 52.

Uncertainty in the knowledge about the beneficial effects

Risks

Unfavourable effects

Infections were more commonly reported in secukinumab-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

Exposure to secukinumab is still limited only to the clinical trial setting. Therefore the safety profile of secukinumab whilst considered acceptable at this time point will be further characterised following post-marketing experience which will be monitored as described in the RMP and will be reported in PSURs.

Effects Table

Effects Table for Cosentyx in the treatment of ankylosing spondylitis (data cut-off: 04 August 2014)

Effect	Short Description	Unit	Active 75 mg	Active 150 mg	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects							
ASAS 20[1)]	% achieving response at Week 16 (primary endpoint) (sc loading regimen as proposed for clinical use)	%	41.1	61.1	28.4	Significant effect in the primary endpoint only with 150 mg secukinumab dose compared to placebo after s.c. loading (p=0.001), supported by the secondary endpoints in this study and similar results over placebo observed in another trial with i.v. loading	Study F2310
Unfavourable Effects							
Infections	Overall rate of infections, SOC[2)] Infections and infestations	%[3)] IR[4)]	30.1 67.9	33.3 68.6	17.9 63.8	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 F2305 and F2310
	Candida infections (HLT[5)])	%[3)] IR[4)]	1.4 1.2	0.0 0.6	0.0 0.0	Candida infections consisting mainly of oral candidiasisand vulvovaginal candidiasis. All cases mild/moderate in severity. None led to discontinuation.	Studies F2305 and F2310
	Oral herpes	%[3)]	0.0	2.8	0.0	Increased incidence of	Studies F2305

Effect	Short Description	Unit	Active 75 mg	Active 150 mg	Placebo	Uncertainties / Strength of evidence	References
	infections (PT[6])	IR[4]	1.8	2.6	0.0	herpes viral infections. No cases of disseminated or CNS herpes.	and F2310
Neutro-penia	Neutropenia (PT[6])	%[3] IR[4]	0.0 2.1	0.0 1.5	0.0 0.0	Cases of grade 2, 3 (n=4), and 4 (n=1) neutropenia were not associated with severe/serious infections.	Studies F2305 and F2310

[1] >20% improvement in Assessment System of SpondyloArthritis International Criteria
[2] SOC = System Organ Class
[3] % rate (first 16 weeks, only patients with sc loading from study F2310, placebo patients from both studies)
[4] IR = exposure adjusted incidence rate (entire treatment period, from both studies F2305 and F2310), expressed as number of subjects with event per 100 patient-years
[5] HLT = High Level Term
[6] PT = Preferred Term

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Statistically significant and clinically highly relevant short-term and long-term efficacy of secukinumab in treatment of AS has been shown. There is a need for additional therapies in moderate to severe AS, particularly for those with inadequate response to TNFαis.

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 AS has been demonstrated. The safety profile appears favourable based on the data currently available.

Discussion on the Benefit-Risk Balance

Robust and clinically relevant efficacy has been shown for secukinumab in the treatment of ankylosing spondylitis. The overall safety profile of secukinumab appears favourable. Unfavourable effects typical for biologic ankylosing spondylitis 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 is approvable for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

4. Recommendations

Outcome

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

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition	Type II	I and IIIB

	of a new therapeutic indication or modification of an approved one		

Extension of indication to add new indication for Cosentyx in the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; consequently, SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 have been revised to include new efficacy and safety information. The Package Leaflet and RMP have been updated accordingly.

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

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).

5. EPAR changes

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

Scope

Extension of indication to add new indication for Cosentyx in the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; consequently, SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 have been revised to include new efficacy and safety information. The Package Leaflet and RMP have been updated accordingly.

Summary

Please refer to the scientific discussion Cosentyx EMEA/H/C/003729/II/0002

Appendix

1. CHMP AR on the novelty of the indication/significant clinical benefit in comparison with existing therapies

22 October 2015
EMA/CHMP/686519/2015
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report on the significant clinical benefit in comparison with existing therapies in accordance with Article 14(11) of Regulation (EC) No 726/2004

Invented name: Cosentyx

International non-proprietary name: secukinumab

Procedure No. EMEA/H/C/003729/II/0002

Marketing authorisation holder (MAH): Novartis Europharm Ltd

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1. Introduction

In accordance with the provisions of Article 14(11) of Regulation (EC) No 726/2004, the Marketing Authorisation Holder (MAH) has applied for an additional one year marketing protection period in the framework of the variation procedure EMEA/H/C/003729/II/0002 (extension of indication).

The request was based on the MAH's position that Cosentyx represents a significant clinical benefit in the treatment of ankylosing spondylitis in adults who have responded inadequately to conventional therapy, in comparison with existing therapies.

2. Justification of significant clinical benefit as presented by the MAH

2.1. Demonstration of new therapeutic indication

Secukinumab (AIN457) is a recombinant high-affinity fully human monoclonal anti-human Interleukin-17A (IL-17A) antibody of the IgG1/kappa isotype that selectively binds with high affinity to interleukin-17A (IL-17A), a downstream product of the Th17 cells, thus neutralizes its bioactivity. Secukinumab targets IL-17A, regardless of its source. IL-17A has been associated with inflammation, neutrophil infiltration, and destruction of cartilage and bone via osteoclastic activity.

Novartis submitted a Marketing Authorisation Application (MAA) for secukinumab lyophilisate in vial (LYO), pre-filled syringe (PFS) and autoinjector/pen (AI) for the treatment of moderate-to-severe plaque-type psoriasis in October 2013. The Committee for Medicinal product for Human Use (CHMP) positive opinion was adopted on 20-Nov-2014 and the European Commission issued a marketing authorisation for the treatment of moderate to severe plaque psoriasis on 15-Jan-2015. In addition, secukinumab was recently approved for the treatment of moderate to severe plaque psoriasis in Australia, Chile and the United States (US), as well as for the treatment of psoriatic arthritis and psoriasis vulgaris in Japan.

Secukinumab is registered under the tradename Cosentyx.

Secukinumab is also being developed by Novartis for the treatment of psoriatic arthritis (PsA) and ankylosing spondylitis (AS). In the current dossier the proposed indication is "ankylosing spondylitis in adults who have responded inadequately to conventional therapy".

Ankylosing spondylitis (AS) is an immune-mediated chronic inflammatory disease which belongs to a group of conditions known as spondyloarthritides (SpA). It is mainly characterized by involvement of the axial skeletons and the sacroiliac joints, but also affects peripheral joints and extra-articular organs. A significant proportion of patients may present with associated extra-articular manifestations such as uveitis, psoriasis, inflammatory bowel disease (IBD), cardiovascular and pulmonary abnormalities. Generalized osteoporosis as well as regional osteopenia are common in AS patients and predispose them to non-traumatic fractures in spite of young age and gender (male). The presence of the HLA-B27 antigen is strongly associated with AS: 90–95% of patients with AS who have European ancestry carry this marker. AS affects up to 1.1% of the population, is associated with significant morbidity and disability and thus constitutes a major socioeconomic burden.

2.2. Details of existing therapies

The first-line drug treatment of mild AS consists of non-steroidal anti-inflammatory drugs (NSAIDs). Treatment of NSAIDs-refractory AS is hampered by the lack of efficacy of virtually all standard disease

modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX), although peripheral arthritis associated with AS may respond to sulfasalazine.

TNFα-blocking agents were successfully added to the armamentarium to treat AS and subsequently demonstrated prolonged efficacy with up to eight years of follow-up. However, upon discontinuation of TNFα-blockers the disease relapses quickly, indicating that the inflammatory process is only suppressed and not completely abolished. Results reported in the ASSERT study, the largest study ever conducted on Magnetic Resonance Imaging (MRI) evaluation of spinal lesions in AS, demonstrated a near complete resolution of inflammatory lesions at the 24- week time point with anti-TNFα therapy. However, in other reports AS inflammatory bone lesions detected by MRI did not completely disappear under TNFα antagonist therapy over a six-month study period. These bone lesions persisted despite full clinical remission, which suggests that the inflammatory process was still smoldering.

Treatment options for patients with intolerance or an inadequate response to anti-TNFα agents are limited and switching patients to a second or third anti-TNFα agent may not be effective choices. Antagonism of IL-17 by secukinumab represents a novel approach to interfere with the chronic inflammatory process by selectively targeting the predominant cytokine of the unique subset of helper Th17 cells, as well as other cells that play a predominant role in the inflammation associated with AS. Thus, there is a high unmet medical need for up to 40% of the AS population which experienced an inadequate response or is intolerant to anti-TNFα agents.

2.3. Significant clinical benefit based on improved efficacy

The significant clinical benefit of secukinumab in comparison to existing therapies is based on its mechanism of action which makes it a targeted treatment, on its pharmacokinetics/pharmacodynamics properties and on the efficacy and safety data in the target indication and population, thus addressing unmet needs. The efficacy and safety data in the target indication and population come from two adequate (n=590 in total) and placebo-controlled confirmatory phase III trials (CAIN457F2305 and CAIN457F2310). The purpose of these studies was to demonstrate the efficacy, safety and tolerability of secukinumab versus placebo in patients with active AS with a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or disease modifying anti-rheumatic drug (DMARD) therapy. In addition, in CAIN457F2305 and CAIN457F2310, respectively, 27% and 38.4% of patients were previously treated with an anti-TNF agent and discontinued the anti-TNF agent for either lack of efficacy or intolerance

As a targeted therapy, secukinumab selectively binds with high affinity to IL-17 which is a downstream product of the Th17 cells involved in the pathogenesis of AS. Secukinumab 150 mg s.c. showed substantial efficacy benefits in the treatment of AS. Treatment with secukinumab resulted in significant improvements in signs and symptoms, physical function and health related quality of life, spinal mobility and inhibition of inflammation compared to placebo at Week 16. These improvements were all sustained up to week 52. The magnitude of response on signs and symptoms at week 16 was similar in TNF-naïve and TNF-inadequate responder (TNF-IR) patients in both studies. Efficacy was maintained in the TNF-naïve and TNF-IR patients up to week 52. Based upon cross-study comparisons to other phase 3 biologics development programs in AS, the efficacy response of secukinumab 150 mg administered subcutaneously is comparable to anti-TNF agents for ASAS 20 and 40.

2.4. Significant clinical benefit based on improved safety

The safety profile of secukinumab in AS patients is comparable to the safety profile of secukinumab in psoriasis patients.

2.5. Significant clinical benefit based on major contribution to patient care

The following is presented by the MAH under the Section "Unmet medical need":

There is a well-known unmet medical need in AS patients for additional therapeutic options, especially for the AS patients who are intolerant to or who have inadequate response to anti-TNF agents as there is no other treatment option currently on the market. These patients represent 40% of the AS population. This population includes patients who experience primary treatment failure with no response to treatment after initially starting an anti-TNF agent, secondary treatment failure who experience recurrence of disease manifestations after an initial period of improvement, and intolerance or contraindication to the use of anti-TNF agents.

Most previous AS trials with TNFα-targeted biologics did not include patients who had failed previously therapy with an anti-TNFα biologic. Notably, the current secukinumab studies include 25-40% of patients with the highest unmet medical need who have failed anti- TNFα therapy. Secukinumab has proven to be efficacious in all components of AS disease in both anti-TNF naïve and TNF-inadequate responder patients. With its novel mechanism of action targeting interleukin-17A (IL-17A), secukinumab will be the first non-anti-TNF biologic treatment registered for the treatment of AS, thus bringing new treatment opportunities for AS patients. The anti-IL-17 Mechanism of Action (MOA) of secukinumab is the only other class of biologics now proven to be effective in ankylosing spondylitis. In contrast to other types of arthritis, non-TNFα biologics such as rituximab, tocilizumab, and abatacept are not effective in ankylosing spondylitis.

In conclusion, secukinumab has a significant clinical benefit in comparison with existing therapies for AS patients, as it was shown to be efficacious in all components of the disease with a rapid onset of action, thus reducing all burdens caused by the disease, without showing any tolerability or unexpected safety issues. In addition, secukinumab will address unmet needs as it will be the first biologic non-anti-TNF treatment that will be registered for the treatment of AS.

3. Assessment of the MAH's justification of significant clinical benefit[1]

3.1. Demonstration of new therapeutic indication

Article 14(11) of Regulation (EC) No 726/2004 refers to significant clinical benefit in comparison with existing therapies. The European Commission´s guidance (Guidance on elements required to support the registration of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period, European Commission, Brussels, November 2007) outlines the level of evidence required to support the application.

Cosentyx has been approved for the treatment of moderate to severe plaque psoriasis in January 2015. It is agreed that AS represents a new therapeutic indication.

[1] In accordance with guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period http://ec.europa.eu/health/files/eudralex/vol-2/c/guideline_14-11-2007_en.pdf

3.2. Details of existing therapies

According to the clinical guidelines, physical therapy and NSAIDs (intermittent or continuous use) comprise the first-line treatment in AS. In contrast, the clinical data do not support the use of traditional non-biological disease-modifying antirheumatic drug in the treatment of AS, with the exception of consideration of sulphasalazine in AS with peripheral arthritis. The treatment with TNFα-blockers is recommended for the patients with persistently high disease activity despite conventional treatment with NSAID and physiotherapy.

To date, there are five TNFα-inhibitors which have been approved for treatment of AS in Europe. Two of these (infliximab and golimumab) are indicated for the treatment of severe active ankylosing spondylitis in adults who have responded inadequately to conventional therapy. In contrast, etanercept, adalimumab and certolizumab-pegol are indicated also for non-radiological axial SpA.

According to the just recently published Cochrane analysis, there are no evident differences in efficacy between the registered TNFα-blockers. In the registration studies for AS, the Assessment of SpondyloArthritis International Society (ASAS) 20 response (the primary efficacy variable used in the Cosentyx AS studies) varied between 51.6% (adalimumab) and 63.6% (certolizumab-pegol). Therefore, it can be estimated that 40-50% of the AS patients experience an inadequate response for TNFα-blockers.

According to the experience derived from a few small observational studies, around 50% of the AS patients intolerant or unresponsive to the first TNFα-blocker respond to the second TNFα-blocker. These preliminary findings have however not been verified in randomized clinical trials.

The conclusions of the MAH are endorsed, *i.e.*, that an unmet need still exists and secukinumab represents a novel therapeutic option based on antagonism of IL-17.

3.3. Significant clinical benefit based on improved efficacy

Justification for significant clinical benefit in comparison with existing therapies should generally be supported by results of comparative clinical studies. As stated in the European Commission´s guidance, the choice of the comparator (existing therapy) in clinical trials should be justified by relevant scientific literature, CHMP guidelines, or scientific advice. Placebo controlled studies or even uncontrolled studies may be sufficient only in the unusual event of exceptional benefit which could not be due to chance or a confounding factor.

A clinically relevant level of efficacy has been demonstrated for secukinumab in comparison to placebo. However, no active control (*i.e.*, TNFα-blocker) was included in the AS studies, although this is recommended in the EMA AS guideline. The efficacy of secukinumab dose of 150 mg in achieving the ASAS 20 response in Study F2310 (61.1%) was at least comparable to the efficacy of previously approved TNFα-blockers for treatment of AS. The ASAS 20 response rate was numerically greater in TNFα naïve population (68.2%) compared to TNF-IR population (50.0%), but the difference over placebo was significant in both sub-populations.

Finally, it is not possible to make any robust comparisons of efficacy with other existing therapies without a direct comparative trial. The MAH has also not provided any detailed comprehensive discussion and comparison of efficacy parameters between secukinumab and existing therapies hence the one year additional marketing protection period cannot be granted based on improved efficacy

The MAH has been asked to justify the lack of a dedicated actively controlled study in AS.

3.4. Significant clinical benefit based on improved safety

According to the MAH, the safety profile of secukinumab in AS patients is comparable to the safety profile of secukinumab in psoriasis. This is generally agreed on, although there are some safety-related issues that need clarification during the current procedure. Overall, the safety profile of secukinumab was considered favourable in the psoriasis population, also in relation to other products available. However, it is not possible to make any robust comparisons of safety with other existing therapies without a direct comparative trial. The MAH has also not provided any detailed comprehensive discussion and comparison of safety parameters between secukinumab and existing therapies and hence the one year additional marketing protection period cannot be granted based on improved safety.

3.5. Significant clinical benefit based on major contribution to patient care

The discussion of the issues related to "significant clinical benefit based on major contribution to patient care" has been in principle provided by the MAH under the section "Unmet medical need".

The mode of administration and the dosing frequency of secukinumab are similar to other products available (sc injection q4w during the maintenance treatment) and therefore do not provide any additional benefit.

According to the European Commission´s guidance, medicinal product having shown a benefit risk balance at least similar to existing therapies could be considered of significant clinical benefit if it acts through a different principal mechanism of action and thus provides a treatment alternative. Secukinumab interrupts the signalling pathway of IL-17-induced inflammation in AS. Compared to the other products in the market, it can be considered a more specific and selective drug in targeting the specific downstream cytokine IL-17. This could result in the quite favourable safety profile observed thus far.

In addition, according to the above-mentioned guidance, a claim for the significant clinical benefit could be considered if the medicinal product produces a response different from other treatments in a substantial part of the targeted population. To date, there is no trial evidence of the efficacy of switching a TNF-IR patient to another TNFα-blocker/biologic. Since the secukinumab trials in the treatment of AS included a considerable proportion of patients (27-39%) with previous use and inadequate response to TNFα-blocker who also experienced a favourable treatment effect, secukinumab treatment could be considered a major contribution to patient care based on these findings.

4. Conclusion

Secukinumab is a novel recombinant monoclonal anti-human Interleukin-17A (IL-17A) antibody for the treatment of psoriasis. The MAH is now seeking for AS-indication together with additional one year marketing protection.

40% of AS patients are intolerant to or have inadequate response to anti-TNF agents; there is no other treatment option currently available on the market for these patients. Secukinumab phase 3 trials included also a substantial amount of TNF-IR patients, in whom efficacy was demonstrated.

Due to the novel mechanism of action, and benefit-risk profile at least similar to existing therapies, secukinumab could be considered to offer a significant clinical benefit in comparison with existing therapies based on major contribution to patient care, as it provides a treatment alternative and produces a response different from other treatments in a substantial part of the targeted population.

5. Recommendation

The CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No. 726/2004 and the "Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period", and considers, that the new therapeutic indication brings a significant clinical benefit in comparison with existing therapies.