EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 March 2020
EMA/199991/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cosentyx

International non-proprietary name: secukinumab

Procedure No. EMEA/H/C/003729/II/0053/G

Note

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

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List of abbreviations

ADA	Anti-drug antibodies
ADR	Adverse drug reaction
AE	Adverse event
AIN457	Secukinumab
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AS	Ankylosing spondylitis
ASAS	Assessment of Spondyloarthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASspiMRI-a	Ankylosing spondylitis spine MRI score for activity
ASQoL	Ankylosing Spondylitis Quality of Life
AST	Aspartate aminotransferase
axSpA	Axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BSL	Baseline
CRP	C-reactive protein
CRP+	Patient with a CRP value above the ULN at Screening
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database lock
DMARD	Disease-modifying anti-rheumatic drug
EAIR	Exposure-adjusted incidence rates
ESR	Erythrocyte sedimentation rate
EQ-5D Euro-QoL	5-Dimension Health Status Questionnaire
EMA	European Medicines Agency
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
HLA	Human leukocyte antigen
HLT	High level term
hsCRP	High sensitivity C-Reactive Protein
IL-17A	Interleukin-17A
IR	Inadequate responder
MACE	Major adverse cardiovascular events
MAR	Missing at random
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score

MCS	Mental component summary score
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model repeated measures
MRI	Magnetic resonance imaging
MRI+	Patient with a MRI considered positive for sacroiliitis at Screening
MRI-	Patient with a MRI considered negative for sacroiliitis at Screening
NMQ	Novartis MedDRA Query
nr-axSpA	Non-radiographic axial spondyloarthritis
NSAID	Non-steroidal anti-inflammatory drug
PCS	Physical component summary score
PK	Pharmacokinetics
PFS	Pre-filled syringe
PsA	Psoriatic arthritis
Pso	Psoriasis
PT	Preferred term
PY	Patient years
QoL	Quality of Life
RMP	Risk Management Plan
SAE	Serious adverse event
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SF-36	Short Form-36
SI-joint	Sacroiliac joint
SMQ	Standardized MedDRA Query
SOC	System organ class
SpA	Spondyloarthritis
SPP	Safety profiling plan
TNF	Tumor Necrosis Factor
TNF-IR	TNF-alpha inhibitor inadequate responder
ULN	Upper limit of normal
VAS	Visual analogue scale
WPAI-GH	Work Productivity and Activity Impairment - General Health

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 5 August 2019 an application for a group of variations.

The following variations were requested in the group:

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

Grouping of two variations:
One type II variation II C.I.6.a: Extension of indication to include the treatment of Non-radiographic axial spondyloarthritis (nr-axSpA) / axial spondyloarthritis (axSpA) without radiographic evidence for Cosentyx. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 of the SmPC are amended. The package leaflet is amended in accordance. The updated RMP version 5.0 has also been submitted.
One type IB C.I.11.z to change the due date of the Psoriasis Registry (category 3 study) within the RMP.

The group of variations requested 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/0372/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0372/2018 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Tuomo Lapveteläinen

Timetable	Actual dates
Submission date	05 August 2019
Start of procedure:	14 September 2019
CHMP Rapporteur Assessment Report	08 November 2019
PRAC Rapporteur Assessment Report	11 November 2019
PRAC members comments	20 November 2019
PRAC Outcome	28 November 2019
CHMP members comments	02 December 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	05 December 2019
Request for supplementary information (RSI)	12 December 2019
CHMP Rapporteur Assessment Report	21 February 2020
PRAC Rapporteur Assessment Report	21 February 2020
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	12 March 2020
CHMP members comments	16 March 2020
Updated CHMP & PRAC Rapporteur Assessment Report	19 March 2020
Opinion	26 March 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The concept of spondyloarthritis (SpA) as described in the EU Guideline (EMA/CPMP/EWP/4891/03 Rev.1, Corr 1) comprises a group of diseases which share common clinical and genetic features, and includes ankylosing spondylitis (AS), psoriatic arthritis, arthritis/spondylitis with inflammatory bowel disease, reactive arthritis, as well as undifferentiated SpA. All of these can present with a predominantly peripheral or axial arthritis.

Axial SpA (axSpA) is defined as a chronic inflammatory disease that involves primarily the sacroiliac joints and the axial skeleton. Clinical manifestations usually begin in late adolescence or early adulthood (mean age of onset 26 years) and onset after age 45 is rare. Clinical manifestations include lower back pain with predominant nocturnal pain, morning stiffness and impaired physical function. Also chest pain, pain and swelling of peripheral joints and extra-articular tenderness may occur as well as several extra-skeletal manifestations such as anterior uveitis, psoriasis, and inflammatory bowel disease.

The diagnosis of ankylosing spondylitis, the most frequent subtype of axial SpA, requires the presence of radiographic sacroiliitis. However, it is now well established that patients with axial SpA who do not meet radiographic criteria for sacroiliitis may experience a significant burden of disease that is comparable to patients with well-defined AS. The 2009 ASAS criteria thus define the entity of axial spondyloarthritis (axial SpA) which includes a broader set of patients than the original 1984 criteria for AS. The new group is captured under the term "non-radiographic axial SpA" and can be identified by the presence of clinical features of axial SpA combined with either "imaging" evidence (active sacroiliitis seen on the MRI scan) or HLA-B27 positivity ("clinical arm").

The prevalence of axial SpA (including AS and non-radiographic forms) is estimated to be 0.3-0.8%. The prevalence of AS is estimated around 0.1 % - 0.5 % of the European population. While AS is more common in males (male to female ratio is estimated to be 2-3:1), women are slightly more often affected compared to men in the nr-axSpA stage. AxSpA tends to be more severe in men, in whom the spine is more frequently involved.

Management

According to clinical guidelines, physical therapy and non-steroidal anti-inflammatory drugs (NSAIDs) comprise the first line treatment in axial SpA. Physical therapy has a positive effect on stiffness and on spinal mobility and even on pain. NSAIDs are used to control pain with good response in up to 50-70% of axial SpA patients, and due to their high symptomatic efficacy and possible disease-modifying properties, NSAIDs are considered the treatment of choice for the majority of patients with axial SpA and if tolerated, these are usually maintained as background therapy in patients with insufficient response.

Several biological products, including anti-TNF agents and secukinumab, are authorised for use in patients with AS who continue to have active disease despite NSAIDs. In Europe, several anti-TNF agents (adalimumab, certolizumab pegol, etanercept and golimumab) are also authorised for nr-axSpA with objective signs of inflammation.

Whereas anti-TNF agents have been shown to be efficacious in the treatment of nr-axSpA, a substantial proportion of patients do not show a good therapeutic response to these agents. The impact of these agents on axSpA-associated structural damage and diseases progression also remains to be established. There is a need for new therapies, including therapies with alternative mechanisms of action beyond TNF inhibition.

2.1.2. About the product

Cosentyx (secukinumab) is a fully human monoclonal anti-human interleukin-17A (IL-17A) antibody of the Immunoglobulin G1 (IgG1)/κ-class. It binds to IL-17A and neutralises the activity of this cytokine. Cosentyx was initially approved in the EU for the treatment of plaque psoriasis on 15 Jan 2015; indications for psoriatic arthritis (PsA) and ankylosing spondylitis (AS) were approved on 19 Nov 2015. Cosentyx is currently approved in over 90 countries worldwide.

The AS indication was originally approved within procedure EMEA/H/C/003729/II/0002. This approval was based on studies CAIN457F2305 and F2310, and the approved indication reads as follows:

"*Cosentyx is indicated for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy*."

The originally approved posology was based on a 150 mg monthly maintenance dose. More recently, a third AS study (CAIN457F2314) was assessed within procedure EMEA/H/C/003729/II/0051, for which a positive CHMP opinion was adopted in September 2019. Study F2314 provided support for a higher 300 mg maintenance dose, and as a result, the revised posology for AS reads as follows:

"*The recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Based on clinical response, the dose can be increased to 300 mg. Each 300 mg dose is given as two subcutaneous injections of 150 mg*."

2.1.3. The development programme

The current submission provides data from an ongoing Phase 3 study (Study CAIN457H2315 or PREVENT; hereinafter H2315) in patients with non-radiographic axial spondyloarthritis (nr-axSpA). According to the MAH, patients with nr-axSpA can progress to develop AS, and nr-axSpA along with AS should therefore be considered to be part of the spectrum of axial spondyloarthritis (axSpA). In the MAH's opinion, the submitted study provides evidence that secukinumab demonstrates clinically meaningful and statistically significant efficacy in patients with active nr-axSpA, including in those who have previously had an inadequate response to TNF-alpha inhibitors, and that the safety data observed in Study H2315 confirm the established safety profile of secukinumab and demonstrate that no new safety signals arise from this patient population. Accordingly, the purpose of this submission is to provide evidence supporting the registration of a 150 mg subcutaneous (s.c.) dose (with loading) of secukinumab for the treatment of patients with active nr-axSpA.

The indication and posology proposed by the MAH were as follows:

"*Secukinumab is indicated for the treatment of active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs)*."

The recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

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

2.3. Clinical aspects

2.3.1. Introduction

This single study submission comprises a clinical study report from an ongoing randomised, placebo-controlled Phase 3 study assessing the efficacy, safety and tolerability of two different regimens of secukinumab, 150 mg with loading and without loading, compared to placebo in patients with nr-axSpA. It should be noted that the MAH is not applying for authorisation for the regimen without loading.

The study population consists of adult patients fulfilling the ASAS classification criteria for axSpA as well as an abnormal CRP and/or evidence of inflammation in the sacroiliac joints (SI-joints) on MRI, but with no radiographic evidence of changes in the SI-joints that would meet the modified New York criteria for AS. Patients were stratified at randomisation according to the subgroup of objective signs of inflammation they belong to. Patients who had experienced an inadequate response to a TNF inhibitor were allowed entry into the study, but inclusion of TNF-IR patients was limited to no more than 20% of the overall randomised population.

GCP

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

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

- Tabular overview of clinical studies

Study Number	Status	Location
CAIN457H2315	Ongoing	Australia, Austria, Belgium, Bulgaria, Czech Republic, France, Germany, Hungary, Israel, Italy, Japan, Korea (Republic of), Mexico, Netherlands, Norway, Poland, Portugal, Russia, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States

2.3.2. Pharmacokinetics

Pharmacokinetics in main study

In Study H2315, secukinumab concentrations were assessed in serum. At Week 4 in the Load arm, the mean serum concentration at trough was approximately 5-fold higher than in the No Load arm and reflected the rise in exposure due to the 3 additional 150 mg doses at Weeks 1, 2 and 3. At Week 16, the mean trough serum concentration was approximately 40% higher in the Load group compared to the No Load group. By Week 52, similar mean trough serum concentrations were observed in all groups, including the group that had initially been randomised to placebo and switched to active medication from Week 20 onward. Table 1 display mean trough concentrations in all treatment groups from Week 0 to Week 52.

Table 1 Serum secukinumab (AIN457) concentrations (mcg/mL) summary statistics up to Week 52 (FAS)

	AIN457 150 mg Load (N=185)	AIN457 150 mg No Load (N=184)	Placebo (N=186)
	Conc (µg/mL) Mean ±SD (n)	Conc (µg/mL) Mean ±SD (n)	Conc (µg/mL) Mean ±SD (n)
Baseline	0 (180)	0 (179)	-
Week 4	53.1 ± 16.0 (169)	10.4 ± 4.33 (173)	-
Week 16	28.4 ± 11.0 (179)	20.5 ± 7.98 (168)	-
Week 52	23.4 ± 10.8 (145)	22.4 ± 10.1 (152)	21.9 ± 8.59 (80)

Conc = secukinumab concentration.

Immunogenicity results in main study

In Study H2315, anti-drug antibodies (ADA) were observed in a total of eight patients. Among these, six patients had ADA at baseline only. One patient had a positive result at baseline and at Week 16 and 52, and one patient had treatment-emergent ADA only at Week 52.

One patient had an AE (dermatitis contact) that was potentially related to immunogenicity; this non-serious AE occurred at Day 522 in a patient with ADA detected at baseline. No influence of ADAs on PK was observed among the four patients in whom assessable PK data was available.

2.3.3. Discussion on clinical pharmacology

No separate clinical pharmacology studies were submitted as part of the current application. In study H2315, trough concentrations of secukinumab in serum were within the expected range, and by Week 52, steady state appeared to have been reached also among patients who were initially randomised to placebo and switched to secukinumab from Week 20 onward.

Immunogenicity results are consistent with observations from the programmes in Pso and AS and continue to indicate a relatively low immunogenic potential for secukinumab.

2.3.4. Conclusions on clinical pharmacology

Reported pharmacokinetic and immunogenicity data from study H2315 are consistent with previous observations within other secukinumab development programmes.

2.4. Clinical efficacy

2.4.1. Dose response study

No dedicated dose response studies were performed. The previously completed Phase 3 studies in AS (F2310 and F2305) were used to support selection of the dosing regimen for Study H2315.

2.4.2. Main study

CAIN457H2315 "A randomized, double-blind, placebo-controlled multicenter study of secukinumab 150 mg in patients with active non-radiographic axial spondyloarthritis (nr-axSpA) to evaluate the safety, tolerability and efficacy up to 2 years, followed by an optional phase of either 150 mg or 300 mg randomised dose escalation for up to another 2 years"

The study is also referred to by the acronym PREVENT.

Methods

Study H2315 is an ongoing randomised, double-blind, placebo-controlled study, consisting of a core phase (up to Week 104) and an extension phase (Week 104 to Week 208). An outline of the study design is displayed in Figure 1. Two separate analysis plans were specified for the study to support regulatory filings in different jurisdictions. Analysis Plan A (to support a filing in EU) assesses the primary endpoint at Week 16, whereas Analysis Plan B (to support a filing in the US) assesses the primary endpoint at Week 52.

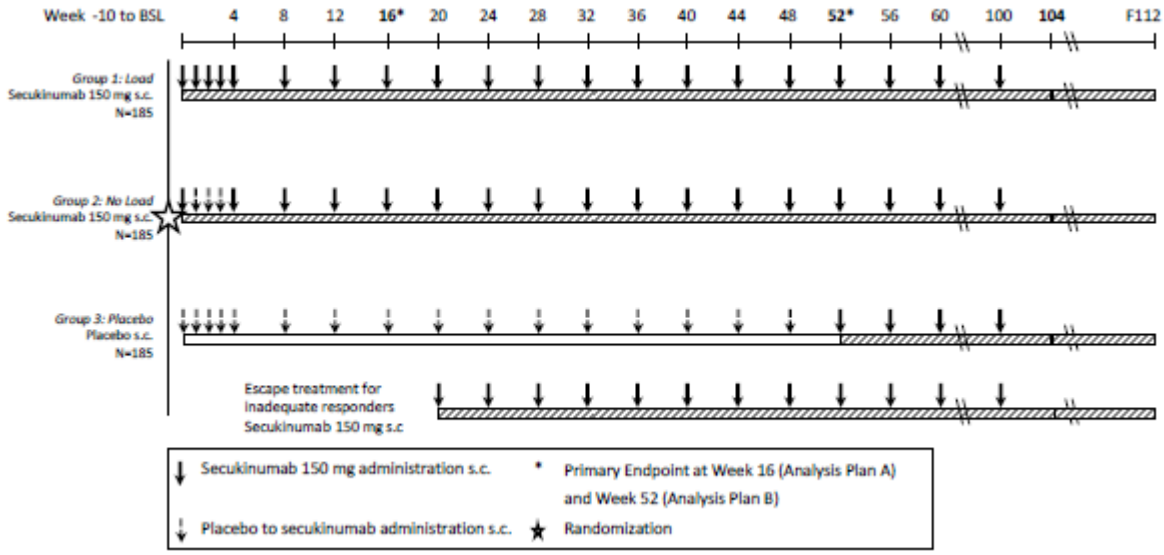


Figure 1 Study design of the core phase

A first interim data cut-off for the study was done on 17 December 2018, when all patients had completed 24 weeks of treatment, and this 24-week database was subsequently locked on 22 February 2019; data from this database lock (supporting Analysis Plan A) forms the basis of the current submission. At the time of the first data cut-off, 71.5% of enrolled patients had reached their Week 52 visit, and an interim analysis for the Week 52 time point (Analysis Plan B) was performed for these patients. These data were also included in the initial submission.

A second data cut-off was done on 01 July 2019, when all patients had completed 52 weeks of treatment, and the database for this cut-off was subsequently locked on 13 September 2019. Analyses of the Week 52 time point (supporting Analysis Plan B) were repeated for the full patient population, and the updated results were submitted for review during the assessment process. Analyses under Analysis Plan A were not repeated.

No data from the extension phase are included in the submission.

Study participants

Inclusion criteria:

- Patient had to be able to understand and communicate with the Investigator and comply with the requirements of the study and had to give a written, signed and dated informed consent before any study assessment was performed
- Male or non-pregnant, non-nursing female patients at least 18 years of age
- Diagnosis of axSpA according to ASAS axSpA criteria:
    - Inflammatory back pain for at least 6 months
    - Onset before 45 years of age
    - Sacroiliitis on MRI with ≥ 1 spondyloarthritis (SpA) feature OR human leukocyte antigen (HLA)-B27 positive with ≥ 2 SpA features
- Objective signs of inflammation at Screening, evident by either
    - MRI with Sacroiliac Joint inflammation

  AND /OR
    - hsCRP > upper limit of normal (ULN) as defined by the central lab (i.e. > 5mg/L)
- Active axSpA as assessed by total BASDAI ≥ 4 cm (0-10 cm) at Baseline
- Spinal pain as measured by BASDAI question #2 ≥ 4 cm (0-10 cm) at Baseline
- Total back pain as measured by visual analog scale (VAS) ≥ 40 mm (0-100 mm) at Baseline
- Patients were to have been on at least 2 different NSAIDs at the highest recommended dose for at least 4 weeks in total prior to randomization with an inadequate response or failure to respond, or less if therapy had to be withdrawn due to intolerance, toxicity or contraindications
- Patients who were regularly taking NSAIDs (including cyclooxygenase (COX)-1 or COX-2 inhibitors) as part of their axSpA therapy were required to be on a stable dose for at least 2 weeks before randomization
- Patients who had been on a TNF-alpha inhibitor (not more than one) had to have experienced an inadequate response to previous or current treatment given at an approved dose for at least 3 months prior to randomization or had been intolerant to at least one administration of an anti-TNF-alpha agent
- Patients who had previously been on a TNF-alpha inhibitor were allowed entry into study after an appropriate wash-out period prior to randomization:
    - 4 weeks for Enbrel® (etanercept) – with a terminal half-life of 102 ± 30 hours (s.c. route)
    - 8 weeks for Remicade® (infliximab) – with a terminal half-life of 8.0-9.5 days (i.v. infusion)
    - 10 weeks for Humira® (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) (s.c. 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

- Patients taking MTX (≤ 25 mg/week) or sulfasalazine (≤ 3 g/day) were allowed to continue their medication and had to have taken it for at least 3 months and had to be on a stable dose for at least 4 weeks prior to randomization
- Patients on MTX had to be on stable folic acid supplementation before randomization
- Patients who were on a DMARD other than MTX or sulfasalazine had to discontinue the DMARD 4 weeks prior to randomization, except for leflunomide, which had to be discontinued for 8 weeks prior to randomization unless a cholestyramine washout had been performed
- Patients taking systemic corticosteroids had to be on a stable dose of ≤ 10 mg/day prednisone or equivalent for at least 2 weeks before randomization.

Exclusion criteria:

- Patients with radiographic evidence for sacroiliitis, grade ≥ 2 bilaterally or grade ≥ 3 unilaterally (radiological criterion according to the modified New York diagnostic criteria for AS) as assessed by central reader
- Inability or unwillingness to undergo MRI (e.g., patients with pacemakers, aneurysm clips or metal fragments /foreign objects in the eyes, skin or body that are not MRI compatible)
- Chest X-ray or MRI with evidence of ongoing infectious or malignant process, obtained within 3 months of Screening and evaluated by a qualified physician
- Patients taking high potency opioid analgesics (e.g., methadone, hydromorphone, morphine)
- Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or IL-17 receptor
- 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 was longer
- History of hypersensitivity to the study drug or its excipients or to drugs of similar chemical classes
- Any therapy by intra-articular injections (e.g., corticosteroid) within 4 weeks before randomization
- Any intramuscular corticosteroid injection within 2 weeks before randomization
- Patients previously treated with any biological immunomodulating agents, except those targeting TNF-alpha
- Patients who had taken more than one anti-TNF-alpha agent
- Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 or investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)
- Pregnant or nursing (lactating) women
- Women of child-bearing potential, unless they were using effective methods of contraception during entire study
- Active ongoing inflammatory diseases other than axSpA that might have confounded the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease or uveitis

- Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions, which in the opinion of the Investigator immunocompromised the patient and/or placed the patient at unacceptable risk for participation in an immunomodulatory therapy
- Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥ 160/95 mmHg), congestive heart failure (New York Heart Association status of class III or IV), uncontrolled diabetes, or very poor functional status unable to perform self-care
- History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as aspartate aminotransferase (SGOT or AST), alanine aminotransferase (SGPT or ALT), alkaline phosphatase, or serum bilirubin. The Investigator was to be guided by the following criteria:
    - Any single parameter was not to exceed 2x upper limit of normal (ULN). A single parameter elevated up to and including 2x ULN was to be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out lab error.
    - If the total bilirubin concentration was increased above 2x ULN, total bilirubin was to be differentiated into the direct and indirect reacting bilirubin.
- History of renal trauma, glomerulonephritis, or patients with one kidney only, or a serum creatinine level exceeding 132.6 µmol/L
- Screening total white blood cell (WBC) count < 3000/µL, or platelets < 100 000/µL or neutrophils < 1500/µL or hemoglobin < 85 g/L
- Active systemic infections during the last 2 weeks prior to randomization (exception: common cold)
- History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive purified protein derivative (PPD) skin test or a positive QuantiFERON TB-Gold test. Patients with a positive test could participate in the study if further work up (according to local practice/guidelines) established conclusively that the patient had no evidence of active tuberculosis. If presence of latent tuberculosis was established, then treatment according to local country guidelines had to be initiated.
- Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at Screening or randomization
- History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that had been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that had been removed)
- Current severe progressive or uncontrolled disease which, in the judgment of the clinical Investigator, rendered the patient unsuitable for the trial
- Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins)
- Inability or unwillingness to receive injections with PFS
- Any medical or psychiatric condition which, in the Investigator's opinion, would have precluded the participant from adhering to the protocol or completing the study per protocol

- Donation or loss of 400 mL or more of blood within 8 weeks before dosing
- History or evidence of ongoing alcohol or drug abuse, within the last 6 months before randomization
- Plans for administration of live vaccines during the study period or 6 weeks prior to randomization

Treatments

Eligible patients were randomised to one of 3 treatment groups (secukinumab 150 mg Load, secukinumab 150 mg No Load, or placebo) in a ratio of 1:1:1.

- Group 1 (secukinumab 150 mg Load): secukinumab 150 mg (1 mL, 150 mg/mL) s.c. prefilled syringe (PFS) at baseline, Weeks 1, 2 and 3, followed by administration every 4 weeks starting at Week 4
- Group 2 (secukinumab 150 mg No Load): secukinumab 150 mg (1 mL, 150 mg/mL) s.c. PFS at baseline, placebo at Weeks 1, 2 and 3, followed by secukinumab 150 mg PFS administration every 4 weeks starting at Week 4
- Group 3 (placebo): placebo (1 mL) s.c. PFS at baseline, Weeks 1, 2, 3, followed by administration every 4 weeks starting at Week 4

From Week 16 onward, background medications, such as NSAIDs and DMARDs, could be modified or added to treat signs and symptoms of nr-axSpA, based on the clinical judgment of disease activity by the Investigator and the patient.

Furthermore, from Week 20 onward, patients who were repeatedly (e.g., at 2 or more consecutive visits) considered to be inadequate responders, based on the clinical judgment of disease activity by the Investigator and the patient, could receive open-label secukinumab 150 mg s.c. or other biologics as standard of care treatment. Patients switching to a biologic therapy (e.g. anti-TNF) other than secukinumab were not to receive any further study medication and had to observe a 12 week wash out period after the last application of study treatment prior to starting any other biologic treatment.

Starting at Week 52, all patients were assigned to receive secukinumab 150 mg s.c. in an open-label fashion except for those patients who discontinued study treatment (secukinumab 150 mg or placebo) during the initial 52 weeks of the study.

Objectives

There were 2 sets of primary and secondary objectives based on regional regulatory precedent and feedback. These objectives were tested in separate analysis plans. Analysis Plan A was designed to support an EU MAA and is the primary basis of the current assessment.

The primary objective (Analysis Plan A) was to demonstrate that secukinumab 150 mg s.c. (with load) at Week 16 was superior to placebo in TNF-alpha naïve patients with active nr-axSpA based on the proportion of patients achieving an Assessment of Spondyloarthritis International Society (ASAS) 40 response.

The secondary objectives (Analysis Plan A) were:

1. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the proportion of all patients achieving an ASAS40 response

2. To demonstrate that the efficacy of secukinumab 150 mg s.c., without loading, at Week 16 was superior to placebo based on the proportion of TNF naïve patients achieving an ASAS40 response
3. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the proportion of patients meeting the ASAS 5/6 response criteria
4. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the change from baseline in total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
5. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the proportion of patients achieving BASDAI 50
6. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the change from baseline of high sensitivity C-Reactive Protein (hsCRP)
7. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the change from baseline in total Bath Ankylosing Spondylitis Functional Index (BASFI)
8. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the change from screening in sacroiliac (SI) joint edema on MRI
9. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the proportion of patients achieving an ASAS20 response
10. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the change from baseline in Short Form-36 Physical Component Summary Score (SF-36 PCS)
11. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) scores
12. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the proportion of patients achieving ASAS partial remission
13. Overall safety and tolerability of secukinumab

Assessment of long-term data was performed according to Analysis Plan B. For Analysis Plan B (which is considered a secondary analysis for EU purposes), the primary objective was to demonstrate that secukinumab 150 mg s.c. (without load) at Week 52 was superior to placebo in TNF-alpha inhibitor naïve (TNFi-naïve) patients with active nr-axSpA based on the proportion of patients achieving an ASAS40 response.

The secondary objectives per Analysis Plan B were:

1. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 52 was superior to placebo based on the proportion of all patients achieving an ASAS40 response
2. To demonstrate that the efficacy of secukinumab 150 mg s.c., with loading, at Week 52 was superior to placebo based on the proportion of TNFi-naïve patients achieving an ASAS40 response

3. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the proportion of patients achieving an ASAS40 response
4. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the change from baseline in total BASDAI
5. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the proportion of patients achieving BASDAI50
6. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 52 was superior to placebo based on the proportion of patients achieving BASDAI50
7. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the change from baseline of hsCRP
8. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the change from baseline in Short Form-36 (SF-36) PCS
9. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) scores
10. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the proportion of patients meeting the ASAS 5/6 response criteria
11. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the proportion of patients achieving an ASAS20 response
12. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the change from baseline in total BASFI
13. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 was superior to placebo based on the change from screening in sacroiliac joint (SIJ) edema on MRI
14. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 52 was superior to placebo based on the proportion of patients achieving Ankylosing Spondylitis Disease Activity - C-reactive protein (ASDAS-CRP) inactive disease as defined by ASDAS < 1.3
15. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 52 was superior to placebo based on the change from screening in SIJ edema on MRI
16. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 52 was superior to placebo based on the change from baseline in ASQoL scores
17. Overall safety and tolerability of secukinumab

Exploratory objectives were not distinguished by Analysis Plan and included the following:

1. To compare between the secukinumab regimens with and without loading for the primary and secondary objectives

To explore the efficacy of secukinumab 150 mg s.c., with or without loading, versus placebo as specified:

2. ASAS20 response over time
3. ASAS40 response over time

4. Change from baseline in hsCRP
5. Change from baseline in total BASDAI over time
6. BASDAI50 response over time
7. ASAS 5/6 response over time
8. ASAS partial remission over time
9. Change from baseline in ASAS components, including:
    a. Patient's global assessment of disease activity
    b. Total spinal pain
    c. Inflammation as measured by the mean of BASDAI questions 5 and 6
    d. Bath Ankylosing Spondylitis Functional Index (BASFI)
10. Cumulative proportion of patients classified as inadequate responders based on the clinical judgment of disease activity between Week 20 and Week 52
11. Change from baseline in nocturnal back pain
12. Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS)-C-Reactive Protein (CRP) and ASDAS-Erythrocyte Sedimentation Rate (ESR)
13. Spinal mobility assessed by Bath Ankylosing Spondylitis Metrology Index (BASMI) linear scores
14. ASDAS inactive disease as defined by ASDAS < 1.3
15. ASDAS clinically important improvement (change in ASDAS $\geq$ 1.1) and major improvement (change in ASDAS $\geq$ 2.0)
16. Change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and expanded enthesis sites
17. Change from baseline in tender or swollen joint count as determined by the 44-joint assessment
18. Change from baseline in ESR
19. Work Productivity and Activity Impairment - General Health (WPAI-GH), QoL (ASQoL, SF-36 and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue) assessments and utilities (Euro-QoL 5-Dimension Health Status Questionnaire; EQ-5D)
20. Change in concomitant glucocorticoid treatment dose from Week 16 to Week 52
21. Change in concomitant DMARD usage from Week 16 to Week 52
22. Cumulative NSAID intake during the study
23. Change from screening edema score in SIJ and spine at Weeks 16, 52 and 104
24. Change from screening in total quadrant level fatty lesions in SIJ and spine at Weeks 16, 52 and 104
25. Change from screening in sacroiliitis grading of X-rays of the sacroiliac joints according to the modified New York criteria for AS at Week 104
26. Change from screening in X-ray modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) at Week 104

27. The development of immunogenicity against secukinumab
28. The pharmacokinetic/pharmacodynamic (PK/PD) relationship of secukinumab
29. Identification of potential biomarkers associated with treatment response to secukinumab or possibly correlating with the severity or progression of nr-axSpA
30. To perform exploratory pharmacogenetic assessments to examine whether individual genetic variation in genes relating to drug metabolism, the indication, and the drug target pathway confer differential response to secukinumab

Additional exploratory objectives are defined for the extension phase, but in the absence of any data, they will not be further discussed in this assessment.

Outcomes/endpoints

Primary endpoint

In Analysis Plan A, the primary efficacy variable of this study was response to treatment according to the ASAS40 criteria at Week 16 in TNF-alpha naïve patients. The analysis of the primary variable was based on the FAS population. The ASAS Response Criteria (ASAS40) were defined as an improvement of $\geq$ 40% and $\geq$ 2 unit on a scale of 10 in at least 3 of the 4 main domains and no worsening at all in the remaining domain.

In Analysis Plan B, the primary efficacy variable was response to treatment according to the ASAS40 criteria at Week 52 in TNF-alpha naïve patients. The analysis of the primary variable was based on the FAS population at the Week 52 DBL.

Secondary endpoints

Secondary efficacy variables for Analysis Plan A included:

- Response to treatment according to the ASAS40 criteria at Week 16
- Response to treatment according to the ASAS 5/6 criteria at Week 16
- Change from baseline in total BASDAI score at Week 16
- Response to treatment at Week 16 according to the BASDAI50 criteria
- Change from baseline in hsCRP at Week 16
- Change from baseline in total BASFI score at Week 16
- Change from screening in MRI SI joint edema score at Week 16
    - According to the MAH, MRI images of the SI joints and the spine were acquired according to a specific imaging charter and read by trained central readers. The scoring methods used were the Berlin Active Inflammatory Lesions Scoring for the SI-joints and the Berlin score, a validated MRI scoring method of the spine.
- Response to treatment according to the ASAS20 criteria at Week 16
- Change from baseline in SF-36 PCS score at Week 16
- Change from baseline in ASQoL score at Week 16
- Response to treatment at Week 16 according to the ASAS partial remission

The secondary efficacy variables were analysed using the FAS population.

For Analysis Plan B, response to treatment was assessed at both Week 16 and at Week 52, using variables corresponding to Analysis Plan A.

Exploratory endpoints

Treatment responses on ASDAS criteria endpoints and spinal mobility on BASMI were evaluated within the exploratory analyses.

Sample size

A total of 555 patients were to be enrolled into the study.

The statistical power calculation for Analysis Plan A was based on an expected ASAS40 response rate of 47.1% for the secukinumab groups and 27.9% for placebo among TNF naïve patients at Week 16. Based on these assumptions, 185 patients per treatment arm was expected to provide 91% power to reject a hypothesis of equal treatment response based on Fisher's exact test.

Randomisation

At baseline, all eligible patients were randomized to one of the treatment arms via IRT.

At randomization, patients were stratified according to which subgroup of objective signs of inflammation they belonged to (based on their CRP and MRI status at Screening). CRP+ was defined as a value above the upper limit of normal as defined by the central lab (hsCRP > 5mg/L); MRI+ was defined as SIJs MRI with presence of inflammatory lesions according to the ASAS/OMERACT (Outcome Measures in Rheumatology) Definition.

The only condition that was placed on enrollment was that no less than 15% of patients were to belong to either of the 3 subgroups of objective signs of inflammation:

- CRP+ and MRI+,
- CRP+ and MRI-,
- CRP- and MRI+.

Additionally, it was planned to enroll no more than approximately 20% TNF-alpha inhibitor inadequate responder (TNF-IR) patients in the study. Randomization was conducted in blocks of size 6. Forced randomization was allowed, and used twice.

Blinding (masking)

This was a double-blind randomized treatment study. Although unblinding did occur after the Week 24 DBL, the original randomization to active treatment vs. placebo continued to remain blinded to the study team conducting the trial, all investigators, site personnel and patients until all patients have completed the treatment period 2 (Week 52) and the Week 52 DBL has occurred. A separate restricted study team conducted the Week 24 interim analysis and no access to the interim data was given to the study team conducting the ongoing trial until Week 52 DBL as detailed in the CAIN457H2315 blinding charter.

Statistical methods

Analysis populations

Randomized set was defined as all patients who were randomized. Unless otherwise specified, mis-randomized patients (mis-randomized in IRT) were excluded from the randomized set.

Mis-randomized patients were defined as those patients who were mistakenly randomized into the IRT prior to the site confirming all eligibility criteria had been met and to whom no study medication was given. Mis-randomized patients were treated as screen failures.

Full analysis set (FAS): The FAS was comprised of all analyzable patients from the randomized set to whom study treatment had been assigned. Following the intent-to-treat principle, patients were evaluated according to the treatment assigned to at randomization, but actual stratum.

Full analysis set 2 (FAS2): The FAS2 was comprised of all patients from the randomized set to whom study treatment had been assigned and who had been in enrolled at least 379 days (upper limit of visit window for Analysis Plan B primary endpoint) before date cut-off. Following the intent-to-treat principle, patients were evaluated according to the treatment assigned to at randomization, but actual stratum, if stratified randomization was used. This analysis set was used to analyse the Week 52 efficacy endpoints in Analysis Plan B only at the time of the interim analysis (Week 24 DBL), and results based on this analysis set are not presented within this Assessment Report.

Safety set: The safety set included all patients who took at least one dose of study treatment during the treatment period. Patients were evaluated according to treatment received.

Primary endpoint

The primary efficacy variable of this study was response to treatment according to the ASAS40 criteria at Week 16 in TNF-alpha naïve patients. The analysis of the primary variable was based on the FAS. The ASAS Response Criteria (ASAS40) were defined as an improvement of $\geq$ 40% and $\geq$ 2 unit on a scale of 10 in at least 3 of the 4 main domains and no worsening at all in the remaining domain.

The primary estimand was defined as follows:

a. Population - defined through appropriate inclusion/exclusion criteria to reflect the targeted nr-axSpA population

b. Variable - composite of remaining on the study and on randomized treatment through 16 weeks and achieving ASAS40 response at 16 weeks

c. Intercurrent event: the intercurrent event was captured through the variable definition

d. Population-level summary - odds ratio of response proportions between treatment conditions

The primary analysis was conducted via logistic regression with treatment and stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) as factors and weight as a covariate. Odds ratios and 95% CI were presented comparing each secukinumab regimen to placebo. Odds ratio and 95% CI were also presented comparing the 2 secukinumab regimens.

Sensitivity analyses and supportive analyses were conducted in order to provide evidence that the results seen from the primary analysis were robust. Interactions between treatment and selected baseline demographics and disease characteristics were explored for ASAS40 response in TNF-alpha naïve patients at Week 16.

The impact of missing data on the analysis results of ASAS40 in TNF-alpha naïve patients was assessed as well by repeating the logistic regression model using different ways to handle missing data:

- Multiple imputation
- Tipping point analysis

Assuming significance was shown for the primary analysis using non-responder imputation, the tipping point analysis investigated if, and at which point, significance was not achieved anymore as patients imputed as non-responders were increasingly reclassified as responders independently for each treatment group.

Secondary efficacy variables are categorized below to binary - response to treatment and "continuous" - change from baseline/screening.

Following response to treatment at week 16 endpoints were used: ASAS40, ASAS 5/6 criteria, BASDAI50 criteria, ASAS20, and ASAS partial remission. The proportion of patients meeting each response criteria was evaluated using a logistic regression model with treatment group, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP- /MRI+) and TNF-alpha status as factors and weight as a covariate. For BASDAI50 criteria also BASDAI score at baseline was included as covariate in the model.

For continuous endpoints MRMM or ANCOVA if there was no other time point than week 16 post baseline, was applied. The model included with treatment group, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP- /MRI+) and TNF-alpha status as factors, baseline value and weight as covariates, and in case of MRMM treatment by visit and baseline value and visit as interaction terms in the model. For hsCRP, prespecified log-transformation was applied.

Multiplicity

The following null hypotheses were included in the sequential testing strategy, and type-I-error was set such that a family-wise type-I-error of 5% was kept:

Primary objective:

H_1: secukinumab 150 mg (with load) is not different to placebo regimen with respect to ASAS40 response in TNF-alpha naïve patients at Week 16

Secondary objectives:

H_2: secukinumab 150 mg (with load) is not different to placebo regimen with respect to ASAS40 response at Week 16

H3: secukinumab 150 mg (with load) is not different to placebo regimen with respect to ASAS 5/6 response at Week 16

H4: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from baseline in total BASDAI at Week 16

H5: secukinumab 150 mg (with load) is not different to placebo regimen with respect to BASDAI50 at Week 16

H6: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from baseline in hsCRP at Week 16

H7: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from baseline in BASFI at Week 16

H8: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from screening in SI joint edema on MRI at Week 16

H9: secukinumab 150 mg (with load) is not different to placebo regimen with respect to ASAS20 at Week 16

H10: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from baseline in SF-36 PCS at Week 16

H11: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from baseline in ASQoL at Week 16

H12: secukinumab 150 mg (with load) is not different to placebo regimen with respect to ASAS partial remission at Week 16

H13 - H26 are otherwise the same as H1to H12 but secukinumab 150mg *without load* is compared to placebo

Subgroup analysis

The primary endpoint was evaluated within stratification factor levels (CRP+/MRI+, CRP+/MRI-, and CRP-/MRI+).

Secondary endpoints were evaluated within TNF-alpha inhibitor status (TNF-alpha naïve and TNF-IR) and within stratification factor levels (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+).

Results

Participant flow

A total of 1,583 patients were screened for this study, of which 555 patients (35.1%) were randomised. Overall, 1,028 patients (64.9%) discontinued prior to screening phase completion, most due to screen failure (1,000 patients, 63.2%). The most common reasons for screen failure were lack of objective signs of inflammation at screening (466/1,028 patients; 45.3%), presence of radiographic evidence of sacroiliitis (295/1,028 patients; 28.7%), and lack of diagnosis of axSpA per ASAS axSpA criteria (205/1,028 patients; 19.9%). Overall, at least one inclusion or exclusion criterion was not met for 1,005/1,028 patients (97.8%) who discontinued prior to screening phase completion. Other reasons for not completing the screening phase were subject/guardian decision (26 patients, 1.6%), AEs (1 patient, 0.1%) and pregnancy (1 patient, 0.1%).

A summary of patient data disposition at Week 16 (time point for primary efficacy analysis) is provided below. While the schedule of study assessments did not contain a dedicated Week 16 completion form, the table summarises availability of efficacy data for each group at the Week 16 time point. Overall, efficacy data was available for 95.1% of patients (528/555) at Week 16, similar to the disposition at Week 24.

Table 2 ***Efficacy data disposition at Week 16 (FAS)***

Disposition/Reason	AIN457 150 mg Load N = 185 n (%)	AIN457 150 mg No Load N = 184 n (%)	Placebo N = 186 n (%)	Total N = 555 n (%)
Efficacy data available at Week 16	175 (94.6)	176 (95.7)	177 (95.2)	528 (95.1)
Efficacy data not available at Week 16	10 (5.4)	8 (4.3)	9 (4.8)	27 (4.9)
Missing visit or data	7 (3.8)	3 (1.6)	3 (1.6)	13 (2.3)
Discontinuation	3 (1.6)	5 (2.7)	6 (3.2)	14 (2.5)
Reason for discontinuation				
ADVERSE EVENT	0 (0.0)	2 (1.1)	1 (0.5)	3 (0.5)
LACK OF EFFICACY	0 (0.0)	1 (0.5)	2 (1.1)	3 (0.5)
LOST TO FOLLOW-UP	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
PHYSICIAN DECISION	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
PROTOCOL DEVIATION	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
SUBJECT/GUARDIAN DECISION	1 (0.5)	1 (0.5)	3 (1.6)	5 (0.9)

Patient disposition at Week 24 is provided in Table 3. Overall, 95.0% of the randomised patients completed Week 24 of the study, with similar proportions across all 3 treatment groups. AEs leading to discontinuation were reported for 2.2% of patients in the secukinumab 150 mg No Load group and 1.1% of patients in the secukinumab 150 mg Load and placebo groups. Overall, the most frequent reason for discontinuation was subject/guardian decision (2.2% in the secukinumab 150 mg Load group, 0.5% in the secukinumab 150 mg No Load group, and 2.7% in the placebo group).

Table 3 ***Patient disposition at Week 24 (Randomized Set/FAS)***

Disposition/Reason	AIN457 150 mg Load N=185 n (%)	AIN457 150 mg No Load N=184 n (%)	Placebo N=186 n (%)	Total N=555 n (%)
Completed Week 24	175 (94.6)	177 (96.2)	175 (94.1)	527 (95.0)
Discontinued before or at Week 24	10 (5.4)	7 (3.8)	11 (5.9)	28 (5.0)
Primary reason for discontinuing				
Adverse event	2 (1.1)	4 (2.2)	2 (1.1)	8 (1.4)
Lack of efficacy	2 (1.1)	1 (0.5)	2 (1.1)	5 (0.9)
Lost to follow-up	0	1 (0.5)	1 (0.5)	2 (0.4)
Physician decision	1 (0.5)	0	1 (0.5)	2 (0.4)
Protocol deviation	1 (0.5)	0	0	1 (0.2)
Subject/guardian decision	4 (2.2)	1 (0.5)	5 (2.7)	10 (1.8)

N = Number of patients randomized.

Patient disposition at Week 52 is provided in Table 4. Overall, 86.7% of patients completed Week 52, with similar percentages across treatment groups. In the secukinumab 150 mg Load group, the most common primary reason for discontinuation was due to subject/guardian decision (6.5%) whereas in the secukinumab 150 mg No Load group and placebo group, it was lack of efficacy (3.8% and 5.9%, respectively).

By Week 52, 94/185 (50.8%) patients in the secukinumab 150 mg Load group, 87/184 (47.3%) patients in the secukinumab 150 mg group and 119/186 (64.0%) patients in the placebo group had switched to either open-label secukinumab 150 mg (N=297) or standard of care (N=3).

Table 4 ***Patient disposition at Week 52 (Randomized Set/FAS)***

Disposition/Reason	AIN457 150 mg Load N=185 n (%)	AIN457 150 mg No Load N=184 n (%)	Placebo N=186 n (%)	Total N=555 n (%)
Completed Week 52	156(84.3)	165(89.7)	160(86.0)	481(86.7)
Discontinued before or at Week 52	29(15.7)	19(10.3)	26(14.0)	74(13.3)
Primary reason for discontinuing				
Adverse event	4(2.2)	5(2.7)	3(1.6)	12(2.2)
Lack of efficacy	10(5.4)	7(3.8)	11(5.9)	28(5.0)
Lost to follow-up	1(0.5)	1(0.5)	1(0.5)	3(0.5)
Physician decision	1(0.5)	1(0.5)	2(1.1)	4(0.7)
Pregnancy	0(0.0)	2(1.1)	0(0.0)	2(0.4)
Protocol deviation	1(0.5)	0(0.0)	0(0.0)	1(0.2)
Subject/guardian decision	12(6.5)	3(1.6)	9(4.8)	24(4.3)

N = Number of patients randomized.

Recruitment

Study H2315 was conducted across 144 Investigator sites in 24 participating countries: 5 centers in Australia, 2 centers in Austria, 3 centers in Belgium, 3 centers in Bulgaria, 6 centers in Czech Republic, 8 centers in France, 14 centers in Germany, 6 centers in Hungary, 4 centers in Israel, 5 centers in Italy, 6 centers in Japan, 2 centers in Republic of Korea, 4 centers in Mexico, 3 centers in Netherlands, 2 centers in Norway, 6 centers in Poland, 5 centers in Portugal, 8 centers in Russia, 15 centers in Spain, 3 centers in Sweden, 2 centers in Switzerland, 1 center in Turkey, 9 centers in United Kingdom, and 18 centers in the United States.

Patient enrolment by participating country is summarised in Table 5. Countries with the highest numbers of enrolled patients included Spain (72), Czech Republic (71), Poland (65), Russia (54), and Germany (52).

Table 5 ***Patient enrolment by participating country***

Country	Total number of patients enrolled
Australia	27
Austria	3
Belgium	10
Bulgaria	7
Czech Republic	71
France	19
Germany	52
Hungary	21
Israel	11
Italy	14
Japan	13
Korea, Republic of	2
Mexico	6
Netherlands	9
Norway	8
Poland	65
Portugal	14
Russia	54
Spain	72
Sweden	7
Switzerland	8
Turkey	2
United Kingdom	24
United States	36
Total	555

Conduct of the study

The original protocol for Study H2315 had an effective date of 30 September 2015, and first patient first visit took place on 29 April 2016. The first data cut-off date for the current submission was 17 December 2018, and the database was subsequently locked on 22 February 2019. The second data cut-off was 01 July 2019, when all patients had completed 52 weeks of treatment, and the database for this cut-off was subsequently locked on 13 September 2019.

The study protocol was amended on two occasions. In Amendment 1, dated 28 November 2016, significant changes included a change in the testing hierarchy, a change in the population for the primary analysis to TNF-alpha naïve patients only, and a change in the maximally allowed proportion of TNF-IR patients from 30% to 20% (Table 6).

Table 6 ***Key changes in Protocol Amendment 1, dated 28 Nov 2016***

Version and date	Summary of key changes
Amendment 1 28-Nov-2016	The powering of the study was re-evaluated, triggering a changed order in the testing hierarchy as well as adjustments of the population for the primary endpoint to TNF-alpha naïve patients only. After feedback from the FDA, changes were made to Analysis Plan B to focus on the no-load dosing regimen The test for HLA-B27 was moved from the Baseline Visit to Screening Visit 2 to facilitate the screening process for the sites. The maximally allowed proportion of TNF-IR patients was changed from 30% to 20% Historic MRIs were accepted, if taken within 3 months of Baseline and in alignment of the imaging criteria to facilitate the re-screening process for patients and sites The wording in the SAE reporting section was updated to be aligned with current and future SAE reporting processes A decision was taken to replace the eSource system and collect the data for the study in OC/RDC in all countries

Amendment 2, dated 11 July 2018, added an extension phase into the study as well as a Week 24 interim analysis for the Week 52 time point for Analysis Plan B (Table 7).

Table 7 ***Key changes in Protocol Amendment 2, dated 11 Jul 2018***

Version and date	Summary of key changes
Amendment 2 11-Jul-2018	Addition of an extension phase to the current core protocol The order of the secondary endpoints of the Analysis Plan B in the hierarchy was updated to elevate several Load regimen endpoints to reflect their clinical relevance Addition of group sequential testing for the Week 24 interim analysis of the Week 52 time points (Analysis Plan B) The wording for the Withdrawal of Consent section was updated to align with the European Economic Area (EEA) General Data Protection Regulation (GDPR) requirements

Protocol deviations were reported for 22.0% of patients overall, with similar percentages across treatment groups. Approximately half of the patients with protocol deviations took prohibited concomitant medication such as opioids or unstable doses of NSAIDs (10.1% overall). Selection criteria were not met for 4.5% of patients overall (5 patients in the secukinumab 150 mg Load group, and 10 patients each in the secukinumab 150 mg No Load and placebo groups), and 1.8% of patients overall had a treatment deviation (e.g., administration of incorrect or additional study medication in four patients). The category of Other deviations included deviations related to informed consent, incorrect stratum assignment, non-compliance with investigator responsibilities, etc. Protocol deviations by deviation category are summarised in Table 8.

Table 8 ***Protocol Deviations by deviation category (Randomized Set)***

Protocol deviation	AIN457 150 mg Load N=185 n (%)	AIN457 150 mg No Load N=184 n (%)	Placebo N=186 n (%)
Patients With At Least One Protocol Deviation	**41 (22.2)**	**40 (21.7)**	**41 (22.0)**
Selection Criteria Not Met	5 (2.7)	10 (5.4)	10 (5.4)
Patient Not Withdrawn As Per Protocol	0	0	0
Treatment Deviation	1 (0.5)	5 (2.7)	4 (2.2)
Prohibited Concomitant Medication	20 (10.8)	14 (7.6)	22 (11.8)
Other	22 (11.9)	20 (10.9)	15 (8.1)

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

Baseline data

Demographic characteristics were similar across the treatment groups (Table 9). In the overall population, 91.5% of patients were white. Mean (SD) age was 39.4 (11.5) years with a range of 18 to 80 years; 98.4% of patients were less than 65 years of age. Mean (SD) BMI was 27.1 (5.6) kg/m2. There were slightly more female patients in each treatment group; overall, 54.1% of patients were female.

Table 9 ***Demographic characteristics (Randomized set)***

Demographic variable	AIN457 150 mg Load N=185	AIN457 150 mg No Load N=184	Placebo N=186	Total N=555
Age group in years, n(%)				
< 65	183 (98.9)	180 (97.8)	183 (98.4)	546 (98.4)
65-74	2 (1.1)	3 (1.6)	2 (1.1)	7 (1.3)
≥ 75	0	1 (0.5)	1 (0.5)	2 (0.4)
Age (Years)				
N	185	184	186	555
Mean	39.1	39.8	39.3	39.4
SD	11.45	11.68	11.47	11.52
Median	39.0	38.5	39.0	39.0
Min - Max	18 – 67	19 - 77	18 - 80	18 - 80
Gender, n(%)				
Female	105 (56.8)	100 (54.3)	95 (51.1)	300 (54.1)
Male	80 (43.2)	84 (45.7)	91 (48.9)	255 (45.9)
Race, n(%)				
American Indian or Alaska Native	0	2 (1.1)	0	2 (0.4)
Asian	4 (2.2)	8 (4.3)	11 (5.9)	23 (4.1)
Black or African American	0	2 (1.1)	1 (0.5)	3 (0.5)
White	176 (95.1)	165 (89.7)	167 (89.8)	508 (91.5)
Other	5 (2.7)	7 (3.8)	7 (3.8)	19 (3.4)
Ethnicity, n(%)				
Hispanic or Latino	9 (4.9)	8 (4.3)	7 (3.8)	24 (4.3)
Not Hispanic or Latino	165 (89.2)	162 (88.0)	161 (86.6)	488 (87.9)
Not reported	2 (1.1)	5 (2.7)	6 (3.2)	13 (2.3)
Unknown	9 (4.9)	9 (4.9)	12 (6.5)	30 (5.4)
BMI (kg/m**2)				
N	185	184	184	553
Mean	27.13	27.17	26.87	27.06
SD	5.497	5.753	5.614	5.613
Median	26.37	25.85	26.12	26.16
Min - Max	17.3 - 51.3	17.1 - 50.0	17.8 - 49.4	17.1 - 51.3
Smoker at baseline, n (%)				
No	140 (75.7)	144 (78.3)	139 (74.7)	423 (76.2)
Yes	45 (24.3)	40 (21.7)	47 (25.3)	132 (23.8)

AIN457= secukinumab, BMI= body mass index.
Age is calculated from date of screening and date of birth.

Disease characteristics and history at baseline were also similar between the treatment groups (Table 10). Mean time since onset of back pain was 8.56 years and mean time since first diagnosis of axSpA was 2.61 years. Over 90% of randomised patients were naive to TNF-alpha inhibitors, with 9.7% of patients having received 1 prior TNF-alpha inhibitor. The mean global assessment of disease activity on a 100 mm VAS was 70.8 mm and median hsCRP was 4.5 mg/L. Mean Berlin scores for SI joint oedema on the MRI were 2.80 (SD 3.83) in the secukinumab Load group, 2.24 (SD 3.29) in the No Load group, and 2.70 (SD 3.96) in the placebo group. Regarding objective signs of inflammation used for stratification, 42.3% of patients were CRP- and MRI+, 29.9% were CRP+ and MRI+, and 27.7% were CRP+ and MRI-. There were no patients with radiographic evidence for sacroiliitis according to the modified NY criteria for AS.

Table 10 **Baseline disease characteristics (Randomized set)**

Background Characteristics	AIN457 150 mg Load N=185	AIN457 150 mg No Load N=184	Placebo N=186	Total N=555
Time since first diagnosis of AxSpA (years)				
N	185	184	186	555
Mean	2.748	2.118	2.955	2.609
SD	4.6289	3.0502	5.0136	4.3255
Median	0.895	0.824	0.943	0.884
Min - Max	0.02 - 30.69	0.07 - 17.35	0.01 - 31.95	0.01 - 31.95
Time since onset of back pain (years)				
n	183	184	186	553
Mean	8.724	8.573	8.385	8.560
SD	9.2659	8.6355	8.3413	8.7389
Median	5.782	5.437	5.644	5.561
Min - Max	0.53 - 46.54	0.51 - 47.20	0.58 - 44.44	0.51 - 47.20
Patient's global assessment of disease activity (0-100 mm)				
n	182	183	186	551
Mean	72.6	71.0	68.8	70.8
SD	15.31	15.21	14.32	15.00
Median	73.0	72.0	67.5	71.0
Min - Max	8 - 100	27 - 100	5 - 100	5 – 100
Total back pain (0-100 mm)				
n	185	184	186	555
Mean	73.3	72.0	70.9	72.1
SD	13.02	14.48	12.52	13.37
Median	74.0	72.5	71.0	72.0
Min - Max	45 - 100	43 - 100	43 - 98	43 – 100
Nocturnal back pain (0-100 mm)				
n	185	184	186	555
Mean	70.9	70.8	70.1	70.6
SD	17.42	16.43	14.72	16.20
Median	72.0	71.0	70.0	71.0
Min - Max	12 - 100	3 - 100	15 - 100	3 – 100
MASES				
n	185	184	186	555
Mean	3.7	3.6	2.7	3.3
SD	3.40	3.71	2.82	3.35
Median	3.0	3.0	2.0	2.0
Min - Max	0 - 13	0 - 13	0 - 13	0 – 13
Erythrocyte sedimentation rate (mm/h)				
n	184	184	186	554
Mean	23.6	23.1	21.4	22.7
SD	22.01	17.66	19.47	19.78
Median	17.5	18.0	16.0	17.0
Min - Max	1 - 129	1 - 90	1 - 94	1 – 129
hs C-reactive protein (mg/L)				
n	185	184	186	555
Mean	13.17	9.67	10.76	11.20
SD	27.209	15.815	21.335	21.969
Median	4.60	4.50	4.20	4.50
Min - Max	0.3 - 222.8	0.4 - 99.3	0.4 - 166.2	0.3 - 222.8
Abnormal hs C-reactive protein				
No	81 (43.8)	77 (41.8)	81 (43.5)	239 (43.1)
Yes	104 (56.2)	107 (58.2)	105 (56.5)	316 (56.9)
Sacroiliac joint inflammation on MRI*				
Negative	53 (28.6)	50 (27.2)	47 (25.3)	150 (27.0)
Positive	132 (71.4)	134 (72.8)	139 (74.7)	405 (73.0)

Background Characteristics	AIN457 150 mg Load N=185	AIN457 150 mg No Load N=184	Placebo N=186	Total N=555
CRP and MRI status				
CRP+ and MRI+	54 (29.2)	57 (31.0)	55 (29.6)	166 (29.9)
CRP+ and MRI-	52 (28.1)	51 (27.7)	51 (27.4)	154 (27.7)
CRP- and MRI+	79 (42.7)	76 (41.3)	80 (43.0)	235 (42.3)
HLA-B27				
Negative	48 (25.9)	65 (35.3)	55 (29.6)	168 (30.3)
Positive	136 (73.5)	117 (63.6)	129 (69.4)	382 (68.8)
Missing	1 (0.5)	2 (1.1)	2 (1.1)	5 (0.9)
Naive to TNF alpha inhibitors				
No	21 (11.4)	18 (9.8)	15 (8.1)	54 (9.7)
Yes	164 (88.6)	166 (90.2)	171 (91.9)	501 (90.3)
Number of prior TNF alpha inhibitors				
=0	164 (88.6)	166 (90.2)	171 (91.9)	501 (90.3)
=1	21 (11.4)	18 (9.8)	15 (8.1)	54 (9.7)
Radiographic evidence for sacroiliitis according to the MNYC criteria				
No	185 (100.0)	184 (100.0)	186 (100.0)	555 (100.0)

AIN457= secukinumab, AxSpA= axial spondyloarthritis, BASDAI= Spondylitis Disease Activity Index, BASMI= Bath Ankylosing Spondylitis Metrology Index, BASFI= Bath Ankylosing Spondylitis Functional Index, CRP= c-reactive protein, HLA= Human Leukocyte Antigen, MASES= Maastricht Ankylosing Spondylitis Enthesitis Score, MNYC = Modified New York Criteria, MRI= magnetic resonance imaging, SD= standard deviation, TNF= tumor necrosis factor. Abnormal hsCRP: > 5 mg/L.*Sacroiliac joint inflammation by historical or current MRI

At baseline, mean BASFI score was 6.02 (SD 1.99), mean BASDAI score was 6.92 (SD 1.34), and mean linear BASMI score was 2.82 (SD 1.24). There were no substantial differences between treatment groups in BASFI, BASDAI or linear BASMI at baseline.

At baseline, 9.9% of all patients used methotrexate with a median dose of 15 mg/week; 14.8% used sulfasalazine (median dose of 2 g/day), and 8.6% used corticosteroids (median dose of 6.67 mg/day).

Numbers analysed

Analysis sets used for this study are shown in Table 11. All 555 randomised patients were included in the Full Analysis Set and in the Safety set. The FAS2 (used only for the Week 52 interim analyses) comprised 397 patients (71.5% of the randomised set), including 133 patients in the secukinumab 150 mg Load group, 132 patients in the secukinumab 150 mg No Load group, and 132 patients in the placebo group.

Table 11 ***Analysis sets in study H2315***

Analysis Population	AIN457 150 mg Load n (%)	AIN457 150 mg No Load n (%)	Placebo n (%)
Randomized set (RAN)	185 (100.0)	184 (100.0)	186 (100.0)
Full analysis set (FAS)	185 (100.0)	184 (100.0)	186 (100.0)
Full analysis set 2 (FAS2)	133 (71.9)	132 (71.7)	132 (71.0)
Safety set (SAF)	185 (100.0)	184 (100.0)	186 (100.0)

The FAS2 comprised all patients from the randomized set to whom study treatment had been assigned and who had been in enrolled at least 379 (upper limit of visit window for primary endpoint) days before date cut off. Percentages were computed using the number of Randomized in each treatment group as the denominator.

Outcomes and estimation

The study met its pre-defined primary and secondary objectives according to Analysis Plan A. Secukinumab 150 mg Load and No Load groups were both superior to placebo on the hierarchically tested endpoints (Table 12). The primary endpoint of ASAS40 response in TNF-naïve patients at Week 16 was statistically significantly higher for both secukinumab groups versus placebo. For the secondary variables at Week 16, both secukinumab groups showed significantly higher rates of ASAS 20 and ASAS40 response, ASAS5/6 response, BASDAI50 response, ASAS partial remission, as well as significantly greater changes from baseline in BASDAI, hsCRP, BASFI, SI-joint edema on MRI, SF-36 PCS and ASQoL, as compared with the placebo group.

Table 12 ***Results of hypothesis tests within the hierarchical testing strategy (Full Analysis Set)***

				Adjusted p-value	
Hypothesis	**Endpoint**	**Comparison vs. Placebo**	**Unadjusted p-value**	**Testing hierarchy**	**Statistically Significant**
H1	ASAS40 in TNF naive patients at Week 16	AIN457 150 mg Load	0.0197	0.0197	Yes
H2	ASAS40 at Week 16	AIN457 150 mg Load	0.0108	0.0197	Yes
H3	ASAS5/6 at Week 16	AIN457 150 mg Load	0.0005	0.0197	Yes
H4	BASDAI at Week 16	AIN457 150 mg Load	0.0006	0.0197	Yes
H5	BASDAI50 at Week 16	AIN457 150 mg Load	0.0001	0.0197	Yes
H6	hsCRP at Week 16	AIN457 150 mg Load	0.0002	0.0197	Yes
H7	BASFI at Week 16	AIN457 150 mg Load	0.0041	0.0197	Yes
H8	SI joint edema on MRI at Week 16	AIN457 150 mg Load	<.0001	0.0197	Yes
H9	ASAS20 at Week 16	AIN457 150 mg Load	0.0260	0.0260	Yes
H10	SF-36 PCS at Week 16	AIN457 150 mg Load	0.0006	0.0260	Yes
H11	ASQoL at Week 16	AIN457 150 mg Load	0.0008	0.0260	Yes
H12	ASAS Partial Remission Criteria at Week 16	AIN457 150 mg Load	<.0001	0.0260	Yes
H13	ASAS40 in TNF naive patients at Week 16	AIN457 150 mg No Load	0.0146	0.0260	Yes
H14	ASAS40 at Week 16	AIN457 150 mg No Load	0.0087	0.0260	Yes
H15	ASAS5/6 at Week 16	AIN457 150 mg No Load	0.0094	0.0260	Yes
H16	BASDAI at Week 16	AIN457 150 mg No Load	0.0002	0.0260	Yes
H17	BASDAI50 at Week 16	AIN457 150 mg No Load	0.0002	0.0260	Yes
H18	hsCRP at Week 16	AIN457 150 mg No Load	0.0002	0.0260	Yes
H19	BASFI at Week 16	AIN457 150 mg No Load	0.0143	0.0260	Yes
H20	SI joint edema on MRI at Week 16	AIN457 150 mg No Load	<.0001	0.0260	Yes
H21	ASAS20 at Week 16	AIN457 150 mg No Load	0.0149	0.0260	Yes
H22	SF-36 PCS at Week 16	AIN457 150 mg No Load	0.0011	0.0260	Yes
H23	ASQoL at Week 16	AIN457 150 mg No Load	0.0002	0.0260	Yes
H24	ASAS Partial Remission Criteria at Week 16	AIN457 150 mg No Load	0.0001	0.0260	Yes

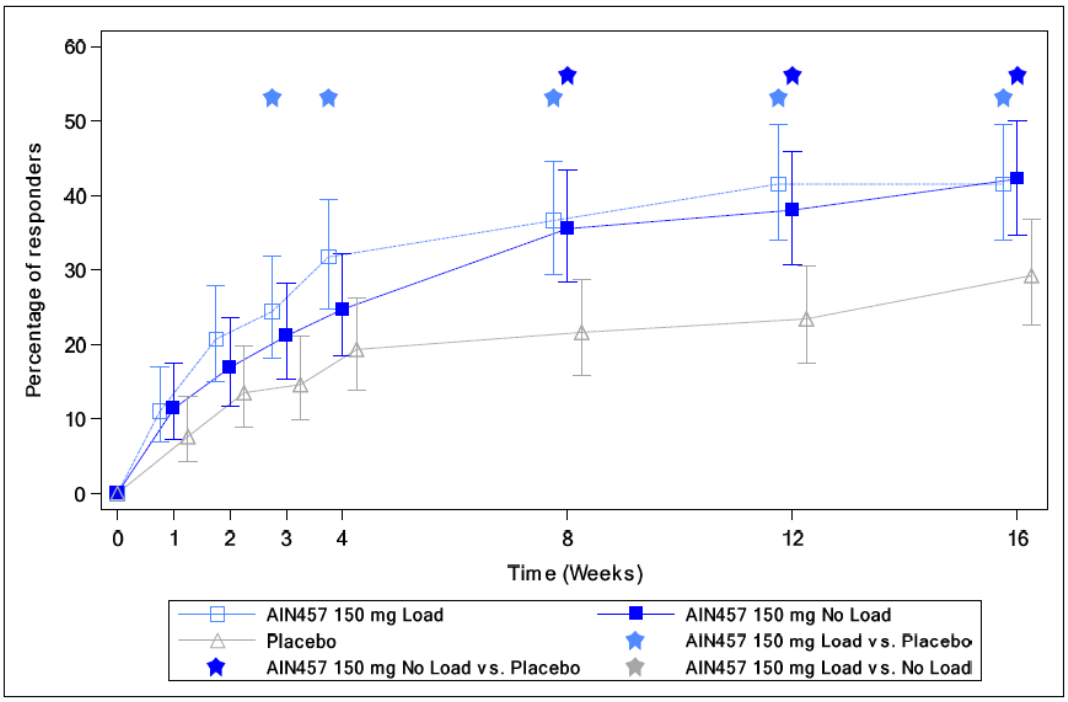
Primary Endpoint

The primary efficacy variable was the response to treatment according to the ASAS40 criteria in TNF-naïve patients at Week 16. As seen in Table 14, both secukinumab groups showed statistically significantly higher ASAS40 response rates among TNF-naïve patients at Week 16; response rates of 41.5% and 42.2% were reported in the secukinumab 150 mg Load and No Load groups, respectively, compared to 29.2% in the placebo group. At Week 16, the ASAS40 response rates were similar between the Load and No Load groups, but the onset of action was faster in the Load group (Figure 2).

Table 13 ***ASAS40 response at Week 16 in TNF-naïve patients using non-responder imputation (Full Analysis Set)***

Analysis Visit	Treatment Group	n/M(%)	Comparison	Odds Ratio	95% CI	p-value
Week 16	AIN457 150 mg Load (N=164)	68/164 (41.5)	vs. No Load	0.98	(0.63, 1.51)	0.9165
			vs. Placebo	1.72	(1.09, 2.70)	0.0197
	AIN457 150 mg No Load (N=166)	70/166 (42.2)	vs. Placebo	1.76	(1.12, 2.76)	0.0146
	Placebo (N=171)	50/171 (29.2)				

CI= confidence interval
Odds ratio, 95% CI, and p-value were from a logistic regression model with treatment and stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) as factors and baseline weight as a covariate.
Missing responses for any reason were imputed as non-responders.
n: The number of patients who responded.
M: The total number of patients in the treatment group of the specified analysis set.



*Unadjusted p-value ≤ 0.05

Figure 2 ASAS40 response in TNF- naïve patients with 95% CI using non-responder imputation - up to Week 16 (Full Analysis Set)

Secondary Endpoints

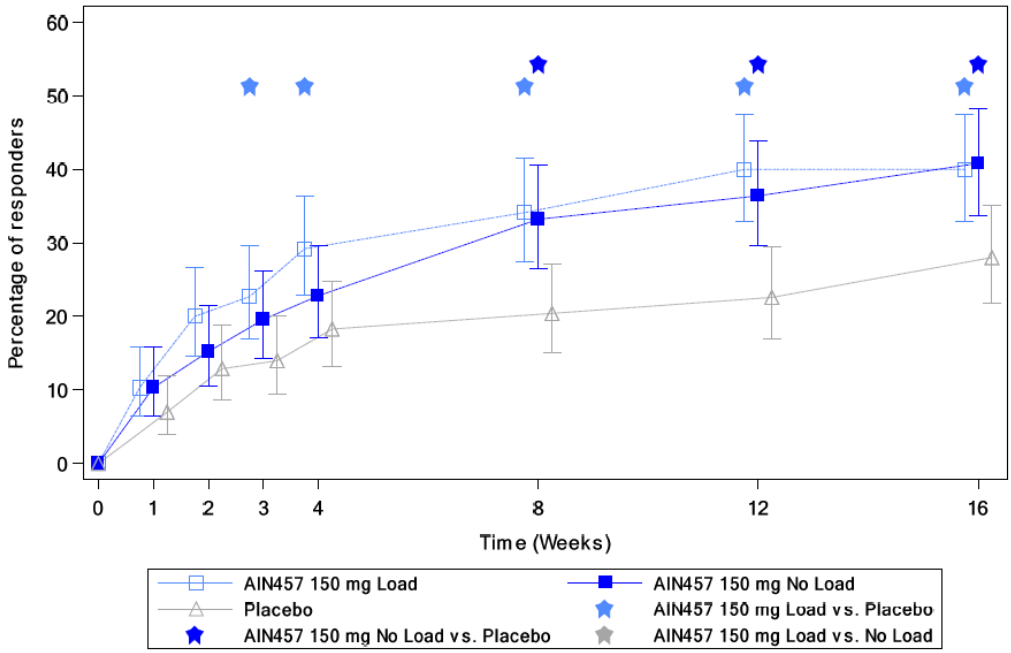
Overall ASAS40 response at Week 16

At Week 16, ASAS40 response in the overall population was statistically significantly higher in the secukinumab 150 mg Load and no Load groups compared to the placebo group (40.0% and 40.8% vs. 28.0%; Table 14). Statistically significant differences vs. placebo (based on unadjusted p values) were noted from Week 3 onward for the secukinumab 150 mg Load group, and from Week 8 onward for the secukinumab 150 mg No Load group (Figure 3).

Table 14 ***ASAS40 response for overall population using non-responder imputation - at Week 16 (Full Analysis Set)***

Analysis Visit	Treatment Group	n/M (%)	Comparison	Odds Ratio	95% CI	p-value
Week 16	AIN457 150 mg Load (N=185)	74/185 (40.0)	vs. No Load	0.98	(0.65, 1.50)	0.9412
			vs. Placebo	1.77	(1.14, 2.74)	0.0108
	AIN457 150 mg No Load (N=184)	75/184 (40.8)	vs. Placebo	1.80	(1.16, 2.78)	0.0087
	Placebo (N=186)	52/186 (28.0)				

CI=confidence interval,
Odds ratio, 95% CI, and p-value were from a logistic regression model with treatment, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and TNF-alpha status as factors and baseline weight as a covariate.
Missing responses for any reason were imputed as non-responders.
n: The number of patients who responded.
M: The total number of patients in the treatment group of the specified analysis set.



*Unadjusted p-value ≤ 0.05

Figure 3 ASAS40 response with 95% CI for overall population using non-responder imputation - up to Week 16 (Full Analysis Set)

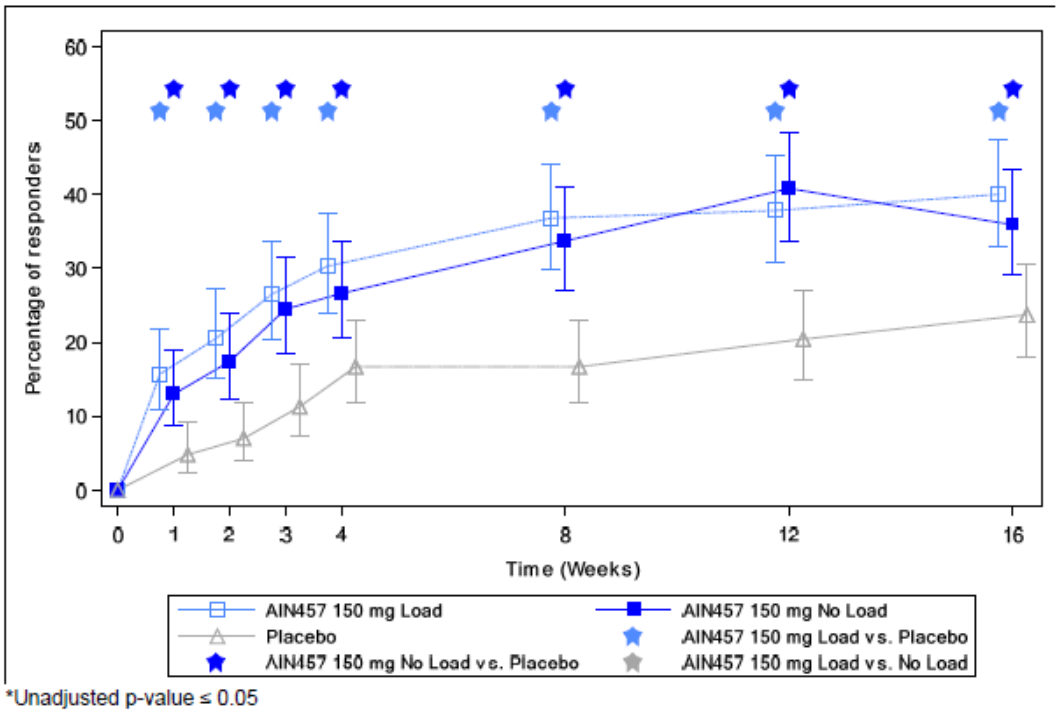
ASAS 5/6 response at Week 16

At Week 16, ASAS5/6 response using non-responder imputation was statistically significantly higher in the secukinumab 150 mg Load and No Load groups than in the placebo group (40.0% and 35.9% vs. 23.7%; Table 15). Statistically significant differences vs. placebo (based on unadjusted p values) were noted from Week 1 onward for both secukinumab groups, with little difference between the Load and No Load groups (Figure 4).

Table 15 ***ASAS5/6 response using non-responder imputation - at Week 16 (Full Analysis Set)***

Analysis Visit	Treatment Group	n/M (%)	Comparison	Odds Ratio	95% CI	p-value
Week 16	AIN457 150 mg Load (N=185)	74/185 (40.0)	vs. No Load	1.22	(0.79, 1.88)	0.3640
			vs. Placebo	2.26	(1.43, 3.58)	0.0005
	AIN457 150 mg No Load (N=184)	66/184 (35.9)	vs. Placebo	1.85	(1.16, 2.94)	0.0094
	Placebo (N=186)	44/186 (23.7)				

CI=confidence interval
Odds ratio, 95% CI, and p-value were from a logistic regression model with treatment, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and TNF-alpha status as factors and baseline weight as a covariate.
Missing responses for any reason were imputed as non-responders.
n: The number of patients who responded.
M: The total number of patients in the treatment group of the specified analysis set.



*Unadjusted p-value ≤ 0.05

Figure 4 - ASAS5/6 response with 95% CI using non-responder imputation - up to Week 16 (Full Analysis Set)

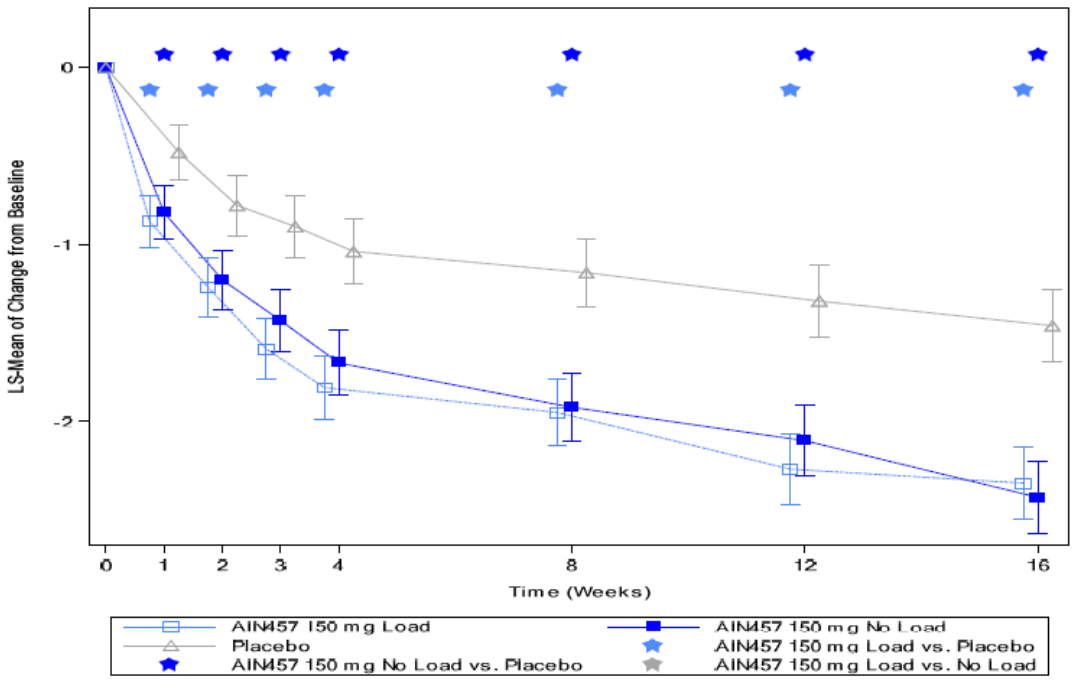
Change from baseline in total BASDAI score at Week 16

At Week 16, a statistically significant improvement (i.e., decrease) from baseline in total BASDAI score was observed for secukinumab 150 mg Load and No Load groups compared with placebo (LS mean change: -2.35 and -2.43 vs. -1.46; Table 16). Onset of action was rapid, and similar, statistically significant differences vs. placebo (based on unadjusted p values) were observed in both secukinumab groups starting at Week 1 (Figure 5).

Table 16 ***Total BASDAI change from baseline using MMRM - at Week 16 (Full Analysis Set)***

			Within treatment			Treatment contrast in LS mean (Change)			
Analysis visit	Treatment group	n	LS Mean Change	(SE)	Comparison	LS Mean	(SE)	(95% CI)	p-value
Week 16	AIN457 150 mg Load (N=185)	181	−2.35	(0.201)	vs. No Load	0.08	(0.255)	(−0.42, 0.58)	0.7479
					vs. Placebo	−0.89	(0.256)	(−1.39, −0.38)	0.0006
	AIN457 150 mg No Load (N=184)	177	−2.43	(0.203)	vs. Placebo	−0.97	(0.255)	(−1.47, −0.47)	0.0002
	Placebo (N=186)	177	−1.46	(0.205)					

CI= confidence interval
LS Mean, 95% CI, and p-value were from a mixed model repeated measures (MMRM) with treatment group, analysis visit, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and TNF-alpha status as factors, weight and baseline score as covariates, treatment by analysis visit and baseline score by analysis visit as interaction terms, using an unstructured covariance structure.
n: The number of patients with measures at both baseline and the corresponding post baseline visit.
N: The number of patients in each treatment group of the specified analysis set.



*Unadjusted p-value ≤ 0.05

Figure 5 Total BASDAI change from baseline +/- SE using MMRM - up to Week 16 (Full Analysis Set)

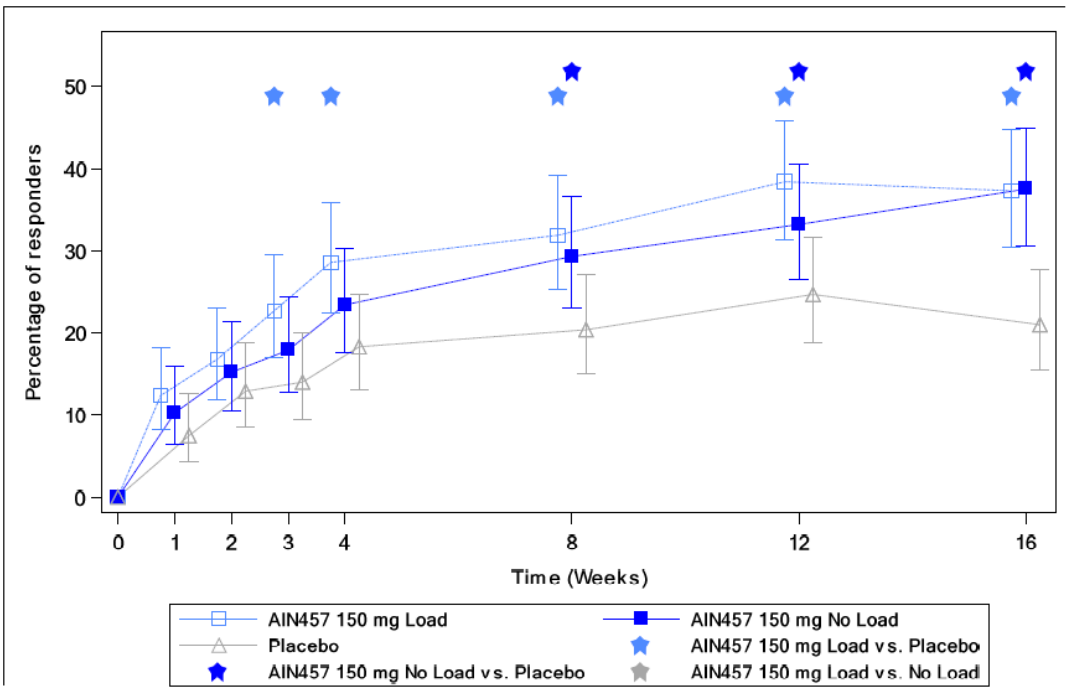
BASDAI50 response at Week 16

At Week 16, BASDAI50 response using non-responder imputation was statistically significantly higher in the secukinumab 150 mg Load and No Load groups than in the placebo group (37.3% and 37.5% vs. 21.0%; Table 17). Statistically significant differences vs. placebo (based on unadjusted p values) were noted from Week 3 onward for the secukinumab 150 mg Load group and, from Week 8 onward, also for the secukinumab 150 mg No Load group (Figure 6).

Table 17 ***BASDAI50 response using non-responder imputation - at Week 16 (Full Analysis Set)***

Analysis Visit	Treatment Group	n/M (%)	Comparison	Odds Ratio	95% CI	p-value
Week 16	AIN457 150 mg Load (N=185)	69/185 (37.3)	vs. No Load	1.04	(0.68, 1.61)	0.8464
			vs. Placebo	2.53	(1.58, 4.07)	0.0001
	AIN457 150 mg No Load (N=184)	69/184 (37.5)	vs. Placebo	2.43	(1.51, 3.89)	0.0002
	Placebo (N=186)	39/186 (21.0)				

CI= confidence interval
Odds ratio, 95% CI, and p-value were from a logistic regression model with treatment, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and TNF-alpha status as factors and baseline weight and baseline score as covariates.
Missing responses for any reason are imputed as non-responders.
n: The number of patients who responded.
M: The total number of patients in the treatment group of the specified analysis set.



*Unadjusted p-value ≤ 0.05

Figure 6 BASDAI50 response with 95% CI using non-responder imputation - up to Week 16 (Full Analysis Set)

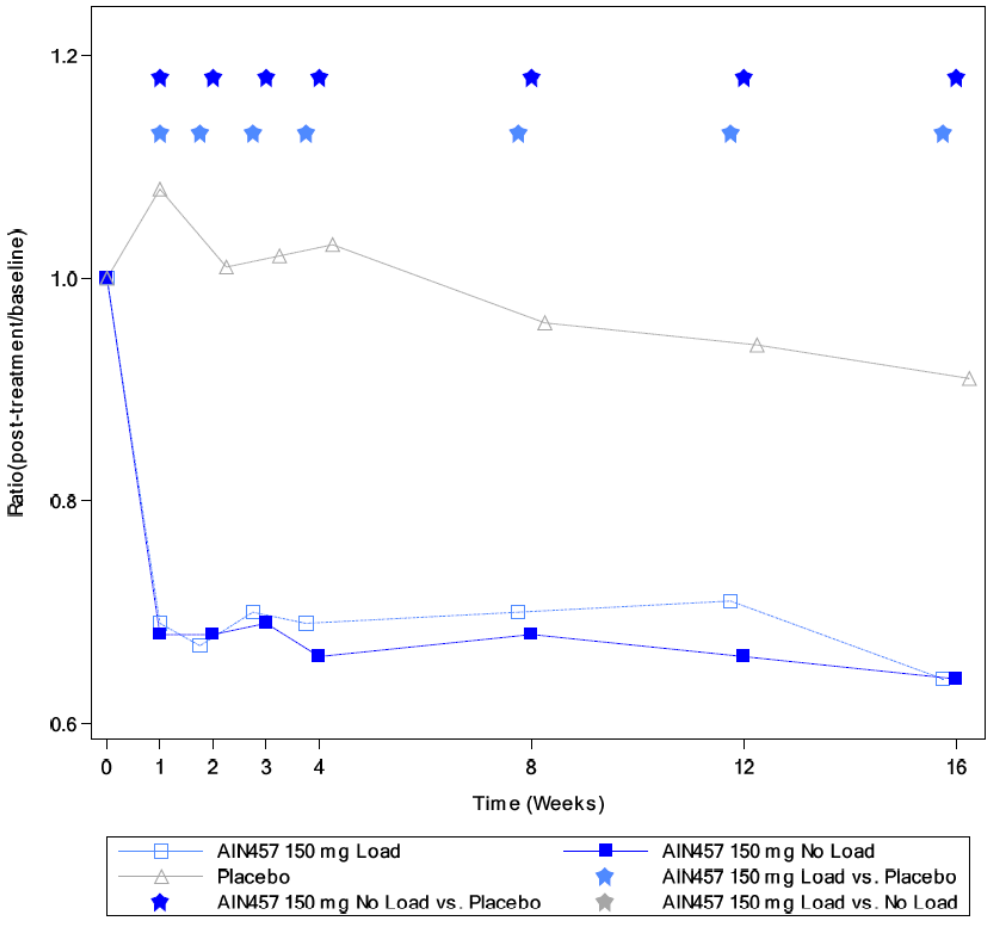
Change from baseline in hsCRP at Week 16

At Week 16, a statistically significant decrease from baseline in hsCRP was observed for the secukinumab 150 mg Load and No Load groups compared with placebo (LS mean change: 0.64 for both secukinumab groups vs. 0.91 for placebo; Table 18). Prompt decreases in the post-baseline/baseline ratios of hsCRP were observed in both secukinumab groups starting at Week 1, with no appreciable difference between the Load and No Load groups (Figure 7).

Table 18 ***hsCRP change from baseline using MMRM - at Week 16 (Full Analysis Set)***

			Within treatment			Treatment contrast in LS mean (Change)		
Analysis visit	**Treatment group**	**n**	**Exp (LSM)[1]**	**Exp (SE)**	**Comparison**	**Relative treatment effect[2]**	**(95 % CI of Ratio)**	**p-value**
Week 16	AIN457 150 mg Load (N=185)	180	0.64	(1.078)	vs. No Load	1.00	(0.83,1.20)	0.9942
					vs. Placebo	0.70	(0.58,0.84)	0.0002
	AIN457 150 mg No Load (N=184)	176	0.64	(1.079)	vs. Placebo	0.70	(0.58,0.84)	0.0002
	Placebo (N=186)	175	0.91	(1.080)				

AIN457= secukinumab, CI= confidence interval, LSM= least squares mean.
Analysis was done on the log(e) ratio of the treatment value vs. baseline value to normalize the distribution of the hsCRP at each visit. LS Mean, SE, 95% CI and p-value were from mixed-effect model repeated measures (MMRM) with treatment, visit, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and TNF-alpha status as factors, log(e) baseline and weight as covariates, treatment by visit and log(e) baseline by visit as interaction terms and an unstructured covariance structure.
[1] Exponentially transformed LSM, the geometric mean ratio of post-baseline/baseline.
[2] Relative treatment effect = exponential of the difference in LSM on the log(e) scale or the geometric LSM ratio on the original scale.
n = number of patients with measurements at both baseline and the post-baseline visit.



*Unadjusted p-value ≤ 0.05

Figure 7 hsCRP change from baseline using MMRM - up to Week 16 (Full Analysis Set)

Change from baseline in total BASFI score at Week 16

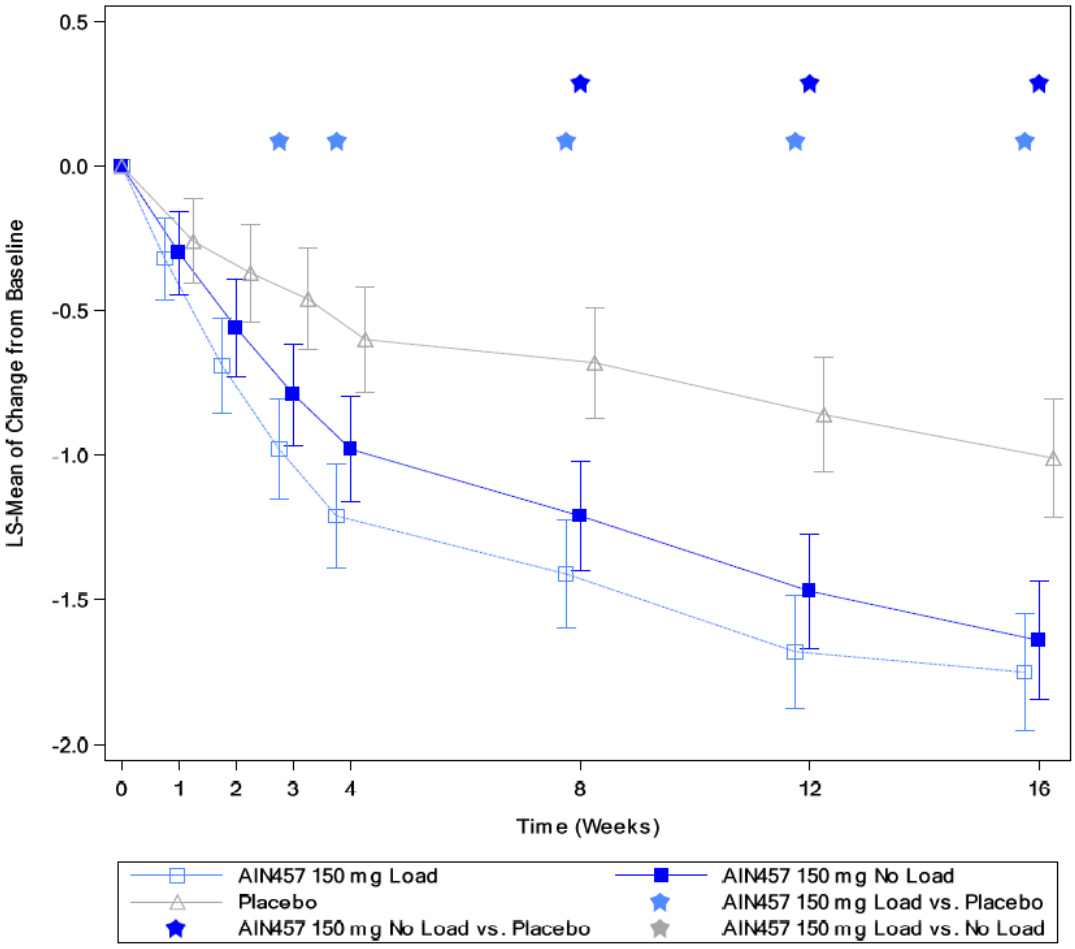
At Week 16, the change from baseline in BASFI using MMRM was statistically significantly greater for secukinumab 150 mg Load and No Load groups than for placebo (LS mean change: -1.75 and -1.64 vs.

-1.01; Table 19). Differences vs. placebo were observable from Week 2 for the secukinumab 150 mg Load group and from Week 8 for the secukinumab 150 mg No Load group (Figure 8).

Table 19 ***BASFI change from baseline using MMRM - at Week 16 (Full Analysis Set)***

			Within treatment			Treatment contrast in LS mean (Change)			
Analysis visit	**Treatment group**	**n**	**LS Mean Change**	**(SE)**	**Comparison**	**LS Mean**	**(SE)**	**(95% CI)**	**p-value**
Week 16	AIN457 150 mg Load (N=185)	181	-1.75	(0.202)	vs. No Load	-0.11	(0.260)	(-0.62,0.40)	0.6727
					vs. Placebo	-0.75	(0.259)	(-1.26,-0.24)	0.0041
	AIN457 150 mg No Load (N=184)	177	-1.64	(0.204)	vs. Placebo	-0.64	(0.259)	(-1.15,-0.13)	0.0143
	Placebo (N=186)	177	-1.01	(0.206)					

AIN457= secukinumab, CI=confidence interval, LS= least squares, SE= standard error
LS Mean, 95% CI, and p-value were from a mixed model repeated measures (MMRM) with treatment group, analysis visit, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and TNF-alpha status as factors, weight and baseline score as covariates, treatment by analysis visit and baseline score by analysis visit as interaction terms, using an unstructured covariance structure.
n: Number of patients with measures at both baseline and the corresponding post baseline visit.
N: Number of patients in each treatment group of the specified analysis set.



*Unadjusted p-value ≤ 0.05

Figure 8 BASFI change from baseline using MMRM - up to Week 16 (Full Analysis Set)

Change from screening in MRI SI joint oedema score at Week 16

At Week 16, the change from baseline in MRI SI joint oedema score (i.e., decrease) was statistically significantly greater for secukinumab 150 mg Load and No Load groups compared to placebo (mean change: -1.68 and -1.03 vs. −0.39; Table 20).

Table 20 ***MRI measurement of SI joint oedema score change from baseline using ANCOVA based on multiple imputation (MAR assumption) - at Week 16 (Full Analysis Set)***

Treatment Group	n	Mean	SE	Comparison	Estimate	SE	p-value
AIN457 150 mg Load (N=185)	180	-1.68	0.24	vs. No Load	-0.38	0.20	0.0612
				vs. Placebo	-1.24	0.20	<0.0001
AIN457 150 mg No Load (N=184)	177	-1.03	0.18	vs. Placebo	-0.86	0.20	<0.0001
Placebo (N=186)	174	-0.39	0.15				

AIN457= secukinumab, CI= confidence interval, SE= standard error
LS Mean, 95% CI, and p-value were from an ANCOVA model with treatment group and stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and TNF status as factors, weight and baseline score as covariates.
Missing data were imputed using multiple imputation (MI, MAR assumption) prior to running ANCOVA.
n: Number of patients with measures at both baseline and the corresponding post baseline visit.
N: Number of patients in each treatment group of the specified analysis set.

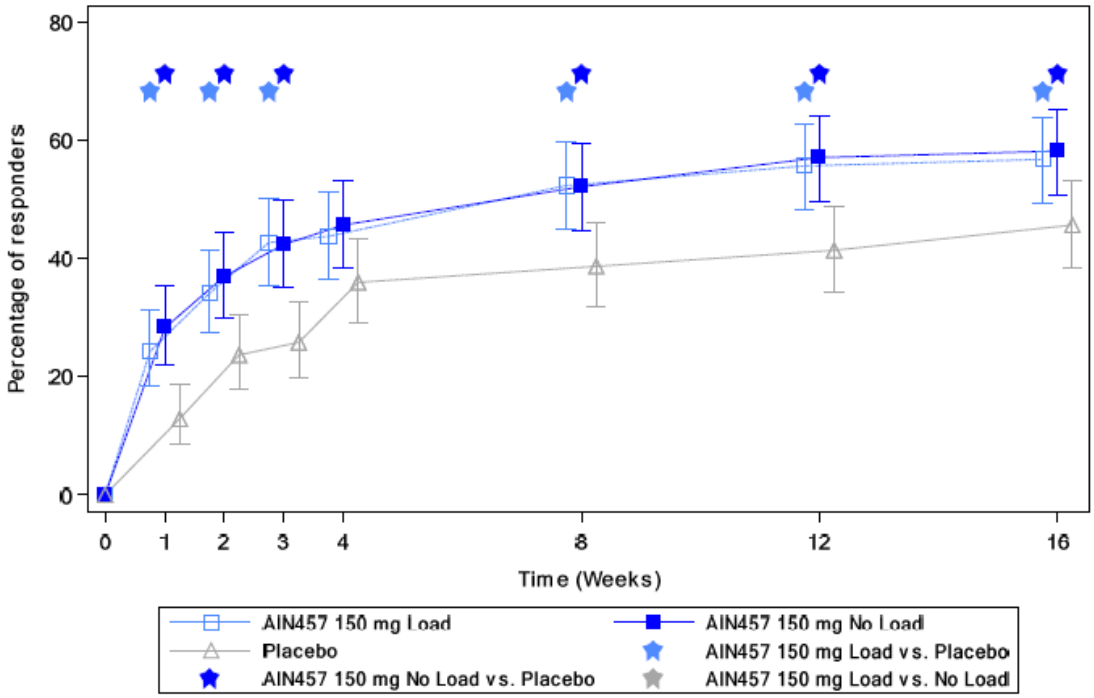
ASAS20 response at Week 16

At Week 16, ASAS20 response was statistically significantly higher for secukinumab 150 mg Load and No Load than for placebo (56.8% and 58.2% vs. 45.7%; Table 22). The time course and magnitude of response was very similar between the Load and No Load groups (Figure 9).

Table 21 ***ASAS20 response using non-responder imputation - at Week 16 (Full Analysis Set)***

Analysis Visit	Treatment Group	n/M (%)	Comparison	Odds Ratio	95% CI	p-value
Week 16	AIN457 150 mg Load (N=185)	105/185 (56.8)	vs. No Load	0.96	(0.63, 1.45)	0.8321
			vs. Placebo	1.60	(1.06, 2.43)	0.0260
	AIN457 150 mg No Load (N=184)	107/184 (58.2)	vs. Placebo	1.68	(1.11, 2.54)	0.0149
	Placebo (N=186)	85/186 (45.7)				

CI= confidence interval
Odds ratio, 95% CI, and p-value were from a logistic regression model with treatment, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and TNF-alpha status as factors and baseline weight as a covariate.
Missing responses for any reason were imputed as non-responders.
n: The number of patients who responded.
M: The total number of patients in the treatment group of the specified analysis set.



*Unadjusted p-value ≤ 0.05

Figure 9 ASAS20 response with 95% CI using non-responder imputation - up to Week 16 (Full Analysis Set)

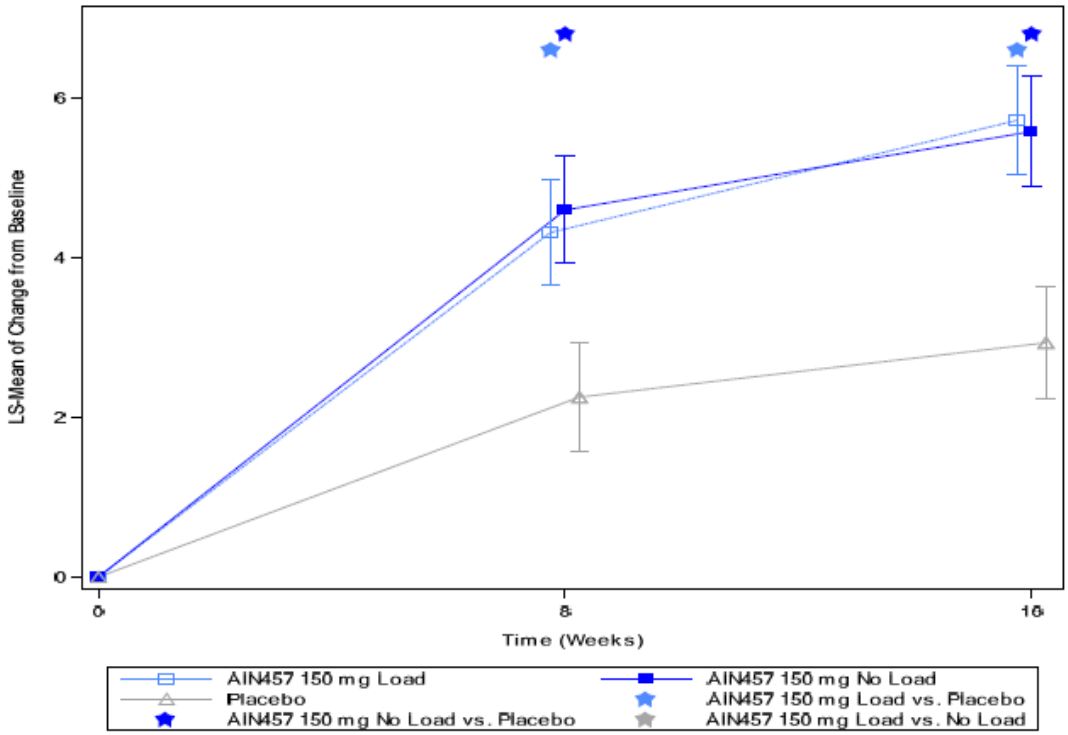
Change from baseline in SF-36 PCS score at Week 16

At Week 16, the improvements observed in SF-36 PCS (i.e., increases in score) were statistically significant for secukinumab 150 mg Load and No Load groups than for placebo (LS mean change: 5.71 and 5.57 vs. 2.93; Table 22). The time course and magnitude of response was very similar between the Load and No Load groups (Figure 10).

Table 22 ***SF-36 PCS change from baseline using MMRM - at Week 16 (Full Analysis Set)***

			Within treatment			Treatment contrast in LS mean (Change)			
Analysis visit	Treatment group	n	LS Mean Change	(SE)	Comparison	LS Mean	(SE)	(95% CI)	p-value
Week 16	AIN457 150 mg Load (N=185)	182	5.71	(0.683)	vs. No Load	0.13	(0.801)	(-1.44,1.71)	0.8665
					vs. Placebo	2.77	(0.799)	(1.20,4.34)	0.0006
	AIN457 150 mg No Load (N=184)	176	5.57	(0.694)	vs. Placebo	2.64	(0.803)	(1.06,4.22)	0.0011
	Placebo (N=186)	178	2.93	(0.705)					

AIN457=secukinumab, CI=confidence interval, LS=least squares, SE=standard error
LS Mean, 95% CI, and p-value were from a mixed model repeated measures (MMRM) with treatment group, analysis visit, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and TNF-alpha status as factors, weight and baseline score as covariates, treatment by analysis visit and baseline score by analysis visit as interaction terms, using an unstructured covariance structure.
N: Number of patients in each treatment group of the specified analysis set.
n: Number of patients with measures at both baseline and the corresponding post baseline visit.
Note: The change from baseline in SF-36 was not evaluated at Week 20.



*Unadjusted p-value ≤ 0.05

Figure 10 SF-36 PCS change from baseline +/- SE using MMRM - up to Week 16 (Full Analysis Set)

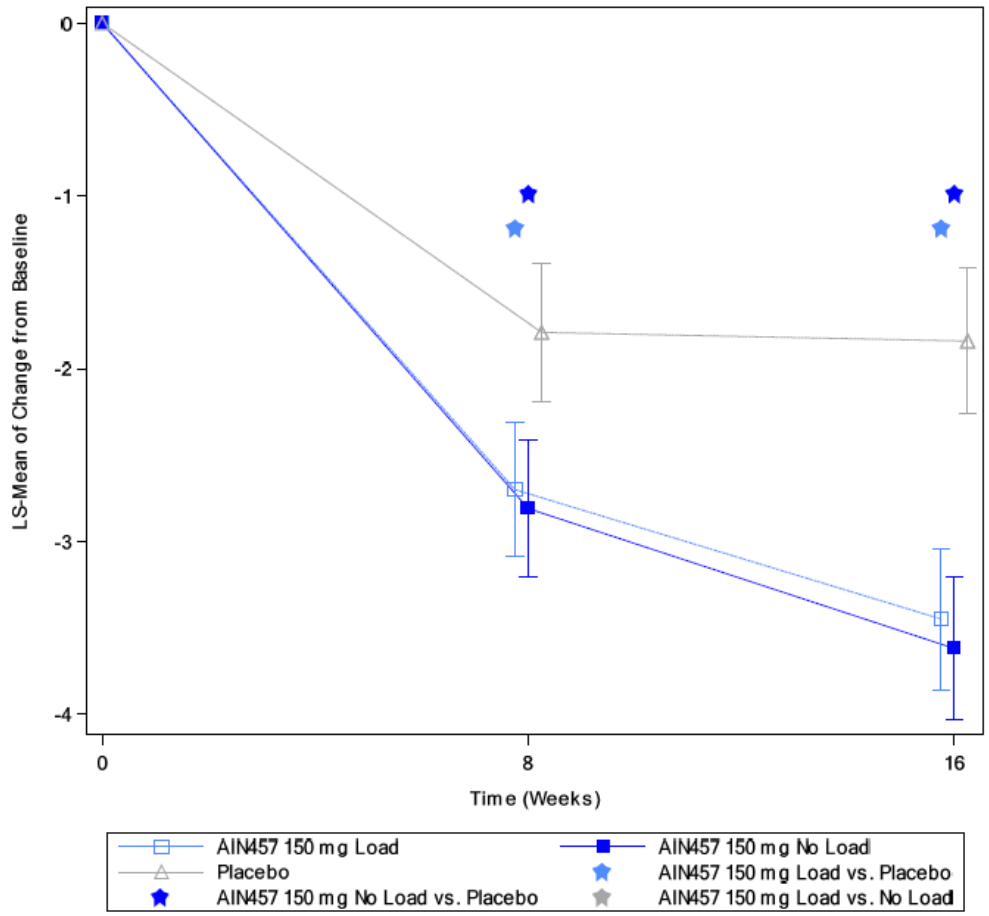
Change from baseline in ASQoL score at Week 16

At Week 16, the decreases in ASQoL score from baseline (improvements) were statistically significantly greater for secukinumab 150 mg Load and No Load than for placebo (LS mean change: -3.45 and -3.62 vs. -1.84; Table 23). The time course and magnitude of response was very similar between the Load and No Load groups (Figure 11).

Table 23 ***ASQoL change from baseline using MMRM - at Week 16 (Full Analysis Set)***

			Within treatment			Treatment contrast in LS mean (Change)			
Analysis visit	**Treatment group**	**n**	**LS Mean Change**	**(SE)**	**Comparison**	**LS Mean**	**(SE)**	**(95% CI)**	**p-value**
Week 16	AIN457 150 mg Load (N=185)	181	-3.45	(0.408)	vs. No Load	0.17	(0.478)	(-0.77,1.11)	0.7194
					vs. Placebo	-1.61	(0.478)	(-2.54,-0.67)	0.0008
	AIN457 150 mg No Load (N=184)	176	-3.62	(0.414)	vs. Placebo	-1.78	(0.479)	(-2.72,-0.84)	0.0002
	Placebo (N=186)	177	-1.84	(0.421)					

AIN457= secukinumab, CI= confidence interval, LS= least squares, SE= standard error
LS Mean, 95% CI, and p-value are from a mixed model repeated measures (MMRM) with treatment group, analysis visit, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and TNF-alpha status as factors, weight and baseline score as covariates, treatment by analysis visit and baseline score by analysis visit as interaction terms, using an unstructured covariance structure.
N: Number of patients in each treatment group of the specified analysis set.
n: Number of patients with measures at both baseline and the corresponding post baseline visit.



*Unadjusted p-value ≤ 0.05

Figure 11 ASQoL change from baseline +/- SE using MMRM - up to Week 16 (Full Analysis Set)

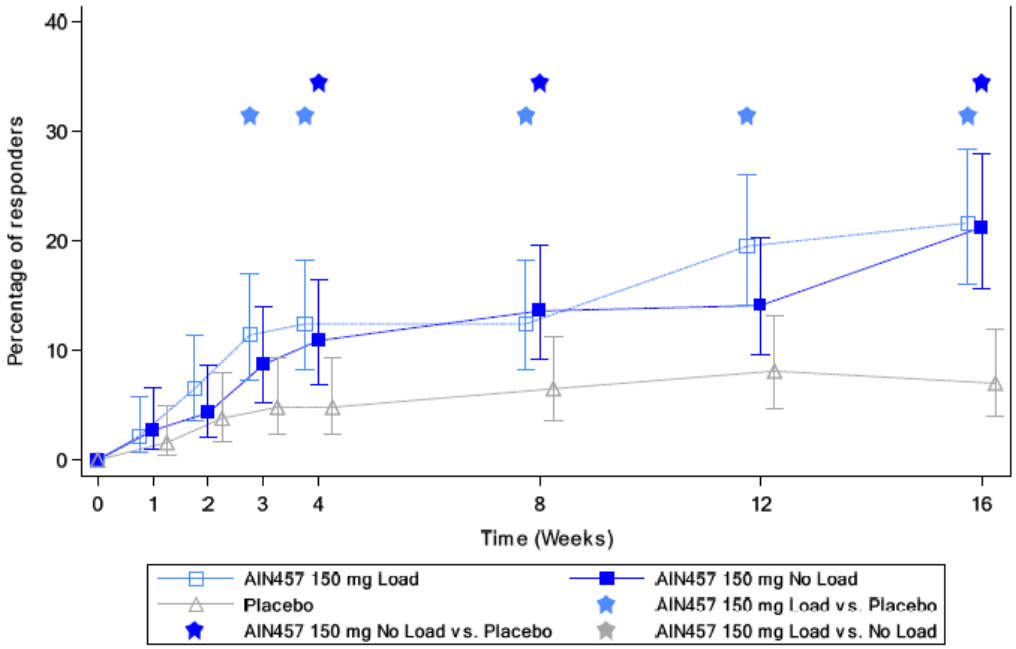
ASAS partial remission response at Week 16

At Week 16, ASAS partial remission response was statistically significantly higher in the secukinumab 150 mg Load and No Load groups compared to placebo (21.6% and 21.2% vs. 7.0%; Table 24). At early time points (Weeks 2-4), the proportion of patients with ASAS partial remission was numerically higher in the secukinumab 150 mg Load group compared to the secukinumab 150 mg No Load group. Differences vs. placebo, in favor of secukinumab 150 mg Load/No Load, were observable from Week 3 for the secukinumab 150 mg Load group and from Week 4 for the secukinumab 150 mg No Load group (Figure 12).

Table 24 ***ASAS partial remission response using non-responder imputation - at Week 16 (Full Analysis Set)***

Analysis Visit	Treatment Group	n/M (%)	Comparison	Odds Ratio	95% CI	p-value
Week 16	AIN457 150 mg Load (N=185)	40/185 (21.6)	vs. No Load	1.04	(0.63, 1.72)	0.8714
			vs. Placebo	3.80	(1.95, 7.39)	<.0001
	AIN457 150 mg No Load (N=184)	39/184 (21.2)	vs. Placebo	3.64	(1.87, 7.10)	0.0001
	Placebo (N=186)	13/186 (7.0)				

AIN457= secukinumab, CI= confidence interval
Odds ratio, 95% CI, and p-value were from a logistic regression model with treatment, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and TNF-alpha status as factors and baseline weight as a covariate.
Missing responses for any reason were imputed as non-responders.
n: The number of patients who responded.
M: The total number of patients in the treatment group of the specified analysis set.



*Unadjusted p-value ≤ 0.05

Figure 12 ASAS partial remission with 95% CI using non-responder imputation - up to Week 16 (Full Analysis Set)

Exploratory endpoints - Week 16

ASDAS-CRP and ASDAS-ESR

The LS mean change from baseline in ASDAS-CRP and ASDAS-ESR using MMRM was greater in the secukinumab 150 mg Load and No Load groups than in the placebo group (ASDAS-CRP: −1.07 and −1.12 vs. −0.60; ASDAS-ESR: −1.03 and −1.09 vs. −0.64 for placebo).

Response rates for ASDAS-CRP and ASDAS-ESR clinically important improvement (using non-responder imputation) in the secukinumab 150 mg Load and No Load groups vs. the placebo group were: ASDAS-CRP: 49.2% and 53.3% vs. 30.6%; ASDAS-ESR: 43.8% and 52.7% vs. 33.3%, respectively.

Response rates for ASDAS-CRP and ASDAS-ESR clinically major improvement (using non-responder imputation) in the secukinumab 150 mg Load and No Load groups vs. the placebo group were: ASDAS-CRP: 24.9% and 25.5% vs. 9.7%; ASDAS-ESR: 24.3% and 26.1% vs. 9.1%, respectively.

Response rates for ASDAS-CRP and ASDAS-ESR inactive disease (using non-responder imputation) in the secukinumab 150 mg Load and No Load groups vs. the placebo group were: ASDAS-CRP: 20.5% and 21.7 vs. 8.1%; ASDAS-ESR: 14.6% and 14.1% vs. 6.5%, respectively.

Other disease signs and symptoms

The LS mean change from baseline in patient's assessment of total back pain using MMRM was −24.96 and −25.52 for secukinumab 150 mg Load and No Load vs. −15.64 for placebo.

The LS mean change from baseline in inflammation (decrease in morning stiffness; mean of BASDAI questions 5 and 6) using MMRM was −2.76 and −2.84 for secukinumab 150 mg Load and No Load compared to −1.71 for placebo.

The LS mean change from baseline in patient's global assessment of disease activity using MMRM was −24.10 and −26.17 for secukinumab 150 mg Load and No Load compared to −13.78 for placebo.

The LS mean change from baseline in MASES using MMRM was −1.19 for secukinumab 150 mg Load, −1.29 for secukinumab 150 mg No Load, and −1.16 for placebo.

At Week 16, the mean change in Berlin modified ASspiMRI-a score was greater for secukinumab 150 mg Load group compared to placebo (−0.33 vs. −0.04; p=0.0224) but not for secukinumab 150 mg No Load group compared to placebo (−0.17 vs. −0.04; p=0.1354).

Spinal mobility - BASMI linear

The LS mean change from baseline in BASMI linear using MMRM was −0.26 for secukinumab 150 mg Load and −0.27 for secukinumab 150 mg No Load, compared to −0.13 for placebo.

Exploratory Quality of Life endpoints - SF-36 response rates, FACIT-Fatigue, EQ-5D

SF-36 PCS response rates were 65.4%, 65.8% and 57.5% for secukinumab 150 mg Load, No Load and placebo groups, respectively, with no statistically significant differences between treatment groups. SF-36 MCS response rates were higher for secukinumab 150 mg Load and No Load groups than for placebo (58.9% and 60.3% vs. 47.8%; p=0.0320 and p=0.0047, respectively).

The LS mean change from baseline in FACIT-Fatigue using MMRM was greater for both secukinumab 150 mg Load and No Load groups compared to placebo (7.19 and 6.94 vs. 3.43; p=0.0001 and p=0.0004).

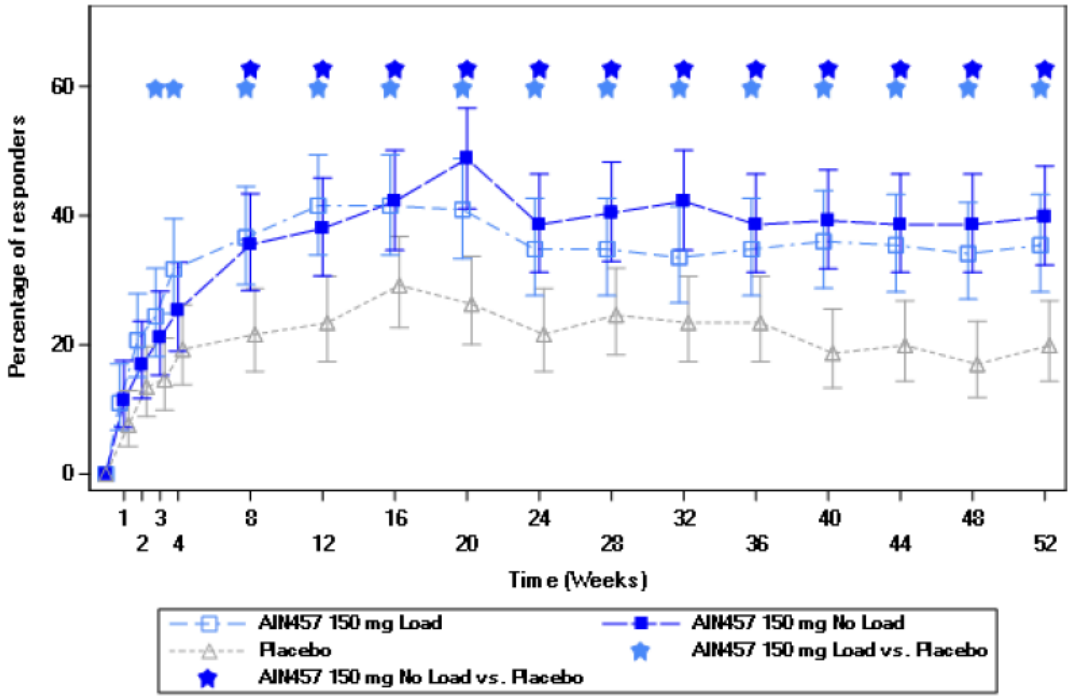
The LS mean change from baseline in EQ-5D health state assessment using MMRM was greater for both secukinumab 150 mg Load and No Load groups compared to placebo (14.10 and 16.12 vs. 7.14; p=0.0011 and p< 0.0001).

Ancillary analyses

Persistence of effect - analyses at Week 52

Long-term efficacy data were assessed using Analysis Plan B. As seen in Figure 13 and Table 25, the ASAS40 response rate using non-responder imputation was sustained over time and remained significantly higher in both secukinumab groups compared to placebo at Week 52 (p=0.0127 vs placebo for both secukinumab groups based on hierarchical testing per Analysis Plan B).

Table 25 presents a comparison of the interim data presented in the original submission (FAS2) vs the updated analysis based on the complete Week 52 dataset (FAS).



*unadjusted p-value ≤ 0.05

Figure 13 ASAS40 response in TNF-alpha naive patients with 95% CI using non-responder imputation - up to Week 52 (FAS)

Table 25 ***ASAS40 response in TNF-alpha naïve patients using non-responder imputation - at Week 52 (FAS2/FAS)***

Analysis	Treatment Group	n/M (%)	Comparison	Odds Ratio	95% CI	p-value*
Interim (Week 24 DBL, FAS2)	AIN457 150 mg Load (N=114)	44/114 (38.6)	vs. No Load	1.01	(0.59, 1.73)	0.9682
			vs. Placebo	2.56	(1.42, 4.63)	0.0019
	AIN457 150 mg No Load (N=115)	44/115 (38.3)	vs. Placebo	2.53	(1.40, 4.58)	0.0021
	Placebo (N=119)	24/119 (20.2)				
Final (Week 52 DBL, FAS)	AIN457 150 mg Load (N= 164)	58/164 (35.4)	vs. No Load	0.83	(0.53, 1.29)	0.4062
			vs. Placebo	2.21	(1.35, 3.63)	0.0017
	AIN457 150 mg No Load (N= 166)	66/166 (39.8)	vs. Placebo	2.67	(1.64, 4.36)	<.0001
	Placebo (N= 171)	34/171 (19.9)				

Odds ratio, 95% CI, and p-value were from a logistic regression model with treatment and stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) as factors and baseline weight as a covariate.
Missing responses for any reason are imputed as non-responders.
Patients were considered as non-responders after treatment switch decision.
n: The number of patients who responded.
M: The total number of patients in the treatment group of the specified analysis set.
*unadjusted p-value

BASDAI50 response rate using non-responder imputation was 30.8% for secukinumab 150 mg Load vs. 19.9% for placebo (OR 1.99 [95% CI 1.22, 3.24]); for the No Load group, a BASDAI50 response rate of 35.3% was observed (OR 2.34 [95% CI 1.45, 3.78] vs. placebo). ASDAS-CRP Inactive disease response rates using non-responder imputation were also numerically higher in the secukinumab Load and No Load groups compared to placebo (15.7% and 23.9% vs. 10.2%).

Subgroup analyses - Week 16 and Week 52

MRI and CRP status - stratification factor

An exploratory analysis was carried out to assess ASAS40 response in TNF-naïve patients using non-responder imputation by the protocol-defined randomisation strata (i.e. CRP and MRI status at screening). At Week 16, there was a significant response to treatment among patients who were CRP+ and MRI+ at screening, whereas the effect was much less marked among the CRP+/MRI- and CRP-/MRI+ patients (Table 26). Figure 14 displays line graphs for the ASAS40 response over time in the different randomisation strata. Similar patterns of response were generally observed on secondary endpoints, including ASAS5/6, BASDAI50, and BASFI.

Table 26 ***ASAS40 response in TNF-alpha naive patients using non-responder imputation at Week 16 by randomisation strata (FAS)***

Randomization strata	Treatment Group	n/M (%)	Comparison	Odds Ratio	95% CI	p-value
CRP+ and MRI+	AIN457 150 mg Load (N=49)	26/49 (53.1)	vs. No Load	0.86	(0.38, 1.93)	0.7162
			vs. Placebo	4.02	(1.65, 9.77)	0.0022
	AIN457 150 mg No Load (N=52)	28/52 (53.8)	vs. Placebo	4.66	(1.91,11.39)	0.0007
	Placebo (N=50)	11/50 (22.0)				
CRP+ and MRI-	AIN457 150 mg Load (N=45)	16/45 (35.6)	vs. No Load	1.05	(0.44, 2.53)	0.9098
			vs. Placebo	1.10	(0.46, 2.62)	0.8348
	AIN457 150 mg No Load (N=44)	15/44 (34.1)	vs. Placebo	1.04	(0.43, 2.52)	0.9255
	Placebo (N=45)	15/45 (33.3)				
CRP- and MRI+	AIN457 150 mg Load (N=70)	26/70 (37.1)	vs. No Load	0.94	(0.47, 1.88)	0.8530
			vs. Placebo	1.25	(0.62, 2.52)	0.5288
	AIN457 150 mg No Load (N=70)	27/70 (38.6)	vs. Placebo	1.34	(0.67, 2.67)	0.4124
	Placebo (N=76)	24/76 (31.6)				

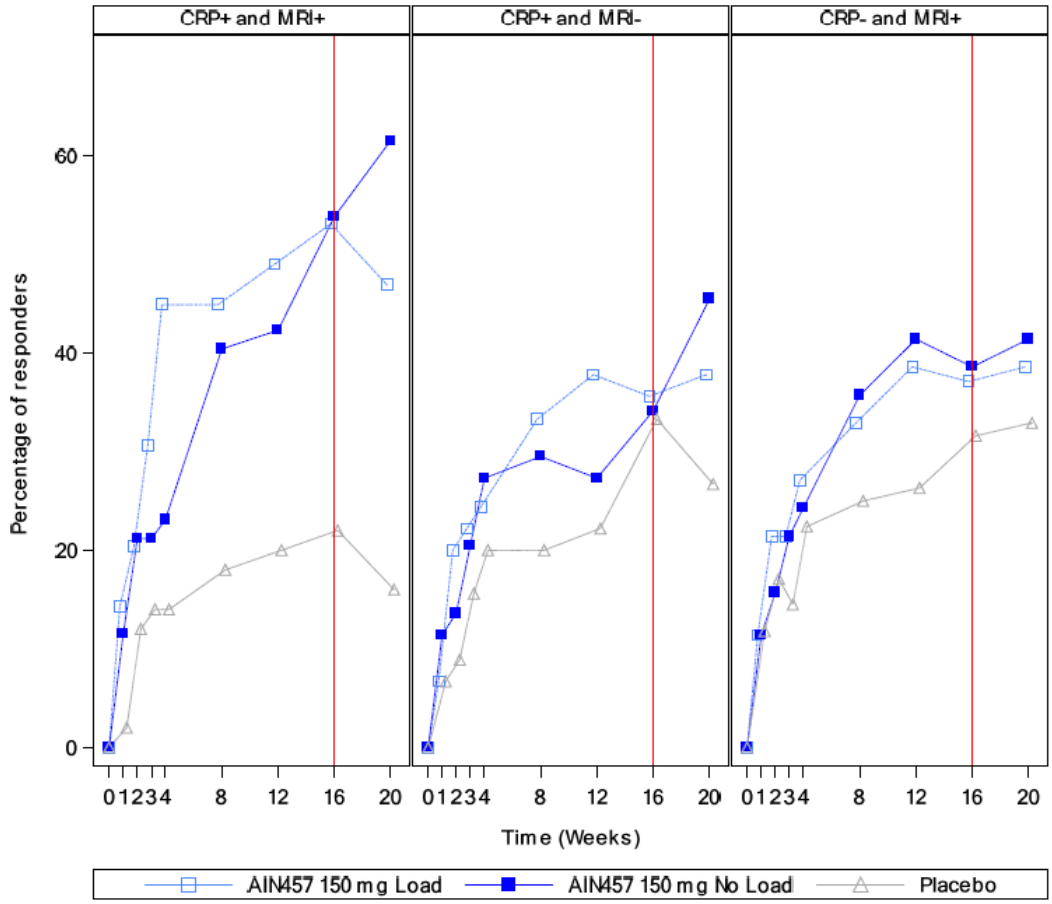
AIN457= secukinumab, CI= confidence interval

Odds ratio, 95% CI, and p-value were from a logistic regression model with treatment as a factor and baseline weight as a covariate.

Missing responses for any reason were imputed as non-responders.

n: The number of patients who responded.

M: The total number of patients in the treatment group of the specified analysis set.



The red line at Week 16 denotes the primary time point for efficacy analyses.
CRP+ and MRI+: Secukinumab 150 mg Load (N=49), Secukinumab 150 mg No Load (N=52), Placebo (N=50)
CRP+ and MRI-: Secukinumab 150 mg Load (N=45), Secukinumab 150 mg No Load (N=44), Placebo (N=45)
CRP- and MRI+: Secukinumab 150 mg Load (N=70), Secukinumab 150 mg No Load (N=70), Placebo (N=76)

Figure 14 ASAS40 response in TNF-naïve patients using non-responder imputation by randomisation strata - up to Week 20 (FAS)

ASAS40 responses by randomisation strata at Week 52 are shown in Table 27.

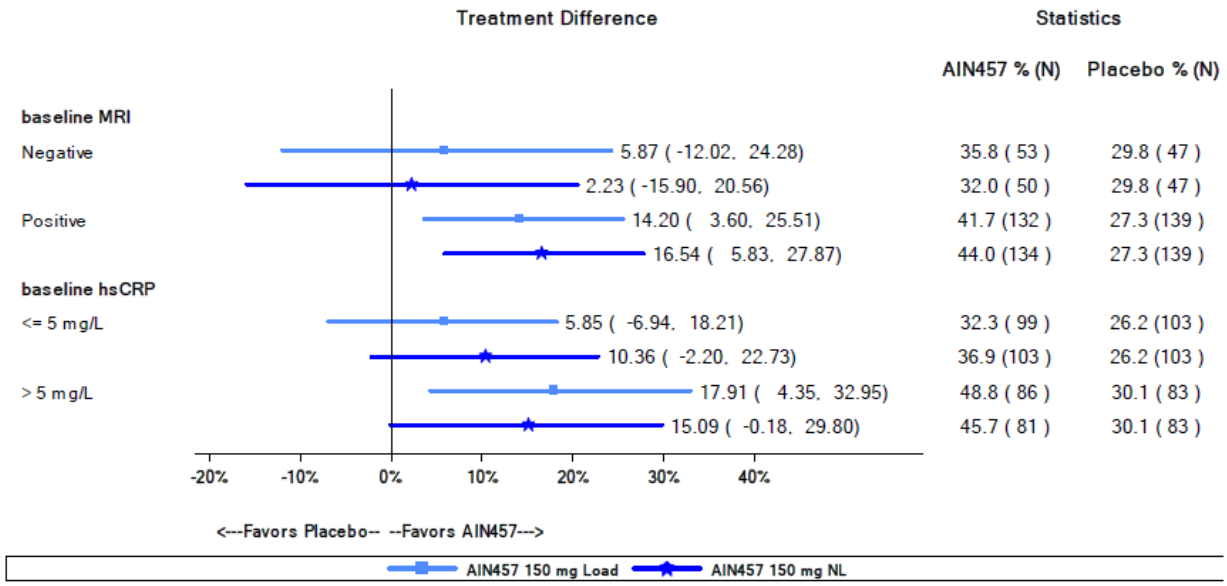
Table 27 ***ASAS40 response in TNF-alpha naive patients using non-responder imputation by randomisation strata - at Week 52 (FAS)***

Randomization strata	Treatment Group	n/M(%)	Comparison	Odds Ratio	95% CI	p-value
CRP+ and MRI+	AIN457 150 mg Load (N=49)	21/49 (42.9)	vs. No Load	0.71	(0.32, 1.56)	0.3911
			vs. Placebo	5.42	(1.94, 15.14)	0.0012
	AIN457 150 mg No Load (N=52)	26/52 (50.0)	vs. Placebo	7.68	(2.77, 21.31)	<.0001
	Placebo (N=50)	6/50 (12.0)				
CRP+ and MRI-	AIN457 150 mg Load (N=45)	19/45 (42.2)	vs. No Load	1.33	(0.56, 3.16)	0.5113
			vs. Placebo	2.31	(0.93, 5.71)	0.0703
	AIN457 150 mg No Load (N=44)	16/44 (36.4)	vs. Placebo	1.73	(0.69, 4.34)	0.2429
	Placebo (N=45)	11/45 (24.4)				
CRP- and MRI+	AIN457 150 mg Load (N=70)	18/70 (25.7)	vs. No Load	0.66	(0.32, 1.37)	0.2693
			vs. Placebo	1.20	(0.56, 2.57)	0.6412
	AIN457 150 mg No Load (N=70)	24/70 (34.3)	vs. Placebo	1.81	(0.87, 3.76)	0.1130
	Placebo (N=76)	17/76 (22.4)				

Odds ratio, 95% CI, and p-value were from a logistic regression model with treatment as a factor and baseline weight as a covariate.
Missing responses for any reason were imputed as non-responders.
Patients were considered as non-responders after treatment switch decision.
n: The number of patients who responded.
M: The total number of patients in the treatment group of the specified analysis set.

Considering that the observed treatment response was clearly higher in the CRP+/MRI+ subpopulation, the MAH was requested to provide further justification for recommending use of secukinumab in CRP+/MRI- and CRP-/MRI+ subpopulations of nr-axSpA patients. To further explore these trends and increase the size of the subgroups, the MAH conducted additional analyses based on only the CRP or the MRI status at baseline (either CRP+ vs CRP- or MRI+ vs MRI-) along with logistic regression analyses to determine the propensity to achieve ASAS40 at Week 16 based on baseline CRP or MRI values.

When considering MRI and CRP status at baseline independently as indicators of systemic inflammation, ASAS40 responses at Week 16 in the secukinumab 150 mg Load and No Load groups in patients with either positive MRI or abnormal CRP at baseline were consistently higher than for patients with negative MRI or normal CRP at baseline. Specifically, for the subgroup of patients with positive MRI at baseline, the absolute treatment differences of ASAS40 between both secukinumab groups versus placebo (14.20% for secukinumab 150 mg Load, 16.54% for secukinumab 150 mg No Load) were higher than for patients who were MRI negative at baseline (5.87% for secukinumab 150 mg Load, 2.23% for secukinumab 150 mg No Load). Similarly, treatment differences were higher for the subgroup of patients whose baseline CRP level was > 5 mg/L (referred to as positive CRP at baseline) compared to the subgroup of patients whose baseline CRP level was ≤ 5 mg/L (referred to as negative CRP at baseline). For the subgroup of patients with positive CRP at baseline, the absolute treatment differences of ASAS40 between both secukinumab groups versus placebo (17.91% for secukinumab 150 mg Load, 15.09% for secukinumab 150 mg No Load) were higher than for patients who were CRP negative at baseline (5.85% for secukinumab 150 mg Load, 10.36% for secukinumab 150 mg No Load). These data are summarised in Figure 15.



NL: No Load
N: The total number of patients in the treatment group of the specified analysis set based on CRP at baseline and final MRI reading.

Figure 15 Differences in ASAS40 response between secukinumab and placebo at Week 16 by MRI and CRP status at baseline (FAS)

In addition, a logistic regression analysis of ASAS40 response using non-responder imputation by treatment and baseline MRI and CRP values as continuous covariates demonstrated a correlation between the baseline MRI and CRP values and the propensity to achieve ASAS40 at Week 16. As shown in Table 28, the propensity to achieve ASAS40 at Week 16 was correlated with increasing MRI score and CRP value at baseline in the secukinumab treatment groups, whereas this was not the case for the placebo group. In the model, baseline MRI SI-joint oedema score and baseline CRP (log transformed) were added to estimate the impact within treatment. The parameter estimate coefficients can be interpreted as change in log (odds) for achieving ASAS40 with one unit change in baseline MRI SI-joint oedema score or baseline log(CRP) value. Within the secukinumab 150 mg Load group, the odds ratio for achieving ASAS40 with 1 unit increase in baseline MRI SI-joint oedema score was 1.18 (p-value = 0.001) and for a unit increase in baseline log(CRP) the odds ratio was 1.31 (p-value = 0.0208), both implying a positive relationship with a p-value lower than 0.05. For placebo, the corresponding odds ratios were 0.99 (p-value = 0.7984) for baseline MRI SI-joint oedema score and 0.96 (p-value = 0.7524) for baseline log(CRP).

Table 28 ***ASAS40 response using non-responder imputation by treatment and baseline MRI and CRP as covariates at Week 16 (FAS)***

Parameter	Source of Variation	Degrees of freedom	Estimate	(SE)	Chi Sq	P-value	Comparison	Comparison to Odds Ratio Estimate	95% LCL	95% UCL
Intercept		1	-0.998	0.473	4.446	0.0350				
TRT01P	AIN457 150 mg Load	1	0.482	0.229	4.420	0.0355	AIN457 150 mg No Load	0.89	0.58	1.38
TRT01P	AIN457 150 mg Load	1	0.482	0.229	4.420	0.0355	Placebo	1.62	1.03	2.53
TRT01P	AIN457 150 mg No Load	1	0.593	0.226	6.904	0.0086	Placebo	1.81	1.16	2.81
TRT01P	Placebo	0	0.000							
WEIGHT		1	0.001	0.006	0.016	0.8986				
Baseline MRI	AIN457 150 mg Load	1	0.163	0.049	10.896	0.0010	1 unit increase	1.18	1.07	1.30
Baseline MRI	AIN457 150 mg No Load	1	0.099	0.050	3.873	0.0491	1 unit increase	1.10	1.00	1.22
Baseline MRI	Placebo	1	-0.011	0.044	0.065	0.7984	1 unit increase	0.99	0.91	1.08
Baseline CRP	AIN457 150 mg Load	1	0.271	0.117	5.345	0.0208	1 unit increase	1.31	1.04	1.65
Baseline CRP	AIN457 150 mg No Load	1	0.208	0.130	2.555	0.1099	1 unit increase	1.23	0.95	1.59
Baseline CRP	Placebo	1	-0.040	0.128	0.099	0.7524	1 unit increase	0.96	0.75	1.23

The MAH also presented an analysis of adverse event data based on MRI and CRP status at baseline. These analyses did not reveal any differences of note between the subgroups.

TNF-naïve vs. TNF-IR patients

As described above, the primary endpoint of the study was the ASAS40 response at Week 16 among TNF-naïve patients, and among these patients, ASAS40 response using non-responder imputation was higher in the secukinumab 150 mg Load (41.5%) and secukinumab 150 mg No Load (42.2%) groups compared to placebo (29.2%). Among TNF-IR patients, ASAS40 response using non-responder imputation at Week 16 was also higher in the secukinumab 150 mg Load (6/21 patients; 28.6%) and secukinumab 150 mg No Load (5/18 patients; 27.8%) groups compared to placebo (2/15 patients; 13.3%); the calculated OR for Load vs. placebo was 2.80 (95% CI 0.43, 18.23).

The MAH also presented a side-by-side comparison of additional efficacy responses between TNFi-naïve and TNF-IR patients to support similar efficacy in both subgroups (Table 29).

Table 29 ***TNFi-naïve vs TNF-IR efficacy responses based on non-responder imputation at Week 16 (FAS)***

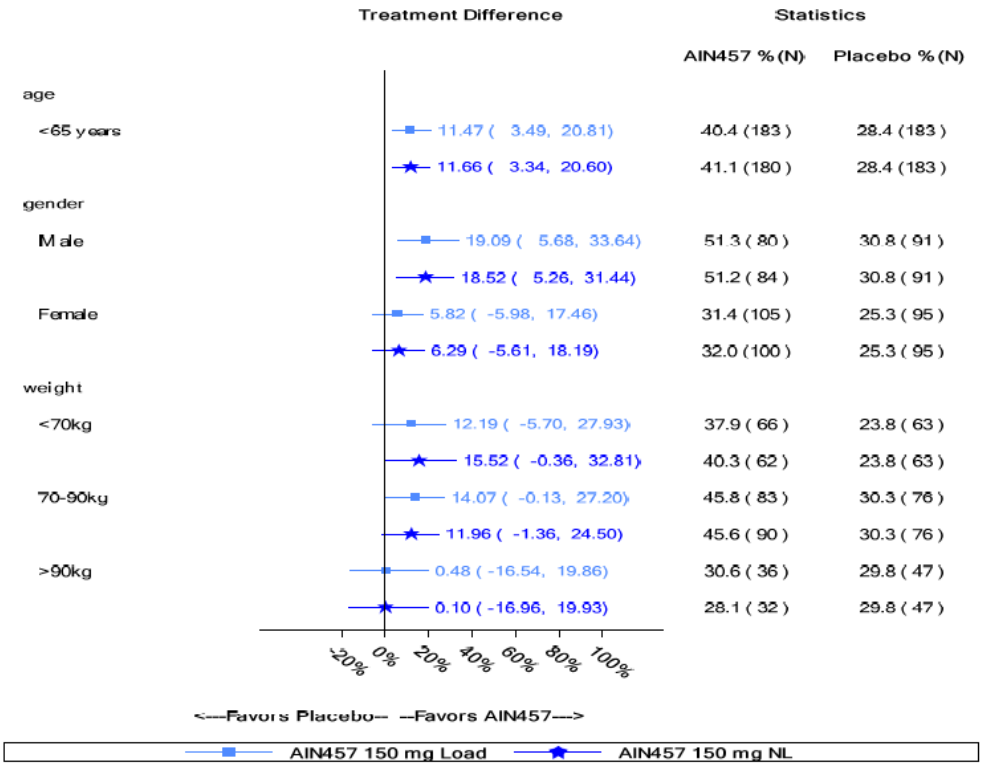
	TNFi-naïve			TNF-IR		
	AIN457 150 mg Load	**Placebo**	**Calculated difference between the rates of AIN457 150 mg Load and placebo[1]**	**AIN457 150 mg Load**	**Placebo**	**Calculated difference between the rates of AIN457 150 mg Load and placebo[1]**
ASAS40, n/M (%)	68/164 (41.5)	50/171 (29.2)	**12.3%**	6/21 (28.6)	2/15 (13.3)	**15.3%**
ASAS 5/6, n/M (%)	68/164 (41.5)	43/171 (25.1)	**16.4%**	6/21 (28.6)	1/15 (6.7)	**21.9%**
BASDAI50, n/M (%)	64/164 (39.0)	38/171 (22.2)	**16.8%**	5/21 (23.8)	1/15 (6.7)	**17.1%**
ASAS20, n/M (%)	97/164 (59.1)	81/171 (47.4)	**11.7%**	8/21 (38.1)	4/15 (26.7)	**11.4%**
ASAS partial remission, n/M (%)	37/164 (22.6)	13/171 (7.6)	**15%**	3/21 (14.3)	0/15 (0.0)	**14.3%**

n: number of patients who responded; M: total number of patients in the treatment group of the specified analysis set

[1] Percentages are based on observed data of the primary estimand with using non responder imputation for treatment switch and missing data.

Demographic factors - gender and weight

ASAS40 responses at Week 16 in subgroups based on age, gender and in different weight groups are shown in Figure 16. In these analyses, the original age cut-off deployed by the MAH (65 years) was considered inappropriate, and an additional analysis based on a more relevant cut off was requested. In other subgroup analyses, males were observed to respond better than females, and in the subgroup of weight >90 kg, the difference between either secukinumab group and placebo was virtually 0.



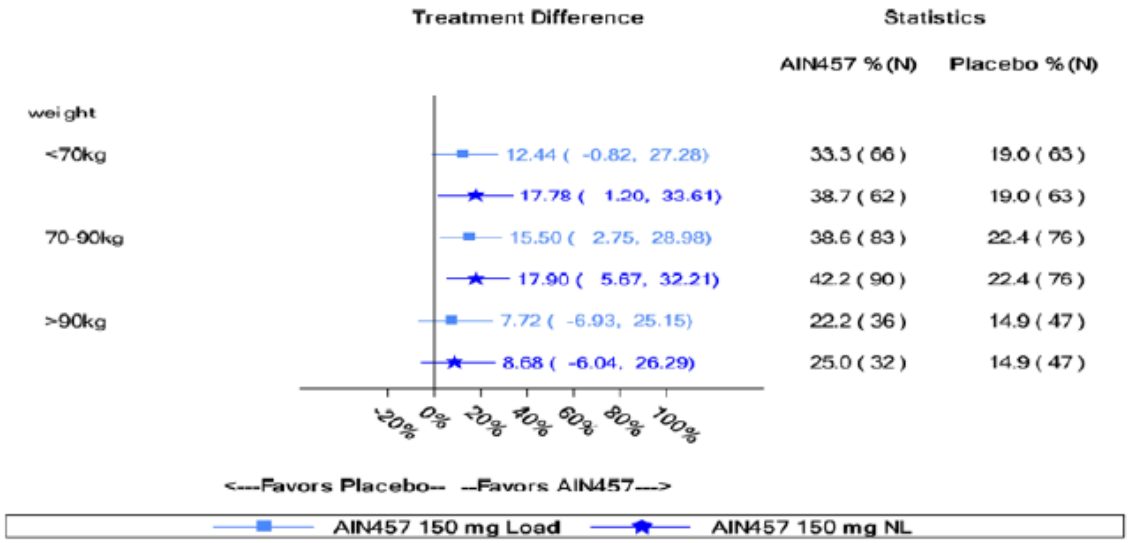
Age group >65 years not displayed owing to the small sample size and the convergence status of the logistic model which made it impossible to calculate the estimates and 95% confidence intervals of risk difference.
NL: No Load

Figure 16 Forest plot for the difference of ASAS40 response between secukinumab and placebo at Week 16 by subgroups based on age, gender, and weight (Full Analysis Set)

The MAH presented an additional analysis of age groups based on a cut-off of 50 years. In this analysis, there were 435 patients < 50 years of age and 120 patients ≥ 50 years of age. The estimated treatment differences of ASAS40 against placebo at Week 16 were all in favour of secukinumab 150 mg Load and No Load groups. For patients < 50 years of age, the treatment differences versus placebo were 11.0% for the secukinumab 150 mg Load group and 12.2% for the secukinumab 150 mg No Load group. For patients ≥ 50 years of age, the treatment differences versus placebo were 11.7% and 7.3%, respectively.

With respect to gender effects, the MAH contended that females with spondyloarthritis generally demonstrate a trend toward lower efficacy responses than males, even if the patient burden in terms of baseline disease activity parameters is similar or worse in females compared to males. At Week 52, ASAS40 response rates in females were about 28% for secukinumab and around 15% for placebo, and in males, the rates ranged from 41% (secukinumab 150 mg Load group) to 50% (secukinumab 150 mg No Load group) vs 24% for placebo. The MAH thus claimed that in the longer term, there was an additional benefit observed for females with the treatment difference versus placebo increasing over time, although a difference in relative response remained between males and females.

With respect to weight, the MAH presented additional data from the Week 52 analysis, in which the placebo-adjusted treatment effect for both secukinumab groups in patients weighing > 90 kg increased to 7.7% and 8.7%, respectively (Figure 17). According to the MAH, while this remains somewhat lower than the other weight subgroups, it indicates that in the longer term, secukinumab 150 mg does provide benefit to patients weighing > 90 kg.

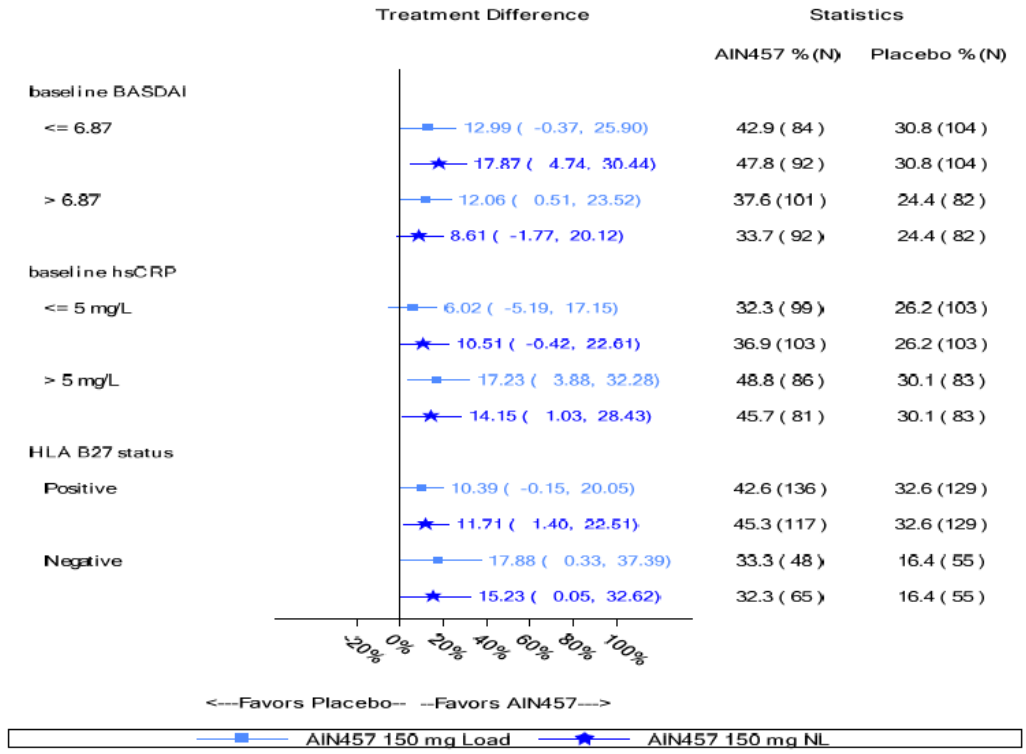


NL: No Load

Figure 17 Forest plot for the difference of ASAS40 response between secukinumab and placebo at Week 52 by subgroups based on weight (FAS)

Disease factors - baseline BASDAI, baseline hsCRP and HLA-B27 status

At Week 16, ASAS40 responses in secukinumab 150 mg Load and no Load groups were generally higher compared with placebo in subgroups based on baseline total BASDAI score, baseline hsCRP level, and HLA-B27 status (Figure 18).



NL: No Load

Figure 18 Forest plot for the difference of ASAS40 response between secukinumab and placebo at Week 16 by subgroups based on baseline BASDAI, baseline hsCRP and HLA-B27 status (Full Analysis Set)

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 30 ***Summary of Efficacy for trial H2315***

Title: A randomized, double-blind, placebo-controlled multicenter study of secukinumab 150 mg in patients with active non-radiographic axial spondyloarthritis (nr-axSpA) to evaluate the safety, tolerability and efficacy up to 2 years, followed by an optional phase of either 150 mg or 300 mg randomized dose escalation for up to another 2 years		
Study identifier	CAIN457H2315; PREVENT	
Design	Randomised, double-blind placebo-controlled study	
	Duration of main phase:	16 weeks (time point for primary analysis, Analysis Plan A)
	Duration of Extension phase:	No data included in current submission
Hypothesis	Superiority to placebo	
Treatment groups	Secukinumab 150 mg Load	Secukinumab 150 mg s.c. at baseline, Weeks 1, 2 and 3, followed by administration every 4 weeks starting at Week 4; N = 185.
	Secukinumab 150 mg No Load	Secukinumab 150 mg s.c. at baseline, placebo at Weeks 1, 2 and 3, followed by secukinumab 150 mg administration every 4 weeks starting at Week 4; N = 184.

	Placebo		Placebo s.c. at baseline, Weeks 1, 2, 3, followed by administration every 4 weeks starting at Week 4; N = 186.
Endpoints and definitions (Analysis Plan A)	Primary endpoint	ASAS40 response in TNF-naïve patients at Week 16	Improvement of ⩾40% and ⩾2 units on a scale of 10 in at least three of the four ASAS scale main domains and no worsening at all in the remaining domain, at week 16. TNF-naïve patients only.
	Secondary endpoint	Overall ASAS40 response at Week 16	Improvement of ⩾40% and ⩾2 units on a scale of 10 in at least three of the four ASAS scale main domains and no worsening at all in the remaining domain, at week 16. All enrolled patients.
	Secondary endpoint	ASAS 5/6 response at Week 16	Improvement of ⩾20% in at least five ASAS scale domains, at week 16. All enrolled patients.
	Secondary endpoint	Change from baseline in total BASDAI score at Week 16	Change from baseline to week 16 on a score from 0 to 10 pertaining to the 5 major symptoms of AS (Fatigue, Spinal pain, Joint pain/ swelling, Enthesitis, Morning stiffness duration and severity). All enrolled patients.
	Secondary endpoint	BASDAI50 response at Week 16	Improvement of at least 50% from baseline in BASDAI. All enrolled patients.
	Secondary endpoint	Change from baseline in hsCRP at Week 16	Change from baseline to week 16 in high-sensitivity C-reactive protein. All enrolled patients.
	Secondary endpoint	Change from baseline in total BASFI score at Week 16	Change from baseline to week 16 on a score from 0 to 10 assessing the degree of functional limitation. All enrolled patients.
	Secondary endpoint	Change from screening in MRI SI joint edema score at Week 16	Change from screening to week 16 in MRI sacro-iliac joint oedema score. Berlin Active Inflammatory Lesions Scoring; scale from 0 to 24. All enrolled patients.
	Secondary endpoint	ASAS20 response at Week 16	Improvement of ⩾ 20% and ⩾ 1 unit on a scale of 10 in at least 3 of the 4 main scale domains and no worsening of ⩾ 20% and ⩾ 1 unit on a scale of 10 in the remaining scale domain. All enrolled patients.
	Secondary endpoint	Change from baseline in SF-36 PCS score at Week 16	Change from baseline to week 16 on the Short Form-36 Physical Components Summary scale. All enrolled patients.
	Secondary endpoint	Change from baseline in ASQoL score at Week 16	Change from baseline to week 16 on the Ankylosing Spondylitis Quality of Life scale. All enrolled patients.

	Secondary endpoint	ASAS partial remission response at Week 16	A value not exceeding 2 (on a scale from 0 to 10) in each of the ASAS scale main domains, at week 16. All enrolled patients.
Database lock	22 February 2019 (all patients having completed Week 24)		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set Week 16			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 150 mg Load	Secukinumab 150 mg No Load	Placebo
	Number of subjects	164	166	171
	ASAS40, TNF-naïve (%)	41.5%	42.2%	29.2%
	Number of subjects	185	184	186
	Overall ASAS40 (%)	40.0%	40.8%	28.0%
	ASAS 5/6 (%)	40.0%	35.9%	23.7%
	Change from baseline total BASDAI (LS Mean Change (SE))	-2.35 (0.201)	-2.43 (0.203)	-1.46 (0.205)
	BASDAI50 (%)	37.3%	37.5%	21.0%
	Change from baseline hsCRP (Geo. Mean Ratio (SE) Wk 16/baseline)	0.64 (1.078)	0.64 (1.079)	0.91 (1.080)
	Change from baseline total BASFI (LS Mean Change (SE))	-1.75 (0.202)	-1.64 (0.204)	-1.01 (0.206)
	Change from screening MRI SI joint oedema score (Mean Change (SE))	-1.68 (0.24)	-1.03 (0.18)	-0.39 (0.15)
	ASAS20 (%)	56.8%	58.2%	45.7%
	Change from baseline SF-36 PCS (LS Mean Change (SE))	5.71 (0.683)	5.57 (0.694)	2.93 (0.705)
	Change from baseline ASQoL (LS Mean Change (SE))	-3.45 (0.408)	-3.62 (0.414)	-1.84 (0.421)
	ASAS partial remission (%)	21.6%	21.2%	7.0%

Effect estimate per comparison	Primary endpoint ASAS40 TNF-naive	Comparison groups	Secukinumab 150 mg Load vs Placebo
		OR	1.72
		95% CI	1.09, 2.70
		P-value	0.0197

	Secondary endpoint ASAS40 overall	Comparison groups	Secukinumab 150 mg Load vs Placebo
		OR	1.77
		95% CI	1.14, 2.74
		P-value	0.0108
	Secondary endpoint ASAS5/6	Comparison groups	Secukinumab 150 mg Load vs Placebo
		OR	2.26
		95% CI	1.43, 3.58
		P-value	0.0005
	Secondary endpoint BASDAI change from baseline	Comparison groups	Secukinumab 150 mg Load vs Placebo
		Treatment contrast in LS Mean (Change)	-0.89
		95% CI	-1.39, -0.38
		P-value	0.0006
	Secondary endpoint BASDAI50	Comparison groups	Secukinumab 150 mg Load vs Placebo
		OR	2.53
		95% CI	1.58, 4.07
		P-value	0.0001
	Secondary endpoint hsCRP change from baseline	Comparison groups	Secukinumab 150 mg Load vs Placebo
		Relative treatment effect	0.70
		95% CI of ratio	0.58, 0.84
		P-value	0.0002
	Secondary endpoint BASFI	Comparison groups	Secukinumab 150 mg Load vs Placebo
		Treatment contrast in LS Mean (Change)	-0.75
		95% CI	-1.26, -0.24
		P-value	0.0041
	Secondary endpoint MRI SI joint oedema	Comparison groups	Secukinumab 150 mg Load vs Placebo
		Estimate of treatment difference	-1.24
		SE	0.20
		P-value	<0.0001
	Secondary endpoint ASAS20	Comparison groups	Secukinumab 150 mg Load vs Placebo
		OR	1.60
		95% CI	1.06, 2.43
		P-value	0.0260
	Secondary endpoint SF-36 PCS change from baseline	Comparison groups	Secukinumab 150 mg Load vs Placebo
		Treatment contrast in LS Mean (Change)	2.77
		95% CI	1.20, 4.34
		P-value	0.0006
	Secondary endpoint ASQoL change from baseline	Comparison groups	Secukinumab 150 mg Load vs Placebo
		Treatment contrast in LS Mean (Change)	-1.61
		95% CI	-2.54, -0.67
		P-value	0.0008
	Secondary endpoint ASAS partial remission	Comparison groups	Secukinumab 150 mg Load vs Placebo
		OR	3.80
		95% CI	1.95, 7.39
		P-value	<0.0001

Notes	Effect estimates for Secukinumab 150 No Load vs placebo comparison are not tabulated as posology is not applied for Categorical variables: Non-Responder Imputation Continuous variables: MMRM, except MRI SI joint oedema (ANCOVA based on multiple imputation with MAR assumption)

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The current submission is supported by results from an ongoing randomised, placebo-controlled Phase 3 study assessing the efficacy, safety and tolerability of two different regimens of secukinumab, 150 mg with loading and without loading, compared to placebo in patients with nr-axSpA. The posology without loading is not being applied for by the MAH.

The general design features of this randomised double-blind placebo-controlled study is generally in line with the current EU Guideline EU Guideline on AxSpA (EMA/CPMP/EWP/4891/03 Rev.1, Corr 1). However, the Guideline (including its previous version) foresees the need, for products belonging to new therapeutic classes, of a comparison against an accepted active comparator (e.g. anti TNF treatment) for the target population in order to properly assess the relative B/R balance of the new product. A three-arm trial is recommended, particularly when biological naïve patients are to be studied. The current study lacks an active comparator, and the MAH was therefore requested to provide a critical discussion characterising the place of secukinumab in the treatment armamentarium of nr-axSpA. In its response, the MAH presented and discussed ASAS40 response rates reported across published studies for several TNF inhibitors vs. that reported for secukinumab. The CHMP considered that indirect comparisons across different studies are complicated e.g. by large differences in response rates on placebo, and that the lack of a concurrent comparator therefore remains a shortcoming when attempting to assess the place of a new therapeutic modality with the treatment armamentarium for a given disorder. However, the CHMP agreed that a clinically relevant effect against placebo for secukinumab in the treatment of nr-axSpA had been demonstrated in a large controlled study. Moreover, data from a secukinumab study with a concurrent "TNFi" control group in psoriasis, a partly interrelated indication, demonstrates a favourable benefit/risk profile. Based on the additional justification provided by the MAH, the CHMP concluded that even in the absence of a direct active comparator, an overall favourable benefit/risk profile for secukinumab has been demonstrated, and the issue was not pursued further.

The eligibility criteria represent accepted definitions for active nr-axSpA. With the exception of the X-ray criterion differentiating AS from nr-axSpA, the eligibility criteria were also very similar to those used in the original secukinumab AS studies. Radiographic and MRI images were read centrally, and hsCRP concentrations were analysed by a central laboratory. Inclusion of patients having failed treatment with one TNF-alpha inhibitor was permitted per protocol.

The fixed treatment schedule from baseline to Week 16 enables a robust assessment of efficacy for purposes of Analysis Plan A. In principle, assessment of the natural course of nr-axSpA over a 1-year period was enabled with the selected design; however, it should be noted that the number of patients completing 52 weeks of treatment on placebo was quite limited. See discussion below.

The defined objectives and endpoints support assessment of the effects of secukinumab across inflammatory, symptomatic, structural and functional aspects of nr-axSpA. However, the study was initiated before the current EU Guideline on AxSpA came into effect. There are some deviations to the choice of the endpoints as recommended per the Guideline that were not found by CHMP to impair the suitability of the study to investigate secukinumab in nr-AxSpA. Indeed, the primary endpoint of ASAS40 is considered the preferred ASAS response criterion as per the current Guideline.

ASDAS responder criteria, such as ASDAS-CRP and ASDAS-ESR clinically important improvement; ASDAS-CRP and ASDAS-ESR clinically major improvement; and ASDAS-CRP and ASDAS-ESP inactive disease, represent endpoints that are being increasingly adopted as part of the emerging treat-to-target approach in axSpA and are recommended within the current Guideline. These endpoints, although only included as exploratory endpoints in the current submission, are considered to provide information of clinical relevance to future prescribers. Determination of spinal mobility is considered an important efficacy domain in the current Guideline. However, in the current study, BASMI scores were still evaluated among the exploratory objectives.

The study was conducted across 144 Investigator sites in 24 participating countries. Of the total of 555 patients enrolled, the largest numbers were recruited in Spain (72), Czech Republic (71), Poland (65), Russia (54), and Germany (52).

Overall, only 35.1% of the patients screened for the study were randomised and the most common reason for not being randomised was screening failure. The most common reasons for screen failure were a lack of objective signs of inflammation at screening, presence of radiographic evidence of sacroiliitis, and lack of diagnosis of axSpA per ASAS axSpA criteria.

The overall discontinuation rate until Week 24 was 5%, with no substantial differences between the treatment groups. It thus seems unlikely that premature discontinuations would have a significant impact on the robustness of the dataset used for the primary statistical analyses. At Week 52, the overall discontinuation rate was about 13%, with lack of efficacy and subject/guardian decision constituting the most frequent reasons for discontinuation.

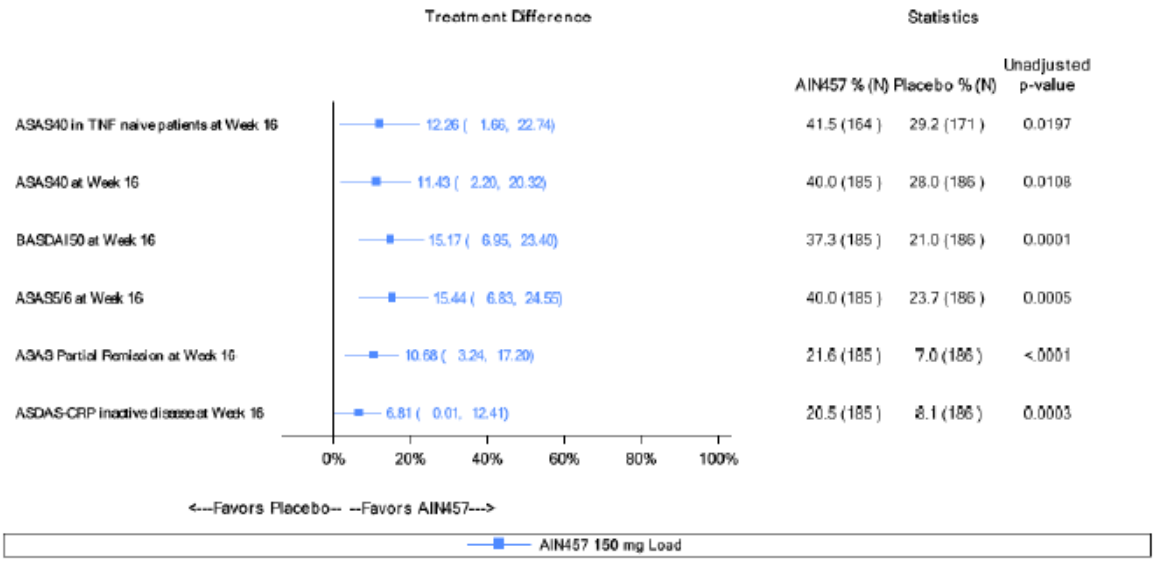
Between Week 20 and Week 52, some 49% of patients in the secukinumab groups opted to switch from double-blind study medication to open-label secukinumab. In the placebo group, the corresponding proportion of switchers was 64%. The numbers thus suggest that fewer patients in the secukinumab groups perceived the treatment as ineffective, and also that a high proportion of patients with active nr-axSpA suffer from persistent symptomatology.

Patients enrolled into the study had a history of about 2.6 years since the first diagnosis of AxSpA, and active disease as evidenced e.g, by a mean value of 70.8 on the global assessment of disease activity, 72.1 on total back pain, and a mean BASDAI score of 6.92. Assessments of disease activity were very comparable to values reported in the AS study F2310, where mean global assessment of disease activity was 67.5, total back pain was 66.8, and mean BASDAI was 6.65. With respect to functional indices, BASFI scores were comparable to the AS study (6.02 in the current study vs. 6.10 in the AS study); however, mean linear BASMI was 2.82 in the current study vs. 3.81 in the AS study, suggesting slightly better spinal mobility among patients in the current study.

Whereas the protocol would have permitted enrolment of up to 20% of TNF-IR patients, the actual proportion of such patients was 9.7% (total N = 54). The CHMP therefore noted that conclusions regarding efficacy in this subpopulation should thus be treated with caution due to the small sample size (see discussions below).

Efficacy data and additional analyses

A forest plot of key efficacy endpoints at Week 16 for the secukinumab 150 mg Load group vs. placebo is displayed in the Figure below.



% is the LSMean from logistic regression with treatment, randomization strata (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and TNF-alpha inhibitor stat

Figure 19 Forest plots of key efficacy endpoints displaying treatment difference of secukinumab 150 mg Load vs. placebo at Week 16 (Full analysis set)

A statistically significant treatment effect was observed on the primary endpoint using a conservative non-responder imputation strategy; ASAS40 response rates of 41.5% in the secukinumab 150 mg Load group vs. 29.2% in the placebo group correspond to an OR of 1.72 favouring secukinumab. The robustness of the observation is supported by appropriate sensitivity analyses.

Although the posology is not being applied for secukinumab 150 mg, No Load also had a significantly better ASAS40 response in TNF-alpha naïve patients than placebo (42.2% vs. 29.2%; p=0.0146).

As reference, the 29.2% response rate observed in the placebo group is somewhat higher than reported in similar studies reported earlier with TNF-alpha inhibitors (e.g. 14.8% at Week 12 in the etanercept study B1801031; 14.9% at Week 12 in the adalimumab study M10-791; 16.3% at Week 12 in the non-radiographic subpopulation of the certolizumab pegol study AS001; and 23.0% at Week 16 in the golimumab study P07642). Conversely, the ASAS40 response rates in the active arms of the respective studies were reported as 33.3% for etanercept; 36.3% for adalimumab; 47.8% for certolizumab pegol; and 56.7% for golimumab, compared to 41.5% for the Load group in the current study. In the original secukinumab AS Study F2310, where a dosing regimen corresponding to the 150 mg Load regimen in the current study was investigated, ASAS40 response rates at Week 16 were 10.8% for placebo and 36.1% for secukinumab 150 mg.

The result on the primary endpoint is supported by analyses of secondary endpoints, where both secukinumab groups consistently demonstrated efficacy on variables related to inflammation and disease activity, function and health-related quality of life:

- ASAS40 response using non-responder imputation at Week 16 was statistically significantly higher in the secukinumab 150 mg Load and No Load groups compared to the placebo group (40.0% and 40.8% vs. 28.0%; p=0.0108 and p=0.0087).

- ASAS 5/6 response using non-responder imputation at Week 16 was statistically significantly higher for secukinumab 150 mg Load and No Load than for placebo (40.0% and 35.9% vs. 23.7%; p=0.0005 and p=0.0094).

- Total BASDAI change from baseline using MMRM at Week 16 was statistically significantly greater in the secukinumab 150 mg Load and No Load groups compared to placebo (−2.35 and −2.43 vs. −1.46; p=0.0006 and p=0.0002).

- BASDAI50 response using non-responder imputation at Week 16 was statistically significantly higher for secukinumab 150 mg Load and No Load compared to placebo (37.3% and 37.5% vs. 21.0%; p=0.0001 and p=0.0002).

- BASFI change from baseline using MMRM at Week 16 was statistically significantly greater for secukinumab 150 mg Load and No Load than for placebo (−1.75 and −1.64 vs. −1.01; p=0.0041 and p=0.0143).

- hsCRP change from baseline using MMRM at Week 16 was statistically significantly greater for the secukinumab 150 mg Load and No Load groups compared to the placebo group (0.64 for both secukinumab groups vs. 0.91 for placebo; p=0.0002 for both comparisons).

- MRI SI joint edema score change from baseline using ANCOVA based on multiple imputation at Week 16 was statistically significantly greater for secukinumab 150 mg Load and No Load than for placebo (−1.68 and −1.03 vs. −0.39; p< 0.0001 for both comparisons).

- SF-36 PCS change from baseline using MMRM at Week 16 was statistically significantly greater for secukinumab 150 mg Load and No Load than for placebo (5.71 and 5.57 vs. 2.93; p=0.0006 and p=0.0011).

- ASQoL change from baseline using MMRM at Week 16 was statistically significantly greater for secukinumab 150 mg Load and No Load than for placebo (−3.45 and −3.62 vs. −1.84; p=0.0008 and p=0.0002).

- ASAS partial remission using non-responder imputation at Week 16 was achieved by a statistically significantly higher proportion of patients in the secukinumab 150 mg Load and No Load groups compared to placebo (21.6% and 21.2% vs. 7.0%; p< 0.0001 and p=0.0001).

- Efficacy was also seen in treat-to-target -oriented variables that were assessed among exploratory analyses. For example, ASDAS-CRP inactive disease (using non-responder imputation) in the secukinumab 150 mg Load and No Load groups vs. the placebo group were 20.5% and 21.7 vs. 8.1%.

Consistent, statistically significant efficacy vs. placebo was observed across the pre-defined secondary endpoints. For some endpoints, a more rapid onset was observed with the Load regimen compared to the No Load regimen; this was seen for higher hurdle endpoints such as ASAS40 and ASAS partial remission, where it can be expected that the hurdle is reached more rapidly with higher initial exposure, whereas ASAS20 responses developed very similarly on both active treatment groups over time. Also for hSCRP, the responses between the Load and No Load regimens were very similar over time. At Week 16, an effect was also observed on active inflammation based on MRI assessment of sacroiliac joint oedema. The CHMP agreed that the overall data support an earlier onset of efficacy for the Load group; as such, the MAH's decision to apply for authorisation for the Load regimen is supported by the CHMP.

The current EU Guideline for AxSpA (EMA/CPMP/EWP/4891/03 Rev.1, Corr 1) gives considerable emphasis to ASDAS response rates, which were analysed among the exploratory endpoints in the current study. Consistently higher response rates were observed for both secukinumab groups compared to placebo on these endpoints; for example, 20.5% of patients in the Load group reached ASDAS-CRP Inactive disease, compared to 8.1% of patients on placebo.

In general, the exploratory endpoint analyses at Week 16 supported analyses of the primary and secondary efficacy endpoints, although little difference between the groups was seen on enthesitis as assessed with the MASES score. It is noted that the results for on BASMI, an additional efficacy domain

that is considered important in the current EU Guideline, were assessed among exploratory endpoints. Some support for efficacy on spinal mobility was observed on BASMI, with numerically greater decreases seen in the active groups compared to placebo.

Week 52 results based on Analysis Plan B were used to assess persistence of therapeutic effect. Maintenance of effect was supported by consistent differences being observed between the secukinumab groups vs. placebo across most endpoints assessed, and statistically significant differences between active groups and placebo (although p values being adjusted within Analysis Plan B only) were observed on the primary endpoint using a conservative imputation strategy. The analysis was primarily intended to support regulatory submissions outside of the European Union, but it was acceptable to CHMP to briefly mention maintenance of effect at Week 52, without reference to specific p-values, within Section 5.1 of the SmPC.

The proposed dosing regimen of 150 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing was considered acceptable by the CHMP.

It is currently not known whether treatment in a well responding nr-axSpA patient should be continued indefinitely, or whether consideration could be given to discontinuing treatment at some point. Studies deploying randomised withdrawal designs are currently ongoing with several TNF-alpha inhibitors to explore this issue. Neutralisation of IL-17A activity would represent a new mechanism of action in the treatment of nr-axSpA, and the CHMP recommended the MAH to explore this question with secukinumab. The MAH agreed to address this issue in an adequately designed clinical study. In accordance with the current EU Guideline, such data will be generated in the post-approval setting.

Earlier studies have shown that the treatment response to TNF inhibitors in nr-axSpA patients is more pronounced in patients with a higher degree of active inflammation at baseline, as determined with an elevated hsCRP and/or joint oedema on MRI. To date, "objective signs of inflammation" for all approved TNF has been defined by either elevated CRP or MRI evidence, i.e., the simultaneous presence of both indicators has not been not required. In the current study, the efficacy was clearly driven by the CRP+/MRI+ subgroup, and observations in both the CRP+/MRI- and CRP-/MRI+ subgroups seem to be characterised by both a) a larger placebo response, and b) a comparatively lesser response to active drug. It was acknowledged that the sample sizes in some of the subgroups are rather small, and the analyses may suffer from possibly random fluctuation in treatment responses over time or other unidentified factors, but the MAH was requested to provide further justification for recommending use of secukinumab in CRP+/MRI- and CRP-/MRI+ subpopulations of nr-axSpA patients. In the response, the MAH argued that the stratified randomisation was based on a request by the US FDA to ensure that a similar number of patients was enrolled into the respective subgroups. When considering MRI and CRP status at baseline independently, ASAS40 responses at Week 16 in the secukinumab 150 mg Load and No Load groups in patients with either positive MRI or abnormal CRP at baseline were consistently higher than for patients with negative MRI or normal CRP at baseline. Based on results of the current study, a subgroup difference in terms of efficacy outcome seems credible. The effect size is more pronounced in patients for whom the inflammation is confirmed by both MRI and CRP. This was further elaborated with log-linear model which showed that higher baseline CRP or MRI would lead to better response rate in terms of ASAS40 with active treatment, and that baseline CRP or MRI has no impact on placebo response. Based on additional justification and analyses presented by the MAH showing that CRP+/MRI- or CRP-/MRI+ derive also benefit from secukinumab, the CHMP agreed that both MRI evidence of active inflammation and an elevated CRP are associated with a greater likelihood of treatment response. Consequently, the indication wording proposed by the MAH "….with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence ….." was considered acceptable by the CHMP.

Based on the reported data and consistent with observations in AS patients, response rates were higher for secukinumab vs. placebo in both TNF-naïve and TNF-IR patients. In principle, this supports the consideration of secukinumab as a useful treatment alternative for nr-axSpA patients not responding to a TNF inhibitor. The MAH ascribed part of the challenge in recruiting TNF-IR patients to the fact that TNFi were not approved, or were only recently approved, for the treatment of nr-axSpA in many countries during conduct of the study, and this explanation was acknowledged by the CHMP. However, due to the small sample size, observations in the TNF-IR nr-axSpA subpopulation still need to be viewed with considerable caution; data in the TNF-IR subgroup is generally limited to less than 20 patients per treatment group, and each individual responder/non-responder thus changes the overall response rate by 5% or more. As the reported data is based on a conservative non-responder imputation, even the limited dataset was considered by the CHMP to generally support efficacy in TNF-IR patients at Week 16. A short statement was included in the Section 5.1 of the SmPC to reflect this conclusion.

In an analysis of age groups based on a cut-off of 50 years, similar efficacy was observed in patients below and above 50 years of age.

In the current study, males were observed to respond better than females. The MAH pointed out that females with spondyloarthritis generally demonstrate a trend toward lower efficacy responses than males, even if the patient burden in terms of baseline disease activity parameters is similar or worse in females compared to males, and that a similar observation has been made in other studies such as the golimumab study P07642. At Week 52, ASAS40 response rates in females were about 28% for secukinumab and around 15% for placebo, and in males, the rates ranged from 41% (secukinumab 150 mg Load group) to 50% (secukinumab 150 mg No Load group) vs 24% for placebo, and the MAH thus claimed that in the longer term, additional benefit is observed for females with the treatment difference versus placebo increasing over time, although a difference in relative response remained between males and females. The MAH's additional justification was acknowledged, and while the response rates on average are lower in females than males, the CHMP accepted that individual female patients can attain benefit from the use of secukinumab.

The treatment response at Week 16 was negligible in patients weighing >90 kg. The MAH acknowledged the finding and presented additional data from the Week 52 analysis, in which the placebo-adjusted treatment effect for the secukinumab groups in patients weighing > 90 kg increased to 7.7% and 8.7%, respectively. While the treatment effect remains smallest in the patient group weighing >90 kg, the CHMP considers that the trend based on weight groups is not consistent, and in contrast to the Week 16 dataset, some efficacy is also seen in in the patient group weighing >90 kg at Week 52. The issue was therefore not pursued further.

Of note, subgroup analyses based on baseline disease characteristics suggested a greater treatment response among patients with an elevated hsCRP level at baseline; this further supports previous observations of improved efficacy among patients with confirmed active inflammation. A comparatively larger treatment response was also seen in HLA B27 negative patients compared to HLA B27 positive patients; however, no conclusion can be drawn in view of the relatively sample size in the HLA B27 negative subgroup.

2.4.4. Conclusions on the clinical efficacy

Secukinumab at a dose of 150 mg by subcutaneous injection, with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing, was studied in a large placebo-controlled study. The study met its primary and secondary endpoints, and robustness of the results is supported by appropriate sensitivity analyses. Maintenance of effect up to 52 weeks of treatment was supported by an additional statistical analysis based on complete Week 52 data from this still ongoing study.

The CHMP concluded that study H2315 provides demonstration of efficacy of secukinumab on symptoms, inflammation, function and quality of life in patients with active nr-axSpA despite treatment with NSAIDs.

The proposed dosing regimen of 150 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing was considered acceptable by the CHMP.

As the required duration of treatment in a well responding patient has not been evaluated, the MAH has committed, based on CHMP's recommendation, to conducting an adequately designed clinical trial (with a randomised withdrawal design) with the goal to assess whether treatment in a well responding nr-axSpA patient should be continued indefinitely. In accordance with the current EU Guideline, the CHMP agreed that this study can be conducted in the post-approval setting.

Based on the data presented, secukinumab can be considered approvable in this indication from an efficacy perspective.

2.5. Clinical safety

Introduction

The pivotal study H2315 in non-radiographic axial spondylarthritis is briefly introduced in Table 31.

Table 31 ***Study H2315***

Study	Study description	No. of patients	Treatment duration	Treatment dose regimen
CAIN457H2315	Efficacy/safety study in target nr-axSpA population - placebo controlled	555	104 weeks (core phase) Data cut-off date: 17-Dec-2018 (LPLV for Week 24)	**Group 1** (AIN457 150 mg Load): 150 mg AIN457 sc at baseline and q1w for the first 4 wks, followed by q4w until Wk 104 **Group 2** (AIN457 150 mg No Load): 150 mg AIN457 sc at baseline and q4w until Wk 104 **Group 3** (Placebo): placebo sc at baseline and q1w for the first 4 wks, followed by q4w until Wk 52

nr-axSpA: non-radiographic axial spondyloarthritis

The pivotal study is designed as a 2-year study (core phase), with an additional 2-year extension phase to assess the efficacy and safety of secukinumab in non-radiographic axial spondylarthritis patients. As of the data cut-off date (17-Dec-2018), safety data are available for all patients up to Week 24 and for some patients up to 104 weeks. No data from the extension phase beyond week 104 for any patient is provided in this submission.

Safety results for both the first 20 weeks (i.e. the period during which all patients remained on the study treatment to which they were originally randomised to) as well as the entire treatment period were evaluated for the following treatment groups:

- Secukinumab (AIN457) 150 mg Load: includes patients randomized at baseline to secukinumab 150 mg s.c. with loading at baseline and Weeks 1, 2, and 3.

- Secukinumab (AIN457) 150 mg No Load: includes patients randomized at baseline to secukinumab 150 mg s.c. without initial loading.
- Any secukinumab (Any AIN457): a combination of the secukinumab 150 mg Load and secukinumab 150 mg No Load groups; placebo switchers after the switch to open-label secukinumab are also included in this category in analyses of the entire treatment period.
- Placebo: includes patients up to Week 20 and those with data past Week 20 who did not switch to open-label secukinumab.

For all three secukinumab groups, events were attributed to secukinumab up to 12 weeks after the last dose and includes patients who switched to standard of care after secukinumab treatment.

In order to evaluate the need for updating the current list of adverse drug reactions for secukinumab with data from study H2315, data pooling was performed on secukinumab studies from multiple indications: non-radiographic spondylarthritis, ankylosing spondylitis (AS), psoriatic arthritis (PsA), and psoriasis (Pso), described in Table 32. Data cut-off was either 12 (Pso) or 16 weeks (AS and PsA) depending on the length of the initial placebo controlled period.

Table 32 ***Population groupings and safety assessments in the pooled dataset***

Database	Studies	Pooled treatment groups	Safety topics
Pool A Pivotal Phase 3 study in non-radiographic axial spondyloarthritis (nr-axSpA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and psoriasis Up to 12/16 weeks duration (randomized, double-blind, placebo-controlled period) N=4224	9 placebo-controlled, randomized, double-blind, Phase 3 studies: CAIN457H2315 (in nr-axSpA); CAIN457F2305 and CAIN457F2310 (in AS); CAIN457F2306, CAIN457F2312 (in PsA); and CAIN457A2302, CAIN457A2303, CAIN457A2308, CAIN457A2309 (in psoriasis)	Secukinumab: 75, 150, and 300 mg/month	Topic: Adverse drug reactions

Patient exposure

A total of 1583 patients were screened for this study, of whom 555 patients (35.1%) were randomized. Overall, 95.0% of the randomized patients completed Week 24 of the study, with similar proportions across all treatment groups. For the demographic and disease baseline characteristics of the patients, refer to the efficacy-sections of this AR. The patient exposure in study H2315 is described in Table 33.

Table 33 ***Duration of exposure to study treatment in study H2315 - entire treatment period (Safety Set)***

Duration of exposure	AIN457 150 mg Load N=185	AIN457 150 mg No Load N=184	Any AIN457 N=543	Placebo N=186
Any exposure	185 (100.0)	184 (100.0)	543 (100.0)	186 (100.0)
≥ 1 week	185 (100.0)	184 (100.0)	541 (99.6)	186 (100.0)
≥ 2 weeks	185 (100.0)	184 (100.0)	541 (99.6)	186 (100.0)
≥ 3 weeks	185 (100.0)	184 (100.0)	541 (99.6)	186 (100.0)
≥ 4 weeks	185 (100.0)	184 (100.0)	541 (99.6)	185 (99.5)
≥ 8 weeks	184 (99.5)	182 (98.9)	537 (98.9)	185 (99.5)
≥ 12 weeks	184 (99.5)	182 (98.9)	534 (98.3)	185 (99.5)
≥ 16 weeks	182 (98.4)	182 (98.9)	529 (97.4)	185 (99.5)
≥ 20 weeks	182 (98.4)	178 (96.7)	516 (95.0)	158 (84.9)
≥ 24 weeks	182 (98.4)	178 (96.7)	511 (94.1)	80 (43.0)
≥ 28 weeks	180 (97.3)	176 (95.7)	502 (92.4)	64 (34.4)
≥ 32 weeks	177 (95.7)	175 (95.1)	492 (90.6)	62 (33.3)
≥ 36 weeks	173 (93.5)	175 (95.1)	476 (87.7)	60 (32.3)
≥ 40 weeks	170 (91.9)	173 (94.0)	462 (85.1)	58 (31.2)
≥ 44 weeks	166 (89.7)	171 (92.9)	447 (82.3)	56 (30.1)
≥ 48 weeks	162 (87.6)	168 (91.3)	436 (80.3)	56 (30.1)
≥ 52 weeks	157 (84.9)	167 (90.8)	420 (77.3)	43 (23.1)
≥ 56 weeks	149 (80.5)	161 (87.5)	391 (72.0)	0 (0.0)
≥ 60 weeks	139 (75.1)	153 (83.2)	367 (67.6)	0 (0.0)
≥ 64 weeks	131 (70.8)	146 (79.3)	345 (63.5)	0 (0.0)
≥ 68 weeks	124 (67.0)	134 (72.8)	320 (58.9)	0 (0.0)
≥ 72 weeks	117 (63.2)	122 (66.3)	293 (54.0)	0 (0.0)
≥ 76 weeks	113 (61.1)	119 (64.7)	279 (51.4)	0 (0.0)
≥ 80 weeks	108 (58.4)	112 (60.9)	259 (47.7)	0 (0.0)
≥ 84 weeks	98 (53.0)	104 (56.5)	226 (41.6)	0 (0.0)
≥ 88 weeks	88 (47.6)	90 (48.9)	185 (34.1)	0 (0.0)
≥ 92 weeks	80 (43.2)	79 (42.9)	162 (29.8)	0 (0.0)
≥ 96 weeks	76 (41.1)	75 (40.8)	151 (27.8)	0 (0.0)
≥ 100 weeks	70 (37.8)	72 (39.1)	142 (26.2)	0 (0.0)
≥ 104 weeks	60 (32.4)	59 (32.1)	119 (21.9)	0 (0.0)
Days				
n	185	184	543	186
Mean	564.8	578.3	509.8	214.6
SD	182.64	172.65	196.68	102.15
Minimum	31	36	1	27
Q1	425.0	455.0	366.0	140.0
Median	612.0	614.5	540.0	145.5
Q3	729.0	729.0	706.0	363.0
Maximum	803	813	813	383
Patient-time (patient-years)	286.1	291.3	757.9	109.3

Duration of exposure to study treatment was defined as the number of days on the study treatment during the considered period.

Patient-time in patient-years was calculated as a sum of individual patient durations in days divided by 365.25.

Patients who were randomized to placebo are counted in the placebo group. Only after switch to open label secukinumab, they were also counted in the Any AIN457 treatment group. Thus, the Any AIN457 column includes patients who were exposed to AIN457 treatment at any time.

Adverse events

Up to week 20

Adverse events that were suspected to be related to study drug were more frequently reported in the secukinumab group compared to placebo at Week 20 (Any secukinumab group: 23.8% vs. placebo group: 14.0%). Refer to Tables 34 and 35.

Infections and infestations were the most frequent, with the largest group difference between secukinumab and placebo (Any secukinumab group: 12.7% vs. placebo group: 7.0%). AEs contributing to this difference in incidence rates were nasopharyngitis, upper respiratory tract infection, and sinusitis. All were mild to moderate and did not lead to study discontinuation. Other AEs with higher rates in the secukinumab group included Gastrointestinal disorders (Any secukinumab group: 4.3% vs. placebo group: 3.2%), mainly due to nausea (all mild or moderate cases, with none leading to discontinuation), and General disorders and administration site conditions (Any secukinumab group: 4.1% vs. placebo group: 2.2%), mainly due to injection site events such as injection site pain, bruising, erythema or haematoma (mainly mild and moderate cases, with one moderate, recovering case that resulted in discontinuation in the placebo group).

Possible suspected treatment-related AEs occurred more frequently for patients in the secukinumab 150 mg Load group (26.5%) compared to the secukinumab 150 mg No Load group (21.2%). This difference was mainly due to nasopharyngitis, upper respiratory tract infection, and urinary tract infection (all mild or moderate cases for all three of these PTs, with only a few drug interruptions and no discontinuations) within the Infections and infestations SOC (secukinumab 150 mg Load group: 16.2% vs. secukinumab 150 mg No Load group: 9.2%).

Table 34 ***Treatment-emergent adverse events by primary system organ class in study H2315 up to week 20 (Safety set)***

Primary system organ class	AIN457 150 mg Load N=185 n (%)	AIN457 150 mg No Load N=184 n (%)	Any AIN457 N=369 n (%)	Placebo N=186 n (%)
Any primary system organ class	118 (63.8)	107 (58.2)	225 (61.0)	100 (53.8)
Infections and infestations	70 (37.8)	61 (33.2)	131 (35.5)	61 (32.8)
Gastrointestinal disorders	33 (17.8)	25 (13.6)	58 (15.7)	20 (10.8)
Musculoskeletal and connective tissue disorders	32 (17.3)	20 (10.9)	52 (14.1)	23 (12.4)
Nervous system disorders	24 (13.0)	12 (6.5)	36 (9.8)	11 (5.9)
General disorders and administration site conditions	15 (8.1)	14 (7.6)	29 (7.9)	8 (4.3)
Respiratory, thoracic and mediastinal disorders	17 (9.2)	12 (6.5)	29 (7.9)	9 (4.8)
Skin and subcutaneous tissue disorders	15 (8.1)	12 (6.5)	27 (7.3)	12 (6.5)
Injury, poisoning and procedural complications	8 (4.3)	11 (6.0)	19 (5.1)	4 (2.2)
Metabolism and nutrition disorders	9 (4.9)	8 (4.3)	17 (4.6)	3 (1.6)
Investigations	3 (1.6)	11 (6.0)	14 (3.8)	2 (1.1)
Psychiatric disorders	8 (4.3)	6 (3.3)	14 (3.8)	3 (1.6)
Blood and lymphatic system disorders	7 (3.8)	5 (2.7)	12 (3.3)	4 (2.2)
Eye disorders	7 (3.8)	2 (1.1)	9 (2.4)	2 (1.1)
Cardiac disorders	6 (3.2)	2 (1.1)	8 (2.2)	4 (2.2)
Vascular disorders	5 (2.7)	2 (1.1)	7 (1.9)	5 (2.7)
Immune system disorders	5 (2.7)	1 (0.5)	6 (1.6)	1 (0.5)
Ear and labyrinth disorders	4 (2.2)	0 (0.0)	4 (1.1)	1 (0.5)
Congenital, familial and genetic disorders	3 (1.6)	0 (0.0)	3 (0.8)	1 (0.5)
Hepatobiliary disorders	2 (1.1)	1 (0.5)	3 (0.8)	0 (0.0)
Reproductive system and breast disorders	1 (0.5)	2 (1.1)	3 (0.8)	2 (1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5)	1 (0.5)	2 (0.5)	1 (0.5)
Renal and urinary disorders	1 (0.5)	0 (0.0)	1 (0.3)	2 (1.1)
Endocrine disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)

A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

Table 35 ***Most common treatment-emergent adverse events by preferred term in study H2315 up to Week 20 (Safety set)***

Preferred term	AIN457 150 mg Load N=185 n (%)	AIN457 150 mg No Load N=184 n (%)	Any AIN457 N=369 n (%)	Placebo N=186 n (%)
Any preferred term	118 (63.8)	107 (58.2)	225 (61.0)	100 (53.8)
Nasopharyngitis	27 (14.6)	19 (10.3)	46 (12.5)	23 (12.4)
Diarrhoea	14 (7.6)	9 (4.9)	23 (6.2)	7 (3.8)
Headache	17 (9.2)	6 (3.3)	23 (6.2)	7 (3.8)
Upper respiratory tract infection	11 (5.9)	11 (6.0)	22 (6.0)	7 (3.8)
Oropharyngeal pain	10 (5.4)	3 (1.6)	13 (3.5)	2 (1.1)
Back pain	7 (3.8)	5 (2.7)	12 (3.3)	2 (1.1)
Nausea	7 (3.8)	5 (2.7)	12 (3.3)	6 (3.2)
Urinary tract infection	8 (4.3)	2 (1.1)	10 (2.7)	3 (1.6)
Abdominal pain upper	4 (2.2)	4 (2.2)	8 (2.2)	2 (1.1)
Tonsillitis	4 (2.2)	4 (2.2)	8 (2.2)	2 (1.1)
Arthralgia	5 (2.7)	2 (1.1)	7 (1.9)	9 (4.8)
Depression	3 (1.6)	4 (2.2)	7 (1.9)	0 (0.0)
Respiratory tract infection	3 (1.6)	4 (2.2)	7 (1.9)	4 (2.2)
Sinusitis	4 (2.2)	3 (1.6)	7 (1.9)	3 (1.6)
Anaemia	5 (2.7)	1 (0.5)	6 (1.6)	0 (0.0)
Axial spondyloarthritis	5 (2.7)	1 (0.5)	6 (1.6)	2 (1.1)
Hypercholesterolaemia	4 (2.2)	2 (1.1)	6 (1.6)	0 (0.0)
Influenza	3 (1.6)	3 (1.6)	6 (1.6)	6 (3.2)
Blood cholesterol increased	2 (1.1)	3 (1.6)	5 (1.4)	0 (0.0)
Cough	2 (1.1)	3 (1.6)	5 (1.4)	3 (1.6)
Hypertension	4 (2.2)	1 (0.5)	5 (1.4)	1 (0.5)
Oral herpes	2 (1.1)	3 (1.6)	5 (1.4)	1 (0.5)
Spondylitis	3 (1.6)	2 (1.1)	5 (1.4)	1 (0.5)
Aphthous ulcer	3 (1.6)	1 (0.5)	4 (1.1)	0 (0.0)
Contusion	1 (0.5)	3 (1.6)	4 (1.1)	1 (0.5)
Cystitis	2 (1.1)	2 (1.1)	4 (1.1)	0 (0.0)
Fatigue	2 (1.1)	2 (1.1)	4 (1.1)	1 (0.5)
Folliculitis	1 (0.5)	3 (1.6)	4 (1.1)	0 (0.0)
Gastroenteritis	2 (1.1)	2 (1.1)	4 (1.1)	3 (1.6)
Gastrooesophageal reflux disease	2 (1.1)	2 (1.1)	4 (1.1)	0 (0.0)
Hyperlipidaemia	3 (1.6)	1 (0.5)	4 (1.1)	0 (0.0)
Nasal congestion	3 (1.6)	1 (0.5)	4 (1.1)	0 (0.0)
Rash	2 (1.1)	2 (1.1)	4 (1.1)	1 (0.5)
Rhinitis	3 (1.6)	1 (0.5)	4 (1.1)	1 (0.5)
Rhinorrhoea	2 (1.1)	2 (1.1)	4 (1.1)	1 (0.5)

The safety profile for secukinumab in non-radiographic axial spondylarthritis patients in study CAIN457H2315 is comparable to that of secukinumab in ankylosing spondylitis patients in study CAIN457F2310, based upon the overall frequency of treatment-emergent AEs in the two studies and the similarities in the most commonly occurring AEs per SOC. The incidence rates in the secukinumab 150 mg Load and the No Load group from Study CAIN457H2315 were overall comparable to those of the secukinumab group (with loading) in Study CAIN457F2310. Refer to Table 36.

Table 36 ***Absolute and relative frequencies for treatment-emergent adverse events by primary system organ class for study F2310 (AS) and study H2315 (nrAxSpA) up to Week 16 (Safety Set)***

	CAIN457F2310		CAIN457H2315		
Primary system organ class	AIN457 150 mg N=72 n (%) 95% CI	Placebo N=74 n (%) 95% CI	AIN457 150 mg Load N=185 n (%) 95% CI	AIN457 150 mg No Load N=184 n (%) 95% CI	Placebo N=186 n (%) 95% CI
Any primary system organ class	47 (65.3) (53.1, 75.9)	47 (63.5) (51.5, 74.2)	110 (59.5) (52.0, 66.5)	100 (54.3) (46.9, 61.6)	91 (48.9) (41.6, 56.3)
Infections and infestations	24 (33.3) (22.9, 45.5)	20 (27.0) (17.7, 38.8)	60 (32.4) (25.9, 39.8)	51 (27.7) (21.5, 34.9)	54 (29.0) (22.7, 36.2)
Musculoskeletal and connective tissue disorders	7 (9.7) (4.3, 19.6)	13 (17.6) (10.0, 28.5)	29 (15.7) (10.9, 21.9)	18 (9.8) (6.1, 15.2)	21 (11.3) (7.3, 17.0)
Gastrointestinal disorders	9 (12.5) (6.2, 22.9)	12 (16.2) (9.0, 27.0)	28 (15.1) (10.5, 21.3)	24 (13.0) (8.7, 19.0)	19 (10.2) (6.4, 15.7)
Nervous system disorders	8 (11.1) (5.3, 21.3)	10 (13.5) (7.0, 23.9)	21 (11.4) (7.3, 17.0)	10 (5.4) (2.8, 10.1)	11 (5.9) (3.1, 10.6)
Respiratory, thoracic and mediastinal disorders	6 (8.3) (3.4, 17.9)	6 (8.1) (3.3, 17.4)	16 (8.6) (5.2, 13.9)	9 (4.9) (2.4, 9.4)	8 (4.3) (2.0, 8.6)
General disorders and administration site conditions	9 (12.5) (6.2, 22.9)	11 (14.9) (8.0, 25.5)	15 (8.1) (4.8, 13.3)	12 (6.5) (3.6, 11.4)	7 (3.8) (1.7, 7.9)
Skin and subcutaneous tissue disorders	6 (8.3) (3.4, 17.9)	7 (9.5) (4.2, 19.1)	12 (6.5) (3.5, 11.3)	11 (6.0) (3.2, 10.7)	11 (5.9) (3.1, 10.6)
Metabolism and nutrition disorders	5 (6.9) (2.6, 16.1)	6 (8.1) (3.3, 17.4)	9 (4.9) (2.4, 9.3)	8 (4.3) (2.0, 8.7)	3 (1.6) (0.4, 5.0)
Psychiatric disorders	3 (4.2) (1.1, 12.5)	3 (4.1) (1.1, 12.2)	8 (4.3) (2.0, 8.6)	6 (3.3) (1.3, 7.3)	2 (1.1) (0.2, 4.2)
Cardiac disorders	0 (0.0 (0.0, 6.3)	2 (2.7) (0.5, 10.3)	6 (3.2) (1.3, 7.3)	2 (1.1) (0.2, 4.3)	4 (2.2) (0.7, 5.8)
Eye disorders	0 (0.0) (0.0, 6.3)	1 (1.4) (0.1, 8.3)	6 (3.2) (1.3, 7.3)	1 (0.5) (0.0, 3.5)	2 (1.1) (0.2, 4.2)
Blood and lymphatic system disorders	0 (0.0) (0.0, 6.3)	2 (2.7) (0.5, 10.3)	5 (2.7) (1.0, 6.5)	4 (2.2) (0.7, 5.8)	4 (2.2) (0.7, 5.8)
Injury, poisoning and procedural complications	3 (4.2) (1.1, 12.5)	6 (8.1) (3.3, 17.4)	5 (2.7) (1.0, 6.5)	10 (5.4) (2.8, 10.1)	4 (2.2) (0.7, 5.8)
Ear and labyrinth disorders	0 (0.0) (0.0, 6.3)	3 (4.1) (1.1, 12.2)	4 (2.2) (0.7, 5.8)	0 (0.0) (0.0, 2.5)	1 (0.5) (0.0, 3.4)
Vascular disorders	2 (2.8) (0.5, 10.6)	1 (1.4) (0.1, 8.3)	4 (2.2) (0.7, 5.8)	2 (1.1) (0.2, 4.3)	5 (2.7) (1.0, 6.5)
Congenital, familial and genetic disorders	0 (0.0) (0.0, 6.3)	0 (0.0) (0.0, 6.1)	3 (1.6) (0.4, 5.0)	0 (0.0) (0.0, 2.5)	1 (0.5) (0.0, 3.4)
Immune system disorders	0 (0.0) (0.0, 6.3)	1 (1.4) (0.1, 8.3)	3 (1.6) (0.4, 5.0)	1 (0.5) (0.0, 3.5)	1 (0.5) (0.0, 3.4)
Investigations	8 (11.1) (5.3, 21.3)	2 (2.7) (0.5, 10.3)	3 (1.6) (0.4, 5.0)	10 (5.4) (2.8, 10.1)	1 (0.5) (0.0, 3.4)
Hepatobiliary disorders	0 (0.0) (0.0, 6.3)	1 (1.4) (0.1, 8.3)	2 (1.1) (0.2, 4.3)	1 (0.5) (0.0, 3.5)	0 (0.0) (0.0, 2.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.4) (0.1, 8.5)	0 (0.0) (0.0, 6.1)	1 (0.5) (0.0, 3.4)	1 (0.5) (0.0, 3.5)	1 (0.5) (0.0, 3.4)
Renal and urinary disorders	0 (0.0) (0.0, 6.3)	2 (2.7) (0.5, 10.3)	1 (0.5) (0.0, 3.4)	0 (0.0) (0.0, 2.5)	2 (1.1) (0.2, 4.2)
Reproductive system and breast disorders	0 (0.0) (0.0, 6.3)	1 (1.4) (0.1, 8.3)	1 (0.5) (0.0, 3.4)	1 (0.5) (0.0, 3.5)	1 (0.5) (0.0, 3.4)

The entire treatment period

Suspected study drug-related treatment-emergent AEs were reported more frequently in the secukinumab group compared to placebo for the entire treatment period (Any secukinumab group: 33.1% vs. placebo group: 18.3%). When taking into account the differences in exposure between secukinumab (mean days of patient exposure: 509.8 days) and placebo (mean days of patient exposure: 214.6 days) for the entire study period, causality assessment was similar between the two groups.

The overall exposure-adjusted incidence rate (EAIR, per 100 PY) of AEs by SOC was lower in the composite secukinumab group compared to placebo (166.2 per 100 PY in the Any AIN457 group vs. 200.1 per 100 PY in the placebo group). This difference was primarily due to the imbalance in EAIRs for AEs belonging to Infections and infestations (76.1 per 100 PY in the Any AIN457 group vs. 100.6 per 100 PY in the placebo group). Other AEs by SOC contributing to this imbalance between treatment groups include Musculoskeletal and connective tissue disorders (22.8 per 100 PY in the Any AIN457 group vs. 29.3 per 100 PY in the placebo group), Gastrointestinal disorders (21.6 per 100 PY in the Any AIN457 group vs. 26.4 per 100 PY in the placebo group), Cardiac disorders (1.5 per 100 PY in the Any AIN457 group vs. 4.7 per 100 PY in the placebo group) and Blood and lymphatic system disorders (3.3 per 100 PY in the Any AIN457 group vs. 6.5 per 100 PY in the placebo group). See Tables 37 and 38.

Treatment comparisons of secukinumab to placebo for the entire treatment period, however, should be interpreted with caution, in case the reported event rates are not constant over time. Moreover, reporting rates, depending on types of AEs, may vary from the initial trial period, with very frequent study visits compared to later study periods with less frequent visits. As noted above, overall exposure was 286.1 patient-years for the AIN457 150 mg Load group, 291.3 patient-years for the AIN457 150 mg No Load group, 757.9 patient-years for the Any AIN457 group, and 109.3 patient-years for the placebo group.

The AIN457 150 mg Load group had higher EAIRs compared to the AIN457 150 mg No Load group (212.7 per 100 PY vs. 158.0 per 100 PY). This was mainly due to differences in Infections and infestations (91.5 per 100 PY vs. 71.6 per 100 PY), and to a lesser extent, differences in Musculoskeletal and connective tissue disorders (29.6 per 100 PY vs. 21.7 per 100 PY), Gastrointestinal disorders (27.3 per 100 PY vs. 21.8 per 100 PY), Nervous system disorders (15.7 per 100 PY vs. 11.5 per 100 PY), and Skin and subcutaneous tissue disorders (13.7 per 100 PY vs. 8.6 per 100 PY). Based upon the detailed review of the events in these SOCs, taking into account the nature, severity, and outcome, there were no clinically meaningful differences between the AIN457 150 mg Load and No Load groups. See Tables 37 and 38.

Table 37 ***Exposure-adjusted incidence rates for treatment-emergent adverse events by primary system organ class in study H2315 entire treatment period (Safety Set)***

Primary system organ class	AIN457 150 mg Load N=185 n/EX (IR)	AIN457 150 mg No Load N=184 n/EX (IR)	Any AIN457 N=543 n/EX (IR)	Placebo N=186 n/EX (IR)
-Any primary system organ class	162/ 76.2 (212.7)	156/ 98.7 (158.0)	431/ 259.3 (166.2)	121/ 60.5 (200.1)
Infections and infestations	128/ 139.9 (91.5)	116/ 162.0 (71.6)	323/ 424.5 (76.1)	79/ 78.6 (100.6)
Musculoskeletal and connective tissue disorders	64/ 216.4 (29.6)	51/ 235.2 (21.7)	140/ 615.0 (22.8)	29/ 98.9 (29.3)
Gastrointestinal disorders	60/ 220.2 (27.3)	51/ 234.3 (21.8)	134/ 619.2 (21.6)	26/ 98.5 (26.4)
Nervous system disorders	38/ 241.3 (15.7)	30/ 261.1 (11.5)	85/ 672.1 (12.6)	13/ 103.6 (12.5)
Skin and subcutaneous tissue disorders	34/ 248.5 (13.7)	23/ 268.4 (8.6)	74/ 686.0 (10.8)	14/ 104.6 (13.4)
Injury, poisoning and procedural complications	27/ 262.2 (10.3)	29/ 261.8 (11.1)	69/ 695.1 (9.9)	10/ 107.1 (9.3)
Respiratory, thoracic and mediastinal disorders	31/ 254.2 (12.2)	23/ 263.8 (8.7)	64/ 692.3 (9.2)	12/ 103.5 (11.6)
General disorders and administration site conditions	25/ 260.3 (9.6)	23/ 267.8 (8.6)	55/ 704.5 (7.8)	10/ 105.7 (9.5)
Eye disorders	19/ 266.7 (7.1)	15/ 279.8 (5.4)	42/ 721.5 (5.8)	4/ 108.1 (3.7)
Investigations	14/ 273.9 (5.1)	16/ 273.0 (5.9)	37/ 723.6 (5.1)	3/ 108.7 (2.8)
Psychiatric disorders	19/ 266.2 (7.1)	11/ 275.6 (4.0)	35/ 721.0 (4.9)	6/ 108.1 (5.6)
Metabolism and nutrition disorders	16/ 269.3 (5.9)	12/ 275.4 (4.4)	33/ 721.5 (4.6)	4/ 107.4 (3.7)
Vascular disorders	9/ 277.0 (3.2)	14/ 279.5 (5.0)	30/ 731.8 (4.1)	7/ 106.5 (6.6)
Blood and lymphatic system disorders	10/ 272.5 (3.7)	9/ 281.8 (3.2)	24/ 732.0 (3.3)	7/ 107.4 (6.5)
Renal and urinary disorders	12/ 277.6 (4.3)	3/ 289.0 (1.0)	18/ 744.2 (2.4)	3/ 108.2 (2.8)
Reproductive system and breast disorders	7/ 280.0 (2.5)	3/ 286.4 (1.0)	15/ 744.0 (2.0)	4/ 108.4 (3.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6/ 281.1 (2.1)	3/ 289.8 (1.0)	14/ 750.5 (1.9)	1/ 108.3 (0.9)
Ear and labyrinth disorders	9/ 278.5 (3.2)	2/ 290.6 (0.7)	13/ 746.8 (1.7)	1/ 108.3 (0.9)
Cardiac disorders	6/ 275.8 (2.2)	4/ 287.7 (1.4)	11/ 743.9 (1.5)	5/ 106.2 (4.7)
Immune system disorders	5/ 281.1 (1.8)	4/ 287.6 (1.4)	10/ 749.2 (1.3)	1/ 108.9 (0.9)
Hepatobiliary disorders	4/ 282.7 (1.4)	2/ 289.9 (0.7)	7/ 751.9 (0.9)	1/ 108.7 (0.9)
Congenital, familial and genetic disorders	4/ 280.2 (1.4)	2/ 290.7 (0.7)	6/ 751.3 (0.8)	1/ 109.1 (0.9)
Endocrine disorders	3/ 283.5 (1.1)	0/ 291.3 (0.0)	3/ 755.3 (0.4)	1/ 109.0 (0.9)
Pregnancy, puerperium and perinatal conditions	0/ 286.1 (0.0)	2/ 291.1 (0.7)	3/ 757.6 (0.4)	0/ 109.3 (0.0)
Social circumstances	1/ 284.5 (0.4)	0/ 291.3 (0.0)	1/ 756.3 (0.1)	0/ 109.3 (0.0)

Primary system organ classes are sorted by descending frequency in the Any AIN457 group.
A patient with multiple TEAEs within a primary system organ class (PSOC) is counted only once in the PSOC.
IR=incidence rate per 100 patient-years. EX=exposure in patient-years.
For patients with event, exposure time is censored at time of first event.

Table 38 ***Exposure adjusted incidence rate for most common treatment emergent adverse events by preferred term in study H2315 entire treatment period (Safety Set)***

Preferred term	AIN457 150 mg Load N=185 n/EX (IR)	AIN457 150 mg No Load N=184 n/EX (IR)	Any AIN457 N=543 n/EX (IR)	Placebo N=186 n/EX (IR)
-Any Preferred term	162/ 76.2 (212.7)	156/ 98.7 (158.0)	431/ 259.3 (166.2)	121/ 60.5 (200.1)
Nasopharyngitis	56/ 220.4 (25.4)	43/ 244.8 (17.6)	122/ 629.9 (19.4)	32/ 98.5 (32.5)
Upper respiratory tract infection	25/ 260.0 (9.6)	24/ 266.3 (9.0)	59/ 699.8 (8.4)	13/ 105.1 (12.4)
Diarrhoea	23/ 262.3 (8.8)	20/ 272.0 (7.4)	50/ 708.8 (7.1)	10/ 105.6 (9.5)
Headache	26/ 257.0 (10.1)	12/ 277.2 (4.3)	46/ 709.2 (6.5)	9/ 104.9 (8.6)
Back pain	19/ 268.4 (7.1)	12/ 276.1 (4.3)	35/ 721.6 (4.9)	4/ 108.1 (3.7)
Arthralgia	20/ 267.8 (7.5)	11/ 279.5 (3.9)	34/ 726.7 (4.7)	11/ 105.2 (10.5)
Urinary tract infection	20/ 266.8 (7.5)	6/ 285.6 (2.1)	32/ 729.9 (4.4)	4/ 108.0 (3.7)
Sinusitis	11/ 277.5 (4.0)	11/ 283.4 (3.9)	27/ 737.9 (3.7)	3/ 108.6 (2.8)
Pharyngitis	4/ 283.7 (1.4)	9/ 283.9 (3.2)	25/ 736.7 (3.4)	1/ 108.9 (0.9)
Hypertension	8/ 277.4 (2.9)	10/ 284.4 (3.5)	24/ 737.2 (3.3)	3/ 108.0 (2.8)
Tonsillitis	9/ 276.5 (3.3)	8/ 283.3 (2.8)	23/ 736.3 (3.1)	2/ 108.9 (1.8)
Oropharyngeal pain	14/ 269.7 (5.2)	7/ 284.1 (2.5)	22/ 733.5 (3.0)	2/ 107.5 (1.9)
Gastroenteritis	8/ 279.1 (2.9)	6/ 284.7 (2.1)	22/ 739.8 (3.0)	3/ 107.7 (2.8)
Nausea	11/ 273.4 (4.0)	9/ 279.4 (3.2)	21/ 732.0 (2.9)	6/ 107.0 (5.6)
Influenza	8/ 277.0 (2.9)	11/ 280.4 (3.9)	21/ 736.1 (2.9)	7/ 106.5 (6.6)
Rash	5/ 279.6 (1.8)	10/ 282.4 (3.5)	19/ 740.3 (2.6)	3/ 108.7 (2.8)
Bronchitis	5/ 281.5 (1.8)	10/ 282.2 (3.5)	19/ 741.2 (2.6)	2/ 108.1 (1.9)
Axial spondyloarthritis	9/ 277.1 (3.2)	6/ 288.2 (2.1)	19/ 744.2 (2.6)	3/ 108.5 (2.8)
Rhinitis	9/ 281.2 (3.2)	6/ 285.5 (2.1)	19/ 745.6 (2.5)	2/ 107.8 (1.9)
Abdominal pain upper	8/ 276.7 (2.9)	6/ 283.4 (2.1)	18/ 737.7 (2.4)	2/ 108.1 (1.9)
Respiratory tract infection	6/ 280.9 (2.1)	7/ 283.0 (2.5)	18/ 741.3 (2.4)	4/ 108.2 (3.7)
Cough	6/ 279.4 (2.1)	7/ 283.0 (2.5)	14/ 741.6 (1.9)	4/ 107.3 (3.7)
Depression	6/ 279.3 (2.1)	6/ 282.2 (2.1)	12/ 742.0 (1.6)	3/ 109.2 (2.7)
Folliculitis	3/ 281.4 (1.1)	7/ 283.6 (2.5)	12/ 743.4 (1.6)	1/ 109.2 (0.9)
Spondylitis	4/ 281.9 (1.4)	4/ 286.5 (1.4)	11/ 746.8 (1.5)	1/ 108.5 (0.9)
Vomiting	5/ 280.9 (1.8)	3/ 289.1 (1.0)	11/ 748.3 (1.5)	2/ 108.5 (1.8)
Pyrexia	6/ 281.4 (2.1)	4/ 289.2 (1.4)	11/ 750.6 (1.5)	1/ 109.1 (0.9)
Anaemia	5/ 277.6 (1.8)	3/ 287.5 (1.0)	10/ 743.7 (1.3)	3/ 108.3 (2.8)
Vulvovaginal candidiasis	5/ 281.3 (1.8)	2/ 288.2 (0.7)	10/ 747.9 (1.3)	0/ 109.3 (0.0)
Dyspepsia	8/ 278.1 (2.9)	2/ 290.5 (0.7)	10/ 749.1 (1.3)	1/ 108.9 (0.9)
Gastritis	7/ 281.4 (2.5)	1/ 291.1 (0.3)	10/ 752.5 (1.3)	0/ 109.3 (0.0)
Dizziness	4/ 279.7 (1.4)	3/ 289.5 (1.0)	9/ 749.4 (1.2)	0/ 109.3 (0.0)
Bursitis	4/ 283.3 (1.4)	3/ 288.0 (1.0)	9/ 749.4 (1.2)	0/ 109.3 (0.0)
Conjunctivitis	2/ 283.0 (0.7)	4/ 287.2 (1.4)	9/ 749.6 (1.2)	1/ 108.8 (0.9)
Uveitis	5/ 280.6 (1.8)	2/ 290.3 (0.7)	9/ 750.6 (1.2)	2/ 108.5 (1.8)
Abdominal pain	6/ 281.0 (2.1)	2/ 289.9 (0.7)	9/ 751.4 (1.2)	5/ 106.7 (4.7)
Mouth ulceration	5/ 281.9 (1.8)	4/ 289.1 (1.4)	9/ 751.5 (1.2)	0/ 109.3 (0.0)
Hypercholesterolaemia	6/ 278.6 (2.2)	2/ 287.7 (0.7)	8/ 746.8 (1.1)	0/ 109.3 (0.0)
Oral herpes	3/ 283.1 (1.1)	3/ 285.9 (1.0)	8/ 748.5 (1.1)	1/ 108.9 (0.9)
Viral upper respiratory tract infection	4/ 281.6 (1.4)	2/ 288.6 (0.7)	8/ 749.6 (1.1)	3/ 108.0 (2.8)
Psoriasis	6/ 280.6 (2.1)	1/ 289.6 (0.3)	8/ 750.2 (1.1)	1/ 109.2 (0.9)
Contusion	1/ 285.2 (0.4)	3/ 286.9 (1.0)	8/ 751.3 (1.1)	2/ 108.7 (1.8)
Cystitis	5/ 283.1 (1.8)	2/ 288.7 (0.7)	8/ 751.4 (1.1)	0/ 109.3 (0.0)
Anxiety	5/ 282.4 (1.8)	2/ 289.3 (0.7)	8/ 751.9 (1.1)	0/ 109.3 (0.0)
Gastrooesophageal reflux disease	3/ 283.9 (1.1)	3/ 289.4 (1.0)	8/ 752.3 (1.1)	0/ 109.3 (0.0)

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

Safety data from secukinumab studies, covering multiple indications, were pooled together to evaluate the need for updating the current list of ADRs with new, additional data from study H2315. Among the studies involving AS, only study F2305 and study F2310 were included in the pool, as these studies were the basis for the registration of the AS indication. However, three other Phase 3 trials have now been completed that add to the safety profile and are included in AIN457 PSUR (26-Dec-2017 to 25-Dec-2018).

The incidence rates for all ADRs according to dosing regimen for all indications (psoriasis, psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondylarthritis) have been evaluated. Out of a total of 2848 patients, 503 patients (Any secukinumab group: 17.7%) reported upper respiratory tract infection (HLT) and 296 patients (10.4%) experienced nasopharyngitis, both of which were designated very common ADRs. Common ADRs included the following: upper respiratory tract infection (3.9%), diarrhea (3.3%), rhinitis (1.3%), oral herpes (1.1%), pharyngitis (1.1%), sinusitis (0.8%), tonsillitis (0.7%), tinea pedis (0.6%), and rhinorrhoea (0.6%). Uncommon events included urticaria (0.7%), conjunctivitis (0.6%), otitis externa (0.5%), oral candidiasis (0.4%), and neutropenia (0.3%). Rare events included anaphylactic reactions (0.04%). The MAH concluded that the information in the SmPC section 4.8 is up to date except for "Tinea pedis" from which the frequency was proposed to be moved from uncommon to common.

Serious adverse event/deaths/other significant events

Deaths

No deaths were reported for the entire treatment period.

Serious adverse events

Non-fatal SAEs occurred more frequently in the secukinumab groups compared to placebo (Any secukinumab group: 7.2% vs. placebo: 4.3%). Discontinuations due to AEs were higher in the secukinumab groups compared to placebo (Any secukinumab: 4.4% vs. placebo: 1.6%). However, when taking into account the longer exposure times in terms of mean days of patient exposure on secukinumab (509.8 days) compared to placebo (214.6 days), the frequency of events was comparable between secukinumab and placebo groups (Table 39).

Table 39 ***Deaths, other treatment-emergent serious or clinically significant adverse events or related discontinuations in study H2315 entire treatment period (Safety Set)***

	AIN457 150 mg Load N=185 n (%)	AIN457 150 mg No Load N=184 n (%)	Any AIN457 N=543 n (%)	Placebo N=186 n (%)
Number of subjects with any AE	162 (87.6)	156 (84.8)	431 (79.4)	121 (65.1)
Number of subjects with serious or other significant events				
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-fatal SAE	20 (10.8)	12 (6.5)	39 (7.2)	8 (4.3)
Discontinued study treatment due to any AE	7 (3.8)	13 (7.1)	24 (4.4)	3 (1.6)

Patients who were randomized to placebo are counted in the placebo group. Only after switch to open label secukinumab, they are also counted in the Any AIN457 treatment group. Thus, the Any AIN457 column includes patients who were exposed to AIN457 treatment at any time.

Until 20 weeks a total of 7 secukinumab patients reported at least one SAE (2 patients, 1.1% from the secukinumab 150 mg Load group and 4 patients, 2.2% from the secukinumab 150 mg No Load group) compared with 4 patients (2.2%) from the placebo group.

In the secukinumab 150 mg Load group, all the SAEs were moderate in severity and consisted of device-related cochlear implant infection, eczema infection (deemed related to study drug by the investigator) and wrist fracture.

Among the 4 patients with SAEs in the secukinumab 150 mg No Load group, severe intervertebral disc disorder and myelopathy (both deemed unrelated to study drug by the investigator) was reported in one patient, which prompted study drug discontinuation. Two patients interrupted study drug treatment during the first 20 weeks due to non-infectious hepatitis (based on LFTs, considered related to the study drug by the investigator) in one case and due to gastroenteritis in another case. The patient with the gastroenteritis SAE also experienced severe diarrhoea, which was considered related to the study drug by the investigator. The fourth patient reported a severe case of sciatica that was deemed unrelated to the study drug by the investigator.

In the placebo group, myocardial infarction, severe pyrexia, back pain, and arteriosclerosis were reported, none leading to interruption of study drug.

Additional SAEs in the secukinumab 150 mg Load group after Week 20 (See also Table 40 which includes all the data until week 52 interim cut-off) comprised infections including tonsillitis, vaccination site cellulitis (deemed related to the study drug by the investigator), and a severe case of post-operative wound infection that resulted in study drug interruption. Injuries included one event of brain contusion and another event of severe tendon injury; the latter led to study drug interruption. Severe Crohn's colitis in one patient (considered related to the study drug) led to study drug withdrawal, and another case of ulcerative colitis (considered related to the study drug) resulted in drug interruption. Musculoskeletal disorders included arthritis and back pain, both severe and unrelated (according to the investigator), in a single patient. Metabolism disorders included diabetes mellitus and diabetic ketoacidosis in 2 patients, both deemed unrelated to the study drug. Renal disorders occurred in 2 patients, one IgA nephropathy and one nephrolithiasis (both severe), the case of IgA nephropathy led to study drug discontinuation and the case of nephrolothiasis led to study drug interruption although both were deemed unrelated to the study drug. One patient reported a mild neoplasm (acrochordon), unrelated to the study drug, leading to study drug interruption. Respiratory disorders included pneumomediastinum and pneumothorax in one patient, considered to be related to the study drug. One patient with a previous history of depression and suicide from the secukinumab 150 mg Load group, who switched to standard of care (TNF-alpha inhibitor), reported a suicide attempt 10 months after the last dose of secukinumab.

New treatment-emergent SAEs in the secukinumab 150 mg No Load group, occurring after Week 20, consisted of Eye disorders (one iridocyclitis), and Infections and infestations. The infections occurred in single patients and consisted of severe tonsillitis, anal abscess, and severe subcutaneous abscess of the abdomen that was considered related to the study drug by the investigator and led to temporary drug interruption.

Seven patients in the placebo group who switched to secukinumab treatment after Week 20 reported one SAE each: diverticulitis, epiglottitis, arthritis, a severe case of skin disorder, ovarian cyst, back disorder, and malignant melanoma. All cases were mild or moderate in severity and deemed unrelated to study treatment by the investigator. The malignant melanoma SAE led to discontinuation of the study drug, as required by the protocol.

Eight patients reported SAEs while on placebo treatment that were mild or moderate and deemed unrelated to the study drug by the investigator. One patient developed acute coronary syndrome and

viral tracheitis and another patient reported arthralgia. The third patient had a radius fracture prior to the switch to secukinumab in the screening period. The fourth patient reported back disorder and the following reproductive SAEs: an abnormal pathology test (endometrium pathology), Bartholin's cyst, cervix enlargement, and vaginal prolapse. Cervix enlargement and vaginal prolapse both led to interruption of the study drug.

Table 40 ***Absolute and relative frequencies for treatment emergent serious adverse events by primary system organ class and preferred term – entire treatment period (Safety Set)***

Primary system organ class Preferred term	AIN457 150 mg Load N=185 n (%)	AIN457 150 mg No Load N=184 n (%)	Any AIN457 N=543 n (%)	Placebo N=186 n (%)
Any primary system organ class				
-Total	20 (10.8)	12 (6.5)	39 (7.2)	8 (4.3)
Cardiac disorders				
-Total	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)
Acute coronary syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Eye disorders				
-Total	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Iridocyclitis	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Gastrointestinal disorders				
-Total	4 (2.2)	2 (1.1)	6 (1.1)	0 (0.0)
Appendiceal mucocoele	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Colitis*	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Colitis ulcerative	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Crohn's disease	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Diarrhoea	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Inguinal hernia	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Lower gastrointestinal haemorrhage	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
General disorders and administration site conditions				
-Total	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Hepatobiliary disorders				
-Total	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Hepatitis acute	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Infections and infestations				
-Total	5 (2.7)	5 (2.7)	12 (2.2)	1 (0.5)
Tonsillitis	1 (0.5)	1 (0.5)	2 (0.4)	0 (0.0)
Anal abscess	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Device related infection	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Diverticulitis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Eczema infected	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Epiglottitis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Gastroenteritis	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Pneumonia	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Postoperative wound infection	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Subcutaneous abscess	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Urinary tract infection	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Vaccination site cellulitis	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Viral tracheitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)

Primary system organ class Preferred term	AIN457 150 mg Load N=185 n (%)	AIN457 150 mg No Load N=184 n (%)	Any AIN457 N=543 n (%)	Placebo N=186 n (%)
Injury, poisoning and procedural complications				
-Total	4 (2.2)	1 (0.5)	5 (0.9)	1 (0.5)
Brain contusion	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Skin laceration	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Tendon injury	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Wound dehiscence	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Wrist fracture	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Clavicle fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Investigations				
-Total	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Arthroscopy	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Metabolism and nutrition disorders				
-Total	2 (1.1)	0 (0.0)	2 (0.4)	0 (0.0)
Diabetes mellitus	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Diabetic ketoacidosis	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Musculoskeletal and connective tissue disorders				
-Total	2 (1.1)	1 (0.5)	5 (0.9)	2 (1.1)
Arthritis	1 (0.5)	0 (0.0)	2 (0.4)	0 (0.0)
Back disorder	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Back pain	1 (0.5)	0 (0.0)	1 (0.2)	1 (0.5)
Intervertebral disc disorder	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Osteoarthritis	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
-Total	2 (1.1)	0 (0.0)	3 (0.6)	0 (0.0)
Acrochordon	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Fibroadenoma of breast	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Malignant melanoma	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Nervous system disorders				
-Total	0 (0.0)	3 (1.6)	3 (0.6)	0 (0.0)
Myelopathy	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Sciatica	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Spinal claudication	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Renal and urinary disorders				
-Total	2 (1.1)	0 (0.0)	2 (0.4)	0 (0.0)
IgA nephropathy	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Nephrolithiasis	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Reproductive system and breast disorders				
-Total	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.5)
Ovarian cyst	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Bartholin's cyst	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Cervix enlargement	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Endometrial disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Vaginal prolapse	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)

Primary system organ class Preferred term	AIN457 150 mg Load N=185 n (%)	AIN457 150 mg No Load N=184 n (%)	Any AIN457 N=543 n (%)	Placebo N=186 n (%)
Respiratory, thoracic and mediastinal disorders				
-Total	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Pneumomediastinum	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Pneumothorax	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Skin and subcutaneous tissue disorders				
-Total	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Skin disorder	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Vascular disorders				
-Total	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Arteriosclerosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)

A patient with multiple adverse events within a primary system organ class is counted only once in the total row. System organ classes are presented in alphabetical order.

Preferred terms are presented by descending frequency in the Any AIN457 group within each SOC.

Patients who were randomized to placebo are counted in the placebo group. Only after switch to open label secukinumab, they are also counted in the Any AIN457 treatment group. Thus, the Any AIN457 column includes patients who were exposed to AIN457 treatment at any time.

Adverse events of special interest

In order to properly manage all safety risks, a safety profiling plan (SPP) was developed for the secukinumab development program. The following SPP risks were evaluated up to Week 20, based upon reported treatment-emergent AEs for all treatment groups: compound and class-related risks, important identified risks, and important potential risks (Tables 41 and 42).

Compound and class-related risks included Immune/administration reactions and various infections (Infectious pneumonia, Fungal infections, Viral herpes, and Skin structure infections). Overall low rates were observed between treatment groups for injection site reactions (HLT) and herpes viral infection (HLT) (secukinumab 150 mg Load group: 3.2%, secukinumab 150 mg No Load group: 1.1%, Any secukinumab: 2.2%, and placebo: 1.6%, for injection site reactions (HLT); secukinumab 150 mg Load group: 2.2%, secukinumab 150 mg No Load group: 1.6%, Any secukinumab: 1.9%, placebo: 1.1%, for herpes viral infections (HLT)). Incidence rates of fungal infectious disorders (HLGT) were similar across treatment groups, and only one case each of Infectious pneumonia (NMQ, broad search) were noted in the secukinumab 150 mg Load group and placebo group. No events for oesophageal candidiasis (narrow search) and mycobacterial infections were reported up to Week 20.

Important identified risks present in both secukinumab and placebo treatment groups included Infections, Hypersensitivity, and Neutropenia, with Infections representing the most frequently reported risk among all risks from the SPP. Comparable rates of Infections and infestations (SOC) were reported across treatment groups (secukinumab 150 mg Load group: 38.4%, secukinumab 150 mg No Load group: 33.2%, Any secukinumab: 35.8%, placebo: 33.3%). Incidence rates of Hypersensitivity (SMQ, narrow search) were also comparable across groups (secukinumab 150 mg Load group: 4.9%, secukinumab 150 mg No Load group: 4.3%, Any secukinumab: 4.6%, placebo: 3.2%). A search of Neutropenia (NMQ, narrow search) yielded comparable rates in the Any secukinumab group compared to placebo.

Important potential risks included malignant or unspecified tumors, MACE, Suicidal ideation and behavior, IBD, Hepatitis B reactivation and Interactions with live vaccines. A search of Inflammatory bowel disease (NMQ, narrow search) for the important potential risk of Crohn's disease revealed one case in the secukinumab 150 mg No Load group of a patient with no prior history of inflammatory disease. A total of seven cases of IBD were reported in the entire study period (5 cases of Crohn’s

disease and 2 cases of ulcerative colitis). Two of the patients had a history of IBD. Three of these cases were reported as SAEs; the other four cases were AEs. Three of the reported AEs were mild or moderate with one event reported as severe (ulcerative colitis). Three of the IBD events resulted in drug discontinuation (two of the SAEs and one AE).

No MACE events were reported in the secukinumab groups. Only one patient in the placebo group reported a MACE event of myocardial infarction.

No cases of Hepatitis B reactivation, Interactions with live vaccines, or Malignancies were found.

One case of attempted suicide occurred off-treatment (44.7 weeks after last dose of secukinumab) in a patient with a previous history of depression and suicide attempt who had switched from secukinumab 150 mg Load to standard of care.

Table 41 ***Absolute and relative frequencies for SPP risks based on all treatment emergent adverse events in study H2315 up to Week 20 (Safety Set)***

Risk Category Risk Name Level 1	AIN457 150 mg Load N=185 n (%)	AIN457 150 mg No Load N=184 n (%)	Any AIN457 N=369 n (%)	Placebo N=186 n (%)
Compound and class-related risk				
Immune/administration reactions				
Injection site reactions (HLT)	6 (3.2)	2 (1.1)	8 (2.2)	3 (1.6)
Infections (Infectious pneumonia)				
Infectious pneumonia (NMQ) (broad)	1 (0.5)	0 (0.0)	1 (0.3)	1 (0.5)
Infections (Fungal)				
Fungal infectious disorders (HLGT)	2 (1.1)	3 (1.6)	5 (1.4)	3 (1.6)
Infections (Herpes viral)				
Herpes viral infections (HLT)	4 (2.2)	3 (1.6)	7 (1.9)	2 (1.1)
Infections (Skin structure)				
Infections of skin structures (NMQ)	9 (4.9)	8 (4.3)	17 (4.6)	7 (3.8)
Important identified risk				
Hypersensitivity				
Hypersensitivity (SMQ) (narrow)	9 (4.9)	8 (4.3)	17 (4.6)	6 (3.2)
Infections				
Infections and infestations (SOC)	71 (38.4)	61 (33.2)	132 (35.8)	62 (33.3)
Neutropenia				
Neutropenia (NMQ) (narrow)	1 (0.5)	3 (1.6)	4 (1.1)	3 (1.6)
Important potential risk*				
Crohns disease				
Inflammatory bowel disease (NMQ) (narrow)	0 (0.0)	1 (0.5)	1 (0.3)	0 (0.0)
Major adverse cardiovascular events (MACE)				
MACE (MI, Stroke, Cardiovascular death) (NMQ)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)

Risk levels are not mutually exclusive.
Preferred terms are sorted within risk level in descending order of frequency in the Any AIN457 column.
A patient with multiple occurrences of a level under one treatment is counted only once for the same risk for that treatment.
*No malignancies (an important potential risk) were reported up to Week 20.

In addition to the same SPP risks reported up to Week 20, additional SPP risks were observed during the period after Week 20. These risks were mainly compound and class-related risks (Central nervous system infections and inflammations, Staphylococcal infections, Malignant or unspecified tumours (except non-melanoma skin cancer (NMSC), and malignant and unspecified skin tumours) and the important potential risk of Malignant or unspecified tumours. The risks reported after Week 20 often occurred in 1-2 patients within a single treatment group. See Table 42.

Table 42 ***Absolute and relative frequencies for SPP risks based on all treatment emergent adverse events in study H2315 - entire treatment period (Safety Set)***

Risk Category Risk Name Level 1	AIN457 150 mg Load N=185 n (%)	AIN457 150 mg No Load N=184 n (%)	Any AIN457 N=543 n (%)	Placebo N=186 n (%)
Compound and class related risk				
Immune/administration reactions				
Injection site reactions (HLT)	7 (3.8)	4 (2.2)	14 (2.6)	3 (1.6)
Infections (Infectious pneumonia)				
Infectious pneumonia (NMQ) (broad)	3 (1.6)	3 (1.6)	7 (1.3)	1 (0.5)
Infections (Central nervous system infections and inflammations)				
Central nervous system infections and inflammations (HLGT)	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Infections (Fungal)				
Fungal infectious disorders (HLGT)	9 (4.9)	11 (6.0)	31 (5.7)	4 (2.2)
Infections (Herpes viral)				
Herpes viral infections (HLT)	9 (4.9)	3 (1.6)	15 (2.8)	3 (1.6)
Infections (Skin structure)				
Infections of skin structures (NMQ)	30 (16.2)	23 (12.5)	67 (12.3)	11 (5.9)
Infections (Staphylococcal)				
Staphylococcal infections (HLT)	0 (0.0)	2 (1.1)	2 (0.4)	0 (0.0)
Malignant or unspecified tumours (except NMSC)				
Malignant or unspecified tumours (SMQ excl BCC and SCC) (NMQ)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Non-melanoma skin cancer (NMSC) (BCC and SCC)				
Non-melanoma skin cancer (BCC and SCC) (NMQ) (broad)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Skin tumours malignant and unspecified				

Risk Category Risk Name Level 1	AIN457 150 mg Load N=185 n (%)	AIN457 150 mg No Load N=184 n (%)	Any AIN457 N=543 n (%)	Placebo N=186 n (%)
Skin tumours malignant and unspecified (NMQ) (broad)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Important identified risk				
Hypersensitivity				
Hypersensitivity (SMQ) (narrow)	19 (10.3)	22 (12.0)	51 (9.4)	8 (4.3)
Infections				
Infections and infestations (SOC)	128 (69.2)	117 (63.6)	324 (59.7)	80 (43.0)
Neutropenia				
Neutropenia (NMQ) (narrow)	2 (1.1)	4 (2.2)	8 (1.5)	3 (1.6)
Important potential risk				
Inflammatory Bowel Disease				
Inflammatory bowel disease (NMQ) (narrow)	3 (1.6)	1 (0.5)	7 (1.3)	0 (0.0)
Interactions with live vaccines				
Vaccination related complications (HLT)	2 (1.1)	0 (0.0)	2 (0.4)	0 (0.0)
Major adverse cardiovascular events (MACE)				
MACE (MI, Stroke, Cardiovascular death) (NMQ)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Malignant or unspecified tumours				
Malignant or unspecified tumours (SMQ)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)

Risk levels are not mutually exclusive.

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

A patient with multiple occurrences of a level under one treatment is counted only once for the same risk for that treatment.

Patients who were randomized to placebo are counted in the placebo group. Only after switch to open label secukinumab, they are also counted in the Any AIN457 treatment group. Thus, the Any AIN457 column includes patients who were exposed to AIN457 treatment at any time.

Immunogenicity

Eight patients showed ADAs, with one of them having a positive result at both baseline and post-baseline. Only one patient was noted to have a treatment-emergent ADA (i.e., negative at baseline and positive post-exposure) at Week 52. Two patients reported AEs that were possibly related to immunogenicity. One patient with ADA detected only at baseline had a non-serious AE (contact

dermatitis) that occurred at Day 522. Another possibly IG-related AE (allergic rhinitis) occurred at Day 525 in the patient with an ADA signal at baseline and post-baseline.

Laboratory findings

Criteria for clinically notable laboratory abnormalities were based on CTCAE grades for the following parameters: heamoglobin, platelets, WBC, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glucose, cholesterol, and triglycerides (TG).

Haematology

Up to week 20, Grade 1 and 2 decreases in haemoglobin and lymphocytes were comparable between the treatment groups. Small numerical differences were observed between treatment groups in Grade 1 leukocyte abnormalities, and Grade 2 leukocyte decreases were infrequent and showed no clinically meaningful differences. No Grade 3 or 4 decreases were reported for haemoglobin, leukocytes, lymphocytes, or platelets. Neutrophil decreases were low in frequency among the Grade 1 and 2 categories. One Grade 3 decrease in neutrophil count was reported in the secukinumab 150 mg Load group and one Grade 4 abnormality was noted in the placebo group. The Grade 3 on-treatment abnormality was deemed related to study drug by the investigator and occurred in a patient with a mild, non-serious upper respiratory tract infection around the same time period. Both the neutropenia and URTI did not require interruption of the study drug. This was a single event occurring early in the study (Week 2). With the exception of a Grade 1 decrease in neutrophil count at Week 52, all other values for this patient before and after Week 2 were within normal range. The Grade 4 abnormality in the placebo patient also occurred at the start of the study (Week 2), with all other values within normal range.

Similar to the data results from the first 20 weeks, most of the haematological abnormalities reported for the entire treatment period were Grade 1 or 2. Among the more severe grades occurring after Week 20, a Grade 3 decrease in lymphocyte count was noted in one patient in the secukinumab 150 mg No Load group. The patient had the following AEs (in chronological order): stomach pain, diarrhoea, IBD, and Crohn's disease starting at Week 16 with Crohn's diagnosis at around the time of the Week 52 visit. The patient entered the study with a lymphocyte cell count screening value of 1 X 109/L, with values below 1 x 109/L for most visits, and no value exceeding 1.3 x 109/L. One new case of a Grade 3 decrease in neutrophil count was reported in a patient who was a placebo-switcher. The Grade 3 neutropenia event resolved without study drug interruption or discontinuation. One case of Grade 3 neutropenia in the AIN457 150 mg Load group, and one case of Grade 4 neutropenia in the placebo group had been reported previously in the first 20 weeks of the study. After Week 20, two new cases of Grade 3 neutropenia were reported in patients who were placebo switchers.

Chemistry

Most of the newly occurring or worsening chemistry laboratory abnormalities up to Week 20 were CTCAE Grade 1 or 2. One Grade 3 AST abnormality was reported each in the secukinumab 150 mg Load group and in the placebo group; there were no Grade 3 or 4 ALT abnormalities. The abnormalities occurring at the highest frequencies among all chemistry parameters were cholesterol and fasting levels of triglycerides. The following shifts in grade of abnormalities were reported:

- An AST shift from normal levels to Grade 3 occurred in one patient in the AIN457 150 mg Load group and in one patient in the placebo group.
- A shift in cholesterol levels from Grade 2 to Grade 3 occurred in one patient in the AIN457 150 mg Load group.

- Decreased fasting serum glucose levels shifted from normal range to Grade 3 in one patient in the AIN457 150 mg No Load group.
- Increased fasting serum glucose levels shifted from Grade 2 to Grade 3 in one patient in the AIN457 150 mg Load group and three patients in the placebo group.
- Triglycerides levels shifted from Grade 2 to Grade 3 in two patients in the AIN457 150 mg Load group and in one patient in the placebo group.

As seen in the data for the first 20 weeks, the majority of patients had values within normal range at baseline with low frequencies of patients shifting to Grade 1 or Grade 2 for the entire treatment period. In addition to the observed shifts in CTCAE grades up to Week 20, the entire treatment period also included shifts in grades for ALT and gamma glutamyl transferase. The additional shifts reported after Week 20 are as follows:

- ALT levels shifted from normal range to Grade 3 in one patient in the secukinumab 150 mg No Load group.
- Additional shifts in AST levels from normal range to Grade 3 were reported after Week 20 in two patients in the secukinumab 150 mg Load group, one patient in the secukinumab 150 mg No Load group and one placebo-switcher.
- A shift from Grade 2 to Grade 3 in cholesterol levels was reported in one patient in the AIN457 150 mg Load group during the first 20 weeks. After Week 20, no additional shifts in cholesterol levels were reported.
- Gamma glutamyl transferase levels had shifted from Grade 1 to Grade 3 in one patient in the AIN457 150 mg Load group, from normal range to Grade 3 in two patients in the AIN457 150 mg No Load group, and from Grade 2 to Grade 3 in one patient in the placebo group.
- Decreased fasting serum glucose levels shifted from normal range to Grade 4 in one patient in the AIN457 150 mg Load group and from Grade 1 to Grade 4 in one patient in the AIN457 150 mg No Load group. A shift from normal range to Grade 3 was reported in the placebo group. A shift from normal range to Grade 3 was previously reported in a patient in the AIN457 150 mg No Load group during the first 20 weeks of the study.
- Increased fasting serum glucose levels shifted from Grade 1 to Grade 3 in two patients in the AIN457 150 mg Load group. Shifts from Grade 2 to Grade 3 in one patient in the AIN457 150 mg Load group and in three patients in the placebo group were reported previously in the first 20 weeks.
- Fasting levels of triglycerides shifted from normal range to Grade 3 in the AIN457 150 mg Load and the AIN457 150 mg No Load groups (one patient in each group). One patient in the AIN457 150 mg Load group experienced a shift from Grade 1 to Grade 3. Shifts from Grade 2 to Grade 3 in two patients in the AIN457 150 mg Load group and in one patient in the placebo group were reported during the first 20 weeks of the study.

Abnormalities in AST levels were observed at > 3 x ULN and > 5 x ULN. There were no patients with AST levels > 8 x ULN. As seen for Week 20, four patients reported total bilirubin (TBL) > 1.5 x ULN only in the secukinumab group. Increased alkaline phosphatase (ALP) levels were also reported during the entire treatment period in the AIN457 150 mg No Load group (one patient each at ALP levels > 2 x ULN, and > 3 x ULN). No patient met the laboratory criteria for Hy's Law.

Vital signs

Rates of elevated systolic blood pressure were similar between all groups (secukinumab 150 mg Load group: 18.0%, secukinumab 150 mg No Load group: 19.7%, Any secukinumab group: 18.9%, and placebo: 19.0%).

Elevations were more frequent than decreases in diastolic blood pressure for all treatment groups. Diastolic blood pressure increases were higher in the secukinumab 150 mg No Load group (19.1%) compared to the secukinumab 150 mg Load group (15.1%), and placebo (16.8%). Decreases in diastolic blood pressure were higher in the secukinumab groups compared to placebo (secukinumab 150 mg Load group: 5.5%, secukinumab 150 mg No Load group: 5.6%, Any secukinumab group: 5.5%, and placebo: 4.3%).

Decreases in pulse rate (secukinumab 150 mg Load group: 14.6%, secukinumab 150 mg No Load group: 13.0%, Any secukinumab group: 13.9%, and placebo: 14.0%) were more frequent than elevated pulse rates (secukinumab 150 mg Load group: 2.2%, secukinumab 150 mg No Load group: 3.3%, Any secukinumab group: 2.7%, and placebo: 3.2%) for all treatment groups. Both elevated and decreased pulse rates were similar across treatment groups.

Observed trends in the entire treatment period were similar to those seen up to Week 20.

There were no clinically significant ECG abnormalities reported for this interim analysis.

Safety in special populations

Intrinsic factors analysed included age, gender, race, and weight while extrinsic factors included prior use of TNF-alpha inhibitors, concomitant use of methotrexate, and concomitant use of corticosteroids.

Since the number of patients were highly imbalanced between age groups (<65, ≥65), no meaningful comparisons could be made between the two age groups. However, the reported AEs by SOC were similar to that of the overall population and consistent between data up to Week 20 and data up to Week 52.

The reported AEs by SOC for each of the subgroups (males, females) were similar to that of the overall population and consistent between data up to Week 20 and data up to Week 52.

Since the number of patients were highly imbalanced between race groups with over 90% of the population being White, no meaningful comparisons could be made between the various race groups. However, the reported AEs by SOC were similar to that of the overall population and consistent between data up to Week 20 and data up to Week 52.

Among the three weight subgroups, the highest incidence rates of AEs for secukinumab were reported in the >90 kg subgroup and the lowest incidence rates of AEs for secukinumab reported in the 70-90 kg subgroup, with higher incidence rates in the secukinumab group compared to placebo in all three groups. The reported AEs were similar to that of the overall population and consistent between data up to Week 20 and data up to Week 52.

The mean duration of exposure was longer in inadequate responders to TNF-alpha inhibitors compared to TNF-alpha inhibitor naive patients (Any secukinumab for inadequate responders: 481.1 days vs. naive patients: 402.5 days). Similar to the initial 20-week period, since the majority of patients in the study were naive to TNF-alpha inhibitor treatment, the trends observed in the incidence rates of AEs and SAEs in this subgroup up to Week 52 were similar to that of the overall population. The reported AEs and SAEs in both subgroups were consistent with that of the overall population.

As observed in the first 20 weeks, since the majority of patients in the study did not take MTX, the patterns of AEs and SAEs reported for MTX non-users up to Week 52 were similar to that of the overall population. Reported AEs in both subgroups were consistent with that of the overall population.

The mean duration of exposure was longer in corticosteroid users compared to corticosteroid non-users (Any secukinumab for corticosteroid users: 433.0 days vs. non-users: 407.6 days). Similar to Week 20, as the majority of patients in the study were not concomitant corticosteroid users, the patterns of AEs and SAEs observed in this subgroup were similar to that of the overall population. The reported AEs and SAEs in both subgroups were consistent with those in the overall population.

Safety related to drug-drug interactions and other interactions

The majority of patients in the study did not take MTX or sulfasalazine (90.1% and 85.2% of the total population); therefore, the patterns of AEs and SAEs reported for MTX or sulphasalazine non-users were similar to that of the overall population. The profile of AEs in each of these subgroups was consistent with that observed for the overall population for both the 20-week and 52-week treatment periods. Thus, concomitant MTX or sulfasalazine use does not change the safety profile of secukinumab in patients with nr-axSpA based on this study.

Discontinuation due to adverse events

All reasons for discontinuation from the study before week 24 are listed in Table 43.

Table 43 ***Patient disposition at Week 24 in Study H2315 (Randomized Set)***

Disposition/Reason	AIN457 150 mg Load N=185 n (%)	AIN457 150 mg No Load N=184 n (%)	Placebo N=186 n (%)	Total N=555 n (%)
Completed Week 24	175 (94.6)	177 (96.2)	175 (94.1)	527 (95.0)
Discontinued before or at Week 24	10 (5.4)	7 (3.8)	11 (5.9)	28 (5.0)
Primary reason for discontinuing				
Adverse event	2 (1.1)	4 (2.2)	2 (1.1)	8 (1.4)
Lack of efficacy	2 (1.1)	1 (0.5)	2 (1.1)	5 (0.9)
Lost to follow-up	0	1 (0.5)	1 (0.5)	2 (0.4)
Physician decision	1 (0.5)	0	1 (0.5)	2 (0.4)
Protocol deviation	1 (0.5)	0	0	1 (0.2)
Patient/guardian decision	4 (2.2)	1 (0.5)	5 (2.7)	10 (1.8)

For the entire treatment period, the incidence of **AEs causing study drug discontinuation** was higher in the secukinumab 150 mg No Load group compared to the secukinumab 150 mg Load group and placebo (secukinumab 150 mg No Load group: 7.1% vs. secukinumab 150 mg Load group: 3.8% and placebo: 1.6%). Refer to Table 46.

Table 44 ***Treatment-emergent adverse events leading to discontinuation by preferred term irrespective of causality in study H2315 entire treatment period (Safety Set)***

Preferred term	AIN457 150 mg Load N=185 n (%)	AIN457 150 mg No Load N=184 n (%)	Any AIN457 N=543 n (%)	Placebo N=186 n (%)
Any preferred term	7 (3.8)	13 (7.1)	24 (4.4)	3 (1.6)
Axial spondyloarthritis	2 (1.1)	0 (0.0)	2 (0.4)	0 (0.0)
Diarrhoea	0 (0.0)	2 (1.1)	2 (0.4)	1 (0.5)
Pregnancy†	0 (0.0)	2 (1.1)	2 (0.4)	0 (0.0)
Abdominal pain	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Ankylosing spondylitis	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Arthralgia	0 (0.0)	1 (0.5)	1 (0.2)	1 (0.5)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Colitis*	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Colitis ulcerative	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Conjunctivitis	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
IgA nephropathy	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Intervertebral disc disorder	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Liver function test increased	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Malignant melanoma	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Myelopathy	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Neuropathy peripheral	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Oral candidiasis	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Polydipsia	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Psoriasis	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Pyrexia	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Rhinitis	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Skin disorder	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Skin infection	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Subcutaneous abscess	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Unintended pregnancy	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Injection site reaction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)

A patient with multiple adverse events within a preferred term is counted only once in the total row.
Preferred terms are presented by descending frequency in the Any AIN457 group.
Patients who were randomized to placebo are counted in the placebo group. Only after switch to open label secukinumab, they are also counted in the Any AIN457 treatment group. Thus, the Any AIN457 column includes patients who were exposed to AIN457 treatment at any time.
*The colitis SAE was confirmed after DBL to be Crohn's disease (see Section 12.3.6.4).
†Pregnancies were reported as being discontinued due to pregnancy, and not discontinued due to AE; therefore, these events have not been included in the narratives.

AEs leading to temporary dose interruption up to Week 20 were reported at similar rates in the secukinumab dose groups and placebo (Any secukinumab group: 8.7% vs. placebo: 7.5%). Similar rates were also observed between the secukinumab treatment groups (secukinumab 150 mg Load group: 8.1% and secukinumab 150 mg No Load group: 9.2%). The most commonly affected SOC was Infections and infestations, occurring at incidence rates of 4.6% in the Any secukinumab group and 4.8% in the placebo group.

Over the entire treatment period, AEs leading to temporary interruption of study treatment were reported at a similar frequency in the secukinumab groups compared to placebo (Any secukinumab: 14.5% vs. placebo: 8.1%) when taking into account the difference in terms of patient years of exposure. Due to

the greater number of patient years (approximately 5 times more) in the secukinumab group than the placebo group for the entire treatment period, these crude rates, when adjusted, would reflect a higher frequency in the placebo group compared to the secukinumab group. Higher incidence rates were reported in the secukinumab 150 mg Load group compared to the secukinumab 150 mg No Load group (21.6% vs. 13.6%, respectively). The majority of dose interruptions were caused by AEs in the SOC Infections and infestations (Any secukinumab group: 8.8% vs. placebo: 4.8%). The majority of Infections and infestations reported in the secukinumab groups were nasopharyngitis (6 events), upper respiratory tract infection (5 events), urinary tract infection (5 events), and pharyngitis (4 events). In the placebo group, only single events occurred within the Infections and infestations SOC.

Post marketing experience

Cosentyx was first registered in Japan on 26 Dec 2014. Through the end of this reporting interval, Novartis (including Sandoz and Alcon) has obtained approvals in 92 countries worldwide (including 31 European Union/European Economic Area [EU/EEA] countries through European Medicines Agency [EMA] approval). Cosentyx is registered in the following indications:

- Moderate to severe plaque psoriasis
- Psoriatic arthritis
- Ankylosing spondylitis
- Pustular psoriasis (Japan only)

The combined exposure to secukinumab and comparators from both completed studies and ongoing studies with interim analysis database locks up to 25 Dec 2018 is presented in Table 47.

Table 45 ***Combined subject exposure to secukinumab by age and gender from both completed studies and ongoing studies with interim analysis database locks***

Age range (years)	Number of subjects*	
	Female	Male
age <18	0	4
age >/=18 and </=65	6,658	10,007
age >65 and </=75	586	532
age >75	81	74

*Includes patients and a small number of healthy volunteers, as of 25 Dec 2018.

An estimate of patient exposure is calculated based on worldwide sales volume in kilograms (kg) of active substance sold during the reporting interval and the average maintenance daily dose (10 mg). The sales volume of Cosentyx during the reporting interval was approximately 501.2 kg (active substance).

The estimated interval exposure was approximately 137,325 patient-treatment years (PTY). During the interval covered by the previous PSUR (26 Dec 2016 to 25 Dec 2017), the estimated cumulative exposure was approximately 148,485 PTY.

The cumulative patient exposure since the International Birth Date of the product is estimated to be approximately 285,811 PTY. Refer to table 48.

Table 46 ***Exposure in patient years from marketing experience by region***

	EU (incl. EEA and CH)	USA and CA	Japan	ROW	Total
Previous cumulative exposure (until 25 Dec 2017 as per PSUR 26 Dec 2016 to 25 Dec 2017)	44,378	34,937	3,794	10,635	**93,744**
Revised figures for previous cumulative exposure*	66,055	60,933	6,993	14,504	**148,485**
Interval exposure	62,674	50,825	2,670	21,156	**137,325**
Cumulative exposure	128,729	111,758	9,664	35,660	**285,811**

Source of data: worldwide sales volume.

EU: European Union; EEA: European Economic Area; CH: Switzerland; USA: United States; CA: Canada; ROW: Rest of world

2.5.1. Discussion on clinical safety

The MAH has evaluated the safety profile of secukinumab and placebo in study H2315 dividing it to two phases, the initial 20 weeks (including all the patients on placebo) and the entire treatment period (some placebo patients converted to secukinumab). In addition, the MAH has pooled safety findings from 9 placebo controlled phase III studies in non-radiographic axial spondylarthritis, ankylosing spondylitis, psoriasis and psoriatic arthritis in order to evaluate the need to update the SmPC section 4.8.

The total exposure of secukinumab in non-radiographic axial spondylarthritis in the interim analysis at week 52 was 286.1 patient-years for the AIN457 150 mg Load group, 291.3 patient-years for the AIN457 150 mg No Load group, 757.9 patient-years for the Any AIN457 group, and 109.3 patient-years for the placebo group. The median secukinumab exposure per patient was roughly 540 days and for placebo 145 days. The CHMP is of the opinion that this provides a sufficient dataset for the safety evaluation.

A slightly elevated incidence of infections in the secukinumab groups was observed compared to the placebo group. Patients with loading regimen appeared to have a slightly elevated incidence of upper respiratory tract infections, diarrhoea, headache, oropharyngeal pain, nausea, and urinary infections compared to non-loading regimen. The increased frequency of infections seems to have increased the need for temporary dose interruptions in the loading secukinumab group. The AE profile during the initial 20-week observation period resembled closely the AE profile in the initial psoriasis submission. Compared to the previous ankylosing spondylitis submission and the initial 16 or 20 week phase with placebo group, the incidence of AEs in different organ classes appeared quite similar, if not less severe.

For the entire treatment period, the differences between the loading and non-loading groups diminished, as the exposures approach each other. Exposure adjusted incidence rates of most of the AEs (preferred terms) did not significantly differ between the secukinumab and placebo groups. There were no new significant AE findings.

Based on the pooled data analysis, from nine randomised phase III studies in psoriasis, ankylosing spondylitis, psoriatic arthritis, and non-radiographic axial spondylarthritis, the SmPC section 4.8 was considered to be up to date except for the change in frequency for "Tinea pedis" from uncommon to common frequency class. This change was acceptable to CHMP.

There were no deaths in study H2315.

Serious adverse events were reported from 10.8%, 6.5%, and 4.3% of patients in loading dose group, non-loading dose group, and placebo group, respectively, during the entire treatment period. SAEs were reported mostly as single occurrences randomly observed from each treatment group.

A total of seven cases of IBD were reported in the entire study period (5 cases of Crohn's disease and 2 cases of ulcerative colitis). Two of the patients had a history of IBD. Three of these cases were reported as SAEs; the other four cases were AEs. One case of Crohn's disease and two cases of ulcerative colitis were considered attributable to secukinumab treatment and resulted in discontinuation. IBD and IL-17 antagonists are currently under evaluation. One suicide attempt took place in a patient 10 months after last secukinumab dose, not implying to a causal relationship. Malignant melanoma was observed in one patient switching from placebo to secukinumab resulting in discontinuation from the study. These findings are not considered of concern or requiring changes to the RMP or SmPC.

The immunogenic potential of secukinumab appeared negligible, as it has been also earlier. There were no new findings regarding the effects of secukinumab on the haematology or chemistry laboratory findings, or vital signs.

The subgroup analyses (intrinsic factors: age <65 or ≥65 years, gender, race, or weight 70-90 or >90 kg, or extrinsic factors: TNF-alpha naïve or non-responders, concomitant MTX or sulphasalazine yes or no, concomitant corticosteroids yes or no) did not reveal any meaningful differences between the subgroups in the AE/SAE profiles.

The discontinuation rates during the initial 24 weeks were 5.4%, 3.8%, and 5.9% in loading secukinumab group, non-loading secukinumab group, and the placebo group, respectively. 2, 4, and 2 patients, respectively, discontinued due to AEs. For the entire study, the discontinuations due to AEs took place in 3.8%, 7.1%, and 1.6% in loading secukinumab group, non-loading secukinumab group, and the placebo group, respectively.

Somewhat higher rates of temporary dose interruptions were reported in the loading secukinumab group compared to the non-loading secukinumab group (21.6% vs. 13.6%, respectively), mainly attributable to the slightly more frequent infections in the loading secukinumab group.

Judged from the discontinuation rates or temporary dose interruption rates, the CHMP concluded that there seems to be no clinically significant difference between the loading or non-loading regimens regarding the tolerability.

2.5.2. Conclusions on clinical safety

The AE and ADR profile of secukinumab is well established from the clinical studies submitted for the already approved indications. There were no new safety concerns identified in the current submission aimed at treatment of moderate to severe non-radiographic axial spondylarthritis. The SmPC section 4.8 was updated to change the frequency for "Tinea pedis" from uncommon to common frequency.

Long term follow-up safety data in the applied for indication is currently lacking. However, this is alleviated by the fact, that there is an extensive database on long term safety follow-up in the approved indications and that the clinical use has been extensive.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive

2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan: the PRAC considered that the risk management plan version 5.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 5.1 with the following content:

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

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

Safety concern	Risk minimization measures	Pharmacovigilance activities
Long-term efficacy data	**Routine risk minimization measures** None proposed **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Use in pediatric patients	**Routine risk minimization measures** SmPC Section 4.1, 4.2 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Patients with severe hepatic impairment	**Routine risk minimization measures** None **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Patients with severe renal impairment	**Routine risk minimization measures** None **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Patients with severe cardiac disease or uncontrolled hypertension	**Routine risk minimization measures** None proposed **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

2.7. Update of the Product information

As a result of this group of variations, sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC are being updated to reflect the extension of indication. The Package Leaflet (PL) is updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- A full user test was performed and found acceptable for the original application of Cosentyx (secukinumab) in the indication of plaque psoriasis. Two additional full user tests of the Cosentyx

PL were performed during the registration of the psoriatic arthritis (PsA) and ankylosing spondylitis (AS) indications.

- The approved Cosentyx PL has now been updated with information related to the new proposed indication of nr-axSpA. The changes proposed to be included in the PL are minor and limited to the following:
    - the indication wording, which is comparable to wording for compounds already approved for the nr-axSpA indication in Europe (Humira/adalimumab, Enbrel/etanercept, Cimzia/certolizumab and Simponi/golimumab),
    - the posology wording, which is the same as the one tested in 2015 for the AS indication, and
    - the change in frequency of one side effect (tinea pedis), a term which was already included in the Cosentyx PL at the time of the previous user testing consultations performed in 2014 and 2015.
- Given that the proposed changes to the PL are not significant and were either already tested in a previous user consultation of the PL or are already used in approved PLs available on the market for the same indication, a new user consultation is not deemed necessary.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The concept of spondyloarthritis (SpA) as described in the EU Guideline (EMA/CPMP/EWP/4891/03 Rev.1, Corr 1) comprises a group of diseases which share common clinical and genetic features, and includes ankylosing spondylitis (AS), psoriatic arthritis, arthritis/spondylitis with inflammatory bowel disease, reactive arthritis, as well as undifferentiated SpA. All of these can present with a predominantly peripheral or axial arthritis.

Axial SpA (axSpA) is defined as a chronic inflammatory disease that involves primarily the sacroiliac joints and the axial skeleton. Clinical manifestations usually begin in late adolescence or early adulthood (mean age of onset 26 years) and onset after age 45 is rare. Clinical manifestations include lower back pain with predominant nocturnal pain, morning stiffness and impaired physical function. Also chest pain, pain and swelling of peripheral joints and extra-articular tenderness may occur as well as several extra-skeletal manifestations such as anterior uveitis, psoriasis, and inflammatory bowel disease.

The diagnosis of ankylosing spondylitis, the most frequent subtype of axial SpA, requires the presence of radiographic sacroiliitis. However, it is now well established that patients with axial SpA who do not meet radiographic criteria for sacroiliitis may experience a significant burden of disease that is comparable to patients with well-defined AS. The 2009 ASAS criteria thus define the entity of axial spondyloarthritis (axial SpA) which includes a broader set of patients than the original 1984 criteria for AS. The new group is captured under the term "non-radiographic axial SpA" and can be identified by the presence of clinical features of axial SpA combined with either "imaging" evidence (active sacroiliitis seen on the MRI scan) or HLA-B27 positivity ("clinical arm").

The prevalence of axial SpA (including AS and non-radiographic forms) is estimated to be 0.3-0.8%. The prevalence of AS is estimated around 0.1 % - 0.5 % of the European population. While AS is more common in males (male to female ratio is estimated to be 2-3:1), women are slightly more often

affected compared to men in the nr-axSpA stage. AxSpA tends to be more severe in men, in whom the spine is more frequently involved.

3.1.2. Available therapies and unmet medical need

According to clinical guidelines, physical therapy and non-steroidal anti-inflammatory drugs (NSAIDs) comprise the first line treatment in axial SpA. Physical therapy has a positive effect on stiffness and on spinal mobility and even on pain. NSAIDs are used to control pain with good response in up to 50-70% of axial SpA patients, and due to their high symptomatic efficacy and possible disease-modifying properties, NSAIDs are considered the treatment of choice for the majority of patients with axial SpA and if tolerated, these are usually maintained as background therapy in patients with insufficient response.

Several biological products, including anti-TNF agents and secukinumab, are authorised for use in patients with AS who continue to have active disease despite NSAIDs. In Europe, several anti-TNF agents (adalimumab, certolizumab pegol, etanercept and golimumab) are also authorised for nr-axSpA with objective signs of inflammation; in the US, only certolizumab pegol is authorised for nr-axSpA.

Whereas anti-TNF agents have been shown to be efficacious in the treatment of nr-axSpA, a substantial proportion of patients do not show a good therapeutic response to these agents. The impact of these agents on axSpA-associated structural damage and diseases progression also remains to be established. There remains a need for new therapies, including therapies with alternative mechanisms of action beyond TNF inhibition.

3.1.3. Main clinical studies

This single study submission comprises a clinical study report from an ongoing randomised, placebo-controlled Phase 3 study assessing the efficacy, safety and tolerability of two different regimens of secukinumab, 150 mg with loading and without loading, compared to placebo in patients with nr-axSpA. The MAH is not applying for authorisation for the regimen without loading.

The study population consisted of adult patients fulfilling the ASAS classification criteria for nr-axSpA and active disease despite treatment with NSAIDs, as evidenced by an abnormal CRP value and/or evidence of inflammation in the sacroiliac joints (SI-joints) on MRI. A limited number of patients who had experienced an inadequate response to a TNF inhibitor were enrolled into the study.

3.2. Favourable effects

Reported pharmacokinetic and immunogenicity data from study H2315 are consistent with previous observations within other secukinumab development programmes.

In the primary analysis at Week 16, secukinumab 150 mg Load was superior to placebo in the ASAS40 response using non-responder imputation in TNF-alpha naïve patients with active nr-axSpA (41.5% vs. 29.2%; p=0.0197).

The result on the primary endpoint is supported by analyses of secondary endpoints, where both secukinumab groups consistently demonstrated efficacy on variables related to inflammation and disease activity, function and health-related quality of life.

In an ancillary analysis based on Analysis Plan B, maintenance of effect until Week 52 was demonstrated based on the primary endpoint as well as most secondary endpoints.

3.3. Uncertainties and limitations about favourable effects

Based on the reported data and consistent with observations in AS patients, response rates were higher for secukinumab vs. placebo in both TNF-naïve and TNF-IR patients. Due to the small sample size, observations in the TNF-IR nr-axSpA subpopulation need to be viewed with considerable caution. However, as the reported data is based on a conservative non-responder imputation, even the limited dataset was considered by the CHMP to generally support efficacy in TNF-IR patients at Week 16.

Furthermore, it is currently unknown whether a nr-axSpA patient responding well to therapy should be treated indefinitely, or whether discontinuation of treatment can be considered at some point. This question is currently being explored in clinical trials with several TNF inhibitors. Considering that secukinumab would represent a new mechanism of action in the treatment of active nr-axSpA, the MAH has committed, based on CHMP's recommendations, to conducting an adequately designed clinical trial (with a randomised withdrawal design) with the goal to assess whether treatment in a well responding nr-axSpA patient should be continued indefinitely. In accordance with the current EU Guideline, the CHMP agreed that this study can be conducted in the post-approval setting.

3.4. Unfavourable effects

The AE and ADR profile of secukinumab is well established from the clinical studies submitted for the already approved indications.

There were no new safety concerns identified in the current submission aimed at treatment of active non-radiographic axial spondylarthritis.

The SmPC section 4.8 was updated to change the frequency for "Tinea pedis" from uncommon to common frequency.

The RMP was updated to change the due date of the Psoriasis Registry (category 3 study). This was considered acceptable.

3.5. Uncertainties and limitations about unfavourable effects

Long term follow-up safety data in the applied for indication is currently lacking. However, this is alleviated by the fact, that there is an extensive database on long term safety follow-up in the approved indications and by the extensive clinical use available to date.

3.6. Effects Table

Table 47 ***Effects Table for Cosentyx in the treatment of active non-radiographic axial spondylarthritis (data cut-off: 17 December 2018). Data is presented only for the posology being applied for (secukinumab 150 mg with a loading regimen)***

Effect	Short description	Unit	Secukinumab 150 mg Load	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
ASAS40 TNF-naïve Wk 16	% TNF-naïve patients achieving ASAS40 response at Week 16	%	41.5%	29.2%	p=0.0197 (using non-responder imputation)	Study H2315

Effect	Short description	Unit	Secukinumab 150 mg Load	Placebo	Uncertainties / Strength of evidence	References
Overall ASAS40 Wk 16	% randomised patients achieving ASAS40 response at Week 16	%	40.0%	28.0%	p=0.0108 (using non-responder imputation)	Study H2315
BASDAI50 Wk 16	% patients achieving BASDAI50 response at Week 16	%	37.3%	21.0%	p=0.0001 (using non-responder imputation)	Study H2315
hsCRP Wk 16	Week16/Baseline ratio of hsCRP concentration	Ratio	0.64	0.91	p=0.0002 (MMRM)	Study H2315
MRI SI joint oedema Wk 16	Change from screening to Week 16 on score for MRI assessment of SI joint oedema	Units on a scale from 0 to 24	-1.68	-0.39	p<0.0001 (ANCOVA, multiple imputation)	Study H2315
BASFI change Wk 16	Change from baseline to Week 16 in BASFI score	Units on 0-10 scale	-1.75	-1.01	p=0.0041 (MMRM)	Study H2315
ASDAS-CRP Inactive disease Wk 16	% patients reaching ASDAS-CRP Inactive disease at Week 16	%	20.5%	8.1%	Exploratory endpoint	Study H2315
SF-36 PCS Wk 16	Change from baseline to Week 16 in SF-36 PCS score	Units on a norm-based score	5.71	2.93	p=0.0006 (MMRM)	Study H2315
ASQoL Wk 16	Change from baseline to Week 16 in ASQoL score	Units on a 0-18 scale	-3.45	-1.84	p=0.0008 (MMRM)	Study H2315
Unfavourable Effects						
Infectious AE's by Wk 20	Number (%) of patients with AE in SOC Infections by Week 20	N (%)	70 (37.8%)	61 (32.8%)		Study H2315
SAE rate by Wk 52	Number (%) of patients with SAE (entire treatment period)	N (%)	20 (10.8%)	8 (4.3%)	Exposure-adjusted incidence rates are similar between treatment groups	Study H2315
AE discont. Rate by Wk 52	Number (%) patients discontinuing due to an AE (entire	N (%)	7 (3.8%)	3 (1.6%)	Exposure-adjusted incidence rates are similar between	Study H2315

Effect	Short description	Unit	Secukinumab 150 mg Load	Placebo	Uncertainties / Strength of evidence	References
	treatment period)				treatment groups	

Abbreviations: AE: Adverse Event; ANCOVA: Analysis of covariance; ASAS: Assessment of Spondyloarthritis International Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; ASQoL: Ankylosing Spondylitis Quality of Life; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; hsCRP: High sensitivity C-reactive protein; MMRM: Mixed-effect model repeated measures; MRI: Magnetic resonance imaging; PCS: Physical component summary score; SAE: Serious Adverse Event; SF-36: Short Form-36; SOC: System Organ Class in MedDRA; TNF: Tumour Necrosis Factor

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

It seems well established that patients with active nr-axSpA despite treatment with NSAIDs experience a persistent burden from the disease, and currently available TNF inhibitors are not universally effective in the treatment of nr-axSpA. As such, there remains a need for new therapies in this indication, where secukinumab represents a new mechanism of action.

In the current study, robust demonstration of efficacy was obtained at Week 16 across symptomatic and functional aspects of nr-axSpA, and MRI and hsCRP data support a direct effect on the inflammatory component of the disease. A beneficial effect was also seen on quality of life. In an ancillary analysis based on Analysis Plan B, maintenance of effect until Week 52 was demonstrated based on the primary endpoint as well as most secondary endpoints.

Despite the very small number of TNF-IR patients enrolled in the study, data demonstrating activity in TNF-IR patient supports consideration of secukinumab as a valuable treatment option for such patients.

The potential unfavourable effects of secukinumab are already well established based both on clinical trials in other indications as well as its clinical use in the post-marketing setting. No new signals or safety concerns have been identified in the current study.

3.7.2. Balance of benefits and risks

Data presented by the MAH demonstrates the efficacy of secukinumab in the "*treatment of active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs)*", and the safety profile is in line with the known safety profile for Cosentyx. Consequently, the benefit-risk balance is considered positive.

3.8. Conclusions

The overall B/R of Cosentyx is positive.

4. Recommendations

Outcome

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

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	I and IIIB

Grouping of two variations:
One type II variation II C.I.6.a: Extension of indication to include the treatment of active non-radiographic axial spondyloarthritis for Cosentyx. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 of the SmPC are amended. The package leaflet is amended in accordance. The RMP has been updated to version 5.1. Minor editorial change was made in the Annex II.
One type IB C.I.11.z to change the due date of the Psoriasis Registry (category 3 study) within the RMP.

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

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Cosentyx-EMEA-H-C-003729-II-0053-G'