20 November 2014
EMA/CHMP/389874/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cosentyx

International non-proprietary name: secukinumab

Procedure No. EMEA/H/C/003729

Note

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

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Administrative information

Name of the medicinal product:	Cosentyx
Applicant:	Novartis Europharm Ltd Frimley Business Park, Camberley GU16 7SR United Kingdom
Active substance:	secukinumab
International Nonproprietary Name/Common Name:	secukinumab
Pharmaco-therapeutic group (ATC Code):	Secukinumab (L04AC10)
Therapeutic indication(s):	Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy
Pharmaceutical form(s):	Powder for solution for injection; Solution for injection in pre-filled pen; Solution for injection in pre-filled syringe
Strength(s):	150 mg

Route(s) of administration:	Subcutaneous use
Packaging:	syringe (glass) and vial (glass)
Package size(s):	1 pre-filled pen, 2 pre-filled pens, 1 pre-filled syringe, 2 pre-filled syringes and 1 vial

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List of abbreviations

ACR	American College of Rheumatology
ADA	anti-drug antibodies
ADR	adverse drug reaction
AE	Adverse Event
AI	autoinjector/pen
ANCOVA	analysis of covariance
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AS	ankylosing spondylitis
AST	aspartate aminotransferase
AV	atrioventricular
BSA	body surface area
Cav	average concentration
CCV	cardiovascular/cerebrovascular
CHO	Chinese hamster ovary
Cmax	maximum serum concentration after a single dose
CMH	Cochran-Mantel-Haenszel
CRF	case report/record form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLQI	Dermatology Life Quality Index
dPGA	dynamic Physician's Global Assessment
ECG	electrocardiogram
EQ-5D	EuroQOL 5-Dimension Health Questionnaire©
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
FI	fixed interval dosing
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HA	health authority
HAQ-DI	Health Assessment Questionnaire©-Disability Index
HRQoL	health-related quality of life
hBD-2	human beta defensin-2
HLT	high level term
hsCRP	high sensitivity C-reactive protein
IBD	inflammatory bowel disease
IGA	Investigator's Global Assessment
IGA mod 2007	IGA scale used in part of the phase II program, 6-point scale
IGA mod 2009	IGA scale used in part of the phase II program, 6-point scale
IGA mod 2011	IGA scale used in the phase III program, 5-point scale
IgG	Immunoglobulin G
IL-17	interleukin 17
IR	incomplete responder

Ir	incidence rate
i.v.	intravenous(ly)
LDL	low-density lipoprotein
LYO	Lyophilisate in vial
mAB	monoclonal antibody
MACE	major adverse cardiovascular event
MCID	minimal clinically important difference
NAFL	non-alcoholic fatty liver disease
NICE	National Institute for Health and Clinical Excellence
NMQ	Novartis MedDRA Query
PASI	Psoriasis Area and Severity Index
PAR	Proven acceptable ranges
PD	pharmacodynamics
PFS	pre-filled syringe
PK	pharmacokinetics
PsA	psoriatic arthritis
PUVA	psoralen and UVA
q4w	dosing once every four weeks
ROC	receiver-operator characteristic
SAE	Serious Adverse Event
SBP	Summary of Biopharmaceutics
s.c.	subcutaneous(ly)
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SCP	Summary of Clinical Pharmacology
SMQ	Standardized MedDRA Query
SOC	system organ class
SoR	start of relapse (synonymous with retreatment as needed)
ss	steady state
TB	tuberculosis
TBL	total bilirubin
Th17	T helper 17 cell
TNFα	tumor necrosis factor alpha
UGT	UDP glucuronosyltransferase
ULN	upper limit of normal
VAS	visual analog scale

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Ltd submitted on 23 October 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Cosentyx, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 February 2013.

The applicant applied for the following indication:" treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA".

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that secukinumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/154/2009 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/154/2009 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

New active substance status

The applicant requested the active substance secukinumab contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific advice

The applicant received Scientific Advice from the CHMP on 17 March 2011. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer of the active substance

Novartis Pharma S.A.S.
Centre de Biotechnologie
8, rue de l'Industrie
F-68330 Huningue
France

Manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

1.3. Steps taken for the assessment of the product

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

Rapporteur: Janne Komi Co-Rapporteur: Kristina Dunder

- The application was received by the EMA on 23 October 2013.
- The procedure started on 20 November 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 February 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 7 February 2014.
- During the meeting on 6 March 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 20 March 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 March 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 July 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 August 2014.
- During the CHMP meeting on 25 September 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 October 2014.
- During the meeting on 6 November 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 20 November 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Cosentyx.

2. Scientific discussion

2.1. Introduction

Problem statement

Psoriasis is one of the most common human skin diseases affecting 2 to 3% of the general population. It is characterized by increase in epidermal thickness, hyperkeratosis, parakeratosis, dilated blood vessels, and dense clusters of inflammatory T-cells and dendritic cells in the dermis, and neutrophils and $CD8^+$ T-cells in the epidermis. IL-17A directly activates in synergy with other cytokines (such as TNFα, IFNγ or IL-22) keratinocytes and dermal fibroblasts to produce cytokines (e.g. IL-6, TNFα, IL-1β, IL-20 family cytokines, GM-CSF), chemokines (CXCL1, CXCL2, CCL20, CXCL8/IL-8) and anti-microbial peptides. This leads to the recruitment of inflammatory cells such as neutrophils and lymphocytes (e.g. Th17 cells) into the psoriatic lesion thereby maintaining and amplifying local inflammation. Psoriatic arthritis (PsA) is an inflammatory rheumatic disorder occurring in psoriatic patients. IL-17A mRNA and/or protein levels are increased psoriasis and psoriatic arthritis (in synovial tissue lysates). An increased numbers Th17 cells in the periphery have been reported in PsA patients. Genome-wide associations studies in psoriasis patients have identified several risk alleles for genes associated within the IL-23/Th17 axis and IL-17 signalling pathway downstream of the IL-17 receptor (TRAF3IP2 encoding the adapter protein Act1/CIKS). Knock-out mouse studies indicate that IL-17A plays an important role in autoimmune diseases including collagen induced arthritis. IL-17A, a soluble pro-inflammatory cytokine belongs to the IL-17 cytokine family. IL-17A is produced by CD4 T cell derived Th17 cells which are part of the adaptive immune response. IL-17A is also secreted by CD8+ T-cells, γδ T-cells, and a fraction of natural killer cells. In some pathological conditions humans cells of the innate immune system, such as macrophages, astrocytes, mast cells and neutrophils produce IL-17A.

IL-17A shares closest similarity with IL-17F, a soluble cytokine secreted by Th-17 cells. An IL-17A/IL-17F heterodimer with biological activity intermediate between IL-17A and IL-17F have been described, which contribution to human inflammatory and autoimmune disease is not well-known. IL-17A and IL-17F act via the same receptors, IL-17RA and IL-17RC, albeit with different binding affinities. IL-17RA is ubiquitously expressed on cells but the expression of IL-17RC is less prominent on hematopoietic cells. Both, IL-17RA and IL-17RC is required for IL-17A and IL-17F biological function (signalling). The IL-17R complex activates a number of different downstream effector signalling pathways and involves the adapter proteins.

Th17/IL-17A pathway is important in immune surveillance of mucocutaneous barrier tissues (gastrointestinal and respiratory tracts, and skin) and promotes host defense against a narrow range of mainly mucocutaneous infections with bacteria *Candida albicans* and to a lesser extent with fungi *Staphylococcus aureus*. Therefore, neutralizing critical mediators of innate and adaptive immunity may carry the risk of an increased susceptibility to infections.

Approximately 80-90% of psoriasis patients have chronic plaque psoriasis, characterized by recurrent exacerbations and remissions of thickened, erythematous, scaly patches of skin. Psoriatic arthritis (PsA) is an important co-morbidity in up to 40% of psoriasis patients.

Patients with moderate to severe disease represent approximately 15% to 25% of plaque psoriasis patients and generally require systemic therapy. Several low molecular weight systemic drugs (including acitretin, cyclosporin, and methotrexate), and more recently several biologic systemic therapies, including TNF-α antagonists (adalimumab, etanercept, infliximab) and anti-IL12/IL23 (ustekinumab), have been approved for the treatment of psoriasis. Each of the approved small molecule systemic agents has safety limitations. Also, the biologic systemic therapies are accompanied by drug-specific safety concerns (e.g., infection including tuberculosis, malignancies including lymphoma, immunogenicity and

demyelinating neurologic events). Thus, there remains a need for new mechanism that can provide therapeutic alternatives.

About the product

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

The initial patient population studied with secukinumab includes patients with moderate to severe psoriasis. The development program evaluated dose regimens with either 150 mg or 300 mg of secukinumab.

The initially proposed therapeutic indication was: “Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA”.

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

Two different pharmaceutical forms of secukinumab have been used in the development program: lyophilisate formulation and liquid formulation. The pharmaceutical forms proposed for marketing are: 150 mg powder for solution for injection (also referred to as Lyo in vial); 150 mg solution for injection; with two presentations: in pre-filled syringe and in pre-filled pen.

Type of application and aspect on development

A total of over 5,044 subjects have been studied in 39 clinical studies within the clinical development program of secukinumab. These include 4498 patients who were treated with secukinumab in 34 clinical studies in various conditions, representing 3588 patient years of exposure. The clinical program included studies in chronic plaque psoriasis and other autoimmune conditions, including psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, uveitis, multiple sclerosis, Crohn´s disease, and dry eye.

3430 patients with chronic plaque psoriasis have been treated with secukinumab in 10 phase II/III studies providing efficacy data and covering 2725 patient-years of exposure. The clinical program included placebo and active (etanercept) controlled studies in patients with moderate to severe plaque psoriasis. Both short-term and long-term efficacy has been measured with standard efficacy variables, including but not limited to PASI, IGA mod 2011, and DLQI. Four phase II dose-finding studies (A2102, A2211, A2212 and A2220) were used to support the dose selection for phase III. Four phase III placebo-controlled studies (Studies A2302, A2308 and A2309, and 1 placebo- and etanercept-controlled study A2303) support the efficacy claims. There are two additional phase III studies that assessed individualized maintenance regimens (Studies A2304 and A2307). One phase II extension trial (Study A2211E1) was used to support treatment duration beyond 52 weeks.

EMA Scientific Advice (EMEA/H/SA/2050/1/2011/III) has been sought at a late developmental phase in 2011. It was focused on confirmation of the design of the planned phase III studies and the registration

of the proposed pharmaceutical forms. The advice was broadly followed. EMA clinical guidance (Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis CHMP/EWP/2454/02 corr) has been adhered to.

2.2. Quality aspects

2.2.1. Introduction

The active substance in Cosentyx, secukinumab, is a first in class recombinant high-affinity fully human monoclonal antibody (IgG1/κ) that selectively binds to human interleukin-17A (IL-17A) and neutralizes the bioactivity of this cytokine.

IL-17A, produced by a subset of T helper cells, named Th17, but also by other T cells, neutrophils and mast cells, promotes the expression of other pro-inflammatory cytokines as well as effector proteins. This cascade results in the activation of neutrophils and macrophages as well as epithelial cells and fibroblasts, and is considered to play an important role in the pathophysiology of many autoimmune diseases, including psoriasis.

Secukinumab is expressed in CHO (Chinese Hamster Ovary) cells MCB 060428 (CHO-HPT1 cell line) using recombinant DNA technology.

Cosentyx finished medicinal product is presented in three different pharmaceutical forms based on two formulations. These include (1) 150 mg powder for solution for injection in a vial (2) 150 mg/1mL solution for injection in pre-filled syringe and (3) 150 mg/1mL pre-filled bulk syringe assembled in pen / auto-injector. The syringe and the pen / auto-injector forms use the same bulk syringes and have exactly the same formulation.

Two buffer compositions optimised for the lyophilised powder and solution formulations are proposed.

The container closure systems in contact with the finished medicinal product consist either of a vial of Type I colourless glass with fluoropolymer-coated rubber stopper and aluminium seal or a syringe barrel (hydrolytic Type I glass) with staked needle, rigid needle shield and fluoropolymer-coated rubber stopper.

2.2.2. Active Substance

General information

Secukinumab is an IgG1/κ monoclonal antibody that selectively binds to human interleukin-17A (IL-17A) and neutralizes the bioactivity of this cytokine.

The sequence of amino acids for secukinumab light chain (215 amino acids) and heavy chain (457 amino acids) was confirmed by mass spectrometry. The expected disulfide linkages were presented and verified to be correct by peptide mapping. The relative molecular mass of secukinumab based on the amino acid sequence without post-translational modifications (e.g., glycosylation), but including the C-terminal lysine residues at the heavy chains is Mr = 147'944 Da. Due to expression in a CHO cell line, the C-terminal lysine residues of the heavy chains are post-translationally removed, resulting in Mr = 147'688 Da (if both lysines are removed).

Both secukinumab heavy chains are fully glycosylated at Asn307. The predominant oligosaccharides are biantennary complex-type structures having zero (bG0), one (bG1), or two (bG2) terminal galactose residues. The bG0 structure (terminating with two N-acetylglucosamine residues) predominates. There are no O-linked glycosylation sites in secukinumab active substance.

Manufacture, characterisation and process controls

Secukinumab is expressed in CHO (Chinese Hamster Ovary) cells MCB 060428 (CHO-HPT1 cell line) using recombinant DNA technology. The cell culture process (Figure 1) is conventional, expanding the culture via T-flasks and roller bottles to a fed batch bioreactor. The cell culture media used for inoculum preparation, for seed expansion, and for the production stage are serum-free, with low protein content and do not contain animal- or human-derived raw materials. The cell culture fluid is harvested as a single-harvest batch which is subsequently purified as a single active substance batch. The purification process consists of 9 steps including harvest, chromatography and filtration with final freezing and storage at ≤- 60℃.

Prior to execution of process evaluation studies, a preliminary classification and definition of the input parameter ranges was conducted based on experience gained during early phase process development, clinical manufacturing, or described in the general literature. Based on a risk assessment the Applicant defined critical and non-critical process parameters, which were further characterised and analysed to define the in-process controls and proven acceptable ranges. Within the non-critical classification, additional sub-categories (key and non-key) were defined to assess the impact of parameters on process performance. The Applicant provided data to justify the classification of different process parameters.

Cell banking system, characterisation, and testing

A two-tiered cell banking system using MCB and WCB is in place. The source, history and production of the CHO cells, MCB and WCB have been described and documented in detail, including methods and reagents used during culture, in-vitro cell age, storage conditions according to ICH Q5B. Both MCB and WCB have been qualified and characterised by extensive testing for mycoplasma, sterility and adventitious viruses to establish purity. The expression system contains both human immunoglobulin heavy and light chains containing the IL-17A binding region.

Process validation was performed thoroughly. The validation batches met the target limits. The batch results for validation batches were consistent and therefore the process is considered robust.

Comparability of the processes

During development of secukinumab, expression was performed in two different cell lines: Sp2/0 and CHO. Secukinumab active substance was initially manufactured with Sp2/0 production cell line. The CHO process was further optimised in order to develop a robust process suitable for commercial supply. This final process was transferred to Novartis Pharma S.A.S., Huningue, France as the final manufacturing site for the active substance used for commercial finished product manufacture. Comparability between the development and commercial processes has been studied extensively. This comparability between the CHO processes is considered as important, because the main pivotal studies are claimed to be performed with development and commercial material. The Applicant has properly addressed the characteristics of the molecule derived from the different processes by several analytical methods. Overall, changes to the processes did not significantly affect the molecule.

Specification

The antibody is extensively and well characterised including molecular structure as well as process- and product-related impurities. The proposed potency assay is a cell-based assay. No binding assay has been introduced to the release testing regimen and the cell-based bioassay is considered sufficient to control biological activity of secukinumab.

The same reference material is used both for active substance and finished product in analytical testing and is sufficiently described.

The active substance specification includes tests and limits for: appearance of the solution, color of the solution, pH, identity by peptide mapping and cell based assay, potency assay, assay for protein by UV, purity and impurities assays, determination of CHO host cell protein, determination of free SH- groups, microbiological quality and bacterial endotoxins.

All analytical methods have been described in detail and non-compendial methods have been validated according to ICH Q2 with acceptable criteria and results.

Stability

The antibody is stored for long term at ≤ -60 °C. Stability studies data show good stability at ≤ - 60 °C. No significant trend is seen at +5 °C either. At both temperatures the results are within the current proposed active substance specifications. A shelf life of 24 months is agreed when stored at ≤-60 °C (± 10 °C) in the primary packaging.

2.2.3. Finished Medicinal Product

Three presentations are proposed for Cosentyx finished product. These include (1) 150 mg powder for solution for injection in a vial (2) 150 mg/1mL solution for injection in pre-filled syringe and (3) 150 mg/1 mL pre-filled bulk syringe assembled in auto-injector. The syringe and the pen / auto-injector use the same bulk syringes and have exactly the same formulation.

Two buffer compositions optimised for the lyophilised powder and solution formulations are proposed. Both formulations have been developed in experimental formulation studies and evaluated in stability studies at long-term, accelerated and stressed conditions to find appropriate excipients for sustaining adequate quality of the finished product.

Powder for solution for injection reconstituted with 1 ml of water for injections contains sucrose (270 mM), histidine (30 mM) and polysorbate 80 (0.06% w/v), at pH 5.8.

Solution for injection (1 ml) consists of trehalose (200 mM), histidine (20 mM), methionine (5 mM), polysorbate 80 (0.02% w/v) at pH 5.8. Finished product manufacturing consists of thawing, pooling and mixing of bulk active substance, dilution to a target concentration using an excipient solution, aseptic filling in syringes and assembly with either a plunger rod and a safety device (pre-filled syringe) or into an auto-injector / pen. An overfill is applied to ensure an extractable volume of 1.0 ml.

All excipients are of Ph. Eur. grade commonly used in marketed parenteral pharmaceutical products.

Container closure system

The primary and secondary packaging of all finished product presentations have been properly described and their quality and testing presented. All components coming into contact with the finished product comply with Ph. Eur. requirements. The container closure systems in contact with the finished product consist either of a vial of Type I colourless glass with fluoropolymer-coated rubber stopper and aluminium seal or a syringe barrel (hydrolytic Type I glass) with staked needle, rigid needle shield and fluoropolymer-coated rubber stopper. BD Hypak syringe was chosen for the commercial presentation considering the stability, general quality aspects of AS and syringe performance. The pre-filled syringe can be assembled into safety device (Safety Syringe Inc. UltraSafe Passive Needle GuardXI00L) or with disposable auto-injector (Delta 02 auto-injector) for fixed-dose administration. There is no contact of finished product with any of the auto-injector components. The suitability of the auto-injector has been extensively studied to identify potential hazards and their severity, the potential harm to the user and design control activities, finally these were evaluated in formative study and validation testing. Studies were conducted to derive information from user interaction with the device. Furthermore, the risk management plan for Delta-02 is provided. The plan details how safety risks will be identified, mitigated,

monitored and recorded throughout the entire product life cycle of Delta-02. Phase 3 clinical trial supplies have been manufactured using commercial scale active substance process for all three presentations at Novartis Pharma Stein AG. The batches used in the Phase 3 clinical trials are described in “Clinical Trial Formulae”. Finally, adequate compatibility studies have been performed for the containers including tungsten and silicone oil leachates for the syringes.

Manufacture and process validation

The finished product is manufactured by Novartis Pharma Stein AG in Switzerland. The finished product manufacturing process involves solution thawing, pooling and mixing of bulk active substance, dilution to a target concentration using an excipient solution, sterile filtration, filling and lyophilisation (vial formulation) or aseptic filling in syringes and assembly with either a plunger rod and a safety device (PFS) or into an auto-injector. An overfill is applied to ensure an extractable volume of 1.0 ml in syringes. The manufacturing processes for the powder for solution for injection and solution for injection formulations consist of six unit operations. Process flow charts are provided for individual steps of the unit operations and they are briefly described for both processes. According to data provided in the dossier the Cosentyx finished product manufacturing processes were developed based on an evaluation of the process steps and parameters both at laboratory and commercial scale. Process validation studies are based on a traditional approach. All validation batches complied with the established in-process and release specifications as well as additional process monitoring data. No critical deviations were observed. One optional re-filtration has been acceptably validated. Operational and proven acceptable ranges (PAR) of the process parameters were derived thereof. The robustness of critical process parameters (CPP) was confirmed by manufacturing both at target parameter set-point and at a setting at the upper limit of the operational/proven acceptable range during scale-up to the commercial manufacturing site. The process validation results demonstrate that the processes are robust and no clear deviations either in the processes or the resulting products could be seen.

Data demonstrating that the antibody’s quality attributes prior to and after additional filtration steps remained unchanged were presented in the dossier and supports the definition of one optional re-filtration for the commercial process.

Comparability of the processes

In order to assess the comparability of the powder for solution for injection manufacturing processes two batches from each finished product manufacturing process and three process validation / stability batches from final commercial process, were used. Comparability was assessed by physicochemical and biological testing including comparison of process performance by (1) release testing, (2) additional characterization and (3) stability studies under long-term (+5°C, 6 months), accelerated (25°C) and stress (40°C) conditions (6 months). Batch release results for finished product batches throughout development are within specifications and coherent. Additional characterisation was performed supporting the comparability of finished manufactured by the processes. The impurity profiles for the development and commercial Processes are comparable, commercial Process material showing slightly less impurities and higher purity. An analytical comparison study was performed comparing both powder for solution for injection and solution for injection formulations to support the introduction of the solution for injection formulation. Two solution for injection batches were compared to five powder for solution for injection formulation batches for development and commercial processes using release testing, finished product stability testing and additional characterisation.

Specifications

Descriptions for all analytical methods used for both the powder for solution for injection and the solution for injection are included and all methods are validated in accordance with ICH guidelines.

The powder for solution for injection specifications include tests and limits for: appearance of the container and lyophilisate, color, pH and osmolality of the reconstituted solution, reconstitution time, water, identity by chromatographic method and cell based assay, potency assay, assay for protein by UV in the reconstituted solution, determination of free SH- groups purity assays (e.g., CEX, SEC, CE-SDS, RP-HPLC) and impurities assay (e.g., SDS-Page), particulate matter, visible particles in the reconstituted solution, uniformity of dosage units, assay of stabilizer in the reconstituted solution, tightness of containers by dye intrusion, sterility and bacterial endotoxins.

The solution for injection specifications include tests and limits for: appearance of the solution and container, color, identity by chromatographic method and cell-based assay, pH, extractable volume, osmolality, purity assays (e.g., CEX, SEC, RP-HPLC) and impurities assay (e.g., SDS-Page), visible particles and subvisible particulate matter, assay of stabilizer, determination of methionine, potency assay, assay for protein by UV, determination of free SH- groups, sterility and bacterial endotoxins, break out and sliding force of the prefilled syringe.

Stability

Stability of the finished product in lyophilised form (in vials) has been studied with 3 representative batches and real-time data has been provided for 36 months in the proposed storage temperature (+ 5 ± 3 °C). Additionally, photostability and freeze-thaw cycles of the vial formulation have been studied. All results are within specifications and only minor degradation can be seen in accelerated and stressed conditions. The shelf-life of 36 months at + 5 ± 3 °C is considered acceptable.

Real time stability data at + 5 ± 3 °C for the pre-filled syringe and the pre-filled pen (auto-injector) cover 9 and 6 months data, respectively, at time of submission of the marketing authorisation application. Although the supportive 24 months data from the bulk pre-filled syringes are considered as relevant since the safety device and the pen does not have direct contact with the finished product solution, the additional data available for the assembled products was requested. As part of their responses, the Applicant proposed 18 month shelf life for the liquid product for the proposed storage conditions in order to assure that clinically justified limits of purity parameters (CEX, SEC, CE-SDS as well as RP-HPLC) can be fulfilled throughout the shelf life of the product. The shelf life of 18 months at + 5 ± 3 °C is considered acceptable.

Adventitious agents

The Applicant has addressed both non-viral and viral contaminants. In the commercial manufacturing process no material from animal or human origin is used. In manufacturing only recombinant insulin is used. The production process of insulin uses components of bovine milk that was determined fit for human consumption, thus posing no risk. The risk of TSE contamination from the raw materials used at the time of establishment of the cell banks is negligible. The CHO cell line used for the production is well characterised. MCB, WCB and end-of production cells have been characterised for the absence of contaminating viruses according to ICH Q5A. Extensive tests for rodent viruses, bovine and porcine viruses as well as sterility and mycoplasma have been conducted for the cell banks. A virus validation study was performed according to CPMP/BWP/268/95. The capability of the four orthogonal process steps (Protein A chromatography, anion exchange chromatography, low pH treatment and nanofiltration) to reduce the amount of adventitious viruses has been adequately demonstrated using these four model viruses for spiking studies in scale-down models. Viruses for the clearance studies can be considered to

represent a wide range of physicochemical properties that demonstrate the ability of the process to eliminate viruses.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The manufacturing processes are well described and properly controlled both for active substance and finished product. The description of different finished product development batches (lyophilised and liquid formulations), their exact formulations and use in clinical studies has been updated. The lyophilised form has been widely used in clinical studies, but the use of the liquid formulation has been more restricted, however, several on-going Phase III clinical trials are to be finalised by December 2014. As part of their responses, the Applicant provided further information about the batches used in clinical trials and a summary of clinically qualified specification limits. The proposed tightened specification limits are considered acceptable, but the Applicant is recommended to review the specifications when more commercial batch analysis data is available. For the review of the purity specifications, it is also recommended to take into account efficacy data (52 w) from relevant ongoing trials.

Based on data from release testing, additional characterisation and stability studies it could be agreed that the bulk-prefilled syringe (PFS), PFS and auto-injector are comparable and it has been shown that they have similar stability behaviour and degradation pathways. However, it seemed that secukinumab in the liquid formulation is not as stable as in lyophilisate, which is quite normal for therapeutic proteins. The Applicant was requested to either show that the bioassay is stability indicating or otherwise introduce further assays (binding assay, RP-HPLC) to be employed for quality control. The Applicant performed additional stress studies to demonstrate that the cell-based assay is sensitive enough to detect the possible subpotent batches. In addition the Applicant demonstrated that the binding assays (ELISA, FRET) are inferior to the cell-based potency assay to detect all secukinumab forms that arose under forced degradation conditions. However, for the purpose of future comparability evaluations (e.g. instigated by significant changes in production of secukinumab), the use of a valid binding assay is recommended.

The Applicant provided more detailed information regarding the manufacturing process and process controls for manufacturing including holding times and included them into Module 3, as requested.

After receipt of supplementary information, the process development was considered well described. For the active substance, the process control strategy was summarised in sufficient detail to give a full understanding of the classification of process parameters into non-critical (operational) and critical.

For both formulations and all finished product presentations (vial, pre-filled syringe (PFS), auto-injector), process validation was performed using a sufficient number of batches. The Applicant provided a summary of process parameters, the acceptable ranges and corresponding data for the developmental or commercial batches manufactured to demonstrate the continuous functionality of manufacturing processes, as requested. The information is included in Module 3 and thus the issue was considered solved.

Overall, the control strategy and test methods applied for the finished product are considered sufficient and well balanced to control the quality of the finished product at release. However, limits applied for purity and product-related impurities were not justified in relation to their clinically qualified levels in the finished product. In their Day 180 responses, the Applicant clarified in detail which batches are used in clinical trials and that the bioassay has been shown to be stability indicating and able to detect quality changes in the active substance and finished product, if any.

A purity analysis by RP-HPLC was introduced during clinical phase III development of the solution for injection. Previously, the Applicant argued that the product-related impurities detected with RP-HPLC are

already controlled by specification limits from other tests (e.g. CE-SDS and CEX). Accordingly, no limit for RP-HPLC had been applied for active substance and finished product (powder); and the assay had been implemented only for the liquid form, which is somewhat less stable. As part of pre-authorisation testing, performed by the OMCL laboratory of Fimea, it was shown that the RP-HPLC was equally usable for analysing both formulations and that the results were also almost identical. Results from purity tests using other methods have suggested better quality profile for the lyophilised form. As RP-HPLC measures different aspects than CEX-HPLC and SEC-HPLC, it was considered appropriate to include it into the test panel of the lyophilisate as well. The Applicant provided examples for RP-HPLC chromatograms for both formulations, identified the peaks and proposed specifications. The issue was considered resolved.

Glycosylation was not addressed as part of release testing, which has been justified by the fact that glycosylation plays no role in the biological activity of secukinumab and the batch results are extremely consistent.

Additional justifications and data were provided in relation to the limits proposed for SEC (monomer, aggregates and fragments), CEX (main variant, acidic and basic variants) and CE-SDS (monomer). The proposed specification limits are considered acceptable, but a recommendation is given to review the specifications when more commercial batch analysis data is available.

Methods used for testing the amount of water and osmolality listed in the Ph. Eur. monograph - 'Monoclonal antibodies for human use' have been justified in the Day 121 responses.

Concerning the finished product liquid formulation in PFS/auto-injector, only partial stability data was initially provided from the 3 representative batches for 9 months (PFS) or 6 months (auto-injector) together with supportive data from 3 different development batches with varying batch sizes not fully comparable with the representative batches. As part of Day 121 responses, new stability data up to 18 months were provided. The Applicant proposed within the Day 180 responses that the shelf life for the liquid formulation is restricted to 18 months, which is agreed.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of Cosentyx is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. However, for the purpose of future comparability evaluations (e.g. instigated by significant changes in production of secukinumab), the use of a valid binding assay is recommended.

Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

The overall Quality of Cosentyx is considered acceptable.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended four points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

Secukinumab is a recombinant human monoclonal antibody directed against human IL-17A and belongs to the IgG1/κ isotype subclass. It is expressed in a recombinant Chinese Hamster Ovary (CHO) cell line and contains two heavy chains and two light chains. Both heavy chains contain oligosaccharide chains linked to the protein at Asn307.

Non-clinical development was performed in accordance with the ICH S6(R1) guideline. Two antibodies have been used to characterize the safety profile of secukinumab (also designated as AIN457, NVP-AIN457 or NVP-AIN457-NX-1): secukinumab itself and a mouse anti-mouse IL-17A surrogate antibody BZN035. Since secukinumab cross-reacts with cynomolgus, rhesus and marmoset monkey IL-17A but not with rodent IL-17A, the cynomolgus monkey was selected for toxicological evaluations of secukinumab. The murine surrogate antibody against mouse IL-17A (BZN035) was used for reproductive toxicity studies in mice.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Nonclinical pharmacodynamics studies are summarised in the Table 3.

Table 3 Summary of primary pharmacodynamics studies conducted with secukinumab.

Study Type	Test System	Batch	Cell system	Process	Study Number
Cloning	RT-PCR	N/A	N/A	N/A	RD-2002-04620
Structural characterisation (Fv fragment)	X-ray crystallography	PN42745	E. coli	N/A	RD-2013-00118
Binding affinity to IL-17A (hu, cy, rm, mar) ; Cross-reactivity IL-17 family members (hu) and IL-17A (mouse)	SPR (Biacore)	MAB110-28 & KB03303A	Hybridoma, Sp2/0	N/A	RD-2004-01490
Binding affinity to IL-17A (hu, cy, rm, mar) ; Cross-reactivity to cytokines (hu)	SPR (Biacore)	lot 041101	Sp2/0	N/A	RD-2005-01595
Binding affinity to IL-17A, A/F, F (hu, cy)	SPR (Biacore)	BF0013	CHO	D	RD-2012-00620
Cross-reactivity IL-17A (hu, mouse, rat, cy) ; IL-17 family members (hu) ; cytokines (hu)	SPR (Biacore)	BF0013	CHO	D	RD-2013-00135
Inhibition of binding of IL-17A (hu) to IL-17RA	ELISA	KB03303A	Sp2/0	N/A	RD-2013-00196

Study Type	Test System	Batch	Cell system	Process	Study Number
Binding to FcRn (h,cm)	SPR (Biacore)	BF0007	CHO	D	RD-2013-00072
In vitro functional activity, inhibition of IL-17A (hu) induced secretion of IL-6	hu dermal fibroblasts	(340)-110-28	Hybridoma	N/A	RD-2002-01987
In vitro functional activity, inhibition of IL-17A (hu, cy, rm) induced secretion of IL-6	hu dermal fibroblasts	E10908.71 & KB03303A	Hybridoma, Sp2/0	N/A	RD-2004-01178
In vitro functional activity, inhibition of IL-17A, A/F and F (hu, cy) induced secretion of IL-6	Primary hu cynoviocytes from RA patients	71201	CHO	B1	RD-2013-00026
In vitro functional activity, inhibition of IL-17A and F (cy) induced secretion of IL-6	Primary (cy) cynoviocytes	BF0013	CHO	D	RD-2013-00148
In vivo functional activity, inhibition of neutrophil migration	mouse air pouch model	KB03303A	Sp2/0	N/A	RD-2004-01063
In vivo functional activity, inhibition of PG synthesis	mouse arthritis model	(340)-110-28	Hybridoma	N/A	RD-2004-01347
In vitro binding affinity, on and off rates to IL-17A ; Cross-reactivity to cytokines	SPR (Biacore), ELISA	BZN035	N/A	N/A	RD-2005-01595
In vitro functional activity; inhibition of IL-17A induced secretion of CXCL-1	murine rectal carcinoma cells, ELISA	surrogate	N/A	N/A	RD-2005-01595
In vivo functional activity; inhibition of joint swelling	mouse AIA model	BZN035 surrogate	N/A	N/A	RD-2013-00148

hu: human, cy: cynomolgus monkey, rm : rhesus monkey, mar : marmoset monkey, N/A : not applicable

***In vitro* binding affinity to human IL-17A, IL-17AF and IL-17F**

K_D rates of secukinumab are summarised in the Table 4 (studies RD-2004-01490, RD-2005-01595 and RD-2012-00620).

Table 4 K_D of secukinumab for human and cynomolgus monkey IL-17A and IL-17AF

Antigen tag	Cell source and batch	KD (nM) Mean ± SEM huIL-17A	KD (nM) Mean ± SEM cyIL-17A	Difference*	Data Source
C-term APP	Hybridoma MAB110-28	0.12 ± 0.02	N/A	N/A	RD-2004-01490
C-term APP	Sp2/0 lot KB3303A	0.23 ± 0.03	6.0 ± 0.7	26x	RD-2004-01490

Untagged	Sp2/0 lot 041101	0.37 ± 0.12	4.0 ± 0.6	11x	RD-2005-01595
N-term APP	CHO batch BF0013	0.09 ± 0.03	1.2 ± 0.1	13x	RD-2012-00620
Untagged	CHO batch BF0013	0.06 ± 0.02	0.9 ± 0.2	15x	RD-2012-00620
		huIL-17AF	**cyIL-17AF**		
N-term APP	CHO batch BF0013	2.4 ± 0.2	4.3 ± 0.5**	1.8x	RD-2012-00620

N/A : not applicable; *Binding affinity difference cyIL-17/huIL-17; **due to variability in the study, the value is an approximate.

Binding affinities of secukinumab to human IL-17A homodimer

The kinetic constants of secukinumab produced by hybridoma cells (MAB110-28) or by Sp2/0 cells (NVP-AIN457-NX-1) were analysed in Study RD-2004-01490. Mean K_D value for secukinumab produced by hybridoma was 122 ± 22 pM, and k_{on} = (4.1 ± 0.1) x 10^5 1/M*s; k_{off} = (3.8 ± 0.5) x 10^{-4} 1/s. K_D value for secukinumab produced by Sp2/0 cells was 227 ± 30 pM, and k_{on} = (2.8 ± 0.2) x 10^5 1/M*s; k_{off} = (5.8 ±0.5) x 10^{-4} 1/s.

Mean K_D value for secukinumab produced by Sp2/0 cells (NVP-AIN457-NX-1) was 370 ± 120 pM, and k_{on} = (1.8 ± 0.24) x 10^5 1/M*s; k_{off} = (6.3 ±1.2) x 10^{-5} 1/s according to the Study RD-2005-01595 (Table 5).

Table 5 Kinetic constants for the secukinumab (nonbiotinylated) produced by Sp2/0 cells (Lot#041101) (Data source Study RD-2005-01595).

Conc [nM]	kon [1/Ms]	koff [1/s]	KD [M]	SEM [nM]
4	2.06E+05	8.55E-05	4.15E-10	Run 1
8	1.40E+05	7.20E-05	5.16E-10	
12	1.37E+05	7.39E-05	5.41E-10	
16	1.37E+05	8.46E-05	6.18E-10	
20	1.43E+05	6.56E-05	4.59E-10	
Mean (run1)	**1.53E+05**	**7.63E-05**	**0.51E-09 ± 0.05E-09 (SEM)**	
4	2.21E+05	2.31E-05	1.04E-10	Run 2
8	1.93E+05	3.35E-05	1.74E-10	
12	1.73E+05	6.06E-05	3.51E-10	
16	1.75E+05	5.16E-05	2.95E-10	
20	1.73E+05	7.30E-05	4.22E-10	
Mean (run2)	**1.79E+05**	**5.47E-05**	**0.31E-09± 0.05E-09 (SEM**	
4	2.66E+05	6.69E-05	2.52E-10	Run 3
8	1.84E+05	3.60E-05	1.96E-10	
12	1.91E+05	3.43E-05	1.80E-10	
16	1.91E+05	9.58E-05	5.03E-10	
20	1.77E+05	5.11E-05	2.89E-10	
Mean (run3)	**2.02E+05**	**5.68E-05**	**0.28E-09 ± 0.06E-09 (SEM)**	
Mean (all runs)	**1.78E+05**	**6.26E-05**	**0.37E-09**	
SEM	0.24E+05	1.19E-05	1.2E-10	

Six independent experiments were performed using 50 – 0.8 nM of IL-17A. Results are shown in in Table 6. Kinetic constant measurements for cynomolgus monkey IL-17A, IL-17AF and IL-17F are included into the table for enabling comparison. Mean K_D value for secukinumab produced by CHO cells with process D was 60 ± 16 pM, and k_{on} = (4.3 ± 0.6) x 10^5 1/M*s; k_{off} = (2.6 ± 0.8) x 10^{-5} 1/s. Representative K_D value using APP6-tagged IL-17A was 90 ± 25 pM. Specific binding to the IL-17A was also seen in the Study RD-2013-00135 which was conducted to analyse selectivity and cross-reactivity. In this assay, K_D values were not determined.

Table 6 Kinetic constants for the secukinumab produced by CHO cells with process D (Batch BF0013).

Antigen	K_D [M]	k_a [$M^{-1}s^{-1}$]	k_d [s^{-1}]	n	R_{max} [RU]	Chi^2 [RU^2]
huIL-17A (BTP27240)	6.0 ± 1.6E-11	4.3 ± 0.6E+5	2.6 ± 0.8E-5	6	70 - 137	0.195 - 0.986
APP6-huIL-17A (BTP27134)	9.0 ± 2.5E-11	2.8 ± 0.1E+5	2.5 ± 0.7E-5	6	69 - 137	0.066 - 0.796
cyIL-17A (BTP27241)	9.0 ± 1.6E-10	4.8 ± 0.5E+5	4.3 ± 0.6E-4	6	58 - 118	1.690 - 6.360
APP6-cyIL-17A (BTP27133)	1.2 ± 0.1E-9	5.7 ± 0.8E+5	6.7 ± 1.1E-4	6	55 - 112	1.080 - 5.190
APP6-huIL-17A/F (BTP27197)	2.4 ± 0.2E-9	1.1 ± 0.1E+5	2.5 ± 0.1E-4	2	49 - 52	0.908 - 0.938
APP6-cyIL-17A/F (BTP27198)	4.3 ± 0.5E-9	1.1 ± 0.1E+5	4.7 ± 0.3E-4	3	49 - 104	5.508 - 16.20
APP6-huIL-17F (BTP27135)	n.d.	n.d.	n.d.	2	n.a.	n.a.
APP6-cyIL-17F (BTP27136)	n.d.	n.d.	n.d.	2	n.a.	n.a.

n.d. = Not determined: heterogeneous interactions and non-specific binding of the antigens to the reference flow cell at the highest antigen concentrations (10 – 1.25 µM) were observed.
n.a. = Not applicable.

Binding affinities of secukinumab to human IL-17AF heterodimer

The K_D value of secukinumab produced by CHO cells with process D was 2.4 ± 0.2 nM (Study RD-2012-00620), and k_{on}= (1.1 ± 0.1) x 10^5 1/M*s; k_{off}= (2.5 ± 0.1) x 10^{-4} 1/s (Table 6). The results are from two experiments using 210 – 3.3 nM of N-terminal APP6-tagged IL-17AF. Representative K_D value for IL-17A was 90 ± 25 pM, indicating ~26-fold lower binding affinity for the IL-17AF than for homodimeric IL-17A. Same batch of secukinumab was analysed in the Study RD-2013-00135 which confirmed the binding of secukinumab to IL-17AF.

Binding of secukinumab to human IL-17F homodimer

Binding to the IL-17F homodimer is specific but weak. Due to the weak interaction (~ µM) no K_D could be determined. The affinity is so low that the binding activity was not recognised in all experiments conducted (Study RD-2004-01490), or was barely recognisable (Study RD-2013-00135). In the Study RD-2012-00620**,** the binding affinity or interactions of secukinumab produced by CHO cells to the IL-17F were not measurable. However, the specificity of the binding to IL-17F was shown by the competition study, in which the binding of secukinumab to the IL-17F (N-terminal tagged) after different degrees of pre-blocking the secukinumab binding sites (0 - 100%) with IL-17A was analysed. Different degrees of binding site saturation were achieved using variable injection times. The binding to the IL-17F was dependent on the degree of the binding site saturation (Table 7). Average binding capacity of secukinumab to the IL-17A of 0.294 (calculated by dividing R_{max}, binding response at surface saturation, by corresponding secukinumab capture level) was determined prior the competition experiment using 12.5 – 200 nM APP6-IL-17A.

Table 7 Competitive binding of IL-17F to secukinumab produced with Process D, by CHO cells, Batch BF0013.

Flow cell	AIN457 capture level [RU]	Surface capacity [RU][1]	1st injection: huIL-17A on AIN457			2nd injection: huIL-17F on AIN457/huIL-17A complex	
			injection time [s]	response [RU]	response [% of surface capacity][2]	response [RU]	response [% of surface capacity][2]
2-1	229 ± 3	67	0 (buffer)	1 ± 0	1	59 ± 1	88
4-1	196 ± 3	58	10	20 ± 0	34	22 ± 0	38
4-1	196 ± 3	58	18	31 ± 1	52	11 ± 0	19
3-1	220 ± 3	65	26	42 ± 1	65	13 ± 0	20
2-1	229 ± 3	67	34	52 ± 1	78	4 ± 0	7
3-1	220 ± 3	65	95	63 ± 2	97	-1 ± 0	-2

[1]Calculated by multiplying capture levels with the previously determined binding capacity of 0.294.
[2]Binding response [%] = (binding response [RU] / surface capacity [RU]) x 100
Average values were calculated from measurements in duplicate.

Blocking the binding to the IL-17RA receptor

The potential of secukinumab (produced by Sp2/0, KB03303A) to block IL-17A/IL-17RA interaction was analysed in the Study RD-2013-00196. The concentration of secukinumab resulting in 50% inhibition of biotinylated IL-17A binding to receptor IL-17RA (IC50) was 0.51 ± 0.01 nM.

Affinity of unmodified IL-17A and biotinylated IL-17A to IL-17RA was analysed, and revealed that the biotinylation reduced the affinity of IL-17A to IL-17RA by one log (K_D being 0.5 x 10^{-9} for nonbiotinylated and 3.8 x 10^{-9} for biotinylated IL-17A).

Selectivity of secukinumab with other human IL-17 family members and cytokines

Secukinumab (produced by SP2/0 cells, KB03303A and produced by CHO cells with Process D) did not bind to IL-B, C, D and E according to the Study RD-2004-01490 and to the Study RD-2013-00135.

Cross-reactivity to human cytokines was analysed in two assays (Study RD-2005-1595, Study RD-2013-00135). No binding of secukinumab to TGFβ1, TGFβ2, IL-8, IL-13, IL-18, IL-19, IL-20, IL-22 and IL-23 cytokines was observed in these studies. Some binding, which according to the SPR binding curves could be specific for IFNγ, (13.3%), IL-2 (9.1%), IL-6 (8.6%), TNFα (6.8%) and IL-1β (1.4%) was seen in the Study RD-2005-1595 using the highest 100 nM concentration (i.e. 200-fold above the K_D for huIL17-A) of these cytokines with secukinumab produced by Sp2/0 cells. Of these, binding was also seen to IFNγ (2.9%) and TNFα (4.7%) when using 20 nM concentration (*i.e.* 40-fold above the K_D for huIL-17A) of cytokines. Re-evaluation of the data and binding kinetics of IL-2, TNFα and IFNγ (as a response to the concern issued by the CHMP) revealed no specific interaction of secukinumab with IL-2 or TNFα, and a low level unspecific or specific binding to IFNγ, which in turn was considered unlikely to have clinical relevance at the concentrations reached for secukinumab and the IFNγ present in psoriasis patients.

In the Study RD-2013-00135 cross-reactivity of secukinumab produced with Process D by CHO cells with IL-6 and IL-1β of the above tested cytokines which gave positive binding result, and with IL-18, IL-19, IL-20, IL-22, IL-23 and TGFβ2, were analysed using SPR. This assay revealed no binding to any of tested cytokines. Binding responses were normalised to the immobilisation level.

Cross species comparison of secukinumab interaction with IL-17A, IL-17A/F and IL-17F

Secukinumab cross-reacts with IL-17A from cynomolgus, rhesus and marmoset monkey. The binding affinity of secukinumab to cynomolgus monkey IL-17A ranged from 1.2 nM to 6.0 nM thus being ~13-26 fold lower affinity than for human IL-17A.

Rate and dissociation constants of cynomolgus, rhesus and marmoset monkeys IL-17A together with comparison of human IL-17A to secukinumab (KB03303A) were determined in the Study RD-2004-01490. Mean K_D value for cynomolgus monkey IL-17A binding to secukinumab produced by Sp2/0 cells (KB03303A) was 6.01 ± 0.7 nM, and k_{on}= (1.2 ± 0.2) x 10^5 1/M*s; k_{off}= (6.2 ±0.4) x 10^{-4} 1/s. This indicates 26-fold less binding affinity of secukinumab to cyIL-17A as compared to the human IL-17A. The K_D value for marmoset was 1.2 ± 0.1 nM and for rhesus monkey 9 ± 1 nM. Roughly 2 -fold differences were seen in the K_D values between the two different methods used (direct or indirect coupling of secukinumab).

Rate and dissociation constants of cynomolgus, rhesus and marmoset monkeys IL-17A (and huIL-17A) to another lot of secukinumab produced in SP2/0 cells were determined in the Study RD-2005-01595. Mean K_D value was 4.0 ± 0.6 nM, and k_{on}= (1.2 ± 0.2) x 10^5 1/M*s; k_{off}= (4.5 ±0.3) x 10^{-4} 1/s. This indicates 11 -fold lower binding affinity of secukinumab to cyIL-17A as compared to the huIL-17A. Biotinylation of secukinumab resulted in similar mean K_D value of 3.0 nM. The K_D value for the marmoset IL-17A was 1.9 ± 0.6 nM and for the rhesus monkey IL-17A 8.8 ± 0.8 nM.

The Study RD-2013-00135 confirmed binding of secukinumab (produced with Process D by CHO cells) to cynomolgus monkey IL-17A. Binding was approximately 65% to cyIL-17A as compared to 93% huIL-17A, K_D values were not determined. Kinetic constants were determined in the Study RD-2012-00620. 50 – 0.8 nM of untagged or N-terminal APP6-tagged cyIL-17A were used. K_D value was determined as 0.9 ± 0.16 nM and k_{on}= (4.8 ± 0.5) x 10^5 1/M*s; k_{off}= (4.3 ±0.3) x 10^{-4} 1/s when using untagged cyIL-17A and 1.2 ± 0.1 nM using APP6-tagged cyIL-17A. This indicates ~13 -15 fold lower binding affinity of secukinumab to cyIL-17A as compared to the human IL-17A.

In the Study RD-2012-00620, the K_D value for binding to cyIL-17AF could not be reliably calculated due to substantial deviations between the data and fitted curves, and high Chi^2 values. However, estimate of K_D 4.3 ± 0.5 nM was provided. This was close to the affinity to the huIL-17AF (*i.e.* 2.4 nM).

Secukinumab's K_D value for the cyIL-17F binding could not be determined, similarly to the huIL-17F. The specificity of the binding to cyIL-17F was shown in the competition study similarly to specificity to binding to huIL-17F. In the study the binding of secukinumab to the IL-17F (N-terminal tagged) was analysed after different degrees of pre-blocking the secukinumab binding sites (0 - 100%) with cynomolgus monkey IL-17A. Secukinumab bound with similar affinity to cynomolgus monkey IL-17F and to human IL-17F. Binding to the IL-17F was dependent on the degree of the binding site saturation, and showed a close resemblance to the huIL-17F (albeit lower in the degree of binding).

Secukinumab (produced with Process D, by CHO cells) do not bind to mouse and rat IL-17A (Study RD-2013-00135). Binding of secukinumab produced by Sp2/0 cells to mouse and rat IL-17A was also analysed in the Study RD-2004-01490, in which some unspecific binding was observed. Due to lack of cross–reactivity, mouse surrogate antibody was generated.

In vitro functional activity

In vitro relative potency of secukinumab was analysed by measuring the inhibitory potential of IL-17A (and IL-17AF, IL-17F) induced release of IL-6 in primary fibroblast like synoviocytes isolated from arthritis patients and in dermal fibroblasts (Study RD-2013-0026 and Study RD-2004-01178). Similarly the potency to inhibit the cynomolgus monkey IL-17A (and cyIL-17F) induced IL-6 secretion was studied in the cynomolgus monkeys primary synoviocytes and human dermal fibroblasts (Study RD-2013-00148 and Study RD-2004-01178). Neutralisation potency (shown as half maximal inhibitory concentration) is summarised in the Table 8.

Table 8 The *in vitro* relative potency of secukinumab: IC50 of the IL-17 -induced production of IL-6.

Secukinumab cell source / batch	Cytokine	Cell source used in assay	IC50 (nM) Mean ± SEM	Data Source
Hybridoma/ En E-10333/53 RD-2002-01987	IL-17A	dermal fibroblasts (hu)	2.07± 0.12 nM	
CHO Process B1/lot 71201	IL-17A	primary synoviocytes (hu)	0.14 ± 0.02 nM	RD-2013-0026
	IL-17AF		3.30 ± 0.20 nM	
	IL-17F		1.80 ± 0.17µM	
Hybridoma/E10908 RD-2004-01178	IL-17A	dermal fibroblasts (hu)	0.37 nM*	
Sp2/0 cells/KB03303A	IL-17A		0.40 nM*	
Hybridoma/E10908 RD-2004-01178	cyIL-17A	dermal fibroblasts (hu)	44.8 nM*	
Sp2/0 cells/KB03303A	cyIL-17A		52.0 nM*	
CHO Process D/ RD-2013-00148	cyIL-17A	cynomolgus monkey	(~µM)**	
Batch BF0013	cyIL-17F	primary synoviocytes	(~µM)***	

(hu): human, *No ± SEM provided; **IC50 not calculated, inhibitory effect seen at concentration ≥ 0.1µM. ***IC50 not calculated, inhibitory effect seen at concentration ≥1µM.

Inhibition of IL-17A, IL-17AF and IL-17F -induced IL-6 release

The *in vitro* neutralising activity of secukinumab for IL-17A-induced production of IL-6 was studied in human primary synoviocyte like fibroblasts and dermal fibroblasts. The ability of secukinumab (produced by CHO cells with process B1) to inhibit IL-17A, IL-17AF or IL-17F –induced IL-6 release was studied in primary rheumatoid arthritis patient fibroblast-like synoviocytes (Study RD-2013-0026). IL-17A alone did not stimulate significantly the release of IL-6 alone in this experiment, but in combination with TNFα the IL-6 release was increased and was ~1180 pg/ml, being ~2.7–fold compared to induction by TNFα alone (430 pg/ml). Secukinumab neutralized dose-dependently the release of IL-6 induced by IL-17A (0.03 nM) and TNFα with IC50 0.14 ± 0.02 nM. Secukinumab also neutralised IL-17AF (1 nM)/ TNFα induced effects at nanomolar concentrations with IC50 3.30 ± 0.20 nM, which is 24-fold weaker than for neutralising effect for IL-17A. Secukinumab had a weak neutralizing activity on IL-6 release induced by IL-17F (33 nM)/TNFα at micromolar concentrations of secukinumab; with IC50 1.80 ± 0.17µM.

Secukinumab produced by hybridoma (E10908) and Sp2/0 cells (KB03303A) neutralised the IL-17A induced IL-6 production dose-dependently also in human dermal fibroblasts (Study RD-2004-01178), with IC50 of 0.37 nM (E10908) and 0.40 nM (KB03303A). Secukinumab concentrations of 0.1 – 300 nM were used in the study. The release of IL-6 was measured with ELISA. When the same conditions were

applied to stimulating the cells with cynomolgus monkey IL-17A (0.1 – 300 nM), the neutralisation potency was much weaker (hundred fold), IC50 being 44.8 nM for hybridoma E10908 and 52 nM for Sp2/0 KB03303A. The rhesus monkey IL-17A gave IC50 values in similar range as compared to the cynomolgus monkey IL-17A. Production of IL-6 in human primary fibroblasts was induced by human and monkey IL-17A.

Inhibition of cyIL-17A and cyIL-17F -induced IL-6 release

The inhibition activity of secukinumab in the cyIL-17A and cyIL-17AF induced release of IL-6 was assessed in primary synoviocytes isolated from cartilage of two cynomolgus monkeys (Study RD-2013-00148). Concentration-dependent inhibition of IL-6 release induced by IL-17A was observed with secukinumab concentration of ≥0.1 µM. The inhibitory effect of secukinumab on IL-17F –mediated stimulation was weaker occurring at concentrations from >1µM. The IC50 could not be determined in the study. Secukinumab at concentration of 10 µM blocked the release of IL-6 completely (induced either by cyIL-17A or cyIL-17F).

Differences in the response to IL-17 –mediated IL-6 production were seen in the human and cynomolgus monkey synoviocytes; in human primary synoviocytes, IL-17A stimulated IL-6 production ~120-fold more than IL-17F, whereas cyIL-17A induced ~10-fold more IL-6 production as compared to the cyIL-17F. Although cynomolgus monkey synoviocytes were not as responsive to the IL-17 –stimulus as compared to the human synoviocytes, the neutralising activity of secukinumab was much weaker. The inhibitory effect of secukinumab on IL-17A induced IL-6 release was seen at concentration of <0.1 nM on human cells and ≥0.1 µM on cynomolgus cells.

***In vivo* functional activity**

The mode of action studies considering the interference of the immediate effect of blocking the IL-17A binding to its receptor were conducted in two IL-17A -related inflammatory mouse models. These studies addressed immediate/short-term effects of secukinumab i.e. 2-3 days post-delivery. No *in vivo* studies have been conducted with secukinumab in animal models of psoriasis-like pathology. The *in vivo* functional activity was analysed using secukinumab produced by hybridoma and Sp2/0 cells.

The mouse arthritis model: The model was generated by implantation of NIH3T3 cells ($5x10^4$) transfected with huIL-17A-GFP and secreting human IL-17A into the right knee joint of DBA-1 mouse (Study RD-2004-10347). This triggers inflammatory reaction, joint swelling and inhibition of chondrocyte-mediated proteoglycan (PG) synthesis. Results showed that secukinumab inhibited knee joint swelling significantly ($p<0.0001$, $n=8$) and protected cartilage from inhibitory effect of IL-17A on chondrocyte PG synthesis *ex vivo* ($p<0.05$, $n=6$). Results were expressed as the ratio between the right (treated) and left (untreated) joint. Histological analysis revealed reduced cellular infiltration and PG depletion as compared to the control antibody –treated mouse joint.

The mouse air pouch model: in this model, air pouches were formed to the back of the mice (Study RD-2004-01063). Secukinumab (produced by Sp2/0 cells) was injected *i.p.* at 1, 3, 10 and 30 mg/kg day before implantation of NIH3T3 cells expressing human IL-17A into the air pouch. Secukinumab inhibited IL-17A induced infiltration of polymorphonuclear leucocytes (neutrophils, eosinophils, basophils) to the pouch with ED50 being 5.4 mg/kg. The maximal inhibition (87%) of polymorphonuclear leucocyte infiltration was seen at secukinumab concentration of 30 mg/kg (highest dose tested), which is regarded as complete inhibition as compared to the negative control value (91%).

Mouse surrogate antibody BZN035

The Mouse surrogate antibody BZN035 was developed due to lack of cross-reactivity of secukinumab with mouse IL-17A (Study 5001452_R:BZN035_975_1). BZN035 recognizes mouse and rat IL-17A and binds

mouse IL-17A with a K_D of ~67 ± 10 pM, which is close to the affinity reported for secukinumab produced by CHO cells (Study RD-2013-00135).

On the contrary to the secukinumab, BZN035 does not bind to IL-17F. The binding to the IL-17AF was not studied. Like its human counterpart, it does not cross-react with other IL-17 family members (IL-17B, IL-17C, IL-17D, IL-17E). BZN035 does not cross-react with IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, IL-17F, IL-18, IL-23, TNFα, IFNγ, and CXCL1/KC (Study RD-2010-00373).

Functionally, BZN035 neutralizes the production of CXCL1/KC by murine rectal epithelial carcinoma cell line CMT-93 stimulated with 0.3 nM of recombinant mouse IL-17A with an IC50 of 0.04 ± 0.004 nM (Study RD-2010-00373). Biological activity of BZN035 *in vivo* was studied in the mouse antigen induced arthritis (AIA) model (Study RD-2010-00416). BZN035 reduced knee swelling in a dose-dependent manner when administered *s.c.* as a single dose (0.015. 0.15, 1.5 and 15 mg/kg) 2 days prior the arthritis induction. The ED50 calculated combining the both data sets was 2.11 (1.34 – 3.71) mg/kg, with a confidence interval of ~2.4 mg. The biological response for BZN035 was dependent on the dosing time in relation to the induction of arthritis; when BZN035 (200 µg, *i.p.* 3x week) was dosed 2 days before the induction of arthritis, it resulted in 72% reduction in knee swelling by 7 days. When BZN035 (200 µg) was dosed 2 days after the initiation of arthritis it resulted in nonsignificant, 20% reduction in knee swelling.

Secondary pharmacodynamic studies

Binding of secukinumab to Fcγ receptors

Secukinumab is a soluble monoclonal antibody carrying a human IgG1 Fc-domain and thus, in theory is able to interact with Fcγ receptors. However the Fc-mediated effector functions are not considered as a mode of action of secukinumab. Secukinumab did not elicit ADCC (Study RD-2005-00898).

Binding of secukinumab to FcRn receptor

Secukinumab binds to recombinant human and cynomolgus monkey FcRn at pH 6.0, and does not bind to human FcRn at a physiological pH (pH 7.4) (Study RD-2013-00072). The affinity of secukinumab at pH 6.0 to human FcRn was ~3 µM and to cynomolgus monkey FcRn ~4 µM.

Safety pharmacology programme

A GLP safety pharmacology study in cynomolgus monkeys was conducted to evaluate the CNS, respiratory and cardiovascular effects of secukinumab (Study 0580140). Slow bolus injection of secukinumab (produced by Sp2/0 cells) at doses of 10, 30 and 100 mg/kg was given to male monkeys (n=4/dose group). Each animal received 4 doses of control and/or secukinumab by *i.v.* delivery.

There were no clinical signs recorded, or deaths during the study. There were occasional effects ($p<0.05$) seen with 100 mg/kg of secukinumab on the systolic, diastolic and mean arterial blood pressure and heart rate. There were no biologically relevant secukinumab related effects noted on heart's electrical cycle; activation of the right and left ventricles and heart rate corrected QT (QTc) intervals on the electrocardiograms. A single ventricular premature complex was noted in one animal 30 minutes following the *i.v*. administration of secukinumab of 30 mg/kg. The arrhythmia was not considered related to the secukinumab treatment, as this did not occur in the high dose group, and ventricular premature complexes can be normal variant in cynomolgus monkeys. Evaluation of ECG tracings showed no evidence of drug induced waveform abnormalities.

There were no adverse treatment related effects noted on any of the neurological parameters examined, and no adverse treatment related effects on respiratory function were observed following exposure to secukinumab. No adverse treatment-related effects on pH, pO_2, pCO_2 or SO_2 where observed following treatment.

The no observed adverse effect level (NOAEL) was considered to be 100 mg/kg.

Pharmacodynamic drug interactions

No pharmacodynamics drug interaction studies were conducted as secukinumabis a fully human antibody and there is no direct evidence for the role of IL 17A in the expression of CYP450 enzymes. This was considered acceptable by the CHMP.

2.3.3. Pharmacokinetics

Pharmacokinetic studies

Evaluation of pharmacokinetics was performed in cynomolgus monkeys in three single dose studies to investigate the disposition of secukinumab administered via intravenous and subcutaneous routes (DMPK R0400373, DMPK R0600743-1, DMPK R0800115).

The comparative absorption pharmacokinetics of Sp2/0-derived and CHO-derived secukinumab after a single subcutaneous administration was evaluated (DMPK R0400373, DMPK R0600743-1).

Absorption

Pharmacokinetic study of secukinumab following an intravenous or subcutaneous dose in the cynomolgus monkey (DMPK R0400373)

In this non-GLP study pharmacokinetics of secukinumab was evaluated in male cynomolgus monkeys after a single intravenous dose of 10 mg/kg and a single subcutaneous dose of 15 mg/kg. The serum concentrations were determined with ELISA at selected time points up to 84 days after administration.

The intravenous administration of secukinumab to cynomolgus monkeys resulted in a low inter-individual variability. The $AUC_{0-\infty}$ and C_0 ranged from 3450-4800 µg day/mL and 239-262 µg/mL, respectively. The extrapolated area contributed for 2-11% to the total $AUC_{0-\infty}$ in the individual animals.

After subcutaneous dosing, the dose-normalized Cmax values were lower than after intravenous dosing. The bioavailability was 94% (range 86-101%).

The pharmacokinetics of secukinumab was typical for an immunoglobulin molecule with low serum clearance and long terminal half-life. Immunogenicity was observed in one animal resulting in interference of quantification of secukinumab in the serum.

Pharmacokinetics and bioavailability of secukinumab (from CHO cell) following an intravenous or subcutaneous dose in the cynomolgus monkey (DMPK R0600743-1)

In this non-GLP study pharmacokinetics of secukinumab (from CHO cells) was evaluated in male cynomolgus monkeys after a single intravenous dose of 10 mg/kg and a single subcutaneous dose of 15 mg/kg. The serum concentrations were determined with ELISA at selected time points up to 84 days after administration.

The IV administration of secukinumab to cynomolgus monkeys resulted in a low inter-individual variability. The AUC0-∞ and C0 ranged from 5410-6050 µg day/mL and 315-323 µg/mL, respectively.

Pharmacokinetics of secukinumab (CHO and Sp2/0 cells) following an intravenous dose in the cynomolgus monkey (DMPK R0800115)

In the study with the secukinumab produced from CHO cells, both analytical methods obtained comparable serum concentrations and PK parameters for secukinumab. Similarly, in the study with the secukinumab produced from Sp2/0 cells, both analytical methods obtained comparable serum concentrations and PK parameters for secukinumab. It appeared that the secukinumab material produced

from Sp2/0 cells showed 25% to 54% higher Cmax and 53 to 74% higher AUCinf and lower CL and Vss when compared to the secukinumab material produced from CHO cells regardless of which analytical method was used.

Single intravenous dose (bolus injection) placental transfer study in the cynomolgus and marmoset monkey (R0580148)

The purpose of this GLP-study was to determine if secukinumab could be transferred across the placenta in cynomolgus or marmoset monkeys.

Serum analysis revealed that that secukinumab is transferred across the placenta during the pregnancy in cynomolgus monkeys and in marmosets, and that the fetuses are exposed to secukinumab at the level corresponding approximately 2% of the mean maternal serum concentration.

Distribution

The mean volumes of distribution at steady-state were 74.5 mL/kg and 59.0 mL/kg for Sp2/0- and CHO-derived secukinumab, respectively, and were similar to the blood volume (approximately 73 mL/kg) in cynomolgus monkey (studies DMPK R0400373, DMPK R0600743-1) .

Metabolism

It is known that immunoglobulins are eliminated by protein catabolism. Early investigations conducted with pooled antibody suggested that immunoglobulins are primarily metabolized within sites that are in rapid equilibrium with plasma. However, the exact anatomical locations of antibody catabolism have not been identified. Given the available evidence about catabolism and elimination of immunoglobulins in general, no specific investigations of the metabolism of secukinumab were performed. This was agreed by the CHMP.

Excretion

The vast majority of immunoglobulins is eliminated by protein catabolism. The total systemic serum clearance, 2.76 mL/day/kg and 1.80 mL/day/kg for Sp2/0- and CHO-derived secukinumab, respectively, of the compound was extremely low compared to the hepatic blood flow (approximately 63 L/day/kg), suggesting minimal hepatic metabolism. The half-life of the α phase, T1/2α, was 0.6 days while the terminal (ß) half-life was 20.1 days for Sp2/0 material which was in close agreement with the terminal (ß) half-life of 24.0 days for CHO-cell-derived material.

Pharmacokinetic drug interactions

Preclinical *in vitro* and *in vivo* drug-drug interaction studies with secukinumab or the corresponding mouse surrogate antibody BZN035 have not been conducted, because typical metabolizing enzymes, such as CYP450's and UGT's, etc. are not involved in the proteolytic degradation of immunoglobulins. This was agreed by the CHMP.

2.3.4. Toxicology

Two antibodies have been used to characterize the safety profile of secukinumab and anti-IL17A therapy: secukinumab itself and a mouse anti-mouse IL-17A surrogate antibody BZN035. The cynomolgus monkey was selected as a relevant species for evaluation of toxicity since secukinumab cross-reacts with cynomolgus, rhesus and marmoset monkey IL-17A but not with the rodent IL-17A. In addition, the murine surrogate antibody against mouse IL-17A (BZN035) was used for reproductive toxicity studies in mice. A surrogate anti-mouse antibody (BZN035) has been used in reproductive toxicity studies, including a fertility and early embryonic development and pre- and post-natal development toxicity study in mice. The potency and pharmacodynamic properties of the surrogate antibody as well as the

evolutionary conservation of the IL-17A signalling pathway across the vertebrates support its use for the safety evaluation of secukinumab.

All studies except the Blood compatibility, Antibody-dependent cellular cytotoxicity study, and the infection studies were performed according to the principles of Good Laboratory Practice.

Single dose toxicity

Toxicity after single subcutaneous dosing of secukinumab was evaluated in cynomolgus monkeys after 7 and 28 days observation periods.

A single dose subcutaneous injection toxicity study in the cynomolgus monkey with a 7- and 28-day observation period (Study 0870084)

The purpose of this GLP study was to investigate the potential toxicity, toxicokinetics and tolerability of secukinumab following a single s.c. injection to the monkey and to assess the potential late onset of toxicity or reversal of any effects within a 7 and 28-day observation period. Data showed that single subcutaneous dose of secukinumab at doses of 15 or 150 mg/kg appeared to be well tolerated after a 7- or 28-day observation period as there were no secukinumab-related changes in any parameters evaluated.

Repeat dose toxicity

Toxicity of secukinumab was evaluated in a series of repeat dose toxicity studies after subcutaneous and intravenous administrations to cynomolgus monkeys.

A 4-week intravenous bolus toxicity study of secukinumab (with an 8-week recovery) in the cynomolgus monkey (Study 0480179)

The aim of the study was to investigate the potential toxicity of secukinumab after a weekly intravenous injection to cynomolgus monkeys for a period of 4 weeks, with an 8-week recovery period. The study was conducted in accordance with the GLP requirements. Secukinumab derived from Sp2/0 cell line process A was used in this study.

There were no deaths or treatment-related effects on clinical signs, body weights, appetite, ophthalmology, electrocardiography, bone marrow, hematology or urinalysis. There were no toxicologically significant clinical biochemistry changes.

The dose-normalized $AUC_{0.083\text{-}168h}$ values and Cmax values after the first administration on Day 1 and Day 22 indicate a proportional increase of AUC and Cmax within the dose range of 10 to 100 mg/kg.

Dose-normalized $AUC_{0.083\text{-}168h}$ values increased by 2-3-fold from day 1 to day 22 after 4 administrations. An increase of the Cmax values by 1.5-2-fold was also observed from day 1 to day 22. For the group 4 recovery (100 mg/kg), the concentrations decreased faster for males than for females. The apparent $T_{1/2}$ calculated on the recovery phase from 168 h to 1512 h was 13.7 days for males (n = 2) and 20 days for females (n = 2). No obvious gender differences in toxicokinetics were observed for the main study, although during the recovery phase males showed a faster elimination than females.

A dose-response accumulation of total IL-17A in animals treated with secukinumab was noted. A single animal in the low dose group and all animals in the mid and high dose groups showed an IL-17A response.

Lymphocyte changes were observed in both females and males but the females appeared to be more affected. However, the effects were reversed in the recovery period. The terminal half-life was considerably longer in females (20 days) than in males (13.7 days) which could explain why the females

were more affected. These changes can be considered as non-adverse as associated organ pathologies were not observed.

No immunogenicity was detected in samples collected and analyzed.

No treatment-related organ weight, macroscopic or microscopic changes were noted in main study or recovery animals.

The no observed adverse effect level (NOAEL) was considered to be 100 mg/kg.

A 4 week intravenous injection (once weekly) toxicity study in the cynomolgus monkey with a 10-week recovery period (Study 0770204)

The aim of the study was to investigate the potential toxicity of secukinumab after a weekly intravenous injection to the monkey for a minimum of 4 weeks and to assess the reversibility of toxic effects within a 10-week recovery period. Secukinumab derived from CHO cell line process B1 was used in this study.

There were no deaths during the study or secukinumab-related effects on body weights, appetite, neurological parameters examined, ophthalmology, electrocardiography, hematology, clinical chemistry, urinalysis, organ weights, macroscopic and microscopic observations. There were no secukinumab-related effects on clinical observations with the exception of an increased incidence and severity of soft and/or liquid feces noted in males given 150 mg/kg/dose. There were no secukinumab-related changes in immunotoxicity assessments.

In general, apparent Tmax was 0.083 hrs irrespective of the gender and dose. The $AUC_{0.083\text{-}168h}$ values on day 1 and day 22 were roughly dose proportional within the dose range of 15 to 150 mg/kg regardless of the gender. Dose-normalized $AUC_{0.083\text{-}168h}$ values increased by a factor of 2, from day 1 to day 22, indicating secukinumab accumulation. Cmax values also increased from day 1 to day 22. The apparent terminal half-life, calculated from 24 to 1848 hrs during the recovery phase for the 150 mg/kg dose group, 11.6 days for males and 14.6 days for females.

Similar, likely pharmacology related effects on lymphocyte counts were not observed in this study as were noted in the other 4-week repeat dose toxicity study performed with secukinumab derived from the Sp2/0 cell line. Also, the effects on anti-KLH IgM antibodies were not observed in this study.

No immunogenicity was detected in any of the treated animals. Based on the reported high secukinumab serum concentrations, it cannot be excluded that potential immunogenicity might have been missed. However, the toxicokinetic profiles do not suggest this.

The high dose of 150 mg/kg/dose was considered as the NOAEL.

A 13 week subcutaneous injection (once weekly) toxicity study in the cynomolgus monkey with a 13-week recovery period (Study 0770712)

The aim of the study was to evaluate the potential toxicity and toxicokinetics of secukinumab after a weekly subcutaneous injection to cynomolgus monkeys for 13 weeks and to assess the potential reversal of any toxic effects within a 13-week recovery period. The study was conducted in accordance with the GLP requirements with the exception of total IL-17A measurements and immunogenicity analysis.

There were no deaths during the study, or any apparent secukinumab-related clinical observations, or effects on food intake, body weight, and body weight gain. There were no ocular or neurological findings, or effects on qualitative or quantitative ECG parameters. In week 13, a slight increase in mean globulin in females receiving 150 mg/kg/week was observed. There were no findings in hematology or urinalysis parameters, or differences in organ weights or treatment related macroscopic or microscopic changes observed in this study at any dose level.

At the end of the dosing period, there were moderately lower total lymphocyte counts (~42%) in females at ≥50 mg/kg/week compared with concurrent controls. Following the recovery period, there were no changes observed in the total lymphocyte counts in blood when compared with either the pre-dosing values or the control group.

Decreases in mean levels of anti-KLH IgM response after immunization were observed in males and females at ≥50 mg/kg/week on study Days 79 and 84 when compared to control animals. Mild to moderate secukinumab-related decreases in mean anti-KLH IgG antibody levels were observed in males at doses ≥50 mg/kg/week at days 79 and 84 and at doses ≥15 mg/kg/week at Day 92. Mild to moderate treatment-related decreases in anti-KLH IgG concentrations were also observed in females dosed with 50 mg/kg/week at Days 79 and 84 and in females dosed with 150 mg/kg/week at Day 84. Secukinumab administration did not interfere with the ability to produce detectable levels of anti-KLH IgG antibodies. Decreases in anti-KLH IgG levels were reversible, not associated with clinical signs or histological changes, and were considered non-adverse.

In secukinumab-treated animals, the total IL-17A concentrations were highly variable between animals. Most detected total IL-17A levels were observed 24 hours post dose and increased up to Day 29. Between Days 29 and 92, total IL-17A concentrations were constant, the median value at 50 mg/kg fluctuated between 1000 and 1330 pg/mL and this was similar at 150 mg/kg. During recovery period, total IL-17A concentrations decreased steadily.

A no observed adverse effect level (NOAEL) was established at 150 mg/kg/week.

A 26-week intravenous injection (once weekly) toxicity study in the cynomolgus monkey with a 13-week recovery period (Study 0770203)

The aim of the study was to investigate the potential toxicity of secukinumab following weekly intravenous injections to cynomolgus monkeys for 26 weeks and to assess the reversibility of any toxic effects within a 13-week recovery period.

There were no deaths during the course of this study or adverse secukinumab-related effects on clinical observations, body weights, appetite, ophthalmology, neurological assessments, electrocardiogram, urinalysis parameters, organ weights, macroscopic, microscopic changes, immunogenicity, mean NK cell activity, mean total and absolute lymphocyte subset counts or mean relative percentages of peripheral blood lymphocytes at doses up to 150 mg/kg for 26 weeks and in hematology parameters in males and females given secukinumab at doses of 15 or 50 mg/kg.

Some variations in the primary anti-KLH IgM and anti-KLH IgG response could be observed between groups. In females at 150 mg/kg/week, a secukinumab-related decrease in anti-KLH IgG concentrations could not be entirely ruled-out, however, the decrease was considered minimal, reversible, and non-adverse. Secukinumab administration did not interfere with the ability of treated animals to produce an anti-KLH IgM and IgG response. There were no treatment-related pathological changes on immune tissues during the treatment and recovery periods.

A mild transient skin rash was observed in one high-dose female monkey. An infectious origin of this lesion could not be established, and the findings were mild and self-limiting despite continued treatment. The rash was superficial and was not associated with other clinical changes, such as decreased food consumption/body weight loss. A decreased in NK cell activity and decreased anti-KLH IgM and IgG levels and a minimal splenic lymphoid atrophy were observed in this animal.

A decrease in neutrophil counts (-40% vs. control) was observed at a dose of 150 mg/kg/dose starting from week 13 in males only. At the end of the recovery phase, there was a mild persistent decrease in the neutrophil count (-53% vs. control) in one male, at 150 mg/kg. Minimal reversible changes in red blood

cell parameters were seen in females at a dose of 150 mg/kg. Administration of secukinumab at doses ≥15 mg/kg was associated with minimal to mild increases in globulin concentration compared to the placebo control group and pre-treatment values. There were minimal to mild increases in globulin (7% to 15% compared to control group) in males given 150 mg/kg in week 13, in males given 150 mg/kg and females given ≥15 mg/kg in week 26.

Secukinumab administration was well tolerated at the injection sites. There were no treatment-related pathology changes during the treatment and recovery periods.

The levels of total IL-17A were highly variable between animals and started to be detected from 8h, 24h or later after the first dosing. Complete total IL-17A profiles above the LLOQ were detected for the majority of the animals at all dose levels. Subsequent weekly dosing seems to increase the total IL-17A concentrations in serum. Based on the considerable variability between subjects, a gender specific difference with regard to IL- 17A secretion and capture appears to be unlikely.

No evidence of immunogenicity was found in animals tested for anti-secukinumab antibodies.

The no observed adverse effect level (NOAEL) was considered to be 150 mg/kg.

Interspecies comparison

Using a population PK model based on pharmacokinetic data from several IV and SC studies in psoriasis patients, mean concentration-time profiles resulting from the dose regimens in the phase III program were simulated.

The PK modelling confirms the high exposure multiples from the cynomolgus monkeys to humans.

Genotoxicity

Based on the ICH Guideline for the Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH S6(R1) 2011), genotoxicity studies have not been conducted for secukinumab which is acceptable to CHMP.

Carcinogenicity

Based on the following considerations conventional carcinogenicity studies were considered not appropriate for secukinumab because:

- Secukinumab a human monoclonal antibody is not pharmacologically active in rodents,
- carcinogenicity studies are not feasible in cynomolgus monkey,
- based on the weight of evidence in the literature available to date in preclinical models, neutralizing IL-17A does not suggest an increase tumor promoting risk, and
- the IgG1 chemical structure itself does not represent a carcinogenic risk.

There is strong *in vivo* evidence supporting a role for IL-17A in promoting tumors. Anti-IL-17A may therefore have an anti-tumorigenic effect. Conversely, there is evidence supporting a role for IL-17A therapy in tumor immuno-surveillance. Anti-IL-17A therapy may therefore impair this tumor immuno-surveillance and reduce the effectiveness of anti-tumor immune responses.

Available literature data suggest that IL-17A has both pro-tumor and antitumor activity, depending on the model used and the types and stages of tumors transplanted. Based on the weight of evidence in the literature available to date in preclinical models, neutralizing IL-17A does not suggest an increase tumor promoting risk, and the IgG1 chemical structure itself does not represent a carcinogenic risk. However, the effects of neutralizing IL-17A or other IL-17 family members on tumor growth in humans have yet to

be explored. Secukinumab is not a potent immunosuppressant and the risk of tumor induction (e.g. skin cancer, lymphoma) by oncogenic viruses is considered to be low. Furthermore, neutralizing IL-17A should not grossly affect the key anti-tumor immune defense mechanisms (Th1-type responses, CTLs and NK cells), supported by the fact that secukinumab had no adverse effect on immune function parameters (T cell-dependent antibody responses (TDAR) or NK cell function) and did not induce signs of lympho-proliferative disease at dose levels of up to 150 mg/kg within chronic monkey toxicology studies. In addition, so far no indication for an increased incidence or progression of malignancies was observed in psoriasis clinical studies.

Reproduction Toxicity

The potential embryonic and teratogenic effects of secukinumab were investigated following weekly subcutaneous administration to the pregnant cynomolgus monkey during the period of organogenesis.

The potential effects on fertility and early embryonic development as well as pre- and post-natal development were evaluated in the mouse using BZN035, a murine anti-IL-17A antibody.

A once weekly subcutaneous injection fertility study in the mouse (Study S497027)

The objective of this GLP study was to investigate the effects of BZN035, a murine anti-IL-17A antibody, when administered once weekly by subcutaneous injection to CD-1 (Crl:CD1 [ICR]) mice, on the reproduction and fertility of the F0 generation and on the early *in utero* development of the F1 generation.

There were no mortality or test article-related effects on clinical signs in males or females at any dose. Body weights, body weight gains and food consumption were unaffected by BZN035. There were no BZN035-related effects on the estrous cyclicity, including the number of days in estrus, the number of cycles seen and the average cycle length of observed cycles. The mean day to mating, mating and fertility indices and conception rate were unaffected. The uterine parameters assessed (i.e., number of corpora lutea, implantation sites, live and dead fetuses, resorptions, and the pre- and post- implantation losses) were unaffected.

There were no effects on the absolute and relative organ weights or gross pathological findings attributed to BZN035. The administration of the BZN035 did not induce changes on the sperm motility or spermatozoa counts. Animals at all dose levels were exposed to the test article. Dose-dependent BZN035 concentrations were determined for all dose levels and all time points. Mean concentrations of BZN035 on gestation day 13 in females were 18.2, 70.8 and 159 µg/mL and on study day 64 in males were 271, 922 and 1740 µg/mL at doses of 15, 50 and 150 mg/kg/dose, respectively. With the analytical method used, a screening-positive signal was not detected in any of the mouse sera. Remaining drug in the samples may have interfered with the ability to detect an antibody response in the BZN035-treated animals.

The no observed effect level (NOEL) was considered to be 150 mg/kg/dose.

Embryo-fœtal development

A subcutaneous embryo-fetal development toxicity study in cynomolgus monkey (Study 0770202)

The objective of this GLP study was to investigate the embryo-fetal developmental effects of secukinumab, when administered subcutaneously to the pregnant cynomolgus monkey during the period of organogenesis and/or fetal development until day 90 of gestation.

No deaths were observed during the course of the study, and no effect of treatment on the incidence of prenatal loss was noted. There was no treatment-related effect on clinical signs and maternal body

weight. Reduced food consumption was seen sporadically in several animals of all groups, including the controls.

An increase incidence of misaligned vertebrae in the tail region, a well-known variation in cynomolgus monkeys, was observed for fetuses of high dose dams [37.5% (n= 6/16) at 150 mg/kg/once weekly]. The incidence of this skeletal finding in the secukinumab groups treated with 15 or 50 mg/kg [6.25% (n=1/16) and 12.5% (n= 2/16) at 15 and 50 mg/kg/once weekly respectively] was comparable to the occurrence in the control group [7.7% (n=1/13)]. Since misaligned vertebrae were also found in up to 31.3% of control fetuses at embryo-fetal development studies performed at the same contract research organization (Covance Münster, Germany) and, in addition their historical studies have also shown an increased incidence of misaligned vertebrae up to 41 % (in the studies that were concluded as negative. In skeletal assessment (x-ray) data from 63 monkeys (approximately 3 months' old) from 5 pre-and postnatal studies (historical data reference from Covance Münster, Germany) such findings were not detected. Furthermore, a pre-and post natal development study in mice (Study S497028) performed with a mouse surrogate antibody BZN035 did not show any treatment related skeletal findings on the F1 and F2 generation.

The exposure to secukinumab, as measured by Cmax and AUC_{0-168h} day 90 of gestation, increased in a dose-proportional manner over the dose range 15 – 150 mg/kg and the apparent maximum exposure to secukinumab was observed at 53.5 h ± 32.6 h as expected for subcutaneous injection. Compared to maternal serum, 3.4 to 5.1 -times lower secukinumab concentrations were observed in fetal serum and 29 to 37 -times lower secukinumab concentrations in amniotic fluid on Day 100. There was no incidence of anti-drug antibody formation in any animal.

Prenatal and postnatal development, including maternal function

A subcutaneous injection pre and postnatal study in the mouse with dose administration on gestation days 6, 11 and 17, and on post-partum days 4, 10 and 16 (Study S497028)

The aim of this GLP study was to evaluate the effects of a murine anti-IL-17A surrogate antibody (BZN035) upon gestation, parturition and lactation (treated on gestation days 6, 11 and 17, and on *post partum* days 4, 10 and 16) in the dam and the development of the pups and their survival, physical development, behavior and reproductive performance. In addition, toxicokinetic and immunology/immunogenicity evaluations were performed. There were no BZN035-related effects on F0 generation. For the offspring (F1 generation), there were no effects on survival, growth, development, behavior or reproductive performance. BZN035-related changes were observed in lymphocyte populations in the thymus, spleen and blood. These changes are likely pharmacology related. The no observed adverse effect level (NOAEL) for the F0 generation and for the F1 generation was considered to be 150 mg/kg/dose. There was no effect on the F2 generation.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

Since the submission aims at treatment of adult patients juvenile animal studies are not needed. This was agreed by the CHMP.

Toxicokinetic data

The average serum concentrations at steady-state observed in monkeys after 13 weekly sc doses are 217- and 108-fold higher than the predicted average serum concentrations expected in patients treated with monthly maintenance sc doses of 150 mg and 300 mg, respectively. At the end of the induction phase, human exposure is approximately 2-fold higher than during the maintenance phase. Therefore, exposure multiples are approximately half of those described above during the induction phase.

Local Tolerance

Based on the evaluation of injection sites in the repeat dose toxicity studies secukinumab was well tolerated and no significant reactions were noted.

Other toxicity studies

Other studies included human and cynomolgus monkey blood hemolysis and compatibility assays (study RD-2005-00699), and an antibody-dependent cellular cytotoxicity (ADCC) assay with human cells (study RD-2005-00898). In addition, two human and cynomolgus monkey tissue cross-reactivity studies (Studies 0480141 and 0670394) were performed with secukinumab derived from different cell lines (Sp2/0 and CHO).

The data showed that secukinumab proved to be compatible with both human and cynomolgus monkey serum and plasma, and it did not cause blood hemolysis in either species and that secukinumab does not have an ADCC activity.

Most of the secukinumab-specific staining of the human tissues was cytoplasmic. However, this reactivity most likely would be of little to no toxicological importance as the intracellular compartment would not be expected to be available to monoclonal antibodies *in vivo*.

In cynomolgus monkey tissues the cytoplasmic staining observed in kidney tubular epithelium, alveolar macrophages, pituitary pia mater, placental Hofbauer cells, splenic follicular dendritic cells, and thymic capsule and stromal fibers are most likely of little to no toxicologic importance as the intracellular compartment would not be expected to be available to monoclonal antibodies *in vivo*. Due to the potential for *in vivo* exposure of the basal lamina to secukinumab, there would be the potential for antibody binding *in vivo* with subsequent immune response and toxicity. However as no toxicities were recorded *in vivo*, the staining differences in cynomolgus monkey can be considered not to be significant.

The same secukinumab material was used in one of the 4 week repeat dose toxicity studies. Relevant toxicological findings in the same tissues in which basal lamina was stained were not observed, thus, giving reassurance that the reactivity seen in the tissue cross-reactivity study is of negligible significance.

In general, secukinumab-specific staining was similar between human and cynomolgus monkey tissues. A difference in staining pattern between the two species was seen in the staining of mononuclear cells consistent with macrophages in cynomolgus monkey liver and spleen and hematopoietic precursor cells in human bone marrow. As no organ toxicities were noted *in vivo*, the staining differences in cynomolgus monkey can be considered insignificant.

Immunotoxicity

Four studies were conducted to address the risk of infection: lung tuberculosis infection model (iTox RD-2010-00463); oral candidiasis after *in vivo* treatment with neutralizing anti-IL-17 A or anti-IL-17F antibodies (Study 1270309); *Mycobacterium tuberculosis* infection in mice in comparison with neutralizing TNF-a treatment (Study 1280723); acute tuberculosis aerosol infection model (RD-2010-00463). The data did not suggest that secukinumab treatment would increase the risk of Mycobacterium infection. These data suggested that neutralisation of IL-17A cytokine does not impair immunity to acute *M. tuberculosis* infection in the mouse and that neutralization of IL-17 or IL-12/p40 has no significant effect on host resistance to acute Mycobacterium tuberculosis infection over 4 weeks in mice.

2.3.5. Ecotoxicity / environmental risk assessment

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

2.3.6. Discussion on non-clinical aspects

Multiple *in vitro* and *in vivo* studies were conducted with secukinumab. Secukinumab binds with high affinity to human IL-17A (K_D ~ 60 – 370 pM; average approximately 200 pM) and human IL-17AF heterodimer (K_D ~ 2 nM) and with weak affinity to IL-17F homodimer (µM). Although the binding of secukinumab to IL-17F was weak, it was specific.

Secukinumab is selective for IL-17A, and has lower cross-reactivity with IL-17AF and IL-17F. It does not cross-react with the other IL-17 family members i.e. human IL-7B, IL-17C, IL-17D and IL-17E or other unrelated cytokines such as IL-1β, IL-6, IL-13, IL-18, IL-19, IL-20, IL-22, IL-23, TGFβ1, TGFβ2, IFNγ, IL-2 and TNFα. Low level (unspecific or specific) binding to IFNγ was detected by SPR, which was considered unlikely to have clinical relevance.

Secukinumab functions by directly competing with IL-17 receptor for IL-17A and IL-17AF and with low affinity IL-17F binding through steric hindrance. Secukinumab dose-dependently inhibited the release of pro-inflammatory mediator IL-6 induced by IL-17A. Secukinumab neutralizes the biological activity of recombinant human IL-17A and IL-17AF *in vitro* (IC_{50} 0.14 – 0.4 nM and 3.30 nM, respectively) and IL-17F with a lesser extent (IC_{50} ~2µM). According to these *in vitro* potency results, secukinumab primarily acts through inhibiting the activity of IL-17A and potentially also IL-17AF. Although the binding of secukinumab to IL-17F is considered specific, and a weak interaction is evident by SPR, the neutralisation potency *in vitro* was 12 800 -fold weaker as compared to IL-17A. Thus, it is not likely that *in vivo*, IL-17F would contribute to clinical activity of secukinumab at the recommended doses in psoriasis patients.

Functionally *in vivo*, secukinumab inhibited IL-17A induced inflammatory reactions in two mouse models, the knee joint inflammatory model and the air pouch model where human IL-17A was produced locally. Secukinumab inhibited joint swelling significantly and prevented reduction of proteoglycan synthesis *ex vivo* in the mouse arthritis model. Secukinumab also inhibited the IL-17A induced infiltration of polymorphonuclear leucocytes in the mouse air pouch model with ED_{50} being 5.4 mg/kg. No *in vivo* studies have been conducted with secukinumab in animal models of psoriasis-like pathology.

Secukinumab recognizes IL-17A from cynomolgus, rhesus and marmoset monkeys. Secukinumab binds to cynomolgus monkey IL-17A with 11 – 26 –fold lower affinity than to human IL-17A, and with <2 -fold lower affinity to cyIL-17AF heterodimer as compared to huIL-17AF. The binding affinities of secukinumab to cynomolgus monkey and human IL-17F are similar. The *in vitro* neutralisation potency of secukinumab towards cynomolgus monkey IL-17A is significantly lower than towards human IL-17A. Secukinumab concentration of ≥0.1 µM (cyIL-17A) and ≥1 µM (cyIL-17F)was required to have an inhibitory effect on cynomolgus monkey IL-6 release on primary cynomolgus monkey synoviocytes and 10 µM concentration was required to completely block the effects of cyIL-17A and cyIL-17F in cynomolgus monkeys, whereas IC_{50} for human IL-17A was 0.14 nM on human primary synoviocytes.

Secukinumab does not recognize mouse and rat IL-17A, and therefore mouse surrogate antibody BZN035 was developed. BZN035 is specific for rat and mouse IL-17A and does not bind to human IL-17A. BZN035 binds to murine IL-17A with similar binding affinity (K_D ~ 70 pM) as secukinumab binds to the human IL-17A. However, BZN035 does not recognize IL-17F and the affinity to IL-17AF has not been analysed. Similarly to secukinumab, BZN035 does not cross-react with other IL-17 family members or with other

unrelated cytokines. Functionally, BZN035 neutralizes the IL-17A activity *in vitro*. *In vivo*, the biological activity of BZN035 in terms of neutralizing effects of mouse IL-17A (ED_{50} ~2 mg/kg) was comparable to ED_{50} for secukinumab in the human IL-17A.

Secukinumab showed expected binding to recombinant Fcγ- and FcRn receptors typical for a human antibody of the IgG1 isotype. Secukinumab binds to recombinant human and cynomolgus monkey FcRn at pH 6.0 with similar affinity, being ~3 µM for human FcRn and ~4 µM for cynomolgus monkey FcRn. Secukinumab is a soluble monoclonal antibody carrying a human IgG1 Fc-domain and thus, in theory is able to interact with Fcγ receptors. However, the Fc-mediated effector functions are not considered to be part of the mode of action of secukinumab and secukinumab did not elicit ADCC.

A safety Pharmacology study conducted in cynomolgus monkeys revealed no significant adverse treatment related effects on CNS, respiratory and cardiovascular functions after *i.v.* administration of secukinumab up to 100 mg/kg dose (NOAEL = 100 mg/kg).

The evaluation of pharmacokinetics was performed in cynomolgus monkeys in three single dose non-GLP studies to investigate the disposition of secukinumab administered via intravenous and subcutaneous routes. Additionally, a comparative study to evaluate pharmacokinetics of Sp2/0-derived and CHO-derived secukinumab after a single subcutaneous administration was performed.

The absorption pharmacokinetics of Sp2/0-derived and CHO-derived secukinumab after a single subcutaneous administration was evaluated in male cynomolgus monkeys. The pharmacokinetic behavior was typical of an immunoglobulin molecule with low serum clearance and long half-life. The half-lives determined for the Sp2/0 and CHO-derived secukinumab were 20 and 24 days, respectively. The peak concentrations of secukinumab occurred between 48 and 96 hours following subcutaneous administration of a single dose of 15 mg/kg. The bioavailability of secukinumab estimated after a single subcutaneous administration was 94% with Sp2/0-derived material, whereas bioavailability of 62% was observed with CHO-derived secukinumab. The mean AUC values after subcutaneous dosing, however, were very similar in both studies. Taking into account that only two animals per sc or iv dosing arm were used in both studies, no conclusion can be made about this difference in absolute bioavailability across the two studies.

The head-to-head comparative pharmacokinetic study with Sp2/0 and CHO-derived secukinumab did not show relevant differences between the materials but, however, difference cannot be excluded due to a small sample size in this study.

The mean volumes of distribution at steady-state were 74.5 mL/kg and 59.0 mL/kg for Sp2/0- and CHO-derived secukinumab, respectively. This corresponds to the blood volume (approximately 73 mL/kg) in cynomolgus monkey, indicating that the distribution of secukinumab is primarily restricted to blood.

Secukinumab was transferred across the placenta in cynomolgus monkeys and in marmosets after a single intravenous administration during pregnancy at approximately Day 100. Fetal exposure to secukinumab was detected at the level corresponding approximately 2% of the mean maternal serum concentration.

Two antibodies were used to characterize the safety profile of secukinumab and anti-IL17A therapy: secukinumab itself and a mouse anti-mouse IL-17A surrogate antibody BZN035. The cynomolgus monkey was selected as a relevant species for evaluation of toxicity since secukinumab cross-reacts with cynomolgus, rhesus and marmoset monkey IL-17A but not with the rodent IL-17A.

Binding of BZN035 (surrogate anti-mouse antibody) to mouse IL-17A was comparable to binding of secukinumab to human IL-17A and similarly, neutralization of the bioactivity of IL-17A with BZN035 was

comparable to secukinumab. Systemic exposure to BZN035 in mice also showed systemic exposure above the exposure to secukinumab in human.

Single subcutaneous injection of secukinumab to the monkey at doses of 15 or 150 mg/kg followed by a 7- or 28-day observation period was well tolerated. There were no secukinumab-related changes in any parameters evaluated.

Repeat dose toxicity of secukinumab derived from the Sp2/0 (process A) and CHO (process B1) cell lines was evaluated four 4 weeks after once weekly intravenous administration at dose levels of 0, 10, 30 and 100 mg/kg or at 0, 15, 50 and 100 mg/kg, respectively. Secukinumab was well tolerated. The NOAELs were determined to be the highest dose levels tested i.e. 100 or 150 mg/kg for the process A and process B1 secukinumab, respectively. There were no toxicologically or clinically meaningful differences between secukinumab derived from the processes A and B1.

Long term repeat dose toxicity of CHO-derived secukinumab was investigated in cynomolgus monkeys for 13 weeks after once weekly subcutaneous administration and for 26 weeks after once weekly intravenous administration. Secukinumab was well tolerated. The main findings were pharmacology related decrease in lymphocyte counts and decrease in anti-KLH antibody response. Additionally, mild primarily reversible neutropenia was observed in the 26 weeks study. A mild transient skin rash was observed in one high-dose female monkey. It was associated with a decreased NK cell activity and decreased anti-KLH IgM and IgG levels and a minimal splenic lymphoid atrophy.

Toxicokinetics indicated a slight accumulation of secukinumab after repeated dosing. Terminal half-lives across studies were 343±126h and 372±101h for male and female cynomolgus monkeys, respectively.

Immunogenicity was observed in one animal in the 13 week repeat dose toxicity study. However, due to assay interference caused by high serum concentrations of secukinumab, occurrence of anti-secukinumab antibodies cannot be excluded.

In line with the ICH S6 Guideline for the Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH S6(R1) 2011), genotoxicity or carcinogenicity studies were not conducted with secukinumab. A comprehensive carcinogenicity risk assessment was performed providing weight of evidence that secukinumab would not significantly increase the risk of cancer. However, the risk cannot be excluded and thus, secukinumab may carry a potential risk for cancer. This risk has been described in the RMP.

In the mouse fertility and early embryonic development study, the murine surrogate antibody, BZN035 was well tolerated in males and females after weekly subcutaneous dosing and resulted in no evidence of adverse effects on the reproductive function, fertility and early embryonic development in any of the treated groups. The no observed effect level (NOEL) was considered to be 150 mg/kg/dose.

Weekly subcutaneous administration of secukinumab to pregnant cynomolgus monkeys at dose levels of 0, 15, 50 or 150 mg/kg/day from day 20 to 50 or day 20 to 90 of gestation did not elicit maternal toxicity, embryo-fetal toxicity or teratogenicity. The NOAEL was established at 150 mg/kg/dose.

In the pre- and post-natal developmental toxicity study, the data showed that apart from pharmacology related effects on lymphocyte counts no treatment related effects on pre- and post-natal development was observed.

Secukinumab proved to be compatible with both human and cynomolgus monkey serum and plasma, and it did not cause blood hemolysis in either species.

Tissue cross-reactivity of secukinumab was similar between human and cynomolgus monkey tissues. The only difference was the staining of mononuclear cells consistent with macrophages in cynomolgus

monkey liver and spleen and hematopoietic precursor cells in human bone marrow. Tissue cross-reactivity of secukinumab derived from the Sp2/0 (process A) and CHO (process B) cell lines revealed no toxicologically relevant findings. The staining pattern was principally similar between the secukinumab products from different sources.

Human and animal data indicate that there is a risk for certain infections in the context of interfering with IL-17A-mediated immunity. However, IL-17A neutralization does not seem to be broadly immunosuppressive but may impair host resistance to certain infectious agents. Further, an increased incidence of certain types of infections was reported in the clinical studies with secukinumab. Based on this it can be concluded that there may be an infection risk to patients treated with secukinumab and has been described in the product information and in the RMP.

2.3.7. Conclusion on the non-clinical aspects

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

A comprehensive non-clinical data package was submitted which adequately provides evidence on target specificity and mode of action i.e. neutralising the IL-17A related cellular events. Secukinumab is specific to human and non-human primate IL-17A and does not recognise the murine counterparts. Therefore, non-clinical safety testing was partially conducted with a murine IL-17A specific surrogate molecule.

During the development of secukinumab, several drug substance manufacturing changes were introduced. Non-clinical PK comparability study proved to be inclusive with regard to comparability of the secukinumab drug products derived from the two cell lines. In terms of safety, the bridging toxicity studies did not reveal relevant differences between the secukinumab products from the manufacturing processes A and B. Thus, they can be considered comparable.

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

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

The risks of infection and potential for tumour promotion for patients treated with secukinumab have been described in the RMP.

Overall, the non-clinical data is sufficient for authorisation of secukinumab in adult patients with psoriasis.

Secukinumab is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, secukinumab is not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Source of data	Details
Dose-selection trials (Ph II)[a]	5 randomized, double-blind, placebo-controlled, dose finding A2204, A2102, A2211, A2212, A2220
Placebo-controlled trials (Ph III)	4 randomized, double-blind A2302, A2308, A2309 and A2303 (also etanercept-controlled)
Individualized maintenance regimen trials (Ph III)	1 randomized, double-blind, individualized maintenance regimen A2304, with supportive data from 1 randomized, double-blind, maintenance dose comparison A2307
Trials used for combined efficacy analysis (Ph III)	Induction period (12-week efficacy): A2302, A2303, A2308, A2309 Induction and Maintenance periods (52-week efficacy): A2302, A2303, A2304
Long-term data (Ph II-III)	3 pivotal, randomized, double-blind, phase III trials A2302, A2303, A2304 with patient exposure up to 52 weeks 1 open-label extension trial A2211E1 with combined patient exposure of up to 175 weeks (32 weeks in A2211 and up to 143 weeks in A2211E1)
Other sources of efficacy data	No other data (e.g. publications) are used to support the claim

a: Study A2204 was excluded from analyses due to GCP noncompliance issues identified by the sponsor's audit.

2.4.2. Pharmacokinetics

The pharmacokinetic data of secukinumab aim to describe the disposition of the compound to support proposed dose recommendations and to identify subgroups in which exposure might be altered.

Twenty-two studies have been submitted to support the current application (**Table 9**). One study, efficacy of influenza vaccination in subjects exposed with secukinumab, did not include any pharmacokinetic (PK) and is not included in the following assessment (A2224).

Secukinumab, a monoclonal Ab, has been assessed with respect to dose proportionality, absolute bioavailability following s.c. administration, bioequivalence between formulations, ethnic differences and distribution to the skin based on six of these studies. The potential of drug-drug-interactions (DDI) between secukinumab and low molecular weight drugs are expected to be low and no *in vitro* or *in vivo* DDI studies have been performed. Secukinumab was administered as 2h iv infusions in the majority of the phase I/II studies but changed to sc injection before the pivotal studies.

Table 9 Overview of studies included in the clinical pharmacology package of Cosentyx

Description	Subject	Phase	Cell line	Formulation	Comment	Study
FTIM - Single - Multiple	RA pats, HV	I/II	Sp2/0	LYO 50 mg	iv - 0, 0.3, 1, 3, 10mg/kg - 1, 3, 10 mg/kg	A2101
BE	HV	I	CHO	LYO 150 mg PFS 150 mg	300 mg sc	A2106

Description	Subject	Phase	Cell line	Formulation	Comment	Study
F	Psoriasis	I	CHO	LYO 150 mg	- 1 mg/kg iv - 150 mg sc	A2103
Japanese - iv - sc	HV	I	CHO	LYO 150 mg	Single dose - 1, 3, 10 mg/kg - 150, 300 mg	A1101
Skin distribution	HV Psoriasis	I	CHO	LYO 150 mg	300 mg sc	A2225
DRF	Psoriasis	II	CHO	LYO 150 mg	25, 75, 150 mg sc	A2220
Serum monitoring						
PoM	HV	II	Sp2/0	LYO 50 mg	10 mg/kg iv	A2104
Safety/tolerability	HV	I	CHO	LYO 150 mg	10 mg/kg iv	A2228
PoC	Psoriasis	II	Sp2/0	LYO 50 mg	3 mg/kg iv	A2102
Dose finding	Psoriasis	II	Sp2/0	LYO 50 mg	0.3, 1, 3 mg/kg iv	A2204
Efficacy	Psoriasis	II	CHO	LYO 150 mg	150 mg sc	A2211
Dose finding	Psoriasis	II	CHO	LYO 150 mg	3, 10 mg/kg iv	A2212
PoC	Crohn's	II	Sp2/0	LYO 50 mg	10 mg /kg iv	A2202
Safety/tolerability	Crohn's	II	CHO	LYO 150 mg	3 mg/kg iv	A2202E1
PoC	Psoriatric arthritis	II	Sp2/0	LYO 50 mg	10 mg/kg iv	A2206
Safety/tolerability	Psoriatric arthritis	II	CHO	LYO 150 mg	3 mg/kg iv	A2206E1
PoC	Noninfectious uveitis	II	Sp2/0 CHO	LYO 50 mg LYO 150 mg	10 mg/kg iv 1, 3, 10 mg/kg iv	A2208
PoC	Ankylosing spondylitis	II	Sp2/0	LYO 50 mg	0.1, 1, 10 mg/kg iv	A2209
Safety/tolerability	Ankylosing spondylitis	II	Sp2/0	LYO 50 mg	3 mg/kg iv	A2209E1
Safety/tolerability	MS	II	CHO	LYO 150 mg	10 mg/kg iv	B2201
PoC	Dry eye syndrome	II	CHO	LYO 150 mg	10 mg/kg iv	CPJMR0092202
Efficacy	Psoriasis	III	CHO	LYO 150 mg	150, 300 mg sc	A2302
Efficacy	Psoriasis	III	CHO	PFS 150	150, 300 mg sc	A2308
Efficacy	Psoriasis	III	CHO	AI 150 mg	150, 300 mg sc	A2309

Absorption

In the clinical study A2106, after a single 300 mg s.c. dose (liquid formulation) in healthy volunteers, the peak concentration of secukinumab was 43.2 ± 10.4 µg/ml. The t_{max} was between 2 and 14 days after the administration.

Data for the population PK model in psoriasis were collected from the following clinical studies: A2102, A2103, A2211, A2212, A2220, A2302 and A2303. On the basis of this popPK model the following PK characteristics of secukinumab were determined:

- After a single s.c. dose of either 150 mg or 300 mg in plaque psoriasis patients, secukinumab reached peak serum concentrations of 13.7±4.8 µg/ml or 27.3±9.5 µg/ml, respectively, between 5 and 6 days after the administration.
- After initial weekly dosing during the first month, t_{max} was between 31 and 34 days.
- The peak concentrations at steady state ($C_{max,ss}$) following s.c. administration of 150 mg or 300 mg were 27.6 µg/ml and 55.2 µg/ml, respectively. The steady state is reached after 20 weeks with monthly dosing regimens.
- The patients exhibited a 2-fold increase in C_{max} and area under the curve (AUC) following repeated monthly dosing during maintenance compared with the exposure after a single dose of secukinumab.

The absolute bioavailability (F) of secukinumab following sc administration was determined in patients with chronic plaque-type psoriasis (study A2103). An exploratory, open-label, randomised, cross-over-like, multiple-dose design was used. Fourteen subjects participated in the study.

Half of the subjects received a sc injection on Day 1 and the other half a 2-h i.v. infusion of secukinumab and on Day 29 *vice versa.* Blood samples were collected up to 85 days after the first dose. Pre-dose samples were taken prior the second dose. Two different PK analyses were performed, non-compartmental analysis that applied carry-over corrections based on lambda z values observed after the second treatment and a compartmental model in a population framework.

The absolute F was calculated to 55% (90% CI 43-70) by non-compartmental analysis and to 63% (90% CI 55-71) by compartmental population analysis (Table 10).

Table 10 Mean(SD) PK of secukinumab following a single sc injection of 150 mg and a 2-h iv infusion of 1 mg/kg

	Intravenous	Subcutaneous
Dose	1 mg/kg	150 mg
C_{max} (µg/ml)	24.1(3.2)	11.8(3.8)
AUC (µg/ml.day)	441(103)	421(164)
AUC_{last} (µg/ml.day)	378 (70)	364(134)
t_{max}[a] (day)	–	8.5(1.0-14.0)
$t_{1/2}$ (day)	27.1(6.3)	22.2(7.8)
CL (ml/day)	0.22(0.07)	–
V_z (L)	7.1(2.4)	–
$F_{non\text{-}compart\ analysis}$ (%)	–	55% (90% CI 43-70)[a]
$F_{compart\ analysis}$ (%)	–	63 (90% CI 55-71)

[a] arithmetic mean 63(38)

Based on the popPK analysis, an average F of secukinumab was 73% in patients with plaque psoriasis. Across the studies, the F was calculated in the range between 60 and 77%.

Bioequivalence

LYO vs. PFS formulation

The biocomparability of secukinumab (300 mg s.c.) in LYO and PFS formulations was shown in the healthy subjects in the study A2106. The secukinumab was derived from CHO derived material. The 90%CI for ratio of means of AUC_{inf}, AUC_{last}, and C_{max} were (0.92, 1.08), (0.93, 1.08), (0.96, 1.12), which were all within the (0.8, 1.25) bioequivalence range.

LYO vs. PFS vs. AI

The planned pharmaceutical formulations i.e. a 150 mg/ml strength, as a LYO in vial, solution for injection in a PFS and as a 150 mg/ml solution for injection in a pre-filled AI/pen are similar, except sucrose is replaced by trehalose dehydrate and L-methionine is added in the liquid PFS and AI forms. No changes in secukinumab serum exposure were expected with these changes in formulations and injection devices. In the phase III studies, all other studies were conducted with the LYO in vial except in the study A2308 solution for injection in a PFS and in the study A2309 solution for injection in a AI were used.

In the studies A2308 and A2309 the doses and dosing regimens in moderate to severe plaque psoriasis patients were the same (see Table 11). The mean s.c. pre-dose concentrations of secukinumab were at a quite similar level at week 4 and 12 indicating that the device did not affect to the serum concentrations of secukinumab. The CV% in the pre-dose concentrations is large with all formulations/devices. The pre-dose concentrations demonstrate a dose-proportionality between s.c doses of 150 mg and 300 mg.

Table 11 Mean and pre-dose secukinumab serum concentrations (µg/ml) in phase III studies with different formulations/injection devices

	Study CAIN457A2302, LYO			Study CAIN457A2308, PFS			Study CAIN457A2309, AI		
	N	Mean (SD) (µg/mL)	%CV	n	Mean (SD) (µg/mL)	%CV	n	Mean (SD) (µg/mL)	%CV
150 mg, Week 4	230	44.9 (14.6)	32.5	56	42.9 (15.1)	35.2	57	50.7 (18.0)	35.7
300 mg, Week 4	226	87.2 (30.1)	34.5	55	84.8 (28.5)	33.7	56	107 (34.3)	32.2
150 mg, Week 12	216	22.8 (10.2)	44.6	55	24.1 (10.1)	42.0	51	28.0 (11.9)	42.3
300 mg, Week 12	219	44.8 (20.6)	45.8	49	47.4 (21.1)	44.5	55	58.4 (25.8)	44.2

Distribution

No study to determine traditional serum protein binding of secukinumab has been performed which is acceptable to the CHMP for an IgG mAb.

On the basis of the clinical study A2212, the mean volume of distribution during the terminal phase (V_z) following single i.v. administration ranged from 7.10 to 8.60 litres in plaque psoriasis patients, suggesting that secukinumab undergoes limited distribution to peripheral compartments.

Skin distribution in healthy subjects and psoriatic patients (A2225)

The distribution of secukinumab to the skin, in healthy subjects and psoriatic patients, was studied in an exploratory study following a single sc injection of 300 mg. In this study, the skin distribution of secukinumab, in healthy subjects and psoriatic patients, was studied following a single s.c. injection of 300 mg. Comparable dermal interstitial fluid (ISF) concentrations were seen in non-lesional and lesional skin in the psoriasis patients. The mean dermal interstitial fluid (ISF) concentration of secukinumab was 23% of the mean serum concentration on day 15 in healthy subjects. The dermal ISF concentrations in psoriasis patients were in the range between 28 and 39% of the individual serum concentrations.

Biotransformation

No specific *in vitro* or *in vivo* metabolism studies have been performed which is acceptable to the CHMP. The majority of IgG elimination occurs via intracellular catabolism, following fluid phase or receptor mediated endocytosis.

Elimination

The elimination $t_{1/2}$ of secukinumab was calculated to about 27 days independently if administered *via* an i.v. or a s.c. injection and is in the range expected for a human IgG mAb. The individual half-lives ranged from 18 to 46 days across the studies in psoriasis patients.

Mean systemic clearance (CL) following a single i.v. administration to psoriasis patients ranged from 0.13 to 0.36 L/day across the studies. Based on the popPK analysis, the mean systemic CL was 0.19 L/day in plaque psoriasis patients with a body weight of 90 kg. The CL was not impacted by gender and it was dose- and time-independent.

- **Excretion**

No specific elimination studies have been performed following injection with secukinumab. Secukinumab, an IgG Ab with a molecular weight of about 150 kDa is not expected to be excreted in the urine or secreted into the bile so the lack of specific excretion studies is acceptable to the CHMP.

Dose proportionality

The single and multiple dose pharmacokinetics of secukinumab in plaque psoriasis patients were determined in several studies with i.v. doses ranging from 1 x 0.3 mg/kg to 3 x 10 mg/kg and with s.c. doses ranging from 1 x 25 mg to multiple doses of 300 mg.

I.v. dose-proportionality of secukinumab

The dose-proportionality of secukinumab after i.v. administration in psoriasis patients were only examined in one clinical study (A2212). In this study exposure increased in approximately dose-proportional manner in the dose range of 1 x 3 mg/kg, 1 x 10 mg/kg and 3 x 10 mg/kg at days 1, 15 and 29.

The dose-proportionality of i.v. secukinumab was studied also in healthy Japanese males (doses: 1 mg/kg, 3 mg/kg and 10 mg/kg) in the study A1101 and C_{max} increased dose-proportionally and exposure increased almost dose-proportionally although not statistically.

In addition, in rheumatoid arthritis patients in the study A2101 the C_{max} increased approximately dose-proportional manner. A formal dose proportionality assessment was not conducted in this study.

S.c. dose proportionality of secukinumab

In the study A2220 dose-proportional increase in secukinumab trough concentrations at weeks 4, 8 and 12 were found over the studied dose range i.e. from 3 x 25 mg to 3 x 150 mg.

Influence of dose on CL

The estimated CL in the 3 biggest studies (studies A211 n = 393, A2212 n = 85 and A2302 n = 623) was consistent across the study arms.

In two smaller studies (A2103 n = 14, A2220 n =103) the CL deviated from the estimated typical CL of 0.19 l/day. In the study A2103 psoriasis patients appeared to have higher CL (lower exposure) and in the study A2220 psoriasis patients appeared to have a lower CL (higher exposure).

- **Time dependency**

The PK of secukinumab seems to be linear i.e. dose proportional, with no evidence of a time-dependent change in its CL.

The loading dose regimens selected for phase III studies i.e. five s.c. doses of 150 mg and 300 mg administered every week followed by dosing every 4 weeks provided an exposure range that lies within the exposure achieved with the single 3 mg/kg i.v. and 3 x 10 mg/kg i.v. doses. After i.v. administration of secukinumab, there is high peak concentration while the loading with s.c. doses lead to a slower build-up but more sustained exposure levels.

Special populations

- **Impaired renal function**

No study to determine PK in patients with renal insufficiency has been performed. This is acceptable to the CHMP since renal elimination of intact sekukinumab, an IgG mAb, is expected to be low and of minor importance.

- **Impaired hepatic function**

No formal study with administration of secukinumab in patients with hepatic impairment (HI) has been performed. IgGmAbs are mainly eliminated *via* intracellular catabolism and hepatic impairment is not

expected to influence clearance of secukinumab *i.e.* the lack of PK data in patients with hepatic impairment is acceptable to the CHMP.

- **Gender**

Gender was not found to have an influence on the clearance of secukinumab on the basis of the popPK analysis.

- **Race**

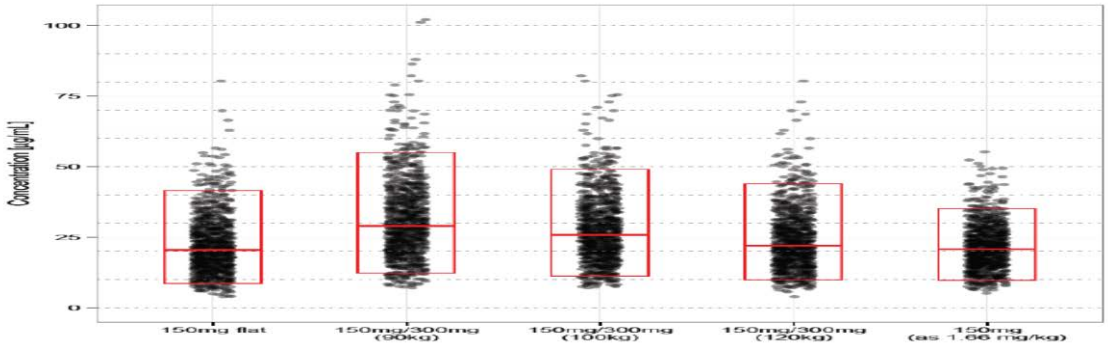
The PopPK model suggests that the race or geographic region has only minor effect on the CL and can be considered clinically not relevant.

- **Weight**

Body weight was found to be significant covariate on CL of secukinumab as determined in the popPK analysis. The relative CL was 38% lower and 55% higher for patients with a body weight of 58 kg and 134 kg, respectively.

Using the PopPK model, simulations of trough concentration at week 12 were performed to evaluate different body weight based dosing regimens. Flat dosing with 150 mg was compared to either dosing based on a bodyweight cut-off (150 mg/300 mg for patients below/above bodyweight thresholds of 90 kg, 100 kg, 120 kg) or to a hypothetical mg/kg s.c. dosing (1.66 mg/kg s.c., resulting in 150 mg for a 90 kg patient). A truncated log-normal distribution (geometric mean 90.9 kg, geometric CV ~28%, range 45 kg to 180 kg) was used to generate individual values of body weight. The result of the simulation is shown in Figure 3. From these simulations it was concluded that body weight based dosing regimens would not substantially decrease the expected variation between individuals.

Figure 3 - Simulated week 12 trough concentrations for different bodyweight based dosing strategies



- **Children**

No pediatric studies have been performed.

- **Elderly**

The database for the popPK model included 1195 psoriasis patients with information available on age, ranging from 18 to 83 years. The amount of plaque psoriasis patients exposed to secukinumab was reported to be 3430. In Table 12, the amount of ≥65 years and ≥ 75 years old psoriasis patients in the popPK model and in clinical studies are shown.

Table 12 Amounts of older (≥ 65 years) psoriasis patients in the PPK model and in the clinical studies.

	Age 65-74	Age 75≥
Patients involved in the popPK model	71 /1195	7/1195
Patients exposure to secukinumab	230/3430	32/3430

The inter-subject variability in the PK parameters

Inter-subject variability in the clinical studies with psoriasis patients was usually moderate or largein Cmax and AUCs of secukinumab. The pre-dose serum concentrations varied a lot and consequently, the CV%s were also large. In the studies with multiple dosing regimen and broad body weight range, the inter-subject variability increases.

Based on the popPK model, the derived inter-subject variability for PK parameters such as Cmin,ss, Cmax,ss, Cav,ss, AUCtau,ss for the 150 mg and 300 mg s.c. regimens in the phase III studies was in the range between 38.9% and 48.0%.

2.4.3. Pharmacodynamics

Mechanism of action

Secukinumab is a fully human anti-human IL-17A monoclonal antibody (IgG1 type) designed to selectively bind to and neutralise the human IL-17A homodimer with high affinity (K_D ~ 60 – 370 pM) and potency (0.14 - 0.4 nM). Via binding to IL-17, secukinumab inhibits the interaction of IL-17A with the IL-17RA receptor chain. While targeted as inhibitor of the IL-17A activity, secukinumab is designed for the treatment of inflammatory or autoimmune diseases entirely or partially driven by IL-17A. Secukinumab is selective for IL-17A, has lower cross-reactivity with IL-17AF and IL-17F and does not cross-react with the other IL-17 family members or cytokines.

Secukinumab binds to IL-17AF heterodimer, whose biological relevance it not well understood, with nM affinity and neutralise human IL-17AF with IC_{50} 3.3 nM. Albeit the affinity to IL-17F has not been determined due to weak interaction (µM), the binding is specific according to the competition experiment. The neutralisation potency of IL-17F *in vitro* is 12 800 -fold weaker as compared to IL-17A (IC_{50} ~2 µM) for secukinumab. Considering the clinical exposures after delivery of 300 mg secukinumab and higher affinity of IL-17F to IL-17RA and IL-17RC receptors (~10^{-7} M, ~10^{-9} M, respectively) as compared to the secukinumab (10^{-6} M), it is not likely that *in vivo*, IL-17F would contribute to clinical activity of secukinumab at the recommended doses in psoriasis patients.

Secukinumab recognizes cynomolgus, rhesus and marmoset monkeys IL-17A with lower affinity (6 – 30 -fold) and neutralisation potency (≥0.1 – 10 µM) as compared to human IL-17A, but does not cross-react with rat or mouse IL-17A. Therefore a mouse surrogate antibody BZN035 was developed.

Secukinumab binds to recombinant human and cynomolgus monkey FcRn at pH 6.0 with similar affinity, being ~3 µM for human FcRn and ~4 µM for cynomolgus monkey FcRn. Secukinumab is a soluble ligand carrying Fc-domain and thus, in theory is able to interact with Fcγ receptors. However the Fc-mediated effector functions are not considered as a mode of action of secukinumab, and secukinumab did not elicit ADCC.

Primary and Secondary pharmacology

Primary pharmacology

IL-17A levels

Total IL-17A

The effect of secukinumab on total IL-17A levels was studied in healthy volunteers (Study CAIN457A1101) and psoriasis patients (Study CAIN457A2309). The used method, MESO Scale Discovery electrochemiluminescence assay, detected both free IL-17A plus IL-17A bound to secukinumab.

Study CAIN457A1101 evaluated the total IL-17A levels after administration of secukinumab as a single intravenous infusion and subcutaneous injection to Japanese healthy male subjects. The results demonstrated high inter-individual variability. Following the 10 mg/kg i.v. dose, the total IL-17A concentrations increased over 14 days and the median peak concentration of 130 pg/ml was reached at approximately 3 weeks. The median duration of increase in total IL-17A increased with secukinumab dose, i.e. from 150 mg s.c. to 10 mg/kg i.v. In contrast to the peak serum concentrations of secukinumab that are reached shortly after infusion of secukinumab, IL-17A concentrations lagged behind the peak secukinumab concentrations after i.v. dosing.

In psoriasis patients (Phase III, Study CAIN457A2309), total IL-17A samples were collected at baseline, Week 4 and Week 12. The dosing regimen consisted of weekly s.c. administration (150 mg and 300 mg) for the first 4 weeks (i.e. 0, 1, 2, 3, and 4) and a further dose at Week 8. Median concentrations at Week 4 were 142 pg/mL and 121 pg/mL for the 150 mg and 300 mg s.c. doses, respectively. The IL-17A concentrations decreased to about 80 pg/mL at Week 12 after the two injections at week 4 and Week 8. Concentrations varied widely across patients.

Free IL-17A

In a small cohort, serum free IL-17A baseline levels was found to be significantly higher in psoriasis patients (n=8) vs. healthy volunteers (n=8) (adjusted geometric mean 0.53 vs. 0.20 pg/mL; $p<0.05$) (Study CAIN457A2225). Due to a complex formation of IL-17A with secukinumab, free IL-17A could not be measured after exposure to secukinumab.

Secondary pharmacology

Effects of secukinumab on tissue and soluble markers

Histology and immunohistochemistry

Sentinel psoriasis plaques were examined in two separate studies in psoriasis patients, (Study CAIN457A2102) and (Study CAIN457A2212), with the objective to assess the effects of secukinumab treatment at the molecular and cellular level in lesional skin. In Study CAIN457A2212, no statistically significant changes were observed in the expression of IL-17A (using semiquantitative scoring: 0, +1 to +4) after secukinumab treatment at doses between 1x3mg/kg and 3x10mg/kg (days 1, 15 and 29) i.v.

Histological changes and comparison to PASI scores

Treatment with secukinumab induced statistically significant reductions in the following parameters in the psoriatic lesional skin: acanthosis (hyperplasia of the epidermis), epidermal thickness, Ki67 (proliferative marker), Munro's abcesses (accumulation of polymorphonuclear leukocytes in the keratinous layer, histological hallmark of psoriasis), parakeratosis (retention of nuclei in the stratum corneum) and MPO positive cell counts (reflecting polymorphonuclear leucocyte count). Reductions in several histopathological features typical for the lesional skin of psoriatic patients were observed after

secukinumab treatment at doses between 1x3mg/kg and 3x10mg/kg i.v. paralleled by clinical PASI improvement.

Analysis of mRNA transcripts in lesional skin

Gene expression patterns from psoriasis lesions were analysed in the psoriasis proof-of-concept study (Study CAIN457A2102) after a single secukinumab dose of 3 mg/kg i.v. using quantitative RT-PCR and microarrays.

Reductions in the IL-17/Th17 pathway related transcripts (downstream markers, pro-inflammatory mediators) were seen after secukinumab treatment.

Studies of soluble protein markers

Studies in dermal interstitial fluid

In Study CAIN457A2225, interstitial levels of selected biomarkers were assessed in normal skin of healthy volunteers, non-lesional skin of psoriasis patients and lesional skin of psoriasis patients using open-flow microperfusion (OFM) technique.

Higher levels of free IL-17A was found in the psoriatic lesions vs. psoriasis non-lesional and HV normal skin in the exploratory open-flow microperfusion experiments.

Human beta defensin-2 (hBD-2) is a downstream marker of the Th17 pathway, i.e. the expression of hBD-2 in keratinocytes is enhanced by IL-17 producing Th17 cells. A significant decrease in the hBD-2 levels in the interstitial fluid were observed after single 300 mg s.c. dose of secukinumab.

Biomarker studies in peripheral blood

Serum IL-17F

Sequential IL-17F measurements were available from patient cohorts with psoriasis (Study CAIN457A2225), ankylosing spondylitis (Study CAIN457A2209) and multiple sclerosis (Study CAIN457B2201). Based on pooled analysis (BMD RCAIN457 IL17A and IL17F pooled analysis), no consistent changes over time were seen in the median serum IL-17F concentrations after secukinumab treatment.

Changes in other serum markers

Serum levels of hBD-2 in psoriasis patients were increased when compared to the healthy volunteers (adjusted geometric mean 5746 vs. 81.78 pg/mL; $p<0.0001$) and decreased after 300 mg s.c. dose of secukinumab. Statistically significant reductions in hBD-2 levels were also seen in psoriatic arthritis patients at 6 weeks after secukinumab 2x10mg/kg i.v. at weeks 0 and 3 (Study CAIN457A2206, secukinumab vs. placebo, $p=0.0009$). These reductions were most evident in patients with elevated baseline hBD-2 levels.

Peripheral immune cell compartment pharmacodynamics

Vaccination study

Effects of a single dose of secukinumab (150 mg s.c.) on the generation of protective antibody titers following either meningococcal or influenza vaccination were examined in Study CAIN457A2224. This was a Phase I, single center, open label, randomized, parallel group, single dose study. After a 14-day screening period the volunteers were randomized into 2 groups of 25 subjects each. Group A was treated with s.c. secukinumab on Day 1 and its subjects received the two vaccinations on Day 15; the control

group C received vaccinations only. An analysis of antibody concentrations (titer) was performed at different time-points up to Day 57.

The vaccines used were Menjugate, Novartis and Agrippal, Novartis. The 2 types of vaccines differ in both the antigenic component and the presence of adjuvant (only Menjugate® contains AlOH3 as an adjuvant). They were chosen in order to obtain evidence of T-cell dependent and independent memory response.

Vaccine efficacy was assessed as antibody titers at 0 (baseline), 2, 3, 4, 6 and 8 weeks, with vaccination at 2 weeks, for each vaccine and serotype. A responder to each vaccine/serotype at each time-point post-vaccination was defined in two ways. For both influenza and meningococcus, response was defined as a ≥4-fold increase in titer post-vaccination. For influenza, overall response was defined as a response in at least 2 out of 3 serotypes. The primary time point was 4 weeks post-vaccination.

Results

The primary endpoint of Study CAIN457A2224 was met e.g. the proportion of subjects with ≥4-fold increase in titer at 4 weeks post-vaccination was similar in patients receiving a single 150 mg s.c. dose of secukinumab vs. control groups for both influenza (at least 2 out of 3 serotypes) and meningitis vaccination. The protective antibody levels for the three influence serotypes (≥1/40) and meningococcal vaccine (≥1/8) were also similar starting at 2 weeks post-vaccination.

The fraction of subjects responding to vaccination was somewhat less in secukinumab treated subjects at the earlier 3 week time point, i.e. at 3 weeks (1 week post-vaccination) the proportion of subjects showing ≥4 increase in titer in secukinumab vs. control groups were 12% vs. 36% for Brisbane serotype, 16% vs. 28% for Perth serotype, 36% vs. 52% for California serotype and 32% vs. 40% for meningitis vaccine. Overall, the geometric mean titres were slightly lower in secukinumab vs placebo-treated subjects.

Infections and headache were reported more frequently in the secukinumab group in this small study.

Analysis of peripheral T cell subpopulations

Changes of peripheral T cell subpopulations during treatment with secukinumab after doses of 3mg/kg, 10mg/kg and 3x10mg/kg i.v. were investigated by Fluorescence-Activated Cell Sorting (FACS) analysis in psoriasis patients with or without ex vivo stimulation (Study CAIN457A2212, Bioanalytical data report: Quantification and characterization of Th17 and Treg cells in PBMCs). No significant changes with regard to visit 1 (screening) were observed in the majority of the T cell populations studied. The only statistically significant changes were observed at a single 12 week time point (increases in the Treg and CD4+/IL-17+/IL-22+ populations with the 3x10 mg dose level), but not at earlier (day 1, weeks 2 or 4) or later time points (week 28). At week 56 (end of study), the number of samples for analysis was limited.

Neutrophil counts

The Applicant conducted a neutrophil count analysis of pooled data from clinical pharmacology studies after secukinumab i.v. and s.c. doses. This pooled analysis was designed to assess the 4 week change in neutrophil count from all phase 1 and phase 2a trials included for the submission for psoriasis.

Secukinumab mildly reduced peripheral neutrophil counts at higher doses, i.e. at doses above 1 mg/kg i.v. and at 300 mg dose s.c. These finding are in line with the role of IL-17 in the homeostatic regulation of blood neutrophil counts (e.g. von Vietinghoff S, Ley KJ: Immunol. 2008 Oct 15;181(8):5183-8. Review) and can be regarded as a pharmacological effect of secukinumab. This pooled analysis has several limitations: the number of patients in subgroups was small, wide range of doses (single and multiple) was used across various indications and only a single time point (4 weeks) was used in the analysis.

Relationship between plasma concentration and effect

On the basis of the population PK/PASI analysis the 300 mg s.c. dose of secukinumab provided a consistent improvement compared to the 150 mg s.c. regimen regarding speed of onset, PASI 75 response at week 12 and PASI 75 response during the maintenance period. The higher exposure leads to higher response across the studied regimens.

Lower doses (75 mg s.c.) were shown to result in substantially lower response at week 12 that did not deliver a clinically meaningful efficacy benefit to psoriasis patients.

The modelled dosing regimen of every 4 weeks administration of secukinumab s.c. in the maintenance period was compared to alternative dosing regimens of every 8 weeks and every 12 weeks and it was shown that increasing the administration interval is likely to result in more patients losing their response over time.

In the pivotal clinical studies (i.e. A2302, A2303, A2308 and A2309) the pre-dose serum concentrations of secukinumab after 150 mg s.c. and 300 mg s.c. were analysed at different weeks. On the basis of the provided pre-dose serum concentration data of secukinumab (from studies A2302 and A2303 up to week 52 and from the studies A2308 and A2309 up to week 12) the mean pre-dose concentrations with 300 mg s.c. are about 2 times higher than with 150 mg s.c. dose.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Pharmacokinetic (PK) data indicated that the PK properties of secukinumab are typical of a human IgG1-type immunoglobulin interacting with a soluble cytokine target (i.e. IL-17A) without any sign of target-mediated disposition. The volume of distribution during the terminal phase and the clearance after a single i.v. administration were low in psoriasis patients. In addition, the elimination half-life is long both after i.v. and s.c. administration.

No PK parameters for 300 mg s.c. in psoriasis patients are available from the clinical studies. Only simulated PK parameters exist for the 300 mg s.c. dose. The selection the 300 mg s.c. dose in pivotal clinical studies was justified on the basis of the phase 2 data, modelling and simulation. The full PK profiles for secukinumab from repeated s.c. dosing regimens at various dose levels for C_{max} and AUC at steady-state are not available from psoriasis patients. In pivotal clinical studies only trough serum secukinumab concentrations were determined.

The CL was dose- and time- independent. Age, gender, race, regional groups and baseline disease severity (PASI) seemed to have no clinically relevant influence on CL of secukinumab after adjusting for body weight. The amount of elderly patients in the studies was, however, small and only cautious conclusions can be made on relation of age and CL.

The inter-patient variations in secukinumab trough serum concentrations, in maximum serum concentrations and in exposure to secukinumab are high on the basis of the provided PK data from studies and also from the simulation PK data and the inter-patient variability increases as body weight range expands. With both doses (150 mg and 300 mg) of secukinumab in psoriasis patients, the higher body weight leads to somewhat lower exposure. In general, the 300 mg secukinumab dose is associated with higher exposure and better clinical responses. An absolute threshold of secukinumab serum concentration for the response cannot be established.

On the basis of the provided PK data it seems that secukinumab pharmacokinetics is quite linear i.e. dose-proportional both after i.v. administration in the dose range from 1 x 0.3 mg/kg to 3 x 10 mg/kg and with s.c. administration from 1 x 25 mg dose to multiple doses of 300 mg, however, the

dose-proportionality conclusions after s.c. administration are justified only by the trough concentrations taken just before the next dose. The absolute bioavailability (F_{abs}) of s.c. secukinumab in psoriasis patients was estimated to be 73% on the basis of the PPK analysis. The range of F_{abs} across clinical studies was between 60 and 77%.

In the exploratory study, the skin distribution of secukinumab, in healthy subjects and psoriatic patients, was studied following a single s.c. injection of 300 mg. Comparable dermal interstitial fluid (ISF) concentrations were seen in non-lesional and lesional skin in the psoriasis patients. The mean dermal interstitial fluid (ISF) concentration of secukinumab was 23% of the mean serum concentration on day 15 in healthy subjects. The dermal ISF concentrations in psoriasis patients were in the range between 28 and 39% of the individual serum concentrations, which was thought to suggest a somewhat stronger distribution of secukinumab into skin of psoriasis patients compared to the healthy subjects.

No formal *in vitro* or *in vivo* DDI studies have been performed. The applicant has theoretically discussed the potential of possible DDI between secukinumab and small molecules and concluded that the clinical relevance of potential changes in CYP mediated metabolism of small molecules in psoriasis patients treated with Cosentyx is deemed unlikely. However, as pointed out by the applicant no reports are available in the literature evaluating the impact of cytokine levels/modulators on IL-17A and potential suppression of metabolising enzymes. The product information has therefore been updated to mention that the risk of DDI between secukinumab and a small molecule cannot be ruled out.

The used programs in secukinumab PK data analyses were appropriate. In most of the studies with secukinumab only descriptive statistics for secukinumab PK parameters was provided. In the studies where the statistical analyses were used, the methods were considered adequate.

The two-compartment PK model is able to adequately describe observed secukinumab concentration time courses. The PK/PASI model was based for the most part on the popPK model. The model may be used for the limited purpose of describing exposure–response at steady-state, but it is currently not capable of describing onset of effect.

Pharmacodynamics

Secukinumab binds to human IL-17A and neutralises its activity. In the clinical PD studies the engagement of IL-17A was seen as an increase in serum total IL-17A levels after secukinumab treatment, followed by a slow release of the IL-17A-secukinumab complex. No significant changes in the systemic levels of the structurally related IL-17F was observed after secukinumab treatment, which is in line with the non-clinical data demonstrating selective binding to the IL-17A. In the lesional skin of psoriatic patients, secukinumab treatment led to significant reductions in histopathological features, including reduced epithelial thickness and parakeratosis, decreased Ki67 positive keratinocyte counts (a measure of keratinocyte proliferation), early decreases of skin-residing innate immune cell populations (e.g. myeloperoxidase-positive neutrophils) and decreases in CD3+ T cell numbers. These changes were paralleled by clinical PASI improvements. Further exploratory studies were conducted by the applicant to demonstrate the anti-inflammatory effects of secukinumab and the effects of IL-17A blockade on the biomarkers of the IL-17A/Th17 pathway, e.g. hBD-2. Together with the preclinical data, these clinical PD data provide a sufficient rationale for the clinical development of secukinumab for the treatment of plaque psoriasis.

In some clinical PD studies, secukinumab was given i.v. at doses between 1 x 3 mg/kg and 3 x 10 mg/kg, instead of the s.c. dosing used in the phase III (150 mg and 300 mg) and the proposed dose in the SmPC (300 mg). According to the PK modelling, the loading dose regimens with five s.c. doses of 150 and 300 mg given every week followed by dosing every 4 weeks provides an exposure range that lies within the exposures achieved with the single 3 mg/kg i.v. and 3 x 10 mg/kg i.v. doses used in the clinical PD

studies. Therefore, the PD data using i.v. dosing is considered relevant for the demonstration of the pharmacological effects of secukinumab.

Secukinumab did not induce major changes in the circulating T cell subpopulations at doses between 3 mg/kg and 3 x 10 mg/kg i.v. in a 28 week study. A slight reduction in the neutrophil counts was observed at 4 weeks with higher doses, including 300 mg s.c., which may be explained by the pharmacological blockade of IL-17A that is involved in the regulation of granulopoiesis. Further, adequate immune responses to meningococcal and influenza vaccines were observed after a single 150 mg s.c secukinumab dose. The fact that secukinumab treatment in doses up to 3x10 mg/kg did not have major effects on the frequency and the balance of peripheral cytotoxic T cell and T helper cell populations suggests that an impact of secukinumab treatment on the immunologic mechanisms residing within these T cell populations is unlikely. Therefore, the applicant considered the probability for an impaired vaccine response at the 300 mg dose level as low and proposed the following update of the product information: "Live vaccines should not be given concurrently with Cosentyx. Patients receiving Cosentyx may receive concurrent inactivated or non-live vaccinations. In a study, after meningococcal and inactivated influenza vaccinations, a similar proportion of healthy volunteers treated with 150 mg of secukinumab and those treated with placebo were able to mount an adequate immune response of at least a 4-fold increase in antibody titres to meningococcal and influenza vaccines. The data suggest that Cosentyx does not suppress the humoral immune response to the meningococcal or influenza vaccines". This was agreed by the CHMP.

2.4.5. Conclusions on clinical pharmacology

The applicant provided in this dossier several studies, in which the PK of secukinumab was one of the objectives in the studies (usually a secondary objective or an exploratory objective); however, quite a lot of practical PK data for s.c. secukinumab are available and for the selected 300 mg s.c. dose in the pivotal clinical studies in psoriasis patients only trough concentration data exist. On the basis of the provided PK data, it can be inferred that for the s.c. administration of secukinumab, the 150 mg was thought to be the most suitable dose. The decision to include the 300 mg s.c. dose (which was proved to be more effective than 150 mg s.c. dose) in the pivotal clinical studies is, however, considered to be sufficiently justified based on the data in the dossier. The main PK parameters which seem to be quite similar after secukinumab administration regardless of the different indications or doses used are low clearance, low volume of distribution and long elimination half-live (after i.v. and s.c. administration almost equally long). The inter-patient variability in trough serum concentrations and in the few PK parameters which have been reported in psoriasis patients is moderate or high.

Together with the preclinical data, the clinical PD studies demonstrated that secukinumab binds and neutralises IL-17A. In psoriasis patients, secukinumab was shown to reduce the various pathological features typical for the lesional psoriatic skin. Therefore, the pharmacological effect in the target tissue has been sufficiently demonstrated.

Adequate immune responses to meningococcal and influenza vaccines were observed after a single 150 mg s.c secukinumab dose.

2.5. Clinical efficacy

2.5.1. Dose response studies

The following table summarizes the phase 2 studies performed in support of the proposed dose regimen for the phase 3 studies. Both intravenous and subcutaneous administration routes and different treatment schedules were used.

Table 13 Summary of short Phase II studies used for dose selection

Study	Description	N	Treatments	Key Efficacy	Key Conclusions
A2102	Single dose (i.v.) in target population	36	3 mg/kg secukinumab PBO	PASI, dPGA	Secukinumab has shown efficacy in psoriasis (proof of concept).
A2220	Dose-ranging (s.c.) in target population	120	25, 75, or 150 mg secukinumab ('monthly') at R, Wks 4, 8 PBO at R, Wks 4, 8	PASI 75, IGA mod 2009 (Wk 12)	Doses below 150 mg do not offer acceptable efficacy.
A2212	Multiple-loading dose regimen (i.v.) in target population	100	1 x 3 mg/kg secukinumab 1 x 10 mg/kg secukinumab 3 x 10 mg/kg secukinumab 3 x PBO	PASI 75, IGA mod 2007 (Wk 12)	Doses above 150 mg might offer improved efficacy.
A2211	Multi-dose regimen finding (s.c.) in target population	404	**Induction:** 1 x 150 mg secukinumab ('single dose') 3 x 150 mg secukinumab at R, Wks 4, 8 ('monthly') 4 x 150 mg secukinumab at R, Wks 1, 2, 4 ('early') 5 x PBO at R, Wks 1, 2, 4, 8 **Maintenance in responders:** *Fixed Interval (every 12 weeks):* 150 mg secukinumab at Wk 12, 24, PBO at relapse *Start of relapse:* 150 mg secukinumab, PBO at Wk 12, & Wk 24 (if did not experience start of relapse) **Treatment in partial or non-responders:** *Open label:* 150 mg s.c. q4w secukinumab until Wk 32	PASI 75, IGA mod 2009 (Wk 12)	An initial increased frequency induction regimen is beneficial. Maintenance treatment should be given monthly (every four weeks). Re-treatment at start of relapse might be beneficial for some patients.

IGA = Investigator's Global Assessment; PASI = Psoriasis Area and Severity Index; PBO = placebo; R = Randomization (baseline); Wks = weeks; dPGA = dynamic Physician's Global Assessment

Study A2102

This was a proof of concept two-arm, single i.v. dose study comparing secukinumab 3 mg/kg i.v. with placebo (18 subjects in each arm). Secukinumab showed reduction in PASI scores and IGA scores at weeks 2, 4, 8 and 12. After 4 weeks, the mean PASI score in the treatment group receiving secukinumab 3mg/kg was 58% lower than their baseline values and in the placebo group the corresponding reduction was 4%. At Week 12, 44% of the secukinumab-treated patients were PASI 75 responders. At 4 weeks,

83% of patients on secukinumab demonstrated reductions in IGA scores of 1 or greater compared with 11% in the placebo group.

Study A2220

Study A2220 was a dose ranging study of subcutaneously administered secukinumab that investigated the lower range of potential doses. The primary objective was the efficacy of 3 different doses of secukinumab s.c. administered monthly (25 mg, 75 mg and 150 mg) or as single administration of 25 mg with respect to PASI 75 achievement at Week 12 compared to placebo. Only the secukinumab 3×150 mg and 3×75 mg dosing regimens were superior to placebo in achieving PASI 75 at Week 12. For the key secondary objective of IGA score for overall psoriatic disease at Week 13, only the 3×150 mg dose was statistically superior to placebo, and only the 3×150 mg cohort achieved a statistically significant PASI 90 response rate in excess of 50% at Week 12.

Study A2212

Study A2212 was a four-arm study to assess the efficacy and duration of response of three different loading-dose regimes of secukinumab infusions administered i.v. (secukinumab 1 x 3 mg/kg, 1 x 10 mg/kg and 3 x 10 mg/kg) compared to placebo. The two primary objectives of the study were to compare the change from baseline in PASI scores at 12 weeks between the placebo and each of the loading-dose regimens of secukinumab, and to compare the proportion of patients who have not relapsed at any time up to week 56. All 3 secukinumab dose regimens resulted in statistically significant reductions in mean PASI score at Week 12 compared to placebo and the largest mean reduction in PASI score was seen with the 3 x 10 mg/kg regimen. There were no statistically significant differences in the proportion of relapse-free patients at any timepoint in the comparison of secukinumab 1 x 3 mg/kg vs. secukinumab 1 x 10 mg/kg single-dose regimens. However, for the 3 x 10 mg/kg vs. 1 x 3 mg/kg comparison, there were statistically significant differences between the groups at each visit from week 14 through week 40 with significantly fewer patients experiencing relapse in the secukinumab 3 x 10 mg/kg vs. the 1 x 3 mg/kg cohort. There is no statistically compelling comparative data available for the three different dosing regimens regarding efficacy at Week 12 but the magnitude of the clinical response increased with the administered dose.

Study A2211

Study A2211 was a regimen finding study of secukinumab 150 mg administered subcutaneously as a single injection, as monthly injections and as early loading injections (administered at weeks 0, 1, 2, 4) with respect to PASI 75 achievement at Week 12, compared to placebo. Key secondary objective was to compare the efficacy of a Fixed Interval (three months) and at Start of Relapse maintenance regimens of secukinumab 150 mg s.c. with respect to PASI 75 response from Week 20 to 28. The primary endpoint at 12 weeks was met in the monthly and early induction regimens when compared to placebo confirming that repeated doses are needed to achieve response. For the two dosing regimens, no statistically compelling comparative data is available but an ‘early’ loading dosing regimen was chosen for the phase III trials. For the maintenance period, a higher proportion of patients in the Fixed Interval treatment arm achieved PASI 75 response compared to the ‘Start of Relapse’ arm indicating the need for repeated continuous dosing of secukinumab to achieve efficacy. With respect to safety, it was considered that there were no clinically relevant regimen-related differences that limited the choice of induction or maintenance regimens.

Study A2211E1 (extension study to A2211) is an ongoing multicenter extension study of the core study CAIN457A2211 and includes an open label arm. The primary objective is to evaluate the long-term safety and tolerability of subcutaneously administered secukinumab 150 mg. All efficacy analyses are thus secondary. The majority of patients in this extension study were in the OL arm and therefore treated

at 4-week intervals. PASI 75 response rates above 50% were observed during the extension study in the OL group, consisting of initial non-responders. The group decreased from 187 to 96 subjects across the study period, though.

Modelling of phase I-II study data

The relationship between dose and regimen, as evaluated by the plasma secukinumab concentration and PASI response based on studies A2102, A2103, A2211, A2212, and A2220, was modelled using a sequential population PK/PD approach. The Applicant justified the 300 mg s.c. fixed dose approach and the 4-week fixed interval dosing for the maintenance period in the phase III trials based on modellingto support these regimens.

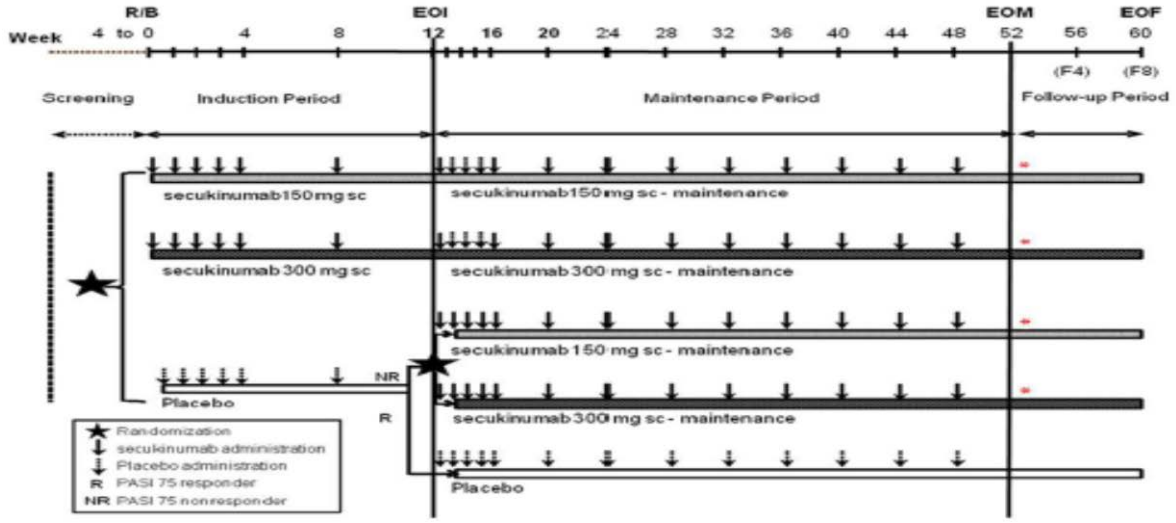
2.5.2. Main studies

Study A2302: Efficacy of Response And Safety of 2 Fixed Secukinumab Regimens in Psoriasis (ERASURE): A randomized, double-blind, placebo controlled, multicenter study of subcutaneous secukinumab to demonstrate efficacy after twelve weeks of treatment, and to assess the safety, tolerability and long-term efficacy up to one year in subjects with moderate to severe chronic plaque-type psoriasis.

Methods

This was a multicenter, randomized, double-blind, placebo-controlled, parallel group trial in 738 patients with moderate to severe chronic plaque-type psoriasis. The study consisted of 4 periods: screening (1-4 weeks), induction (12 weeks), maintenance (40 weeks) and follow-up (8 weeks) (see Figure 4).

Figure 4 - Study design



R/B = Visit 2, Randomization/Baseline visit. sc = subcutaneous.

Study Participants

Main inclusion criteria:

- Adults, at least 18 years of age;
- Diagnosis of chronic plaque-type psoriasis for at least 6 months prior to randomization;
- Moderate to severe psoriasis defined as PASI score of minimally 12 and IGA mod 2011 of at least 3 and a total BSA of minimally 10%;

- Candidate for systemic therapy, defined as having chronic plaque-type psoriasis considered inadequately controlled by:
    - topical treatment and/or
    - phototherapy and/or
    - previous systemic therapy

Main Exclusion Criteria

- Other forms of psoriasis than chronic plaque-type (e.g., pustular, erythrodermic and guttate psoriasis)
- Drug-induced psoriasis (i.e., new onset or current exacerbation from beta-blockers, calcium channel inhibitors or lithium)
- Ongoing use of prohibited psoriasis treatments (e.g. topical or systemic corticosteroids), ultraviolet (UV) therapy) or non-psoriasis prohibited treatments. All other prior non-psoriasis concomitant medications must be on a stable dose for at least four weeks before randomization.
- Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or the IL-17 receptor.
- Patients with the following conditions were excluded:
    - active ongoing inflammatory diseases; active, ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection (if presence of latent tuberculosis is established, then treatment must have been initiated and maintained according to local country guidelines prior to randomization);
    - underlying condition significantly immunocompromising the patient and/or places the patient at unacceptable risk for receiving an immunomodulatory therapy:
        - lymphoproliferative disease, malignancy, history of malignancy within the past 5 years; past medical history of HIV, hepatitis B or hepatitis C;
    - plans for administration of live vaccines during the study period or 6 weeks prior to randomization.
    - significant medical problems (current severe progressive or uncontrolled disease), including uncontrolled hypertension and congestive heart failure;
    - serum creatinine exceeding 176.8 µmol/L (2.0 mg/dL) or screening total white blood cell count <2,500/µL, or platelets <100,000/µL or neutrophils <1,500/µL or hemoglobin <8.5 g/dL;
    - any medical or psychiatric condition including history or evidence of ongoing alcohol or drug abuse up to 6 months before randomization which, in the investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol.
- Patients not willing to limit UV light exposure (e.g., sunbathing and/or the use of tanning devices) during the course of the study.
- Pregnant or nursing (lactating) women, and women of child-bearing potential

Treatments

The study consisted of 4 periods: screening (1-4 weeks), induction (12 weeks), maintenance (40 weeks) and follow-up (8 weeks). Patients were assigned to one of the following 3 treatment arms:

- Secukinumab 150 mg (one s.c. injection of the 150 mg dose + one s.c. injection of placebo) administered at Randomization, Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and placebo (two s.c. injections per dose) administered at Weeks 13, 14 and 15.
- Secukinumab 300 mg (two s.c. injections of the 150 mg dose) administered at Randomization, Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and placebo (two s.c. injections per dose) administered at Weeks 13, 14, and 15.
- Placebo group (two s.c. injections per dose) administered at Randomization, Weeks 1, 2, 3, 4, and 8.

At Week 12 (prior to receiving the Week 12 dose), patients in the placebo group were assigned to one of following treatment arms based on their PASI 75 response at Week 12:

- Placebo PASI 75 non-responder induction period/secukinumab 150 mg maintenance period: secukinumab 150 mg (one s.c. injection of the 150 mg dose + one s.c. injection of placebo) administered at Weeks 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, and 48.
- Placebo PASI 75 non-responder induction period/secukinumab 300 mg maintenance period: secukinumab 300 mg (two s.c. injections of the 150 mg dose) administered at Weeks 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, and 48.
- Placebo PASI 75 Responder induction period/placebo maintenance period: s.c. placebo secukinumab (two s.c. injections per dose) administered at Weeks 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44 and 48.

The study treatment solution was injected in non-affected areas of the skin and administered to one of the following body regions, changing the injection site from visit to visit: right thigh, left thigh, right stomach, left stomach.

Objectives

The primary objective was to demonstrate the superiority of secukinumab in patients with moderate to severe chronic plaque-type psoriasis with respect to both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared to placebo.

The key secondary objectives were:

• To demonstrate the superiority of secukinumab in patients with moderate to severe chronic plaque-type psoriasis with respect to PASI 90 response at Week 12, as compared to placebo.

• To assess the efficacy of secukinumab in maintaining PASI 75 response at Week 52 for patients who were PASI 75 responders at Week 12.

• To assess the efficacy of secukinumab in maintaining IGA mod 2011 0 or 1 response at Week 52 for patients who were IGA mod 2011 0 or 1 responders at Week 12.

• To demonstrate the superiority of secukinumab in patients with moderate to severe chronic plaque-type psoriasis with respect to psoriasis-related itching, pain and scaling as measured by the Psoriasis Symptom Diary at Week 12 compared to placebo.

Outcomes/endpoints

Efficacy assessments:

• Investigator's Global Assessment (IGA mod 2011; scale from 0 – 4): A subject was considered an IGA 0 or 1 responder if the following two conditions were met: score of 0 or 1 was achieved, AND if there was an improvement of 2 points or more compared to baseline

• Psoriasis Area and Severity Index (PASI; score 0 - 72): The following definitions were used:

  • PASI 50/75/90 response: a patient achieving ≥ 50%/≥ 75%/≥ 90%/≥ 100% improvement (reduction) in PASI score compared to baseline; PASI 100 response: complete clearing of psoriasis (PASI=0)

  • PASI non-response: a patient achieving <50% improvement (reduction) in PASI score compared to baseline

  • Partial response: a patient achieving ≥50% improvement (reduction) in PASI score but less than 75% compared to baseline

  • Relapse: >50% reduction in maximal PASI improvement from baseline

• Rebound assessment: an increase in PASI score to >125% of baseline, or the occurrence of new pustular psoriasis, or new erythrodermic psoriasis, or more inflammatory psoriasis within 8 weeks after last study treatment administration.

• Assessments performed at selected study sites on patients with PsA at randomization (defined as ≥ 3 points according to the CASPAR criteria, and ≥3 tender and ≥3 swollen joints): Patient's Global Assessment of disease activity (PtGA Activity); Patient's Global Assessment of psoriatic arthritis pain (PtGA Pain); Physician's global assessment of disease activity (PhGA PsA); Tender and swollen joint count; Erythrocyte sedimentation rate (ESR); and ACR response criteria (ACR20/ 50 /70).

Safety assessments:

• all AEs and SAEs, with their severity and relationship to study drug, and pregnancies

• hematology, blood chemistry, urine and regular assessments of vital signs, ECGs, physical condition, height and body weight

• immunogenicity

Other assessments:

• Waist and hip circumference

• Photography

• Health related quality of life assessments:

  • The Psoriasis Symptom Diary: The applicant developed and validated a novel electronic diary of psoriasis signs and symptoms reported by the patient. Diary assessments were not performed if the patient refused to participate or due to lack of available device at the site at the time of screening.

  • Patient Global Impression of Change (PGIC) via the electronic diary

  • Dermatology Life Quality Index (DLQI)

  • Health Status Questionnaire (EuroQOL 5-Dimension Health Questionnaire, EQ-5D)

• Health Assessment Questionnaire – Disability Index (HAQ-DI): only in patients who had psoriatic arthritis (PsA) prior to randomization.

Sample size

With a targeted total sample size of 720, 240 patients in each treatment group, the power for PASI75 and IGA mod 2011 0 or 1 respectively was above 99%.

Randomisation

Randomization occurred two times; the first one at randomization visit and the second one at Week 12. At Visit 2, all eligible patients were randomized in a 1:1:1 ratio to one of the three treatment groups. Prior to receiving the Week 12 dose PASI 75 non-responders in the placebo group were re-randomized 1:1 to 150 mg or 300 mg secukinumab.

Blinding

Patients, investigator staff, persons performing the assessments and data analysts remained blinded to the identity of the treatment from the time of randomization until end of follow-up database lock.

Statistical methods

The primary analysis method was the stratified Cochran-Mantel-Haenszel (CMH) test. The tests were stratified by geographical region and body weight stratum. In case of response rates of 0% or of 100% in one of the treatment groups, Fisher's exact test was applied.

If all efficacy post baseline values were missing for one efficacy parameter, then these missing values were not imputed and this patient was removed from the analysis. Missing values with respect to response variables based on PASI score and IGA score were imputed with non-response regardless of the reason for missing data. The last observation carried forward (LOCF) method was applied to PASI score and IGA score that were missing after baseline regardless of the reason for missing data. LOCF imputations were not considered for response variables based on PASI score or IGA. Further, additional sensitivity analyses were performed including multiple imputations.

Results

Participant flow

A total of 951 patients were screened at 88 study centers, and 738 were randomized in 86 centers to one of the three treatments groups (245 to secukinumab 150 mg, 245 to secukinumab 300 mg, and 248 to placebo). Of the 213 subjects who discontinued prior to screening phase completion, 196 were screen failures (i.e. did not meet inclusion/exclusion criteria).

Most randomized patients (700 i.e. 94.9%) completed the induction period (see Table 14). The most common reasons for discontinuation of induction treatment were subject/guardian decision (overall 2.4%) and AE (overall 1.6%).

Table 14 Patient disposition – Induction period (Randomized set)

Disposition /Reason	AIN457 150 mg N=245 n (%)	AIN457 300 mg N=245 n (%)	Placebo N=248 n (%)	Total N=738 n (%)
Randomized	245	245	248	738
Completed Induction	230 (93.9)	238 (97.1)	232 (93.5)	700 (94.9)
Discontinued Induction	15 (6.1)	7 (2.9)	16 (6.5)	38 (5.1)
Adverse event	5 (2.0)	3 (1.2)	4 (1.6)	12 (1.6)
Lack of efficacy	1 (0.4)	1 (0.4)	0	2 (0.3)
Lost to follow-up	0	0	3 (1.2)	3 (0.4)
Non-compliance with study treatment	0	0	0	0
Physician decision	0	0	0	0
Pregnancy	0	1 (0.4)	0	1 (0.1)
Protocol deviation	0	1 (0.4)	1 (0.4)	2 (0.3)
No longer requires treatment	0	0	0	0
Study terminated by sponsor	0	0	0	0
Technical problems	0	0	0	0
Subject/guardian decision	9 (3.7)	1 (0.4)	8 (3.2)	18 (2.4)
Death	0	0	0	0

Of the 700 patients who entered the maintenance period, 623 (89.0%) completed this period (see Table 15). The most common reasons for discontinuation were adverse event (overall 24/700, 3.4%), subject/guardian decision (17/700, 2.4%) and lack of efficacy (16/700, 2.3%).

Table 15 Patient disposition – Maintenance period (Randomized set)

Disposition /Reason	AIN457 150 mg N=245 n (%)	AIN457 300 mg N=245 n (%)	Placebo - AIN457 150 mg N=109 n (%)	Placebo - AIN457 300 mg N=105 n (%)	Placebo N=18 n (%)	Total N=722 n (%)
Randomized	245	245	109	105	18	722
Entered Maintenance	230 (93.9)	238 (97.1)	109 (100.0)	105 (100.0)	18 (100.0)	700 (97.0)
Completed Maintenance	201 (82.0)	215 (87.8)	100 (91.7)	92 (87.6)	15 (83.3)	623 (86.3)
Discontinued in Maintenance	29 (11.8)	23 (9.4)	9 (8.3)	12 (11.4)	3 (16.7)	76 (10.5)
Adverse event	12 (4.9)	5 (2.0)	2 (1.8)	4 (3.8)	1 (5.6)	24 (3.3)
Lack of efficacy	10 (4.1)	2 (0.8)	2 (1.8)	2 (1.9)	0	16 (2.2)
Lost to follow-up	2 (0.8)	4 (1.6)	0	3 (2.9)	0	9 (1.2)
Non-compliance with study treatment	0	0	1 (0.9)	0	0	1 (0.1)
Physician decision	0	1 (0.4)	0	0	0	1 (0.1)
Pregnancy	0	4 (1.6)	0	2 (1.9)	0	6 (0.8)
Protocol deviation	1 (0.4)	1 (0.4)	0	0	0	2 (0.3)
No longer requires treatment	0	0	0	0	0	0
Study terminated by sponsor	0	0	0	0	0	0
Technical problems	0	0	0	0	0	0
Subject/guardian decision	4 (1.6)	6 (2.4)	4 (3.7)	1 (1.0)	2 (11.1)	17 (2.4)
Death	0	0	0	0	0	0

Recruitment

Study initiation date: 09 June 2011 (first patient first visit)

Study completion date: 07 March 2013 (last patient last visit for Week 52)

Conduct of the study

The study protocol was amended twice. Amendment 1 was implemented to incorporate changes recommended by FDA. Amendment 2 included text about the extension protocol and described the possibility for qualifying patients to enter the extension study.

Baseline data

In the Induction treatment groups, the mean age of all patients was 45.1 years. 92.1% of subjects were <65 years, 7.9% ≥65 and 0.9% (7 patients) ≥75 years. 69.0% were males and 70.2 % were Caucasian, followed by Asian (20.6%). The mean body weight was 88.6 kg, the mean BMI 30.1 kg/m^2, and 36.9% were current smokers.

Among baseline disease characteristics (see Table 16), the mean PASI score was 22.1 and 45.3% had a baseline PASI score > 20. The mean total BSA affected was 31.9% and all patients had moderate to

severe disease, as measured by IGA mod 2011 and Severity of Psoriasis criteria. The majority of patients (76.8%) did not have a history of psoriatic arthritis.

Table 16 Disease history and baseline disease characteristics – Induction treatment groups (Randomized set)

Background Characteristics	AIN457 150 mg N=245	AIN457 300 mg N=245	Placebo N=248	Total N=738
Baseline PASI score				
n	245	245	247	737
Mean	22.32	22.47	21.44	22.07
SD	9.832	9.226	9.077	9.382
Median	18.40	19.60	18.60	19.00
Min - Max	12.0 - 61.2	11.2 - 72.0	10.6 - 72.0	10.6 - 72.0
Baseline PASI, n (%)				
<=20	139 (56.7)	128 (52.2)	136 (54.8)	403 (54.6)
>20	106 (43.3)	117 (47.8)	111 (44.8)	334 (45.3)
Baseline total BSA				
n	245	245	247	737
Mean	33.253	32.840	29.709	31.928
SD	19.1710	19.3026	15.8882	18.2278
Median	27.400	27.600	27.000	27.100
Min - Max	9.99 - 91.50	10.00 - 100.00	9.98 - 99.00	9.98 - 100.00
Baseline IGA mod 2011 score, n (%)				
3=Moderate disease	161 (65.7)	154 (62.9)	151 (60.9)	466 (63.1)
4=Severe disease	84 (34.3)	91 (37.1)	97 (39.1)	272 (36.9)
Severity of psoriasis, n (%)				
Mild	0	0	0	0
Moderate	69 (28.2)	80 (32.7)	75 (30.2)	224 (30.4)
Severe	176 (71.8)	165 (67.3)	172 (69.4)	513 (69.5)
Psoriatic arthritis present, n (%)				
Yes	46 (18.8)	57 (23.3)	68 (27.4)	171 (23.2)
No	199 (81.2)	188 (76.7)	180 (72.6)	567 (76.8)
Time since first diagnosis of psoriasis (years)				
n	245	245	248	738
Mean	17.526	17.439	17.321	17.429
SD	12.0247	11.0871	12.3556	11.8211
Median	15.088	15.417	14.423	15.069
Min - Max	0.57 - 61.43	0.55 - 56.27	0.62 - 68.13	0.55 - 68.13
Time since first diagnosis of psoriatic arthritis (years)				
n	46	57	68	171
Mean	7.263	8.121	10.991	9.031
SD	8.1470	9.2985	9.4242	9.1496
Median	4.890	5.837	8.445	6.346
Min - Max	0.00 - 41.28	0.04 - 47.30	0.02 - 41.56	0.00 - 47.30

Previous exposure to any systemic therapy was reported by 63.0% of all patients, with a failure rate of 66.5%. Previous exposure to biologic systemic therapy was reported by 29.3% of patients (46.3% to IL-12/23 antagonist and 66.2% to anti-TNF-α), with a failure rate of 33.3%. 48.9% of all patients were previously exposed to non-biologic systemic therapy and 75.6% had failed on such therapy (see Table 17).

Table 17 Previous exposure to psoriasis therapies – Induction treatment groups (Randomized set)

Previous exposure	AIN457 150 mg N=245	AIN457 300 mg N=245	Placebo N=248	Total N=738
Previous exposure to systemic therapy, n/N (%)				
Yes	156 (63.7)	163 (66.5)	146 (58.9)	465 (63.0)
No	89 (36.3)	82 (33.5)	102 (41.1)	273 (37.0)
Previous failure to systemic therapy, n/m (%)				
Yes	109/156 (69.9)	109/163 (66.9)	91/146 (62.3)	309/465 (66.5)
No	47/156 (30.1)	54/163 (33.1)	55/146 (37.7)	156/465 (33.5)
Previous exposure to biologic systemic therapy, n/N (%)				
Yes	73 (29.8)	70 (28.6)	73 (29.4)	216 (29.3)
No	172 (70.2)	175 (71.4)	175 (70.6)	522 (70.7)
Previous failure to biologic systemic therapy, n/m (%)				
Yes	29/73 (39.7)	19/70 (27.1)	24/73 (32.9)	72/216 (33.3)
No	44/73 (60.3)	51/70 (72.9)	49/73 (67.1)	144/216 (66.7)
Previous exposure to non-biologic systemic therapy, n/N (%)				
Yes	125 (51.0)	128 (52.2)	108 (43.5)	361 (48.9)
No	120 (49.0)	117 (47.8)	140 (56.5)	377 (51.1)
Previous failure to non-biologic systemic therapy, n/m (%)				
Yes	95/125 (76.0)	100/128 (78.1)	78/108 (72.2)	273/361 (75.6)
No	30/125 (24.0)	28/128 (21.9)	30/108 (27.8)	88/361 (24.4)
Previous failure to at least 2 non-biologic systemic therapy, n/m (%)				
Yes	24/125 (19.2)	26/128 (20.3)	18/108 (16.7)	68/361 (18.8)
No	101/125 (80.8)	102/128 (79.7)	90/108 (83.3)	293/361 (81.2)

Source: Tables 14.1-11.1, 14.1-12.1, 14.1-13.1
N=number of patients within a treatment group; n=number of patients within the category; m=number of patients with non-missing value
% are based on n/N or n/m, as indicated

Numbers analysed

In the Entire treatment group, the number of patients in the Full analysis set was 737, as one randomized subject was excluded due to major protocol violation (see Table 18).

Table 18 Analysis sets – Entire treatment groups (All patients enrolled) and maintenance treatment groups (below)

Analysis Set	AIN457 150 mg	AIN457 300 mg	Any AIN457 150 mg	Any AIN457 300 mg	Any AIN457 dose	Placebo	Total
Randomized set	245	245	354	350	704	248	738
Full analysis set	245	245	353	350	703	247	737
Safety set	245	245	353	349	702	247	737

Outcomes and estimation

Testing strategy results

The study met both co-primary endpoints and key secondary efficacy endpoints. The p-value adjusted for multiple testing was <0.0001 for all comparisons tested.

Primary efficacy results

Secukinumab demonstrated superior efficacy vs. placebo with respect to PASI 75 and IGA 2011 0/1 response at Week 12 (see Table 19). PASI 75 was achieved by 81.6% of patients treated with 300 mg secukinumab and by 71.6% of patients treated with 150 mg secukinumab, compared with 4.5% of placebo patients. With respect to IGA 0/1, the response rate was 65.3% for 300 mg secukinumab and 51.2% for 150 mg secukinumab versus 2.4% for placebo. The p-values for the differences between 300 mg vs. 150 mg were 0.0080 for PASI 75 and 0.0016 for IGA 0/1.

Table 19 Statistical analysis (Cochran-Mantel-Haenszel test) of IGA mod 2011 0 or 1 and PASI 75 response at Week 12 (non-responder imputation) (FAS)

Response criterion	Treatment comparison "test" vs. "control"	_"test"_ n/m (%)	_"control"_ n/m (%)	odds ratio estimate (95% CI)	p-value
IGA 0/1	AIN457 150 mg vs. Placebo	125/244 (51.2)	6/246 (2.4)	44.18 (18.21,107.18)	<0.0001
	AIN457 300 mg vs. Placebo	160/245 (65.3)	6/246 (2.4)	70.46 (28.75,172.70)	<0.0001
PASI 75	AIN457 150 mg vs. Placebo	174/243 (71.6)	11/246 (4.5)	57.64 (28.43,116.86)	<0.0001
	AIN457 300 mg vs. Placebo	200/245 (81.6)	11/246 (4.5)	82.69 (38.70,176.71)	<0.0001

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

Prespecified sensitivity analyses supported the efficacy data in favor of secukinumab vs. placebo. In a subgroup analysis by body weight (<90 kg, ≥90 kg), results for PASI 75 and IGA were consistent with the superior efficacy of 300 mg and 150 mg secukinumab versus placebo demonstrated in the overall population (Table 20). However, efficacy was somewhat reduced in those weighing ≥90 kg.

Table 20 PASI 75, PASI 90 and IGA mod 2011 0 or 1 response at Week 12 by body weight (non-responder imputation) (FAS)

	< 90 kg			≥ 90 kg		
Response criterion	AIN457 150 mg n/m (%)	AIN457 300 mg n/m (%)	Placebo n/m (%)	AIN457 150 mg n/m (%)	AIN457 300 mg n/m (%)	Placebo n/m (%)
IGA 0/1	75/141 (53.2)	103/142 (72.5)	3/142 (2.1)	50/103 (48.5)	57/103 (55.3)	3/104 (2.9)
PASI 75	104/140 (74.3)	126/142 (88.7)	6/142 (4.2)	70/103 (68.0)	74/103 (71.8)	5/104 (4.8)
PASI 90	63/140 (45.0)	99/142 (69.7)	2/142 (1.4)	32/103 (31.1)	46/103 (44.7)	1/104 (1.0)

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

In the subgroup analysis by previous or ongoing exposure to therapies, response rates on secukinumab treatment were slightly reduced in patients with previous exposure to systemic therapy (63% of patients) compared to systemic treatment-naïve (37% of patients). For secukinumab 300 mg at Week 12, IGA 0/1 responses were 63.2% vs. 69.5%, respectively, PASI 75 responses were 77.9% vs. 89.0%, respectively, and PASI 90 responses were 57.1 vs. 63.4%, respectively. The responses were comparable between

previously exposed patients and those who had failed to respond to previous systemic therapy. In 216 (29.3%) patients previously exposed to biologic systemic therapy, the responses were consistent with the superior efficacy of 300 mg and 150 mg secukinumab vs. placebo demonstrated in the overall population (see Table 21). Response rates were generally lower in patients who had failed to respond to previous biologic therapy.

Table 21 PASI 75, PASI 90 and IGA mod 2011 0 or 1 response at Week 12 by previous exposure to biologic systemic therapy (non-responder imputation) (FAS)

Response criterion	AIN457 150 mg n/m (%)	AIN457 300 mg n/m (%)	Placebo n/m (%)	AIN457 150 mg n/m (%)	AIN457 300 mg n/m (%)	Placebo n/m (%)
	Previously exposed to biologic therapy			Previously exposed to and failed biologic therapy		
IGA 0/1	31/73 (42.5)	42/70 (60.0)	1/73 (1.4)	12/29 (41.4)	11/19 (57.9)	1/24 (4.2)
PASI 75	47/73 (64.4)	53/70 (75.7)	3/73 (4.1)	14/29 (48.3)	11/19 (57.9)	3/24 (12.5)
PASI 90	20/73 (27.4)	37/70 (52.9)	1/73 (1.4)	7/29 (24.1)	6/19 (31.6)	1/24 (4.2)
	Previously exposed to anti-TNF-α therapy			Previously exposed to and failed anti-TNF-α therapy		
IGA 0/1	19/44 (43.2)	30/48 (62.5)	1/51 (2.0)	9/18 (50.0)	11/17 (64.7)	1/21 (4.8)
PASI 75	29/44 (65.9)	35/48 (72.9)	3/51 (5.9)	10/18 (55.6)	11/17 (64.7)	3/21 (14.3)
PASI 90	12/44 (27.3)	23/48 (47.9)	1/51 (2.0)	6/18 (33.3)	6/17 (35.3)	1/21 (4.8)

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

Key secondary efficacy results:

• PASI 90 response at Week 12: Secukinumab 300 mg and 150 mg were both superior to placebo in the PASI 90 response at Week 12 (p-value <0.0001). PASI 90 response for secukinumab 300 mg was 59.2%, compared to 39.1% for secukinumab 150 mg and 1.2% for placebo.

• Maintenance of PASI 75 response at 52 weeks: Among Week 12 PASI 75 responders, the overall decline in the PASI 75 response rate was greater in the 150 mg secukinumab group (−20.1% from 92.5% to 72.4%) than in the 300 mg secukinumab group (−13.0% from 93.5% to 80.5%). The cumulative rate for loss of PASI 75 response was 27.5 for the 150 mg group and 14.2 for the 300 mg group. The rate of PASI 75 loss at 52 weeks was higher in patients with previous exposure to biologic systemic therapy (47.4% with 150 mg and 23.6% with 300 mg secukinumab) than in treatment-naïve patients (20.1% with 150 mg and 10.8% with 300 mg secukinumab).

• Maintenance of IGA 0/1 response at 52 weeks: The majority of secukinumab-treated patients (74.4% with 300 mg and 59.2% with 150 mg) who achieved IGA 0/1 at Week 12 maintained the response at Week 52. The cumulative rate for loss of IGA 0/1 response was 41.4 for the 150 mg group and 28.8 for the 300 mg group.

• Psoriasis Symptom Diary items at Week 12: Patients treated with either 300 mg or 150 mg secukinumab had significantly greater improvements in the Psoriasis Symptom Diary items itching, pain and scaling after 12 weeks of treatment compared with patients on placebo (p-value <0.0001). Improvements from baseline were numerically greater with 300 mg than with 150 mg secukinumab. Differences in response rates favoring secukinumab vs. placebo were apparent by Week 2.

Other secondary efficacy results:

• Higher response rates with secukinumab relative to placebo appeared as early as Week 2. A ≥ 50% mean decrease from baseline in PASI score was achieved by Week 3 in the 300 mg secukinumab group and by Week 4 in the 150 mg secukinumab group. The median time to PASI 75 response was 57.0 days (lower to upper quartiles: 55.0 to 85.0) for 150 mg secukinumab and 57.0 days (29.0 to 59.0) for 300 mg secukinumab.

• DLQ1: At Week 12, the percentage change from baseline in the DLQ1 total score was −77.8, −86.4 and −9.1 for 300 mg and 150 mg secukinumab and placebo, respectively. P-values for treatment difference

vs. placebo were <0.0001 for both secukinumab doses at all time points (Weeks 4, 8, and 12). The improvements in DLQI were sustained up to Week 52.

• EQ-5D: A clear effect of secukinumab treatment was seen in the category of Pain/Discomfort. At Week 12, the proportion of secukinumab-treated patients reporting no pain or discomfort increased from 26.2% and 22.1% (300 mg and 150 mg, respectively) at baseline to 72.8% and 70.8%, respectively. For the placebo group, the corresponding figures were 18.9% at baseline and 28.4% at Week 12. Other categories of the EQ-5D showed similar trend and the improvements were sustained through Week 52.

• For PGIC data only summary statistics are presented. PGIC items showed improvement in the overall impact of psoriasis on life and diminished severity of psoriasis symptoms in both secukinumab groups by Week 12.

Exploratory efficacy results:

• The cumulative probability to relapse at 52 weeks of treatment was 2.1% with 300 mg vs. 6.8% with 150 mg secukinumab dose. In the analysis of time to relapse after last study treatment, based on low number of subjects available the risk was lower in the secukinumab 300 mg group. Rebound was more frequently reported in the placebo group (2/15 patients, 13.3%) than in either secukinumab dose group (4/50 patients, 8.0% for 150 mg and 2/44 patients, 4.5% for 300 mg).

• The highest rate of HAQ-DI response (improvement of at least 0.3 score points compared to baseline level) at Week 12 was reported in the 300 mg secukinumab group (24/51, 47.1%) compared with the 150 mg secukinumab (12/45, 26.7%) and the placebo (14/65, 21.5%) groups. In the maintenance period, the improvements in HAQ-DI were sustained. ACR response was evaluated in five patients who met the criteria (at randomization PsA defined as ≥ 3 points according to the CASPAR criteria, and ≥ 3 tender and ≥ 3 swollen joints). Efficacy data of the five patients is inconsistent.

Study A2308: First study of SEcukinumAb in pre-filled syringes in subjecTs with chronic plaqUe-type psoriasis: REsponse at 12 weeks (FEATURE): a randomized, double-blind, placebo controlled, multicenter study of subcutaneous secukinumab in pre-filled syringes to demonstrate efficacy after twelve weeks of treatment, and to assess the safety, tolerability, usability and long-term efficacy in subjects with chronic plaque-type psoriasis.

Methods

This is an ongoing, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, in 177 patients with moderate to severe, chronic, plaque-type psoriasis. The study was designed to compare 2 doses of secukinumab (150 mg and 300 mg) and placebo in pre-filled syringes (PFS) administered as s.c. self-injections. The study consists of 5 periods: Screening (1 to 4 weeks), Induction (12 weeks), Maintenance (40 weeks), Extension (up to 156 additional weeks), and Follow-up (8 weeks).

Study Participants

The study population consisted of a representative group of adult (≥18 years old) outpatients with moderate to severe chronic plaque-type psoriasis, who were candidates for systemic therapy. Inclusion and exclusion criteria were similar to those in Study A2302. An additional inclusion criterion was “Written informed consent must be obtained before any assessment is performed”. Additional exclusion criteria were “History of hypersensitivity to secukinumab, its constituents or having suffered from severe adverse drug reactions to other anti-IL-17 therapies” and “Inability or unwillingness to… self-injection with a pre-filled syringe”.

Treatments

Patients were assigned equally to 1 of 3 treatment groups. Study treatment consisted of 2 s.c. injections, self-administered (secukinumab 150 mg + placebo, secukinumab 300 mg, or placebo only) at Randomization and Weeks 1, 2, 3, 4 and 8. Final assessments for the Induction period were performed prior to dosing at Week 12.

Objectives

The primary objective was to demonstrate the efficacy of secukinumab (150 mg and 300 mg) in patients with moderate to severe chronic plaque-type psoriasis with respect to both PASI 75 and IGA 0 or 1 response (co-primary endpoints) at Week 12 compared to placebo.

The secondary objectives evaluated at Week 12 were:

• To assess the subject usability (ability to follow instructions for use (IFU) and potential use-related hazards) and satisfaction with the secukinumab PFS utilizing a self-administered Self-Injection Assessment Questionnaire (SIAQ) and investigator/site staff observation

• To assess secukinumab (150 mg and 300 mg) efficacy compared to placebo based on PASI 50/75/90/100 and IGA mod 2011 0 or 1 response, PASI score, IGA mod 2011 score, Health Status Questionnaire (EuroQOL 5-Dimension Health Questionnaire [EQ-5D©]) score, Dermatology Life Quality Index (DLQI) score, and DLQI 0 or 1 response

• To investigate the clinical safety and tolerability of secukinumab (150 mg and 300 mg) as assessed by vital signs, clinical laboratory variables, electrocardiograms (ECGs), and adverse events monitoring compared to placebo up to Week 12

• To investigate the development of immunogenicity against secukinumab

Outcomes/endpoints

Efficacy and safety assessments were identical to Study A2302. Additional assessments were related to the use of the pre-filled syringe: the observer measured and evaluated the usability of the pre-filled syringe using the Self-injection assessment checklist, as they observed the first of the 2 self-injections by the patient (at the Randomization Visit and Week 1). The Possible hazard assessment check list was also used. Pre-filled Syringe patient satisfaction assessment of self-injection (SIAQ) measured overall patient experience with subcutaneous self-injection, and investigated its psychometric properties.

Sample size

177 patients were randomized to treatment, 59 patients per treatment group (secukinumab 150 mg, secukinumab 300 mg, and placebo).

Randomisation

All eligible patients were randomized via the Interactive Response Technology (IRT) to 1 of the 3 treatment groups. Randomization was stratified by body weight (≥90 kg or <90 kg).

Blinding

This was a double-blind study. Patients, investigator staff, and persons performing the assessments remained blinded to the identity of the treatment from the time of randomization until final database lock.

Statistical methods

The primary analysis method was changed from planned stratified Cochran-Mantel-Haenszel test to Fisher's exact test because there was 0% response rate for IGA 0/1 and PASI 75 in the placebo group. Similar sequentially rejective testing procedure to preserve family wise type I error rate at 5% level as in Study A2302 was applied to four hypotheses associated with the two primary endpoints and two doses.

Results

Participant flow

A total of 209 patients were screened and 177 patients were randomized to secukinumab 150 mg, secukinumab 300 mg, or placebo group (n = 59 per group). 170 of the 177 (96.0%) patients completed the 12-week induction period. Two patients discontinued due to an adverse event, three were lost to follow-up and two discontinued due to subject/guardian decision (see Table 22).

Table 22 Induction period patient disposition (Randomized set)

Disposition Reason for discontinuation	AIN457 150 mg N=59 n (%)	AIN457 300 mg N=59 n (%)	Placebo N=59 n (%)	Total N=177 n (%)
Randomized	59	59	59	177
Completed Induction period	58 (98.3)	56 (94.9)	56 (94.9)	170 (96.0)
Discontinued Induction period	1 (1.7)	3 (5.1)	3 (5.1)	7 (4.0)
Adverse event	0 (0.0)	1 (1.7)	1 (1.7)	2 (1.1)
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	1 (1.7)	2 (3.4)	0 (0.0)	3 (1.7)
Non-compliance with study treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Physician decision	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No longer requires treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Technical problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject/guardian decision	0 (0.0)	0 (0.0)	2 (3.4)	2 (1.1)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Recruitment

First patient enrolled: 08 May 2012

Last patient completed the Induction period (data cut-off): 15 Jan 2013 (study is ongoing)

Conduct of the study

The study protocol was amended twice. Amendment 1 was issued prior to study start and included the opportunity for the patient to enter an extension study. Amendment 2 was issued after completion of the Induction period and is currently in the process of being reviewed by ECs, IRBs, and health authorities. It provided continued treatment for another 156 weeks or until the drug is available in the country of participation for eligible patients who were on active therapy during the Maintenance period. It also specified that after the Week 52 data base lock, the study will be open label.

Baseline data

Most patients were male (66.1%), Caucasian (91.5%), with median age of 46.0 years. There were fewer patients ≥65 years old in the secukinumab 300 mg group (1/59, 1.7%) compared with the secukinumab 150 mg group (8/59, 13.6%) or placebo group (6/59, 10.2%). The mean body weight was 91.6 kg and the mean BMI 30.7 kg/m^2. 28.8% of patients were current smokers.

Among baseline disease characteristics, the mean PASI score was 20.8, the affected mean body surface area (BSA) was 32.0%, and the mean time since psoriasis diagnosis was 19.5 years.

Previous psoriasis systemic therapy was reported for 67.2% (119/177) of patients (see Table 23). The most common prior immunomodulating therapies included methotrexate (44/177, 24.3%), etanercept (42/177, 23.7%), ustekinumab (25/177, 14.1%), and adalimumab (24/177, 13.6%). 43.5% (77/177) of patients were exposed previously to biological therapy and over half of them (53.2%) did not respond to their previous therapy. Other previous psoriasis therapies included topical medications (158/177, 89.3%), phototherapy (71/177, 40.1%) and photochemotherapy (24/177, 13.6%).

Table 23 Previous exposure to psoriasis therapy - induction treatment groups (Randomized set)

Background characteristics	AIN457 150 mg N=59	AIN457 300 mg N=59	Placebo N=59	Total N=177
Previous exposure to systemic psoriasis therapy, n/N (%)				
Yes	45 (76.3)	35 (59.3)	39 (66.1)	119 (67.2)
No	14 (23.7)	24 (40.7)	20 (33.9)	58 (32.8)
Previous failure to systemic psoriasis therapy, n/m (%)				
Yes	33/45 (73.3)	22/35 (62.9)	27/39 (69.2)	82/119 (68.9)
No	12/45 (26.7)	13/35 (37.1)	12/39 (30.8)	37/119 (31.1)
Previous exposure to biologic systemic psoriasis therapy, n/N (%)				
Yes	28 (47.5)	23 (39.0)	26 (44.1)	77 (43.5)
No	31 (52.5)	36 (61.0)	33 (55.9)	100 (56.5)
Previous failure to biologic systemic psoriasis therapy, n/m (%)				
Yes	18/28 (64.3)	9/23 (39.1)	14/26 (53.8)	41/77 (53.2)
No	10/28 (35.7)	14/23 (60.9)	12/26 (46.2)	36/77 (46.8)
Previous exposure to non-biologic systemic psoriasis therapy, n/N (%)				
Yes	39 (66.1)	20 (33.9)	29 (49.2)	88 (49.7)
No	20 (33.9)	39 (66.1)	30 (50.8)	89 (50.3)
Previous failure to non-biologic systemic psoriasis therapy, n/m (%)				
Yes	29/39 (74.4)	17/20 (85.0)	20/29 (69.0)	66/88 (75.0)
No	10/39 (25.6)	3/20 (15.0)	9/29 (31.0)	22/88 (25.0)

Numbers analysed

177 patients were randomized at the baseline visit Full analysis set (FAS) (n = 177). All randomized patients were included in both FAS and Safety set.

Outcomes and estimation

Primary efficacy results:

Both secukinumab regimens (150 mg and 300 mg) were superior to placebo with respect to PASI 75 response and IGA 0/1 response at Week 12. The p-value for each comparison was <0.0001 (see Table 24). IGA 0/1 response rate and PASI 90 response showed an incremental improvement in efficacy with secukinumab 300 mg dose. PASI 100 response was achieved by 43.1 % of the patients in the secukinumab 300 mg group vs. 8.5% in the secukinumab 150 mg group and 0% in the placebo group. The onset of efficacy was rapid, as at 4 weeks, 22.0% of the patients in the secukinumab 150 mg group and 55.2% of the patients in the 300 mg group had achieved PASI 75 response.

At 12 weeks, the p-values for the differences between 300 mg vs. 150 mg secukinumab, as assessed by the CMH test, were 0.8195 for PASI 50, 0.4405 for PASI 75, 0.0974 for PASI 90, <0.0001 for PASI 100, and 0.0570 for IGA 0/1.

Table 24 Statistical analysis (Risk-difference and Fisher's exact test) of IGA mod 2011 0 or 1, PASI 75 and PASI 90 response at Week 12 (nonresponder imputation) (FAS)

Response criterion	Treatment comparison "test" vs. "control"	"test" n/m (%)	"control" n/m (%)	Risk difference estimate (%) (95%CI)	p-value*
IGA 0/1	AIN457 150 mg vs. placebo	31/ 59 (52.5)	0/ 59 (0.0)	52.5 (35.1, 67.2)	<0.0001
	AIN457 300 mg vs. placebo	40/ 58 (69.0)	0/ 59 (0.0)	69.0 (53.5, 80.5)	<0.0001
PASI 75	AIN457 150 mg vs. placebo	41/ 59 (69.5)	0/ 59 (0.0)	69.5 (53.9, 81.4)	<0.0001
	AIN457 300 mg vs. placebo	44/ 58 (75.9)	0/ 59 (0.0)	75.9 (61.5, 86.1)	<0.0001
PASI 90	AIN457 150 mg vs. placebo	27/ 59 (45.8)	0/ 59 (0.0)	45.8 (27.8, 61.3)	<0.0001
	AIN457 300 mg vs. placebo	35/ 58 (60.3)	0/ 59 (0.0)	60.3 (43.9, 73.0)	<0.0001

FAS=full analysis set; IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index
n=number of patients with response; m=number of patients evaluable
* Unadjusted p-values. For adjusted p-values, refer to Table 11-7.
Co-primary endpoints are in bold.

In a subgroup analysis by body weight (<90 kg, ≥90 kg), efficacy was somewhat reduced in those ≥90 kg. PASI 75 response rates for the secukinumab 150 mg and 300 mg doses in the <90 kg subgroup were 83.3% and 86.7%, respectively, compared with 55.2% and 64.3%, respectively, in the ≥90 kg subgroup.

In the subgroup analysis by previous systemic therapy, PASI 75 or IGA 0/1 response rates in previously exposed patients were similar to the rates in those not previously exposed. Patients not previously exposed to biologic therapy generally showed numerically higher response rates than those previously exposed (e.g. PASI 75 response in secukinumab 300 mg group 80.0% vs. 69.6%). The IGA 0/1, PASI 75 and PASI 90 response rates in the patients who had failed on previous biologic therapy were similar to those for with previous exposure to biologic therapy (see Table 25).

Table 25 PASI 75, PASI 90, and IGA mod 2011 0 or 1 response at Week 12 by previous biologic therapy exposure (non-responder imputation) (FAS)

Response criterion	AIN457 150 mg N=59 n/m (%)	AIN457 300 mg N=59 n/m (%)	Placebo N=59 n/m (%)	AIN457 150 mg N=59 n/m (%)	AIN457 300 mg N=59 n/m (%)	Placebo N=59 n/m (%)
	Previously exposed to biologic therapy			Previously exposed to and failed biologic therapy		
IGA 0/1	13/ 28 (46.4)	15/ 23 (65.2)	0/ 26 (0.0)	7/ 18 (38.9)	6/ 9 (66.7)	0/ 14 (0.0)
PASI 75	16/ 28 (57.1)	16/ 23 (69.6)	0/ 26 (0.0)	9/ 18 (50.0)	6/ 9 (66.7)	0/ 14 (0.0)
PASI 90	9/ 28 (32.1)	14/ 23 (60.9)	0/ 26 (0.0)	7/ 18 (38.9)	6/ 9 (66.7)	0/ 14 (0.0)
	Previously exposed to anti-TNFα therapy			Previously exposed to and failed anti-TNFα therapy		
IGA 0/1	9/ 24 (37.5)	10/ 15 (66.7)	0/ 15 (0.0)	6/ 16 (37.5)	4/ 7 (57.1)	0/ 11 (0.0)
PASI 75	12/ 24 (50.0)	10/ 15 (66.7)	0/ 15 (0.0)	8/ 16 (50.0)	4/ 7 (57.1)	0/ 11 (0.0)
PASI 90	7/ 24 (29.2)	9/ 15 (60.0)	0/ 15 (0.0)	6/ 16 (37.5)	4/ 7 (57.1)	0/ 11 (0.0)

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

Secondary efficacy results:

• In both secukinumab groups, there was an increase in the percentage of IGA 0/1, PASI 50, PASI 75, PASI 90 and PASI 100 responders over the first 12 weeks of treatment. Except for PASI 50 response, the effects were dose dependent with a higher response rates observed with secukinumab 300 mg compared with secukinumab 150 mg.

• In both secukinumab groups, PASI scores were decreasing at each visit. At Week 12, mean PASI scores decreased by 16.3 points (-78.5% change from baseline) in the secukinumab 150 mg group, by 17.9 points (-86.1% change from baseline) in the secukinumab 300 mg group, and increased (worsened) by 0.5 point (+1.8% change from baseline) in the placebo group.

• The median time to PASI 75 response was 57.0 days (lower to upper quartiles: 51.0 to 86.0) for 150 mg secukinumab and 30.0 days (29.0 to 84.0) for 300 mg secukinumab, but was not estimable for the placebo group.

• The EQ-5D questions where improvements in secukinumab groups were most evident were on pain/discomfort and usual activities. At Week 12, the overall change from Baseline on the EQ-5D health state assessment (from 0 to 100) indicated an improved health state in both secukinumab groups (mean percent change of +24.6% for 150 mg and +24.7% for 300 mg) compared with placebo (+6.8%).

• The proportion of patients achieving DLQI 0 or 1 response (i.e., total score of 0 or 1 out of the maximum of 30) at Week 12 were the same for both secukinumab groups (54.4% for 150 mg and 54.7% for 300 mg), compared to 7.4% in the placebo group.

• 7 patients who discontinued treatment during the Induction period were evaluated for rebound-like events and rebound. There were no such events observed during the first 12 weeks of the study.

• Subject usability and satisfaction with the secukinumab PFS: Using a check list completed by a staff site member at Baseline and Week 1, 9 possible user-related hazards with the PFS were reported for 6 patients. 5 issues related to question H8 ("Was any other problem observed?") and concerned handling of the syringe. Nearly all patients successfully completed all 18 steps of the Instructions for Use (IFU). Slightly lower compliance rate (172/177; 97.2% at Baseline) was Step 18, pertaining to syringe disposal in a sharps container. At Week 1, self-administration of first injection of study drug was successfully performed by all patients (patients in all treatment groups performed all the required 6 critical steps out of 18 steps). Patients completed the Self-Injection Assessment Questionnaire (SIAQ) which measures the overall patient experience with subcutaneous self-injection. Scores on the principal domains of the SIAQ ("feelings about injections", "self-confidence" and "satisfaction with self-injection") improved over time between the Randomization and Week 12 visits for all treatment groups.

Study A2309: Judging the Efficacy of SecUkinumab in Patients With Psoriasis using Autoinjector: a Clinical Trial EvalUating Treatment REsults (JUNCTURE): a randomized, double-blind, placebo-controlled, multicenter study of subcutaneous secukinumab in autoinjectors to demonstrate efficacy after 12 weeks of treatment, and to assess the safety, tolerability, usability and long-term efficacy in subjects with chronic plaque-type psoriasis.

Methods

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in 182 patients with moderate to severe, chronic, plaque-type psoriasis. The study was designed to compare 2 doses of secukinumab (150 mg and 300 mg) and placebo administered subcutaneously (s.c) using an autoinjector/pen (AI).

The study consisted of 4 periods: Screening (1 to 4 weeks), Induction (12 weeks), Maintenance (40 weeks), and Follow-up (8 weeks).

Study Participants

The study population consisted of male and female outpatients (≥ 18 years old) with moderate to severe chronic plaque-type psoriasis that were poorly controlled by topical treatments and/or phototherapy and/or previous systemic therapy.

Inclusion and exclusion criteria were in principle identical to those in Study A2308.

Treatments, Objectives, and Outcomes/endpoints

Treatments, Objectives, and Outcomes/endpoints in Study A2309 were identical to those in Study A2308, with the exception that an AI device was used. For patients who had issues with the AI, it was investigated whether patients with PsA were differentially affected. No other data related to PsA were collected.

Sample size

In order to randomize 171 patients, approximately 220 patients were expected to be screened. Patients who dropped out after they were randomized were not replaced. In total, 182 patients were randomized to three treatment groups: secukinumab 150 mg (61 patients), secukinumab 300 mg (60 patients), or placebo (61 patients).

Randomisation, Blinding, Statistical methods

Randomisation, blinding and statistical methods in Study A2309 were identical to those in Study A2308. Patients were assigned equally to 1 of 3 treatment groups and stratified by body weight (<90 kg or ≥90 kg at the Randomization visit). For the same reason as in Study A2308, the primary analysis method was changed from planned stratified Cochran-Mantel-Haenszel test to Fisher's exact test.

Results

Participant flow

A total of 220 patients were screened, and 182 patients were randomized into 3 treatment groups. 177 patients (97.3%) completed the 12-week Induction period. Among the 5 discontinued patients, two discontinuations were due to AEs, one due to physician and patient/guardian decision, each, and one due to lack of efficacy (the latter in the placebo group) (see Table 26).

Table 26 Induction period patient disposition (Randomized set)

Disposition /Reason	AIN457 150 mg N=61	AIN457 300 mg N=60	Placebo N=61	Total N=182
Randomized	61	60	61	182
Completed Induction	58 (95.1)	60 (100.0)	59 (96.7)	177 (97.3)
Discontinued Induction	3 (4.9)	0 (0.0)	2 (3.3)	5 (2.7)
Adverse event	1 (1.6)	0 (0.0)	1 (1.6)	2 (1.1)
Lack of efficacy	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-compliance with study treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Physician decision	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No longer requires treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Technical problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patient/guardian decision	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Recruitment

First patient enrolled: 17 Oct 2012

Last patient completed the Induction period (data cut-off): 10 Apr 2013 (study is ongoing)

Conduct of the study

The study protocol was not amended. No changes in study conduct were done.

Baseline data

Most patients were male (68.7%) and Caucasian (95.1%) with mean age of 44.7 years. There were more patients ≥65 years old in the secukinumab 300 mg group (8/60, 13.3%) compared with secukinumab

150 mg and placebo groups (8.2% and 4.9%, respectively). The mean body weight was 91.6 kg and the mean BMI 30.2 kg/m^2. 36.3% of patients were current smokers.

Among baseline disease characteristics, the mean PASI score was 20.1, the affected mean body surface area (BSA) was 27.4% and the mean time since psoriasis diagnosis was 20.5 years. Psoriatic arthritis was present in 23.1% of patients, with least PsA patients in the placebo group (19.7%).

Previous exposure to systemic therapy was reported for 55.5% (101/182) of patients (see Table 27). The most common prior immunomodulating therapies included methotrexate (31/182, 17.0%), ustekinumab (17/182, 9.3%), adalimumab (16/182, 8.8%) and etanercept (15/182, 8.2%). Previous exposure to biological therapy was reported for 23.6% (43/182) of patients and nearly half of them (44.2%) did not respond to their previous therapy. 62.8% of those patients (27/43) had received anti-TNFα treatment and over half failed to respond (55.6%). Other previous psoriasis therapies included topical medications (92.3%), phototherapy (35.7%), and photochemotherapy (19.2%).

Table 27 Previous exposure to psoriasis therapy - induction treatment groups (Randomized set)

Background characteristics	AIN457 150 mg N=61	AIN457 300 mg N=60	Placebo N=61	Total N=182
Previous exposure to systemic therapy, n/N (%)				
Yes	34/61 (55.7)	34/60 (56.7)	33/61 (54.1)	101/182 (55.5)
No	27/61 (44.3)	26/60 (43.3)	28/61 (45.9)	81/182 (44.5)
Previous failure to systemic therapy, n/m (%)				
Yes	26/34 (76.5)	26/34 (76.5)	28/33 (84.8)	80/101 (79.2)
No	8/34 (23.5)	8/34 (23.5)	5/33 (15.2)	21/101 (20.8)
Previous exposure to biologic therapy, n/N (%)				
Yes	15/61 (24.6)	15/60 (25.0)	13/61 (21.3)	43/182 (23.6)
No	46/61 (75.4)	45/60 (75.0)	48/61 (78.7)	139/182 (76.4)
Previous failure to biologic therapy, n/m (%)				
Yes	7/15 (46.7)	6/15 (40.0)	6/13 (46.2)	19/43 (44.2)
No	8/15 (53.3)	9/15 (60.0)	7/13 (53.8)	24/43 (55.8)
Previous exposure to non-biologic therapy, n/N (%)				
Yes	31/61 (50.8)	30/60 (50.0)	29/61 (47.5)	90/182 (49.5)
No	30/61 (49.2)	30/60 (50.0)	32/61 (52.5)	92/182 (50.5)
Previous failure to non-biologic therapy, n/m (%)				
Yes	23/31 (74.2)	23/30 (76.7)	26/29 (89.7)	72/90 (80.0)
No	8/31 (25.8)	7/30 (23.3)	3/29 (10.3)	18/90 (20.0)

Numbers analysed

182 patients were randomized at the baseline visit. All randomized patients were included in both FAS and Safety set.

Outcomes and estimation

Primary efficacy results:

The co-primary objectives were met; both secukinumab regimens (150 mg and 300 mg) were superior to placebo with respect to PASI 75 response and IGA mod 2011 0/1 response at Week 12, with p-value for each comparison <0.0001 (see Table 28). PASI 75, IGA 0/1 and PASI 90 response rates all showed an incremental improvement in efficacy with the secukinumab 300 mg dose.

Table 28 Statistical analysis (Risk difference and Fisher's exact test) of IGA mod 2011 0 or 1, PASI 75 and PASI 90 response at Week 12 (non-responder imputation) (FAS)

Response criterion	Treatment comparison "test" vs. "control"	_"test"_ n/m (%)	_"control"_ n/m (%)	Risk difference estimate (%) (95% CI)	p-value*
IGA 0/1	AIN457 150 mg vs. Placebo	32/ 60 (53.3)	0/ 61 (0.0)	53.3 (36.6, 66.7)	<0.0001
	AIN457 300 mg vs. Placebo	44/ 60 (73.3)	0/ 61 (0.0)	73.3 (58.8, 83.9)	<0.0001
PASI 75	AIN457 150 mg vs. Placebo	43/ 60 (71.7)	2/ 61 (3.3)	68.4 (53.1, 79.8)	<0.0001
	AIN457 300 mg vs. Placebo	52/ 60 (86.7)	2/ 61 (3.3)	83.4 (70.7, 91.7)	<0.0001
PASI 90	AIN457 150 mg vs. Placebo	24/ 60 (40.0)	0/ 61 (0.0)	40.0 (22.5, 55.0)	<0.0001
	AIN457 300 mg vs. Placebo	33/ 60 (55.0)	0/ 61 (0.0)	55.0 (38.4, 68.1)	<0.0001

n=number of patients with response, m=number of patients evaluable
* Unadjusted p-values. For adjusted p-values, refer to the results of hypothesis tests within the testing strategy as shown in Table 11-6.

A rapid onset of efficacy was observed with high PASI 50 response rates as early as Week 4 (71.7% with secukinumab 300 mg vs. 51.7% with secukinumab 150 mg). At the same time point, 28.3% of the patients in the secukinumab 300 mg group had already achieved a PASI 75 response.

In subgroup analysis by weight strata, PASI 75 response rates in the <90 kg subgroup were 83.3% and 86.7% for the secukinumab 150 mg and 300 mg dose groups, respectively, compared with 55.2% and 64.3%, respectively, in the ≥ 90 kg subgroup.

In subgroup analysis in 101 patients with previous exposure to systemic therapy, PASI 75 and IGA 0/1 responses at Week 12 were 72.7% and % 51.1%, respectively, for the secukinumab 150 mg group and 82.4% and 61.8%, respectively, for the secukinumab 300 mg group. Among 43 patients previously exposed to biologic therapy, PASI 75 and IGA 0/1 responses were 64.3% and % 28.6%, respectively, for the secukinumab 150 mg group and 66.7% and 46.7%, respectively, for the secukinumab 300 mg group.

Secondary efficacy results:

• In both secukinumab groups, there was an increase in the percentage of IGA 0/1, PASI 50, PASI 75, PASI 90 and PASI 100 responders over the first 12 weeks of treatment. The effects on IGA 0/1 and PASI rates were dose dependent, with a higher response rates observed with secukinumab 300 mg compared with secukinumab 150 mg.

• In both secukinumab groups, PASI scores were decreasing at each visit. At Week 12, mean PASI scores decreased by 15.5 points (-75.1% change from baseline) in the secukinumab 150 mg group, by 16.8 points (-87.8% change from baseline) in the secukinumab 300 mg group, and by 1.26 point (-6.64% change from baseline) in the placebo group, compared to baseline values.

• The median time to PASI 75 response was 85.0 days (95% CI 57.0, 85.0) for 150 mg secukinumab and 57.0 days (95% CI 55.0, 58.0) for 300 mg secukinumab.

• Improvements on each of the questions of the EQ-5D were seen in the secukinumab groups, with the most evident improvement on pain/discomfort. At Week 12, the overall change from Baseline on the EQ-5D health state assessment (from 0 to 100) indicated an improved health state in both secukinumab groups (mean percent change of +12.5% for 150 mg and +14.3% for 300 mg) compared with placebo (0%).

• The proportion of patients achieving DLQI 0 or 1 response at Week 12 was 59.3% for secukinumab 150 mg and 74.6% for secukinumab 300 mg group, compared with 15.3% in the placebo group.

• 5 patients who discontinued treatment during the Induction period were evaluated for rebound-like events and rebound. There were no such events observed.

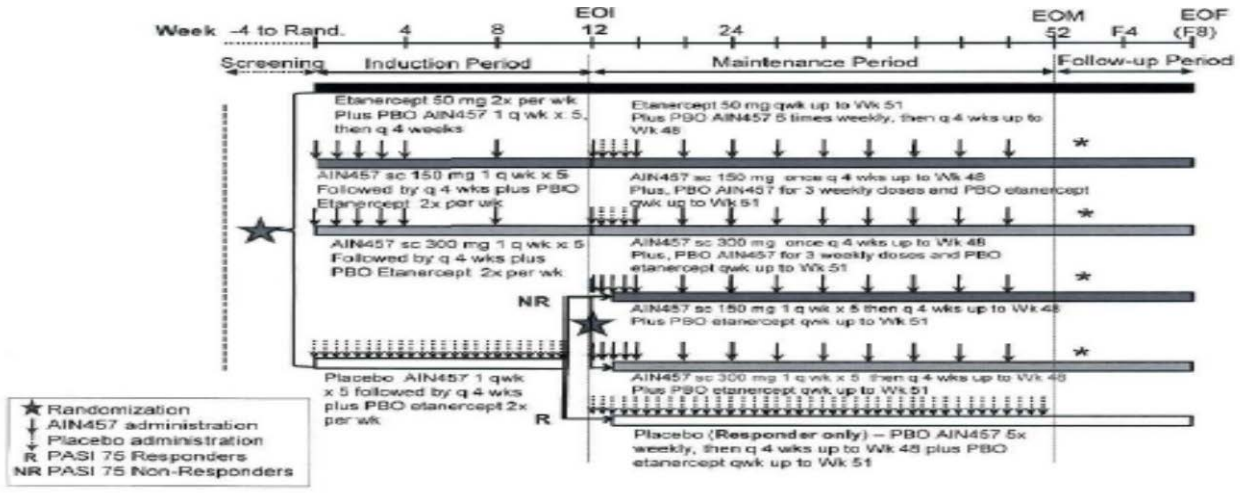
• Subject usability and satisfaction with the secukinumab autoinjector (AI): Using a check list completed by a staff site member at Baseline and Week 1, six possible user-related hazards with the AI were reported for 5 patients. 3 distinct issues were related to question H8 ("Was any other problem observed?") and 3 issues were related to question H9 (Was less than the full dose administered?). Nearly all patients successfully completed the 14 indicated steps of the Instructions for Use (IFU). The steps with a slightly lower compliance rate were Steps 1 and 14, pertaining to washing hands with soap and disposal of the AI into a sharps container (95.1% and 96.7% of patients with successful completion at baseline, respectively). At Week 1, self-administration of first autoinjection of study drug was successfully performed by all patients. Scores of the Self-Injection Assessment Questionnaire (SIAQ) improved over time between the Randomization and Week 12 visits for all treatment groups ("Feelings about self-injection", "Self confidence" and "Satisfaction with self-injection").

Study A2303: FIXTURE (Full year Investigative eXamination of secukinumab vs. eTanercept Using 2 dosing Regimens to determine Efficacy in psoriasis): a randomized, double-blind, double-dummy, placebo controlled, multicenter study of subcutaneous secukinumab to demonstrate efficacy after twelve weeks of treatment, compared to placebo and etanercept, and to assess the safety, tolerability and long-term efficacy up to one year in subjects with moderate to severe chronic plaque-type psoriasis.

Methods

This was a multicenter, double-blind, double-dummy, randomized, parallel-group, active and placebo-controlled study in approximately 1264 patients with moderate to severe chronic plaque-type psoriasis. The study consisted of 4 periods: screening (of at least 1 week and up to 4 weeks), induction (of 12 weeks), maintenance (of 40 weeks) and follow-up period (of 8 weeks) (see Figure 5).

Figure 5 - Study design



AIN457 = secukinumab, EOI = end of induction period, EOM = end of maintenance period, EOF = end of follow-up period, PBO = placebo, Rand = Randomization, wk = week.
F4 is follow-up 4 visit, which was 4 weeks after maintenance but 8 weeks post last dose of secukinumab or placebo secukinumab.
F8 (EOF) is follow-up 8 visit, which was 8 weeks after maintenance but 12 weeks post last dose of secukinumab or placebo secukinumab.

Study Participants

The study population consisted of a representative group of male and female out-patients (≥18 years old) with moderate to severe chronic plaque-type psoriasis that was poorly controlled by topical treatments and/or phototherapy and/or previous systemic therapy.

Inclusion and exclusion criteria were the same as in Study A2302, with the following additional exclusion criteria: Previous exposure to etanercept (criteria no. 6); Investigator discretion should be used for

subjects with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders (criteria no. 11); and Subjects who are allergic to rubber or latex; (the needle covers on the single-use prefilled syringes for etanercept and placebo contain dry natural rubber) (criteria no. 22).

Treatments

Patients were assigned to one of the following 4 treatment arms, with approximately 316 patients per arm:

• Active etanercept comparator group: s.c. etanercept 50 mg twice per week from Randomization until Week 12, followed by s.c. etanercept 50 mg every week from Week 12 through Week 51. Patients self-administered etanercept or etanercept placebo doses at home. To maintain the blind, they also received 2 placebo secukinumab s.c. injections at the following site visits: Randomization, Weeks 1, 2, 3, 4, 8, 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, and 48.

• Secukinumab 150 mg regimen group (1 s.c. injection of the 150 mg dose + 1 s.c. injection of secukinumab placebo) administered at the following site visits: Randomization, Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and secukinumab placebo (2 s.c. injections per dose) administered at Weeks 13, 14 and 15. In addition, to maintain the blind, placebo etanercept was administered twice per week from randomization through Week 12, and then once per week until Week 51. Patients self-administered placebo etanercept doses at home.

• Secukinumab 300 mg regimen group (2 s.c. injections of the 150 mg dose) administered as indicated in the previous bullet point.

• Placebo group: s.c. placebo etanercept twice per week until Week 12 and s.c. placebo secukinumab (2 s.c. injections per dose) administered at Randomization, Weeks 1, 2, 3, 4, and 8. At Week 12 (prior to receiving the Week 12 dose), patients who had been on placebo for the initial part of the study either remained on placebo or were re-randomized to either secukinumab 150 mg or secukinumab 300 mg based on their PASI 75 response to placebo at Week 12:

  • Placebo PASI 75 responders continued to receive placebo secukinumab at Weeks 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, and 48 along with placebo etanercept once a week until Week 51.

  • Placebo PASI 75 non-responders were re-randomized 1:1 to 150 mg or 300 mg secukinumab (AIN457) and received their treatment on Weeks 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, and 48 along with weekly placebo etanercept until Week 51.

Objectives

The primary objective of Study A2303 was identical to previous studies, i.e. demonstration of superiority of secukinumab with respect to PASI 75 and IGA 0/1 response (co-primary endpoints) at Week 12, compared to placebo.

Key secondary objectives were similar to those of Study A2302 but included comparison to the active control etanercept (non-inferiority followed by superiority of secukinumab compared to etanercept at Week 12, and superiority of secukinumab in maintaining PASI 75 and IGA 0/1 response at Week 52 compared to etanercept). Also, no assessments on ACR responses in PsA patients were included among the exploratory objectives.

Criteria for efficacy, safety and other evaluations were generally the same as in Study A2302 (including items of the Psoriasis Symptom Diary but excluding ACR response assessments in PsA patients).

Sample size

The sample size was determined by the key secondary objective to demonstrate the non-inferiority of secukinumab vs. etanercept with respect to PASI 75 response at Week 12. In order to preserve the family wise error rate at 5% among all predetermined sequential comparisons, the type-I-error was set to 0.625% one-sided in non-inferiority comparison. With a non-inferiority margin of 10% and assumed PASI 75 response rates of 50% for etanercept and 55% for secukinumab, 316 patients per treatment group were needed to achieve a power of 90%. With 316 patients per group and assuming a response rate of 5% for PASI 75 response and IGA 0/1 response in the placebo group, the power to show a response rate of 55% for PASI 75 response and 30% for IGA 0/1 response in the secukinumab groups based on Fisher's exact test was above 99%.

Randomisation

The total sample size was 1264 patients, i.e. using a balanced randomization 316 patients were randomized to each treatment group.

Blinding

A double-dummy design was used because the comparator had a different dosing regimen than secukinumab and the identity of the study treatments could not be distinguished due to their different forms. Patients, investigator staff, persons performing the assessments, and data analysts remained blinded to the identity of the treatment from the time of randomization until end of follow-up database lock. If a patient had been in a secukinumab treatment group in the maintenance period and was a PASI 75 responder or partial responder, the IRT system indicated the patient was eligible for an extension study.

Statistical methods

The primary analysis set was the FAS. An analysis based on the per-protocol set was only performed if deemed necessary as additional sensitivity analyses, but it was not planned a priori for the superiority comparison to placebo. For the non-inferiority comparison, the one-sided 99.375% CI was derived. In case the stated non-inferiority limit -10% was smaller than the lower bound of the CI for the difference secukinumab minus etanercept, non-inferiority was concluded.

The primary analysis method for superiority testing was the stratified Cochran-Mantel-Haenszel (CMH) test. The tests were stratified by geographical region and body weight stratum. In case of response rates of 0% or 100% in one of the treatment groups, Fisher's exact test was applied.

Results

Participant flow

1560 patients were screened and 1306 patients (83.7%) completed the screening period. Of the 254 subjects who did not complete the screening phase, 211 had screen failure. The most common criterion for this was "history of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive QuanitFERON TB-Gold test at screening" (90 patients, 35.4%).

1306 patients were randomized to 4 treatment groups in the Induction period: secukinumab 150 mg (n=327), secukinumab 300 mg (n=327), placebo (n=326), or etanercept (n=326). Most patients (94.4%) completed the Induction period (see Table 29). The most common reasons for premature discontinuation was subject/guardian decision (overall 1.9%) followed by adverse event (overall 1.1%).

Table 29 Induction period patient disposition (Randomized set)

Disposition/Reason	AIN457 150 mg N=327 n (%)	AIN457 300 mg N=327 n (%)	Placebo N=326 n (%)	Etanercept N=326 n (%)	Total N=1306 n (%)
Randomized	327	327	326	326	1306
Completed induction period	315 (96.3)	312 (95.4)	301 (92.3)	305 (93.6)	1233 (94.41)
Discontinued induction period	12 (3.7)	15 (4.6)	25 (7.7)	21 (6.4)	73 (5.59)
Adverse event	2 (0.6)	4 (1.2)	2 (0.6)	6 (1.8)	14 (1.07)
Lack of efficacy	0	0	9 (2.8)	2 (0.6)	11 (0.84)
Lost to follow-up	0	0	1 (0.3)	4 (1.2)	5 (0.38)
Physician decision	2 (0.6)	1 (0.3)	2 (0.6)	0	5 (0.38)
Protocol deviation	3 (0.9)	5 (1.5)	0	3 (0.9)	11 (0.84)
Technical problems	0	0	1 (0.3)	1 (0.3)	2 (0.15)
Patient/guardian decision	5 (1.5)	5 (1.5)	10 (3.1)	5 (1.5)	25 (1.91)

Reasons for discontinued were attributed to the treatment that the patient was assigned to at the time of discontinuation

1233 patients entered the Maintenance period, of which 1100 patients (89.2%) completed the Maintenance period (see Table 30). For the 133 patients who discontinued during the maintenance period, the most common reasons for premature discontinuation were patient/guardian decision (overall 3.4%), lack of efficacy (overall 2.11%) and adverse event (1.64%).

Table 30 Maintenance period patient disposition (Randomized set)

Disposition/Reason	AIN457 150 mg N=327 n (%)	AIN457 300 mg N=327 n (%)	Placebo-AIN457 150 mg N=142 n (%)	Placebo-AIN457 300 mg N=142 n (%)	Placebo N=17 n (%)	Etanercept N=326 n (%)	Total N=1281 n (%)
Randomized	327	327	142	142	17	326	1281
Entered maintenance period	315 (96.3)	312 (95.4)	142 (100.0)	142 (100.0)	17 (100.0)	305 (93.6)	1233 (96.25)
Completed maintenance period	276 (84.4)	290 (88.7)	125 (88.0)	131 (92.3)	15 (88.2)	263 (80.7)	1100 (85.87)
Discontinued maintenance period	39 (11.9)	22 (6.7)	17 (12.0)	11 (7.7)	2 (11.8)	42 (12.9)	133 (10.38)
Adverse event	2 (0.6)	7 (2.1)	4 (2.8)	3 (2.1)	0	5 (1.5)	21 (1.64)
Lack of efficacy	10 (3.1)	3 (0.9)	3 (2.1)	0	0	11 (3.4)	27 (2.11)
Lost to follow-up	4 (1.2)	0	1 (0.7)	1 (0.7)	0	5 (1.5)	11 (0.86)
Non-compliance with study treatment	3 (0.9)	1 (0.3)	1 (0.7)	2 (1.4)	0	2 (0.6)	9 (0.70)
Physician decision	0	1 (0.3)	0	0	0	1 (0.3)	2 (0.16)
Pregnancy	1 (0.3)	0	0	0	0	0	1 (0.08)
Protocol deviation	7 (2.1)	4 (1.2)	2 (1.4)	2 (1.4)	0	2 (0.6)	17 (1.33)
Study terminated by sponsor	0	0	0	0	0	1 (0.3)	1 (0.08)
Patient/guardian decision	12 (3.7)	6 (1.8)	6 (4.2)	3 (2.1)	2 (11.8)	15 (4.6)	44 (3.43)

Recruitment

Study initiation date: 14 Jun 2011 (first patient first visit)

Study completion date: 07 Jul 2013 (last patient last visit for Week 52)

Conduct of the study

The study protocol was amended twice. The content of study protocol amendments was similar to those in Study A2302. No relevant changes in study conduct or in planned analyses were done.

Baseline data

The mean age was 44.4 years and the majority of patients (94.0%) were <65 years of age. There were 78 (6.0%) patients ≥65 years and 16 (1.2%) patients ≥75 years, equally distributed across the treatment groups. Caucasian was the predominant race (67.4%) followed by Asians (22.3%), and more than two-thirds of patients were male (71.1%). The mean weight was 83.3 kg, the mean BMI was 28.3 kg/m2 and one-third of patients were smokers at baseline (34.6%).

Among baseline disease characteristics, the mean PASI score was 23.7, the mean affected BSA was 34.4, and the mean time since psoriasis diagnosis was 16.6 years (see Table 31). PsA was diagnosed in 14.7% of patients at baseline. 836 patients (64.0%) were previously treated with systemic psoriasis therapy and

682 patients (81.6%) failed their systemic therapy. Other previous psoriasis therapies included topical medications (85.3%), phototherapy (37.6%), and photochemotherapy (21.0%).

Table 31 Disease history and baseline disease characteristics – induction treatment groups (Randomized set)

Background characteristics	Number (%) of patients				
	AIN457 150 mg N=327	AIN457 300 mg N=327	Placebo N=326	Etanercept N=326	Total N=1306
Baseline PASI score					
n	327	327	326	326	1306
Mean	23.67	23.86	24.05	23.23	23.70
SD	10.499	9.945	10.467	9.811	10.178
Median	20.30	21.50	20.70	20.00	20.50
Min - Max	12.0 - 69.6	12.0 - 64.2	12.0 - 64.4	12.0 - 54.5	12.0 - 69.6
Baseline PASI, n (%)					
≤20	161 (49.2)	149 (45.6)	152 (46.6)	163 (50.0)	625 (47.86)
>20	166 (50.8)	178 (54.4)	174 (53.4)	163 (50.0)	681 (52.14)
Baseline total BSA, n (%)					
n	327	327	326	326	1306
Mean	34.491	34.306	35.210	33.582	34.397
SD	19.4235	19.2096	19.1291	17.9673	18.9286
Median	30.400	29.800	31.500	28.950	30.000
Min - Max	9.99 - 88.50	10.00 - 95.00	9.99 - 93.50	9.97 - 86.00	9.97 - 95.00
Baseline IGA mod 2011 score, n (%)					
3 (moderate)	206 (63.0)	203 (62.1)	202 (62.0)	195 (59.8)	806 (61.72)
4 (severe)	121 (37.0)	124 (37.9)	124 (38.0)	131 (40.2)	500 (38.28)
Severity of psoriasis, n (%)					
Moderate	93 (28.4)	88 (26.9)	79 (24.2)	90 (27.6)	350 (26.80)
Severe	234 (71.6)	239 (73.1)	247 (75.8)	236 (72.4)	956 (73.20)
Psoriatic arthritis present, n (%)					
Yes	49 (15.0)	50 (15.3)	49 (15.0)	44 (13.5)	192 (14.70)
No	278 (85.0)	277 (84.7)	277 (85.0)	282 (86.5)	1114 (85.30)
Time since first diagnosis of psoriasis [years]					
n	327	327	326	326	1306
Mean	17.331	15.839	16.648	16.449	16.567
SD	12.2215	12.2925	11.6300	12.0105	12.0397
Median	15.458	12.758	15.515	14.528	14.548
Min - Max	0.51 - 69.01	0.49 - 61.48	0.51 - 54.62	0.59 - 57.20	0.49 - 69.01
Time since first diagnosis of psoriatic arthritis [years]					
n	49	50	49	44	192
Mean	7.737	8.052	8.595	9.533	8.450
SD	7.4258	7.3220	8.9106	11.6140	8.8532
Median	4.758	6.163	5.478	4.591	5.547
Min - Max	0.15 - 28.20	0.09 - 25.89	0.30 - 38.80	0.00 - 44.60	0.00 - 44.60
Previous exposure to systemic psoriasis therapy, n (%)					
Yes	212 (64.8)	206 (63.0)	204 (62.6)	214 (65.6)	836 (64.01)
No	115 (35.2)	120 (36.7)	122 (37.4)	112 (34.4)	469 (35.91)
Previous failure to systemic psoriasis therapy, n (%)					
m	212	206	204	214	836
Yes	175 (82.5)	168 (81.6)	173 (84.8)	166 (77.6)	682 (81.58)
No	37 (17.5)	38 (18.4)	31 (15.2)	48 (22.4)	154 (18.42)
Previous exposure to biologic systemic psoriasis therapy, n (%)					
Yes	45 (13.8)	38 (11.6)	35 (10.7)	45 (13.8)	163 (12.48)
No	282 (86.2)	288 (88.1)	291 (89.3)	281 (86.2)	1142 (87.44)
Previous failure to biologic systemic psoriasis therapy, n (%)					
m	45	38	35	45	163
Yes	15 (33.3)	16 (42.1)	12 (34.3)	16 (35.6)	59 (36.20)
No	30 (66.7)	22 (57.9)	23 (65.7)	29 (64.4)	104 (63.80)
Previous exposure to non-biologic systemic psoriasis therapy, n (%)					
Yes	198 (60.6)	195 (59.6)	199 (61.0)	204 (62.6)	796 (60.95)
No	129 (39.4)	131 (40.1)	127 (39.0)	122 (37.4)	509 (38.97)
Previous failure to non-biologic systemic psoriasis therapy, n (%)					
m	198	195	199	204	796
Yes	171 (86.4)	163 (83.6)	172 (86.4)	161 (78.9)	667 (83.79)
No	27 (13.6)	32 (16.4)	27 (13.6)	43 (21.1)	129 (16.21)

m = number of patients with measurements
BSA = body surface area, IGA mod 2011 = Investigator's global assessment modified 2011, PASI = psoriasis area and severity index, SD = standard deviation.
Baseline IGA mod 2011 scores: 3 = moderate disease, 4 = severe disease.

Numbers analysed

The number of patients in each analysis is shown in Table 32.

Table 32 Analysis sets - entire treatment group (All patients enrolled)

Analysis set	AIN457 150 mg	AIN457 300 mg	Any AIN457 150 mg	Any AIN457 300 mg	Any AIN457 dose	Placebo	Etanercept	Total
	n	n	n	n	n	n	n	n
Randomized set	327	327	469	469	938	326	326	1306
Full analysis set	327	327	469	468	937	325	326	1305
Safety set	327	326	469	467	936	327	323	1303

The Randomized set was defined as all patients who were randomized.
The Full analysis set was comprised of all patients to whom study treatment had been assigned.
The Safety set included all patients who took at least 1 dose of study drug during the treatment period, and patients were analyzed according to treatment received.

Outcomes and estimation

Co-primary efficacy results:

The results of the statistical analysis of IGA mod 2011 0/1 and PASI 75 response at Week 12 are shown in Table 33. Secukinumab at both doses was superior to placebo at Week 12, with statistically significant difference (p<0.0001). The p-values for the differences between 300 mg vs. 150 mg secukinumab at Week 12 were 0.0046 for PASI 75 and 0.0032 for IGA 0/ 1.

Table 33 Statistical analysis (Cochran-Mantel-Haenszel test) of IGA mod 2011 0/1 and PASI 75 response at Week 12 for secukinumab vs. placebo (non-responder imputation) (Full analysis set); below also efficacy data on etanercept treatment

Response criterion	Treatment comparison "test" vs. "control"	"Test" n/m (%)	"Control" n/m (%)	Odds ratio estimate (95%CI)	p-value
IGA mod 2011 0 or 1	AIN457 150 mg vs. placebo	167/327 (51.1)	9/324 (2.8)	40.62 (19.80, 83.35)	<0.0001
	AIN457 300 mg vs. placebo	202/323 (62.5)	9/324 (2.8)	79.13 (35.97, 174.09)	<0.0001
PASI 75	AIN457 150 mg vs. placebo	219/327 (67.0)	16/324 (4.9)	42.76 (23.57, 77.60)	<0.0001
	AIN457 300 mg vs. placebo	249/323 (77.1)	16/324 (4.9)	65.95 (36.07, 20.59)	<0.0001

IGA mod 2011 = Investigator's global assessment modified 2011, m=number of evaluable subjects, n=number of subjects with response, PASI = psoriasis area and severity index.

Response criterion	Analysis description	Treatment comparison "test" vs. "control"	"test" n/m (%)	"control" n/m (%)	odds ratio estimate (95% CI)	p-value
IGA 0/1	CMH	AIN457 150 mg vs. Placebo	167/327 (51.1)	9/324 (2.8)	40.62 (19.80, 83.35)	<0.0001
		AIN457 300 mg vs. Placebo	202/323 (62.5)	9/324 (2.8)	79.13 (35.97, 174.09)	<0.0001
		AIN457 150 mg vs. Etanercept	167/327 (51.1)	88/323 (27.2)	2.96 (2.11, 4.15)	<0.0001
		AIN457 300 mg vs. Etanercept	202/323 (62.5)	88/323 (27.2)	4.91 (3.46, 6.97)	<0.0001
	log. regr.	AIN457 150 mg vs. Placebo	167/327 (51.1)	9/324 (2.8)	41.93 (20.72, 84.83)	<0.0001
		AIN457 300 mg vs. Placebo	202/323 (62.5)	9/324 (2.8)	68.36 (33.65, 138.86)	<0.0001
		AIN457 150 mg vs. Etanercept	167/327 (51.1)	88/323 (27.2)	2.99 (2.13, 4.20)	<0.0001
		AIN457 300 mg vs. Etanercept	202/323 (62.5)	88/323 (27.2)	4.88 (3.45, 6.90)	<0.0001
PASI 75	CMH	AIN457 150 mg vs. Placebo	219/327 (67.0)	16/324 (4.9)	42.76 (23.57, 77.60)	<0.0001
		AIN457 300 mg vs. Placebo	249/323 (77.1)	16/324 (4.9)	65.95 (36.07, 120.59)	<0.0001
		AIN457 150 mg vs. Etanercept	219/327 (67.0)	142/323 (44.0)	2.73 (1.96, 3.79)	<0.0001
		AIN457 300 mg vs. Etanercept	249/323 (77.1)	142/323 (44.0)	4.69 (3.28, 6.70)	<0.0001
	log. regr.	AIN457 150 mg vs. Placebo	219/327 (67.0)	16/324 (4.9)	47.34 (26.85, 83.45)	<0.0001
		AIN457 300 mg vs. Placebo	249/323 (77.1)	16/324 (4.9)	79.31 (44.36, 141.80)	<0.0001
		AIN457 150 mg vs. Etanercept	219/327 (67.0)	142/323 (44.0)	2.75 (1.98, 3.83)	<0.0001
		AIN457 300 mg vs. Etanercept	249/323 (77.1)	142/323 (44.0)	4.61 (3.24, 6.56)	<0.0001

In a subgroup analysis by weight, PASI 75, PASI 90, and IGA mod 2011 0/1 response rates at Week 12 were higher in both secukinumab dose groups compared to etanercept and placebo for both body weight subgroups (<90 kg and ≥90 kg), and overall higher in the <90 kg subgroup (see Table 34). P-values for the comparison to placebo were <0.0001.

Table 34 PASI 75, PASI 90 and IGA mod 2011 0 or 1 response at Week 12 by body weight (non-responder imputation) (FAS)

Criterion	<90 kg n/m (%)				≥90 kg n/m (%)			
	AIN457 150 mg	AIN457 300 mg	Placebo	Etanercept	AIN457 150 mg	AIN457 300 mg	Placebo	Etanercept
IGA mod 2011 0 or 1	119/215 (55.3)	140/217 (64.5)	8/216 (3.7)	66/215 (30.7)	48/112 (42.9)	62/106 (58.5)	1/108 (0.9)	22/108 (20.4)
PASI 75	157/215 (73.0)	171/217 (78.8)	15/216 (6.9)	100/215 (46.5)	62/112 (55.4)	78/106 (73.6)	1/108 (0.9)	42/108 (38.9)
PASI 90	101/215 (47.0)	127/217 (58.5)	5/216 (2.3)	49/215 (22.8)	36/112 (32.1)	48/106 (45.3)	0/108 (0)	18/108 (16.7)

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

In subgroup analyses by previous exposure to systemic therapy and by previous biologic therapy, secukinumab 300 mg provided the highest response rates compared to all other treatment groups. For secukinumab 300 mg at Week 12, IGA mod 2011 0/1 responses were 61.0% vs. 65.0%, respectively, PASI 75 responses were 77.1% vs. 76.9%, respectively, and PASI 90 responses were 54.6 vs. 53.0%, respectively, in patients with or without previous exposure to systemic therapy (64% and 36% of

patients, respectively). 163 patients had been exposed to previous biologic therapy and 60 patients had received previous anti-TNFα treatment. Response rates were higher for patients with no previous biologic therapy and for patients who did not fail their previous biologic therapy (see Table 35).

Table 35 IGA mod 2011 0 or 1, PASI 75 and PASI 90 response at Week 12 by previous exposure to biologic therapy (non-responder imputation) (FAS)

Response criterion	AIN457 150 mg n/m (%)	AIN457 300 mg n/m (%)	Placebo n/m (%)	Etanercept n/m (%)
Previously exposed to biologic therapy				
IGA mod 2011 0 or 1	15/45 (33.3)	20/38 (52.6)	0/35 (0)	12/45 (26.7)
PASI 75	24/45 (53.3)	29/38 (76.3)	0/35 (0)	24/45 (53.3)
PASI 90	15/45 (33.3)	18/38 (47.4)	0/35 (0)	8/45 (17.8)
Previously exposed to and failed biologic therapy				
IGA mod 2011 0 or 1	3/15 (20.0)	6/16 (37.5)	0/12 (0)	4/16 (25.0)
PASI 75	7/15 (46.7)	11/16 (68.8)	0/12 (0)	6/16 (37.5)
PASI 90	3/15 (20.0)	7/16 (43.8)	0/12 (0)	2/16 (12.5)
Previously exposed to anti-TNFα therapy				
IGA mod 2011 0 or 1	4/15 (26.7)	5/12 (41.7)	0/12 (0)	9/21 (42.9)
PASI 75	8/15 (53.3)	8/12 (66.7)	0/12 (0)	11/21 (52.4)
PASI 90	3/15 (20.0)	6/12 (50.0)	0/12 (0)	4/21 (19.0)
Previously exposed to and failed anti-TNFα therapy				
IGA mod 2011 0 or 1	3/9 (33.3)	4/10 (40.0)	0/3 (0)	3/10 (30.0)
PASI 75	5/9 (55.6)	7/10 (70.0)	0/3 (0)	3/10 (30.0)
PASI 90	3/9 (33.3)	5/10 (50.0)	0/3 (0)	1/10 (10.0)

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

Key secondary efficacy results

Secukinumab at both doses was statistically significantly ($p<0.0001$) superior to placebo with respect to PASI 90 response at Week 12, with a higher odds ratio estimate for the secukinumab 300 mg dose (118.48) than for the secukinumab 150 mg dose (56.10) (see Table 36). A higher proportion of patients in both secukinumab dose groups were PASI 90 responders than in the etanercept group (41.9% for 150 mg secukinumab and 54.2% for 300 mg secukinumab vs. 20.7% for etanercept).

Table 36 Statistical analysis (Cochran-Mantel-Haenszel test) of PASI 90 response at Week 12 (non-responder imputation) (Full analysis set)

Response criterion	Treatment comparison "test" vs. "control"	"Test" n/m (%)	"Control" n/m (%)	Odds ratio estimate (95%CI)	p-value
PASI 90	AIN457 150 mg vs. placebo	137/327 (41.9)	5/324 (1.5)	56.10 (21.41, 147.03)	<0.0001
	AIN457 300 mg vs. placebo	175/323 (54.2)	5/324 (1.5)	118.48 (41.34, 339.58)	<0.0001
	AIN457 150 mg vs. etanercept	137/327 (41.9)	67/323 (20.7)	2.86 (2.01, 4.07)	<0.0001
	AIN457 300 mg vs. etanercept	175/323 (54.2)	67/323 (20.7)	4.67 (3.28, 6.66)	<0.0001

m=number of evaluable subjects, n=number of subjects with response, PASI = psoriasis area and

In non-inferiority analysis of PASI 75 response at Week 12, risk difference estimates were in favor of secukinumab vs. etanercept both for the 150 mg dose (estimate of 23.12%; 99.375% confidence level; CI 14.06, 32.19) and the 300 mg dose (estimate of 32.80%; 99.375% confidence level; CI 24.06, 41.53). As the lower limits of the CIs were above –10%, non-inferiority could be concluded for both secukinumab doses (see Table 37).

Table 37 Non-inferiority analysis (Mantel-Haenszel risk difference) of PASI 75 response at Week 12 (non-responder imputation) (Full analysis set)

Response criterion	Comparison "test" vs. "control"	"Test" n/m (%)	"Control" n/m (%)	Mantel-Haenszel risk difference		
				Estimate (%)	Confidence level (1-sided)	CI
PASI 75	AIN457 150 mg vs. Etanercept	219/327 (67.0)	142/323 (44.0)	23.12	initial 99.375% adjusted 99.375%	(14.06, 32.19)
	AIN457 300 mg vs. Etanercept	249/323 (77.1)	142/323 (44.0)	32.80	initial 99.375% adjusted 99.375%	(24.06, 41.53)

CI = confidence interval, m=number of subjects evaluable, n=number of subjects with response, PASI = psoriasis area and severity index.
Non-inferiority margin is 10%.

In the tests for superiority, response rates at Week 12 were statistically significantly ($p<0.0001$) higher for secukinumab at both doses compared to etanercept both for PASI 75 (67.0% for secukinumab 150 mg and 77.1% for secukinumab 300 mg vs. 44.0% for etanercept) and IGA 0/1 (51.1% and 62.5% vs. 27.2%, respectively) (see previous Table 33).

Maintenance of PASI 75 response at Week 52 (for subjects who were PASI 75 responders at Week 12) was similar in the secukinumab 300 mg group (84.3%) and secukinumab 150 mg group (82.2%), but lower in the etanercept group (72.5%). The cumulative rate for the loss of PASI 75 response was highest in the etanercept group (33.8), and lower in both secukinumab groups (22.5 and 11.9 in secukinumab 150 mg and 300 mg groups, respectively). In the overall population, the PASI 75 response rates achieved on induction treatment with 300 mg and 150 mg secukinumab increased from Week 12 to 16, and were then sustained to Week 52.

Maintenance of IGA 0/1 response at Week 52 (for subjects who were IGA 0/1 responders at Week 12) was higher in the secukinumab 300 mg group (79.7%) than in the secukinumab 150 mg group (67.7%) and etanercept group (56.8%). The cumulative rate for the loss of IGA 0/1 response was highest in the etanercept group (56.9), and lower in both secukinumab groups (37.6 and 23.5 in secukinumab 150 mg and 300 mg groups, respectively).

Psoriasis Symptom Diary items at Week 12: For all comparisons (itching, pain and scaling) vs. placebo, secukinumab at both doses showed statistically significantly higher improvement, with p-values of <0.0001 for all comparisons. Improvements from baseline were numerically greater with 300 mg than with 150 mg secukinumab. Secukinumab at both doses showed statistically significantly higher improvement compared to etanercept, with p-values ranging from 0.0467 to <0.0001 for all comparisons.

Other secondary efficacy results:

Time course of response: From Week 3 on, higher PASI 75 and IGA 0/1 response rates were observed in both secukinumab dose groups than in the etanercept group. During the maintenance period, PASI 75 and IGA 0/1 response rates increased from Week 12 to 16, and were then sustained. In the placebo-secukinumab dose groups, the percentage of PASI 75 and IGA 0/1 responders increased quickly and reached the level of the secukinumab dose groups from Week 20. The time courses for PASI 50, PASI 90, and PASI 100 during the induction period were generally similar. The median time to PASI 75 response was 57.0 days (55.0 to 85.0) for 150 mg secukinumab, 57.0 days (29.0 to 85.0) for 300 mg secukinumab and 86.0 days (59.0 to not specified) for etanercept, and not estimable for the placebo group.

HAQ-DI was assessed for the subset of patients who had PsA at baseline. The mean HAQ-DI score improved up to Week 12 in both secukinumab dose groups and in the etanercept group but not in the placebo group (mean change of scores of −0.19 (−30.53%) for secukinumab 150 mg, −0.41 (−55.04%) for secukinumab 300 mg, −0.29 (−49.47%) for etanercept and 0.02 (8.41%) for placebo). These mean improvements were sustained throughout the maintenance period in all active treatment groups.

The cumulative probability to relapse at >40 weeks after Week 12 was 3.0% in the secukinumab 300 mg group, 6.6% in the secukinumab 150 mg group and 11.1% in the etanercept group. Prior to this time period, the risk was smaller in both secukinumab groups compared to etanercept group. The cumulative probability for the time to relapse >12 to ≤20 weeks after last study treatment administration was 16.6% for secukinumab 300 mg compared to 67.1% for secukinumab 150 mg and 62.1% for etanercept. Rebound was less frequently reported in any active treatment group (23.3% for secukinumab 150 mg, 21.4% for secukinumab 300 mg, and 19.5% for etanercept) than in the placebo group (58.3%). Assessments of post-treatment relapses and rebounds were however biased due to small sample of mainly discontinued patients.

PGIC: Improvement in PGIC items (overall impact of psoriasis on life and severity of current psoriasis symptoms “a great deal better”) were reported in approximately 60% of patients in both secukinumab dose groups, compared to approximately 30% of patients in the etanercept group and approximately 5% of patients in the placebo group.

EQ-5D: Improvements during the induction period were reported for all EQ-5D categories in both secukinumab dose groups and in the etanercept group. The largest differences between baseline and Week 12 were seen in the EQ-5D categories “I have no pain or discomfort” and “I am not anxious or depressed”. Absolute changes from baseline reached a mean score of 22.3 for secukinumab 300 mg, 19.7 for secukinumab 150 mg, 14.4 for etanercept, and 2.2 for placebo. Mean changes from baseline in the EQ-5D health assessment were sustained or even improved further throughout the maintenance period.

DLQ1: Changes in DLQI total score at Week 12 reached a mean of −10.4 (−78.8%) in the secukinumab 300 mg group, −9.7 (−72.7%) in the secukinumab 150 mg group, −7.9 (−56.0%) in the etanercept group and mean score of −1.9 (−3.6%) in the placebo group. The treatment differences vs. placebo and etanercept were statistically significantly for both secukinumab doses at all time points (Weeks 4, 8, and 12) but was not statistically significant between secukinumab 300 mg and secukinumab 150 mg. The improvements achieved for the mean DLQI total score during the induction period were sustained up to Week 52.

Study A2304: Study Comparing secukinumab Use in Long-term Psoriasis maintenance therapy: fixed regimens vs. reTreatment Upon start of RElapse (SCULPTURE): a randomized, double-blind, multicenter study of subcutaneous secukinumab, assessing Psoriasis Area and Severity Index (PASI) response and maintenance of response in subjects with moderate to severe chronic plaque-type psoriasis on either a fixed dose regimen or on a retreatment at start of relapse regimens.

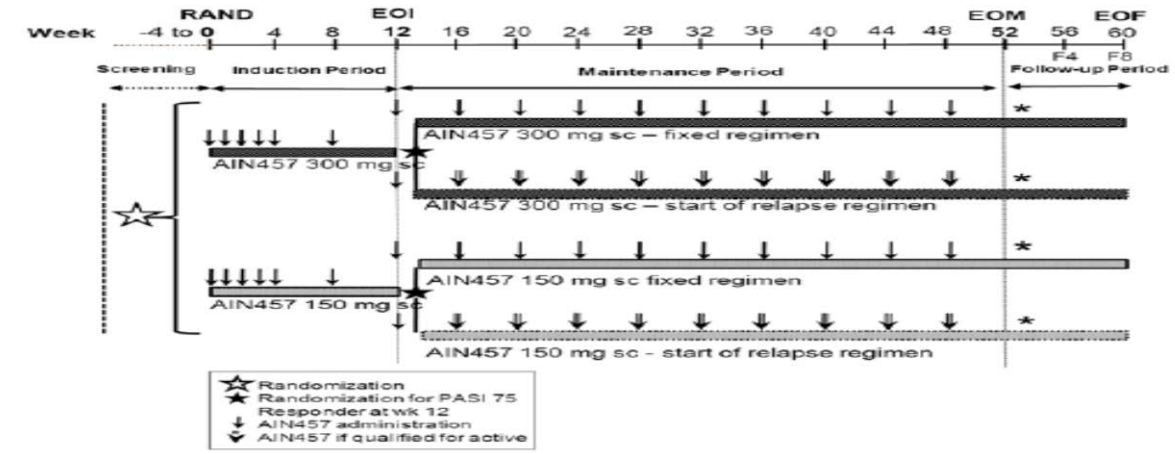
Methods

This was a randomized, double-blind, multicenter trial in patients with moderate to severe chronic plaque-type psoriasis. The study consisted of four periods: screening (at least 1 week and up to 4 weeks), induction (12 weeks), maintenance (40 weeks), and follow-up (8 weeks) (see Figure 6).

Patients who were partial responders at the end of the induction period did not continue in the maintenance period of the study, but were given the option to enter study AIN457A2307. Non-responders did not continue in the maintenance period but entered the treatment-free follow-up period. After the End of Maintenance (EOM) visit was completed, qualifying patients could enter extension study

AIN457A2304E1. Patients not entering the extension after the EOM visit entered the treatment-free follow-up period.

Figure 6 - Study design



EOF = end of Follow-up period; EOI = end of induction period; EOM = end of maintenance period
* After the end of maintenance, qualifying patients entered an extension study (AIN457A2304E1) designed to investigate long-term safety, tolerability, and efficacy with secukinumab. A patient was considered for entry into the extension protocol only at a site where the extension was approved at the time the patient has completed the maintenance period (Week 52 in this study). Subjects not eligible for the extension study for any reason (including extension study screening failure patients) and those who have chosen to not enter the extension entered the treatment-free follow-up period.

Study Participants

Inclusion and exclusion criteria were identical to Study A2302.

Treatments

Patients were randomized using a 1:1 ratio into one of the two induction treatment arms below:

• Secukinumab 150 mg group from Randomization to Week 8 (treatment at Weeks 1, 2, 3, 4 and 8);

• Secukinumab 300 mg group treated with secukinumab 300 mg from Randomization to Week 8.

At Week 12 (end of Induction period), patients were classified and progressed as follows:

• PASI 75 responders were re-randomized into the maintenance period within their same dose group of either 150 or 300 mg subcutaneous secukinumab, in a ratio of 1:1 to one of two treatment schedules: FI or SoR, and stratified according to the same criteria as in the induction period

- A patient in the FI groups received the same dose they received during the induction period every four weeks, from Week 12 up to and including Week 48
- A patient in the SoR group was not dosed with active secukinumab until that patient met start of relapse criteria and continued dosing until PASI 75 response was regained.

• PASI partial responders (patients achieving at least 50%, but less than 75% reduction of PASI compared to baseline) could enter protocol CAIN457A2307. Partial responders who did not want to enter protocol CAIN457A2307 entered the treatment-free follow-up period

• PASI non responders (patients achieving less than 50% reduction of PASI compared to baseline) progressed immediately into the treatment-free follow-up period.

In Study A2304, lyophilisate in vial (LYO) formulation of secukinumab was used, as in Phase III Studies A2302 and A2303.

Objectives

The primary objective was to demonstrate the non-inferiority of 150 mg and 300 mg of secukinumab administered at the start of relapse (SoR) versus fixed interval (FI) regimens of 150 mg and 300 mg of secukinumab respectively, in patients with moderate to severe chronic plaque-type psoriasis who were PASI 75 responders at Week 12, with respect to PASI 75 response:

- at Week 52 for patients in the FI regimen, or
- at Week 40 for patients in the SoR regimen who do not require active treatment at Week 40, or
- at Week 52 for patients in the SoR regimen who do require active treatment at Week 40.

Secondary and exploratory objectives were largely similar to the previous phase III studies. They included efficacy assessment in PsA, as in Study A2302.

Outcomes/endpoints

Criteria for efficacy, safety and other evaluations in Study A2304 were the same as in previous studies but the Psoriasis Symptom Diary was not used. "Start of relapse" was defined as "a loss of ≥ 20% of the maximum PASI gain achieved during the study compared to baseline, and a loss of PASI 75 response".

Sample size

1200 patients were screened and 966 patients were randomized (482 patients in the 150 mg group and 484 patients in the 300 mg group) in the induction period. In the sample size calculation, the used type I error rate of 1.25% (one-sided) controls family wise type I error rate at 2.5% level (one -sided) among the set of two hypotheses H1 and H2.

Randomisation

Eligible patients were randomized 1:1 to treatment with either 150 mg or 300 mg subcutaneous (s.c.) secukinumab. In the maintenance period, PASI 75 responders were re-randomized to either a fixed-time interval (FI) regimen of the dose received during the induction period (150 mg or 300 mg s.c. secukinumab), or a "re-treatment at start of relapse (SoR) regimen" of the dose received during the induction period (150 mg or 300 mg s.c. secukinumab).

Blinding

This was a double-blind study. Blinding was maintained as described in previous studies.

Statistical methods

For the non-inferiority comparison for each of the two doses, the one-sided 98.75% confidence interval was derived. In case the non-inferiority margin of -15% was smaller than the lower bound of the confidence interval for the difference in maintenance responder rates "retreatment at start of relapse regimen" minus "fixed interval regimen," non- inferiority was to be concluded. In the event non-inferiority was shown for one dose, but not for the other dose, the alpha was to be shifted to the other dose and the null hypotheses could be retested at 2.5% level (one-sided). The analysis of the primary variable was based on the FAS.

Results

Participant flow

A total of 1200 patients were screened and 966 patients were randomized to two balanced groups in the Induction period: secukinumab 150 mg (n=482) or secukinumab 300 mg (n=484). The majority (196, 83.8%) of 234 screened patients who did not complete the screening phase were screen failures.

Most randomized patients (928, 96.1%) completed the 12-week Induction period. The most common reasons for premature discontinuation among the 38 discontinued patients were AEs (17, 1.8% overall) and patient/guardian decision (14, 1.4% overall).

Patient disposition during the Maintenance period is shown in Table 38. Of the 928 patients who completed the Induction period, a total of 843 (90.8%) patients were re-randomized to the maintenance period to either FI dosing or SoR dosing at their respective dose level: FI secukinumab 150 mg (N=203), FI secukinumab 300 mg (N=217), secukinumab 150 mg SoR (N=206), or secukinumab 300 mg SoR (N=217). Most patients (767, 91.0%) completed the 52-week maintenance period. The discontinuation rate was highest in the 150 mg SoR group (12.1%) followed by 150 mg FI (8.4%), 300 mg FI (8.3%) and 300 mg SoR (7.4%) groups. The most common reason for premature discontinuation was patient/guardian decision (35, 4.2% overall).

Table 38 Patient disposition – maintenance period (Randomized set)

Disposition /Reason	AIN457 150 mg N=203 n (%)	AIN457 300 mg N=217 n (%)	AIN457 150 mg SoR N=206 n (%)	AIN457 300 mg SoR N=217 n (%)	Any AIN457 dose N=843 n (%)
Randomized	203	217	206	217	843
Completed maintenance	186 (91.6)	199 (91.7)	181 (87.9)	201 (92.6)	767 (91.0)
Discontinued maintenance	17 (8.4)	18 (8.3)	25 (12.1)	16 (7.4)	76 (9.0)
Adverse event	2 (1.0)	8 (3.7)	4 (1.9)	2 (0.9)	16 (1.9)
Lack of efficacy	2 (1.0)	1 (0.5)	3 (1.5)	5 (2.3)	11 (1.3)
Lost to follow-up	0 (0.0)	0 (0.0)	4 (1.9)	0 (0.0)	4 (0.5)
Non-compliance with study treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Physician decision	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)
Protocol deviation	2 (1.0)	2 (0.9)	2 (1.0)	2 (0.9)	8 (0.9)
No longer requires treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Technical problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject/guardian decision	11 (5.4)	7 (3.2)	10 (4.9)	7 (3.2)	35 (4.2)
Death	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)

Recruitment

Study initiation date: 04 Aug 2011 (first patient first visit)

Study completion date: 07 March 2013 (last patient last Week 52 visit)

Conduct of the study

The study protocol was amended twice. Amendment 1 was implemented to incorporate changes recommended by FDA. Amendment 2 included text about the extension protocol (AIN457A2304E1) and described the possibility for qualifying patients to enter the extension study.

Baseline data

In the Induction period, most patients were male (66.0%), Caucasian (71.6%; followed by Asian 24.9%), with median age of 46.0 years. The majority of patients were <65 years old (93.0%) and a total of six patients were ≥75 years. The mean weight was 89.2 kg and mean BMI 29.0 kg/m^2. Overall, 34.1% of patients were current smokers.

The baseline disease characteristics were consistent with moderate to severe plaque-type psoriasis; the mean PASI score was 23.6, the affected mean BSA was 34.7, and the mean time since psoriasis diagnosis was 17.3 years. Baseline PASI was >20 in 53.7% of patients, IGA mod 2011 score 4 = “Severe disease” in 40.6% of patients and “Severity of psoriasis” was assessed as “severe” in 73.5% of patients. Psoriatic

arthritis was present in 20.5% of patients. Previous exposure to psoriasis systemic therapy was reported for 66.6% and to biologic psoriasis systemic therapy for 28.0% of patients. Previous failure to such therapies was reported for 75.6% and 51.1% of patients, respectively.

Most patients who entered the Maintenance period were male (66.4%), Caucasian (70.1%; followed by Asian 26.5%), with median age of 45.5 years. There was a greater proportion of female patients in the 150 mg FI arm (40.4%) compared to the other treatment arms (28.6-34.0%). The mean weight was 83.7 kg and mean BMI 28.6 kg/m^2. 33.3% of patients were current smokers.

Disease history and baseline characteristics as well as previous exposure to psoriasis systemic therapy (see Table 39) were generally well distributed among maintenance treatment arms. Previous failure to psoriasis systemic therapy and to biologic psoriasis systemic therapy was reported more frequently for the secukinumab 300 mg FI group (81.0% and 59.0%, respectively, vs. 75.3% and 48.9%, respectively, in the Any AIN457 dose group). Also previous exposure to biologic psoriasis systemic therapy was more frequent in this group (28.1%).

Table 39 Previous exposure to psoriasis systemic therapy - maintenance / entire treatment period groups (Randomized set)

Background Characteristics	AIN457 150 mg N=203	AIN457 300 mg N=217	AIN457 150 mg SoR N=206	AIN457 300 mg SoR N=217	Any AIN457 dose N=843
Previous exposure to psoriasis systemic therapy, n (%)					
Yes	130/202 (64.4)	147/217 (67.7)	137/206 (66.5)	141/217 (65.0)	555/842 (65.9)
No	72/202 (35.6)	70/217 (32.3)	69/206 (33.5)	76/217 (35.0)	287/842 (34.1)
Previous failure to psoriasis systemic therapy, n (%)					
Yes	99/130 (76.2)	119/147 (81.0)	98/137 (71.5)	102/141 (72.3)	418/555 (75.3)
No	31/130 (23.8)	28/147 (19.0)	39/137 (28.5)	39/141 (27.7)	137/555 (24.7)
Previous exposure to biologic psoriasis systemic therapy, n (%)					
Yes	48/202 (23.8)	61/217 (28.1)	51/206 (24.8)	61/217 (28.1)	221/842 (26.2)
No	154/202 (76.2)	156/217 (71.9)	155/206 (75.2)	156/217 (71.9)	621/842 (73.8)
Previous failure to biologic psoriasis systemic therapy, n (%)					
Yes	21/48 (43.8)	36/61 (59.0)	23/51 (45.1)	28/61 (45.9)	108/221 (48.9)
No	27/48 (56.3)	25/61 (41.0)	28/51 (54.9)	33/61 (54.1)	113/221 (51.1)
Previous exposure to non-biologic psoriasis systemic therapy, n (%)					
Yes	110/202 (54.5)	118/217 (54.4)	121/206 (58.7)	117/217 (53.9)	466/842 (55.3)
No	92/202 (45.5)	99/217 (45.6)	85/206 (41.3)	100/217 (46.1)	376/842 (44.7)
Previous failure to non-biologic psoriasis systemic therapy, n (%)					
Yes	91/110 (82.7)	98/118 (83.1)	91/121 (75.2)	93/117 (79.5)	373/466 (80.0)
No	19/110 (17.3)	20/118 (16.9)	30/121 (24.8)	24/117 (20.5)	93/466 (20.0)

Numbers analysed

Table 40 Analysis sets – maintenance / entire treatment groups (All patients enrolled)

Analysis Set	AIN457 150 mg	AIN457 300 mg	AIN457 150 mg SoR	AIN457 300 mg SoR	Any AIN457 dose
Randomized set	203	217	206	217	843
Full analysis set	203	216	206	217	842
Safety set	203	216	205	217	841
Per protocol set	190	205	193	204	792

The number of subjects with deviations of potential or major impact was 47. In addition to these, three patients were excluded from the Per protocol set due to low compliance and one patient due to no dosing after Week 12.

Outcomes and estimation

Primary efficacy results:

The primary endpoint for this study was not met i.e., it could not be shown that the re-treatment at SoR maintenance regimen was non-inferior to a FI regimen with treatment every four weeks. The lower limit of the adjusted CI for SoR minus FI was approximately -20% for both 150 mg and 300 mg; hence, the non-inferiority margin was exceeded. The 300 mg SoR dosing regimen showed maintenance of response similar to that of the 150 mg FI regimen with respect to PASI 75 response (67.7% vs. 62.1%, respectively) (see Table 40).

Table 40 Non-inferiority analysis (Mantel-Haenszel risk difference) of maintenance of response (non-responder imputation) (FAS)

				Mantel-Haenszel Risk difference		
Response Criterion	Treatment comparison "Test" vs. "Control"	"Test" n/m (%)	"Control" n/m (%)	Estimate (%)	Confidence Level -One sided	Confidence -Interval
Maintenance of response	AIN457 150 mg SoR vs. AIN457 150 mg FI	108/ 206 (52.4)	126/ 203 (62.1)	-9.61	initial 98.75%	(-20.10, 0.88)
					adjusted 98.75%	(-20.10, 0.88)
	AIN457 300 mg SoR vs. AIN457 300 mg FI	147/ 217 (67.7)	169/ 216 (78.2)	-10.34	initial 98.75%	(-19.37, -1.30)
					adjusted 98.75%	(-19.37, -1.30)

Non-inferiority margin was 15%
FAS = Full Analysis set; FI = fixed interval; SoR = start of relapse
"Test" = 150 mg or 300 mg SoR groups
"Control" = 150 mg or 300 mg FI groups
n = number of patients with response, m = number of patients evaluable

Subgroup analyses of maintenance of response: Comparisons were made between treatment groups by age group, gender, race, region, geographical region strata, weight strata, weight, previous therapies, baseline disease characteristics, and PASI 75 response at Week 4 and 8. Comparisons we made initially in order according to the primary endpoint: 300 mg SoR vs. 300 mg FI and 150 mg SoR vs. 150 mg FI, and then by cross-comparison as follows: 300 mg SoR vs. 150 mg FI and 150 mg SoR vs. 300 mg FI.

Secondary efficacy results:

PASI 50, PASI 75, PASI 90, and PASI 100 responses over time up to Week 52: Patients treated with 300 mg secukinumab in general showed numerically higher response rates than those treated with 150 mg during the Induction period, and response rates to secukinumab appeared as early as Week 2 (32.9% of patients in the 300 mg group and 20.2% of patients in the 150 mg group achieving PASI 50). Throughout the Maintenance period, a notable difference in the proportion of patients achieving PASI 50, 75, 90, 100 and IGA 0/1 responses was observed, with FI groups having higher response rates compared with SoR groups. At Week 52, the proportion of patients with PASI 75 response was higher in the 300 mg FI and 150 mg FI groups (78.2% and 62.1%, respectively) compared to the 300 mg SoR and 150 mg SoR groups (41.0% and 35.0%, respectively). The corresponding figures for PASI 90 response were in the 300 mg FI and 150 mg FI groups 59.7% and 45.8%, respectively, compared to the 300 mg SoR and 150 mg SoR groups (13.8% vs. 11.2%, respectively).

The mean PASI scores decreased during the Induction period, and the mean absolute change from baseline at Week 12 was comparable between the 150 mg and 300 mg secukinumab groups (−20.71 and −20.89, respectively). Improvements were sustained through Week 52 for all four treatment groups, however, mean decrease in PASI score was greater in the FI groups (300 mg = -21.47 and 150 mg = -18.79) compared with the SoR groups (300 mg = -16.33 and 150 mg = -17.40).

Maintenance of IGA 0/1 response: The proportion of patients who achieved IGA =0/1 response at Week 12 and maintained this response at Week 52 was higher with the 300 mg and 150 mg FI groups (68.6% and 60.3%, respectively) compared with the 300 mg and 150 mg SoR groups (22.6% and 21.9%, respectively). The cumulative probability of losing IGA 0/1 response was lower with the higher FI

secukinumab dose: 35.2% with 300 mg vs. 49.6% with 150 mg, and 90.3% in both doses groups in the SoR dosing regimen. The median time to loss of IGA =0/1 response for the 150 mg FI dose group was 283 days and not estimable for the 300 mg group, and comparable between the 300 mg and 150 mg SoR groups (141 days and 140 days, respectively).

Time to relapse and start of relapse (SoR): The cumulative probability of having a relapse increased gradually after Week 12 in both 300 mg and 150 mg FI groups. In line with the study design, the probability increased greatly in the SoR groups; initially more quickly in the 150 mg SoR group but at >40 weeks, the cumulative probability of having a relapse was higher in the 300 mg SoR group compared to the 150 mg SoR group (54.7% vs. 37.4%, respectively). 50% of patients in the 150 mg SoR group met "start of relapse" criteria by 143 days (approximately 20 weeks) compared to 169 days (approximately 24 weeks) in the 300 mg SoR group. The cumulative probability was low for both the 150 mg and 300 mg FI groups (13.3% vs. 5.9% at >16 weeks, respectively). Patients in both 300 mg and 150 SoR groups had higher cumulative probabilities of having a relapse (65.9% vs. 33.7% up to Week 16, respectively).

Number of injections needed to regain PASI 75 response after retreatment at SoR: In the 150 mg SoR group, 85.4% (176/206) of patients and in the 300 mg SoR group, 85.2% (185/217) of patients met SoR criteria at least once within the maintenance period. 55.1% in the 150 mg SoR group and 69.2% in the 300 mg SoR group were successful in regaining PASI 75 response during the treatment period. Of those that met SoR criteria a second time, 21/59 (35.5%) in the 150 mg SoR group and 36/85 (42.4%) in the 300 mg SoR group were successful in regaining PASI 75 response a second time during the treatment period. Of patients who regained PASI 75 any time during the trial after meeting SoR criteria for the first time, 68.0% in the 150 mg SoR group and 76.6% in the 300 mg SoR group regained PASI 75 response within 8 weeks; and 79.3% in the 150 mg SoR and 90.7% in the 300 mg SoR regained PASI 75 response within 12 weeks.

Rebound: There were 121/842 (14.4%) evaluable patients for rebound up to 8 weeks after last injection. Rebounds were reported for 4/38 (10.5%) of patients in the 150 mg FI group and for 3/36 (8.3%) patients in the 300 mg FI group.

Psoriatic arthritis: At Week 12, mean absolute decrease in HAQ-DI score from baseline (improvement) were comparable between the 300 mg and 150 mg treatment groups (-0.23 vs. -0.21, respectively). At Week 52, mean absolute decrease in HAQ-DI score from baseline (improvements) was higher in the 300 mg FI group compared with the 150 mg FI group (-0.32 vs. -0.11, respectively). Listings but no summaries of responses according to ACR criteria and ACR components for Japanese PsA patients are provided.

The EQ-5D questions where improvements in secukinumab groups were most evident were on "pain/discomfort", "Anxiety/Depression" and "Usual Activities". At Week 12, mean absolute increase from baseline (i.e., improvement on a scale from 0 to 100) was comparable between the 300 mg and 150 mg treatment groups (+21.2 vs. +20.2, respectively). The improvements were maintained through Week 52 for patients who were randomized to the FI groups while patients in SoR groups saw a decline over time.

The number of patients who had a decrease in DLQI score (improvement) and achieved a score of 0 or 1 increased over time up to Week 12. In the maintenance period, the proportion of patients achieving DLQI 0 or 1 response was statistically significant in both the 300 mg and 150 mg FI groups compared to their respective SoR counterparts ($p<0.0001$) beginning with Week 32 and up to Week 52.

Study A2307: Secukinumab Trial Analyzing the potential of intravenous administration To Upgrade the REsponse in psoriasis (STATURE): a randomized, double-blind, double dummy, multicenter study to assess the safety, tolerability and long-term efficacy of intravenous (10 mg/kg) and subcutaneous (300

mg) secukinumab in patients with moderate to severe chronic plaque-type psoriasis who are partial responders to secukinumab.

Methods

This was a multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group trial in patients with moderate to severe chronic plaque-type psoriasis who were "partial responders" after the first 12 weeks of s.c. injection treatment (150 mg or 300 mg secukinumab) in study A2304. A total of approximately 140 patients worldwide were originally planned to be enrolled. However, since the PASI 75 response rate in study A2304 study was higher than predicted, only 43 patients were randomized into study A2307.

Study participants

The study population consisted of patients who participated in study A2304 and had achieved a partial response after 12 weeks of treatment with no major protocol deviations.

Treatments

At start of the i.v. period, all eligible patients were randomly assigned to one of the following two treatment arms in a ratio of 1:1:

• Secukinumab 300 mg s.c. arm: two s.c. injections of 150 mg secukinumab in 1 mL of diluent, both at randomization and at Week 4, plus an i.v. infusion of 100 mL of normal saline in an infusion bag at randomization and at Weeks 2 and 4.

• Secukinumab 10 mg/kg i.v. arm: An i.v. infusion of secukinumab solution diluted to 100 mL with normal saline in an infusion bag at randomization and at Weeks 2 and 4, plus two s.c. injections of secukinumab placebo, each in 1 mL of diluent, at randomization and at Week 4.

During the Maintenance period, all patients received secukinumab 300 mg s.c. every 4 weeks until Week 40.

Objectives

The primary objective was to evaluate the efficacy of i.v. administration of secukinumab compared with s.c. administration of secukinumab with respect to both PASI 75 and Investigator's Global Assessment (IGA) 0 or 1 response (co-primary endpoints) at Week 8 in study CAIN457A2307 in moderate to severe chronic plaque-type psoriasis in patients who achieved a partial response after 12 weeks of treatment in study CAIN457A2304.

The secondary and exploratory objectives were similar to those in Study A2304 and included assessments at Week 8 and up to Week 40.

Outcomes/endpoints

Criteria for efficacy, safety and other evaluations were similar to previous studies.

Sample size

Based on PASI 75 response rates of 66.7% and 90.5%, and IGA 0/1 response rates of 33.3% and 66.7% in the secukinumab 300 mg s.c. and 10 mg/kg i.v. treatment groups, respectively, the total sample size of 132 (66 in each treatment group) was needed to achieve a power of 90% for both PASI 75 and IGA 0/1. Thus, it was originally planned to enroll approximately 140 patients worldwide. However, since the PASI 75 response rate in Study A2304 was higher than predicted, the number of partial responders was lower than expected and only 43 patients entered Study A2307.

Randomisation

At Visit 1, all eligible patients were randomized via the IRT system to one of two treatment arms. Randomization was stratified by the previous treatment group in Study A2304, i.e. secukinumab 150 mg or 300 mg s.c.

Blinding

The i.v. period of this study was double-blinded, as described in the section "Treatments". All study personnel remained blinded to the identity of treatment from the time of randomization until database lock (after the Week 40 visit of the last patient participating in the study).

Statistical methods

The two null hypotheses associated with co-primary endpoints were both tested at 5% level, and significant results were only achieved if both tests were rejected at level 5%. I.e., if only one hypothesis was rejected in favor of i.v. administration and the other hypothesis was not rejected, efficacy of the i.v. administration was not demonstrated.

Results

Participant flow

A total of 43 patients were randomized into study A2307 and 40 (93.0%) patients completed the i.v. period. Three patients discontinued prior to s.c. secukinumab treatment after the Week 4 Visit: 1 due to the patient being lost to follow-up, 1 due to a protocol deviation, and 1 due to subject/guardian decision. Of the remaining 40 patients, four discontinued during the Maintenance period (one due to lack of efficacy in the secukinumab 150 mg s.c. – 10 mg/kg i.v. treatment group and three due to subject/guardian decision).

A total of 36 patients completed the Maintenance period (19 and 17 patients in the 300 mg s.c. and 10 mg/kg i.v. treatment groups, respectively).

Recruitment

Study initiation date: 02 Dec 2011 (first patient first visit)

Study completion date: 28 Feb 2013 (last patient visit at Week 40)

Conduct of the study

The study protocol was amended once. The amendment introduced update of the primary and secondary objectives to reflect changes in the sample size, introduced the extension study A2304E1 and aligned the language with Study A2304.

Baseline data

Most patients (88.4%) were below 65 years of age, with the mean age of 46.6 years (range: 20 to 71 years), male (67.4%) and Caucasians (74.4%). In the secukinumab 10 mg/kg i.v. group (vs. 300 mg s.c. group) there were more patients <65 years (95.5% vs. 81.0%, respectively), less males (59.1% vs. 76.2%, respectively) and lighter patients (92.4 vs. 102.2 kg, respectively).

Baseline mean PASI score was 21.8, 60.5% had a baseline PASI score ≤ 20 and the mean affected BSA was 32.1%. 67.4% of patients were previously treated with systemic psoriasis therapy and 37.2% with biologic therapy. 25.6% presented with PsA at baseline. There were more patients with baseline PASI ≤20 in the secukinumab 10 mg/kg i.v. group compared to the 300 mg s.c. group (68.2% vs. 52.4%, respectively), more patients with IGA score indicative of moderate disease (50.0% vs. 33.3%,

respectively), less patients with PsA (18.2% vs. 33.3%, respectively), less patients with exposure to systemic psoriasis therapy (59.1% vs. 76.2%, respectively), and less patients with exposure to biologic therapy (31.8% vs. 42.9%, respectively).

Numbers analysed

A total of 43 patients were randomized into study A2307. 43 patients (21 in the secukinumab 300 mg s.c. group and 22 in the secukinumab 10 mg/kg i.v. group) were included in the full analysis and safety sets.

Outcomes and estimation

The primary objective of this study was not met. However, a higher proportion of patients in the secukinumab 10 mg/kg i.v. group had achieved PASI 75 and IGA 0/1 response at Week 8 compared with the secukinumab 300 mg s.c. group (p=0.0649 and 0.0332, respectively) (see Table 41).

Table 41 Statistical analysis (Cochran-Mantel-Haenszel test) of IGA mod 2011 0 or 1, PASI 75 and PASI 90 response at Week 8 (non-responder imputation) (FAS)

Response criterion	Treatment comparison "test" vs. "control"	_"test"_ n/m (%)	_"control"_ n/m (%)	Confidence Interval (95% CI)	p-value
IGA 0/1	AIN457 10 mg /kg i.v. vs. AIN457 300 mg s.c.	14/ 21 (66.7)	7/ 21 (33.3)	(1.12, 14.76)	0.0332
PASI 75	AIN457 10 mg /kg i.v. vs. AIN457 300 mg s.c.	19/ 21 (90.5)	14/ 21 (66.7)	(0.86, 27.38)	0.0649
PASI 90	AIN457 10 mg /kg i.v. vs. AIN457 300 mg s.c.	13/ 21 (61.9)	2/ 21 (9.5)	(2.88, 101.09)	0.0005

Secondary and other efficacy results:

PASI 50, 75, 90 and 100 and IGA 0/1 responses over time: At every visit beginning with Week 2 and up to Week 40, a higher proportion of patients in the secukinumab 10 mg/kg i.v. group achieved PASI_75, PASI 90, and PASI 100 response compared with patients in the secukinumab 300 mg s.c. group. A higher proportion of patients in the secukinumab 10 mg/kg i.v. group achieved IGA 0/1 response beginning with Week 4.

Absolute PASI score and IGA 0/1 categories over time: By Week 8, the mean percent decrease in PASI score was greater for the secukinumab 10 mg/kg i.v. group. Between Weeks 28 and 40, mean percent decrease in PASI scores were comparable between the secukinumab 10 mg/kg i.v. group and secukinumab 300 mg s.c. group. The proportion of patients who achieved the IGA mod 2011 category of “clear” tended to be numerically higher in the secukinumab 10 mg/kg i.v. group.

Maintenance of PASI 75 response and IGA 0/1 response over 40 weeks of treatment: The majority of secukinumab-treated patients who achieved PASI 75 response at Week 8 were able to maintain it at Week 40 (68.4% of patients in the secukinumab 10 mg/kg i.v. group and 64.3% of patients in the 300 mg s.c. group). The overall decline in PASI 75 response rate among Week 8 responders from Week 12 to Week 40 was greater in the secukinumab 10 mg/kg i.v. group (26.3%; from 94.7% to 68.4%) than in the secukinumab 300 mg s.c. group (14.3%; from 78.6% to 64.3%). The proportion of secukinumab-treated patients who achieved IGA 0/1 at Week 8 and maintained this response at Week 40 was higher in the secukinumab 300 mg s.c. group compared with the secukinumab 10 mg/kg i.v. group (57.1% vs. 42.9%, respectively).

Rebound was observed in one patient (in the secukinumab 300 mg s.c. group) among the 6 evaluable patients.

By Week 40, improvements in the EQ-5D and DLQI were reported in both treatment groups, with variability in the improvements between the treatment groups depending on the category/parameter.

Summary of main studies

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

Results of the co-primary and key secondary efficacy analyses of Study A2302 are presented in the table below.

Summary of Efficacy for trial A2302

Title: Efficacy of Response And Safety of 2 Fixed Secukinumab Regimens in Psoriasis (ERASURE)			
Study identifier	CAIN457A2302		
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial		
	Duration of main phase: Duration of Extension phase:		12 weeks (Induction phase) 40 weeks (Maintenance phase)
Hypothesis	Superiority		
Treatments groups	Secukinumab 150 mg		Secukinumab 150 mg. Duration 12 weeks (Induction), 40 weeks (Maintenance). Number randomized 245
	Secukinumab 300 mg		Secukinumab 300 mg. Duration 12 weeks (Induction), 40 weeks (Maintenance). Number randomized 245
	Placebo		Placebo. Duration 12 weeks (Induction), 40 weeks (Maintenance). Number randomized 248
Endpoints and definitions	Co-Primary endpoint	PASI 75 and IGA 0/1 at Week 12	To demonstrate the superiority of secukinumab in patients with moderate to severe chronic plaque-type psoriasis with respect to both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared to placebo

	Key secondary endpoint	PASI 90 at Week 12	To demonstrate the superiority of secukinumab in patients with moderate to severe chronic plaque-type psoriasis with respect to PASI 90 response at Week 12, as compared to placebo
	Key secondary endpoint	Loss of PASI 75 response at Week 52	To assess the efficacy of secukinumab in maintaining PASI 75 response at Week 52 for patients who were PASI 75 responders at Week 12
	Key secondary endpoint	Loss of IGA 0/1 response at Week 52	To assess the efficacy of secukinumab in maintaining IGA mod 2011 0 or 1 response at Week 52 for patients who were IGA mod 2011 0 or 1 responders at Week 12
	Key secondary endpoint	Itching, pain and scaling as measured by the Psoriasis Symptom Diary	To demonstrate the superiority of secukinumab in patients with moderate to severe chronic plaque-type psoriasis with respect to psoriasis-related itching, pain and scaling as measured by the Psoriasis Symptom Diary at Week 12 compared to placebo.
Database lock	07 March 2013 (last patient last visit for Week 52)		

Results and Analysis

Analysis description	**Co-Primary Analysis**			
Analysis population and time point description	Full Analysis Set 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 150 mg	Secukinumab 300 mg	Placebo
	Number of subject	245	245	247
	PASI 75	174/243 (71.6%)	200/245 (81.6%)	11/246 (4.5%)
	IGA 0/1	125/244 (51.2%)	160/245 (65.3%)	6/246 (2.4%)

Effect estimate per comparison	Co-Primary endpoint: PASI 75	Comparison groups	Secukinumab 150 mg vs. Placebo	
		Cochran-Mantel-Haenszel test, odds ratio	57.64	
		95% CI	28.43,116.86	
		P-value	p<0.0001	
	Co-Primary endpoint: PASI 75	Comparison groups	Secukinumab 300 mg vs. Placebo	
		Cochran-Mantel-Haenszel test, odds ratio	82.69	
		95% CI	38.70,176.71	
		P-value	p<0.0001	
	Co-Primary endpoint: IGA 0/1	Comparison groups	Secukinumab 150 mg vs. Placebo	
		Cochran-Mantel-Haenszel test, odds ratio	44.18	
		95% CI	18.21,107.18	
		P-value	p<0.0001	
	Co-Primary endpoint: IGA 0/1	Comparison groups	Secukinumab 300 mg vs. Placebo	
		Cochran-Mantel-Haenszel test, odds ratio	44.18	
		95% CI	18.21,107.18	
		P-value	p<0.0001	
Analysis description	**Key Secondary Analysis: PASI 90 at Week 12**			
Analysis population and time point description	Full Analysis Set 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 150 mg	Secukinumab 300 mg	Placebo
	Number of subject	245	245	247
	PASI 90	95/243 (39.1%)	145/245 (59.2%)	3/246 (1.2%)

Effect estimate per comparison	PASI 90 at Week 12	Comparison groups	Secukinumab 150 mg vs. Placebo	
		Cochran-Mantel-Haenszel test, odds ratio	59.50	
		95% CI	17.24,205.35	
		P-value	p<0.0001	
	PASI 90 at Week 12	Comparison groups	Secukinumab 300 mg vs. Placebo	
		Cochran-Mantel-Haenszel test, odds ratio	186.13	
		95% CI	44.39,780.52	
		P-value	p<0.0001	
Analysis description	**Key Secondary Analysis: Maintenance of PASI 75 at Week 52**			
Analysis population and time point description	Full Analysis Set 52 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 150 mg	Secukinumab 300 mg	
	Number of subject (evaluable)	174	200	
	PASI 75	126 (72.4%)	161 (80.5%)	
Effect estimate per comparison	Loss of PASI 75 response at Week 52	Comparison groups	Secukinumab 150 mg	
		Cumulative rate	27.5	
		95% CI	21.3, 35.1	
		P-value		
	Loss of PASI 75 response at Week 52	Comparison groups	Secukinumab 300 mg	
		Cumulative rate	14.2	
		95% CI	10.0, 20.0	
		P-value		
Analysis description	**Key Secondary Analysis: Maintenance of IGA 0/1 at Week 52**			

Analysis population and time point description	Full Analysis Set 52 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 150 mg	Secukinumab 300 mg	
	Number of subject (evaluable)	125	160	
	IGA 0/1	74 (59.2%)	119 (74.4%)	

Effect estimate per comparison	Loss of IGA 0/1 response at Week 52	Comparison groups	Secukinumab 150 mg
		Cumulative rate	41.4
		95% CI	33.0, 50.9
		P-value	
	Loss of IGA 0/1 response at Week 52	Comparison groups	Secukinumab 300 mg
		Cumulative rate	28.8
		95% CI	22.3, 36.7
		P-value	

Analysis description	**Key Secondary Analysis: Itching, pain and scaling**			
Analysis population and time point description	Full Analysis Set 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 150 mg	Secukinumab 300 mg	Placebo
	Number of subject (evaluable)	86	79	84
	Itching: mean change (SD)	-4.86 (0.299)	-5.45 (0.276)	-0.22 (0.260)
	Pain: mean change (SD)	-3.92 (0.337)	-4.59 (0.322)	0.06 (0.246)
	Scaling: mean change (SD)	-4.74 (0.307)	-5.49 (0.289)	- 0.11 (0.248)

Effect estimate per comparison	Itching	Comparison groups	Secukinumab 150 mg vs. Placebo
		Treatment contrast in LS mean estimate (SE)	-4.35 (0.301)
		95% CI	-4.95, -3.76
		P-value	p<0.0001
	Itching	Comparison groups	Secukinumab 300 mg vs. Placebo
		Treatment contrast in LS mean estimate (SE)	-4.85 (0.308)
		95% CI	-5.45, -4.24
		P-value	p<0.0001
	Pain	Comparison groups	Secukinumab 150 mg vs. Placebo
		Treatment contrast in LS mean estimate (SE)	-3.96 (0.298)
		95% CI	-4.54, -3.37
		P-value	p<0.0001
	Pain	Comparison groups	Secukinumab 300 mg vs. Placebo
		Treatment contrast in LS mean estimate (SE)	-4.20 (0.305)
		95% CI	-4.80, -3.60
		P-value	p<0.0001
	Scaling	Comparison groups	Secukinumab 150 mg vs. Placebo
		Treatment contrast in LS mean estimate (SE)	-4.43 (0.297)
		95% CI	-5.01, -3.84
		P-value	p<0.0001
	Scaling	Comparison groups	Secukinumab 300 mg vs. Placebo

		Treatment contrast in LS mean estimate (SE)	-5.03 (0.304)
		95% CI	-5.63, -4.44
		P-value	p<0.0001

Results of the co-primary efficacy analysis of Study A2308 are presented in the table below.

Table 42 Summary of efficacy for trial A2308

Title: First study of SEcukinumAb in pre-filled syringes in subjecTs with chronic plaqUe-type psoriasis: REsponse at 12 weeks (FEATURE)			
Study identifier	CAIN457A2308		
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial		
	Duration of main phase: Duration of Extension phase:		12 weeks (Induction phase) not applicable
Hypothesis	Superiority		
Treatments groups	Secukinumab 150 mg		Secukinumab 150 mg. Duration 12 weeks (Induction). Number randomized 59.
	Secukinumab 300 mg		Secukinumab 300 mg. Duration 12 weeks (Induction). Number randomized 59.
	Placebo		Placebo. Duration 12 weeks (Induction). Number randomized 59.
Endpoints and definitions	Co-Primary endpoint	PASI 75 and IGA 0/1 at Week 12	To demonstrate the efficacy of secukinumab (150 mg and 300 mg) in patients with moderate to severe chronic plaque-type psoriasis with respect to both PASI 75 and IGA 0 or 1 response (co-primary endpoints) at Week 12 compared to placebo
Database lock	18 March 2013 (last patient last visit 15 Jan 2013)		
Results and Analysis			
Analysis description	**Co-Primary Analysis**		
Analysis population and time point description	Full Analysis Set 12 weeks		

Descriptive statistics and estimate variability	Treatment group	Secukinumab 150 mg	Secukinumab 300 mg	Placebo
	Number of subject	59	59	59
	PASI 75	41/59 (69.5%)	44/58 (75.9%)	0/59 (0.0%)
	IGA 0/1	31/59 (52.5%)	40/58 (69.0%)	0/59 (0.0%)

Effect estimate per comparison	Co-Primary endpoint: PASI 75	Comparison groups	Secukinumab 150 mg vs. Placebo
		Fisher's exact test, Risk-difference estimate	69.5
		95% CI	53.9, 81.4
		P-value	p<0.0001
	Co-Primary endpoint: PASI 75	Comparison groups	Secukinumab 300 mg vs. Placebo
		Fisher's exact test, Risk-difference estimate	75.9
		95% CI	61.5, 86.1
		P-value	p<0.0001
	Co-Primary endpoint: IGA 0/1	Comparison groups	Secukinumab 150 mg vs. Placebo
		Fisher's exact test, Risk-difference estimate	52.5
		95% CI	35.1, 67.2
		P-value	p<0.0001
	Co-Primary endpoint: IGA 0/1	Comparison groups	Secukinumab 300 mg vs. Placebo
		Fisher's exact test, Risk-difference estimate	69.0
		95% CI	53.5, 80.5
		P-value	p<0.0001

Results of the co-primary efficacy analysis of Study A2309 are presented in the table below.

Summary of efficacy for trial A2309

Title: Judging the Efficacy of SecUkinumab in Patients With Psoriasis using Autoinjector: a Clinical Trial EvalUating Treatment REsults (JUNCTURE)			
Study identifier	CAIN457A2309		
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial		
	Duration of main phase: Duration of Extension phase:		12 weeks (Induction phase) not applicaple
Hypothesis	Superiority		
Treatments groups	Secukinumab 150 mg		Secukinumab 150 mg. Duration 12 weeks (Induction). Number randomized 59.
	Secukinumab 300 mg		Secukinumab 300 mg. Duration 12 weeks (Induction). Number randomized 59.
	Placebo		Placebo. Duration 12 weeks (Induction). Number randomized 59.
Endpoints and definitions	Co-Primary endpoint	PASI 75 and IGA 0/1 at Week 12	To demonstrate the efficacy of secukinumab (150 mg and 300 mg) in patients with moderate to severe chronic plaque-type psoriasis with respect to both PASI 75 and IGA 0 or 1 response (co-primary endpoints) at Week 12 compared to placebo
Database lock	13 Jun 2013 (last patient last visit 10 April 2013)		

Results and Analysis

Analysis description	**Co-Primary Analysis**			
Analysis population and time point description	Full Analysis Set 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 150 mg	Secukinumab 300 mg	Placebo
	Number of subject	61	60	61
	PASI 75	43/60 (71.7%)	52/60 (86.7%)	2/61 (3.3%)

	IGA 0/1	32/60 (53.3%)	44/60 (73.3%)	0/61 (0.0%)

Effect estimate per comparison	Co-Primary endpoint: PASI 75	Comparison groups	Secukinumab 150 mg vs. Placebo
		Fisher's exact test, Risk-difference estimate	68.4
		95% CI	53.1, 79.8
		P-value	p<0.0001
	Co-Primary endpoint: PASI 75	Comparison groups	Secukinumab 300 mg vs. Placebo
		Fisher's exact test, Risk-difference estimate	83.4
		95% CI	70.7, 91.7
		P-value	p<0.0001
	Co-Primary endpoint: IGA 0/1	Comparison groups	Secukinumab 150 mg vs. Placebo
		Fisher's exact test, Risk-difference estimate	53.3
		95% CI	36.6, 66.7
		P-value	p<0.0001
	Co-Primary endpoint: IGA 0/1	Comparison groups	Secukinumab 300 mg vs. Placebo
		Fisher's exact test, Risk-difference estimate	73.3
		95% CI	58.8, 83.9
		P-value	p<0.0001

Results of the co-primary and key secondary efficacy analyses of Study A2303 are presented in the table below.

Summary of efficacy for trial A2303

Title: FIXTURE (Full year Investigative eXamination of secukinumab vs. eTanercept Using 2 dosing Regimens to determine Efficacy in psoriasis)	
Study identifier	CAIN457A2303

Design	Multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group trial		
	Duration of main phase: Duration of Extension phase:		12 weeks (Induction phase) 40 weeks (Maintenance phase)
Hypothesis	Superiority to placebo, non-inferiority / superiority to etanercept		
Treatments groups	Secukinumab 150 mg		Secukinumab 150 mg. Duration 12 weeks (Induction), 40 weeks (Maintenance). Number randomized 327.
	Secukinumab 300 mg		Secukinumab 300 mg. Duration 12 weeks (Induction), 40 weeks (Maintenance). Number randomized 327.
	Placebo		Placebo. Duration 12 weeks (Induction), 40 weeks (Maintenance). Number randomized 326.
	Etanercept		Etanercept 50 mg. Duration 12 weeks (Induction), 40 weeks (Maintenance). Number randomized 326.
Endpoints and definitions	Co-Primary endpoint	PASI 75 and IGA 0/1 at Week 12	To demonstrate the superiority of secukinumab in subjects with moderate to severe chronic plaque-type psoriasis with respect to both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared to placebo
	Key secondary endpoint	PASI 90 at Week 12	To demonstrate the superiority of secukinumab in subjects with moderate to severe chronic plaque-type psoriasis with respect to PASI 90 response at Week 12, compared to placebo
	Key secondary endpoint	non-inferiority to etanercept: PASI 75 response at Week 12	To demonstrate the non-inferiority of secukinumab in subjects with moderate to severe chronic plaque-type psoriasis with respect to PASI 75 response at Week 12, compared to etanercept

	Key secondary endpoint	superiority to etanercept: PASI 75 and IGA 0/1 response at Week 12	To demonstrate the superiority of secukinumab in subjects with moderate to severe chronic plaque-type psoriasis with respect to PASI 75 response and IGA mod 2011 0 or 1 response at Week 12, compared to etanercept
	Key secondary endpoint	superiority to etanercept: Loss of PASI 75 response at Week 52	To demonstrate the superiority of secukinumab in maintaining PASI 75 response at Week 52 for subjects who were PASI 75 responders at Week 12, compared to etanercept
	Key secondary endpoint	superiority to etanercept: Loss of IGA 0/1 response at Week 52	To demonstrate the superiority of secukinumab in maintaining IGA mod 2011 0 or 1 response at Week 52 for subjects who were IGA mod 2011 0 or 1 responders at Week 12, compared to etanercept
	Key secondary endpoint	Itching, pain and scaling as measured by the Psoriasis Symptom Diary	To demonstrate the superiority of secukinumab in patients with moderate to severe chronic plaque-type psoriasis with respect to psoriasis-related itching, pain and scaling as measured by the Psoriasis Symptom Diary at Week 12 compared to placebo.
Database lock	07 July 2013 (last patient last visit for Week 52)		

Results and Analysis

Analysis description	**Co-Primary Analysis**			
Analysis population and time point description	Full Analysis Set 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 150 mg	Secukinumab 300 mg	Placebo
	Number of subject	327	327	325

	PASI 75	219/327 (67.0%)	249/323 (77.1%)	16/324 (4.9%)
	IGA 0/1	167/327 (51.1%)	202/323 (62.5%)	9/324 (2.8%)

Effect estimate per comparison	Co-Primary endpoint: PASI 75	Comparison groups	Secukinumab 150 mg vs. Placebo
		Cochran-Mantel-Haenszel test, odds ratio	42.76
		95% CI	23.57, 77.60
		P-value	p<0.0001
	Co-Primary endpoint: PASI 75	Comparison groups	Secukinumab 300 mg vs. Placebo
		Cochran-Mantel-Haenszel test, odds ratio	65.95
		95% CI	36.07, 20.59
		P-value	p<0.0001
	Co-Primary endpoint: IGA 0/1	Comparison groups	Secukinumab 150 mg vs. Placebo
		Cochran-Mantel-Haenszel test, odds ratio	40.62
		95% CI	19.80, 83.35
		P-value	p<0.0001
	Co-Primary endpoint: IGA 0/1	Comparison groups	Secukinumab 300 mg vs. Placebo
		Cochran-Mantel-Haenszel test, odds ratio	79.13
		95% CI	35.97, 174.09
		P-value	p<0.0001
Analysis description	**Key Secondary Analysis: PASI 90 at Week 12**		
Analysis population and time point description	Full Analysis Set 12 weeks		

Descriptive statistics and estimate variability	Treatment group	Secukinumab 150 mg	Secukinumab 300 mg	Placebo
	Number of subject	327	327	325
	PASI 90	137/327 (41.9%)	175/323 (54.2%)	5/324 (1.5%)
Effect estimate per comparison	PASI 90 at Week 12	Comparison groups	Secukinumab 150 mg vs. Placebo	
		Cochran-Mantel-Haenszel test, odds ratio	56.10	
		95% CI	21.41, 147.03	
		P-value	p<0.0001	
	PASI 90 at Week 12	Comparison groups	Secukinumab 300 mg vs. Placebo	
		Cochran-Mantel-Haenszel test, odds ratio	118.48	
		95% CI	41.34, 339.58	
		P-value	p<0.0001	
Analysis description	**Key Secondary Analysis: non-inferiority to etanercept: PASI 75 response at Week 12**			
Analysis population and time point description	Full Analysis Set 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 150 mg	Secukinumab 300 mg	Etanercept
	Number of subject	327	327	326
	PASI 75	219/327 (67.0%)	249/323 (77.1%)	142/323 (44.0%)
Effect estimate per comparison:	PASI 75 at Week 12	Comparison groups	Secukinumab 150 mg vs. Etanercept	

		Cochran-Mantel-Haenszel risk difference, Estimate (%)	23.12 Confidence level (1-sided) initial 99.375% adjusted 99.375%
		Confidence level (1-sided) initial 99.375% adjusted 99.375%	21.41, 147.03
		Non-inferiority margin is 10%	
	PASI 75 at Week 12	Comparison groups	Secukinumab 300 mg vs. Etanercept
		Cochran-Mantel-Haenszel risk difference, Estimate (%)	32.80
		Confidence level (1-sided) initial 99.375% adjusted 99.375%	24.06, 41.53
		Non-inferiority margin is 10%	
Analysis description	**Key Secondary Analysis: superiority to etanercept:** **PASI 75 and IGA 0/1 response at Week 12**		
Analysis population and time point description	Full Analysis Set 12 weeks		

Descriptive statistics and estimate variability	Treatment group	Secukinumab 150 mg	Secukinumab 300 mg	Etanercept
	Number of subject	327	327	326
	PASI 75	219/327 (67.0%)	249/323 (77.1%)	142/323 (44.0)
	IGA 0/1	167/327 (51.1%)	202/323 (62.5%)	88/323 (27.2)

Effect estimate per comparison	PASI 75 at Week 12	Comparison groups	Secukinumab 150 mg vs. Etanercept
		Cochran-Mantel-Haenszel test, odds ratio	2.73

		95% CI		1.96, 3.79
		P-value		p<0.0001
	PASI 75 at Week 12	Comparison groups		Secukinumab 300 mg vs. Etanercept
		Cochran-Mantel-Haenszel test, odds ratio		4.69
		95% CI		3.28, 6.70
		P-value		p<0.0001
	IGA 0/1 at Week 12	Comparison groups		Secukinumab 150 mg vs. Etanercept
		Cochran-Mantel-Haenszel test, odds ratio		2.96
		95% CI		2.11, 4.15
		P-value		p<0.0001
	IGA 0/1 at Week 12	Comparison groups		Secukinumab 300 mg vs. Etanercept
		Cochran-Mantel-Haenszel test, odds ratio		4.91
		95% CI		3.46, 6.97
		P-value		p<0.0001
Analysis description	**Key Secondary Analysis: superiority to etanercept:** **Loss of PASI 75 response at Week 52**			
Analysis population and time point description	Full Analysis Set 52 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 150 mg	Secukinumab 300 mg	Etanercept
	Number of subject (evaluable)	219	249	142
	PASI 75	180 (82.2%)	210 (84.3%)	103 (72.5%)

Effect estimate per comparison	Loss of PASI 75 response at Week 52	Comparison groups	Secukinumab 150 mg vs. Etanercept	
		Hazard ratio secukinumab vs. etanercept	0.57	
		95% CI	0.38, 0.85	
		P-value (Log-rank test) P-value (Wilcoxon test)	0.0088 0.0321	
	Loss of PASI 75 response at Week 52	Comparison groups	Secukinumab 300 mg vs. Etanercept	
		Hazard ratio secukinumab vs. etanercept	0.30	
		95% CI	0.19, 0.47	
		P-value (Log-rank test) P-value (Wilcoxon test)	<0.0001 <0.0001	
Analysis description	**Key Secondary Analysis: superiority to etanercept:** **Loss of IGA 0/1 response at Week 52**			
Analysis population and time point description	Full Analysis Set 52 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 150 mg	Secukinumab 300 mg	Etanercept
	Number of subject (evaluable)	167	202	88
	IGA 0/1	113 (67.7%)	161 (79.7%)	50 (56.8%)
Effect estimate per comparison	Loss of IGA 0/1 response at Week 52	Comparison groups	Secukinumab 150 mg vs. Etanercept	
		Hazard ratio secukinumab vs. etanercept	0.55	
		95% CI	0.38, 0.80	
		P-value (Log-rank test) P-value (Wilcoxon test)	0.0022 0.0103	

	Loss of IGA 0/1 resposne at Week 52	Comparison groups	Secukinumab 300 mg vs. Etanercept	
		Hazard ratio secukinumab vs. etanercept	0.33	
		95% CI	0.22, 0.49	
		P-value (Log-rank test) P-value (Wilcoxon test)	<0.0001 <0.0001	
Analysis description	**Key Secondary Analysis: Itching, pain and scaling**			
Analysis population and time point description	Full Analysis Set 12 weeks			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 150 mg	Secukinumab 300 mg	Placebo
	Number of subject (evaluable)	117	117	109
	Itching: mean change (SD)	−4.92 (0.249)	−4.93 (0.247)	−0.54 (0.201)
	Pain: mean change (SD)	−4.10 (0.277)	−4.48 (0.278)	−0.33 (0.216)
	Scaling: mean change (SD)	−4.89 (0.241)	−4.93 (0.258)	−0.42 (0.217)
Effect estimate per comparison	Itching	Comparison groups	Secukinumab 150 mg vs. Placebo	
		Treatment contrast in LS mean estimate (SE)	−4.00 (0.283)	
		95% CI	−4.56, −3.45	
		P-value	p<0.0001	
	Itching	Comparison groups	Secukinumab 300 mg vs. Placebo	

		Treatment contrast in LS mean estimate (SE)	−4.21 (0.282)
		95% CI	−4.76, −3.65
		P-value	p<0.0001
	Pain	Comparison groups	Secukinumab 150 mg vs. Placebo
		Treatment contrast in LS mean estimate (SE)	−3.30 (0.275)
		95% CI	−3.84, −2.76
		P-value	p<0.0001
	Pain	Comparison groups	Secukinumab 300 mg vs. Placebo
		Treatment contrast in LS mean estimate (SE)	−3.76 (0.275)
		95% CI	−4.30, −3.22
		P-value	p<0.0001
	Scaling	Comparison groups	Secukinumab 150 mg vs. Placebo
		Treatment contrast in LS mean estimate (SE)	−4.10 (0.279)
		95% CI	−4.65, −3.55
		P-value	p<0.0001
	Scaling	Comparison groups	Secukinumab 300 mg vs. Placebo
		Treatment contrast in LS mean estimate (SE)	−4.47 (0.278)
		95% CI	−5.01, −3.92
		P-value	p<0.0001

Clinical studies in special populations

Table 2-8 Number of elderly patients involved in the clinical trial programme (all secukinumab studies)

eCTD Module	Age 65-74 number / total number all ages (%)	Age 75-84 number / total number all ages (%)	Age 85+ number / total number all ages (%)
Efficacy and Safety Studies[1]	321/4818 (6.66)	47/4818 (0.98)	2/4818 (0.04)
Human PK/PD and Pharmaceutical Studies	40/571 (7.0)	4/ 571 (0.7)	0/ 571 (0.0)

[1] Module 5.3.5, Sum of patients involved in controlled, uncontrolled and other studies.
Source: Table A75 1-2

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

The pooled efficacy analyses are based on a Full Analysis Set (FAS) consisting of 3,366 patients with moderate to severe plaque psoriasis. They were enrolled in four placebo-controlled and two individualized maintenance regimen phase III trials, with 2348 patients randomized to secukinumab, 692 to placebo and 326 to etanercept. The 12-week (Induction period) data from four phase III trials (A2302, A2303, A2308, A2309) were pooled to obtain estimates of both the primary treatment effect and variations among subgroups, as well as to conduct exploratory analyses (short-term efficacy). The 52-week (comprising Induction and Maintenance periods) data from three phase III trials (A2302, A2303, A2304) were pooled to obtain estimates of the persistence of efficacy over time (long-term efficacy). Additional data beyond 52 weeks was collected in an ongoing phase II extension study A2211E1 (interim data up to Week 121, with total exposure of 175 weeks).

Co-primary endpoints and some key secondary endpoints evaluated at Week 12, and response rates at Week 52 are summarized below.

Table 43 - Summary of co-primary endpoints and key secondary endpoints evaluated at Week 12 (Studies A2302, A2303, A2308 and A2309)

	AIN457 150 mg	AIN457 300 mg	PBO	Etanercept		AIN457 150 mg	AIN457 300 mg	PBO	Etanercept
PASI 90 - % achieving response					**IGA mod 2011 0/1 - % achieving response**				
A2302	39.1*	59.2*	1.2	-	A2302	51.2*	65.3*	2.4	-
A2303	41.9*	54.2*	1.5	20.7	A2303	51.1*	62.5*	2.8	27.2
A2308	45.8*	60.3*	0.0	-	A2308	52.5*	69.0*	0.0	-
A2309	40.0*	55.0*	0.0	-	A2309	53.3*	73.3*	0.0	-
pooled	41.1*	56.6*#	1.2	20.7	*pooled*	51.4*	65.0*#	2.2	27.2
PASI 100 - % achieving response					**IGA mod 2011 - % achieving score of 0**				
A2302	12.8*	28.6*	0.8	-	A2302	16.4	32.2	0.8	-
A2303	14.4*	24.1*	0.0	4.3	A2303	15.3	28.2	0.3	5.3
A2308	8.5	43.1*	0.0	-	A2308	10.2	44.8	0.0	-
A2309	16.7*	26.7*	0.0	-	A2309	18.3	30.0	0.0	-

	AIN457 150 mg	AIN457 300 mg	PBO	Etanercept		AIN457 150 mg	AIN457 300 mg	PBO	Etanercept
pooled	13.5*	27.6*#	0.3	4.3	*pooled*	15.5	31.2	0.4	5.3
PASI 75 - % achieving response					**DLQI 0/1 - % achieving response**				
A2302	71.6*	81.6*	4.5	-	A2302	46.1*	58.8*	10.3	-
A2303	67.0*	77.1*	4.9	44.0	A2303	50.6*	56.7*	6.6	34.5
A2308	69.5*	75.9*	0.0	-	A2308	54.4*	54.7*	7.4	-
A2309	71.7*	86.7*	3.3	-	A2309	59.3*	74.6*	15.3	-
pooled	69.2*	79.4*#	4.2	44.0	*pooled*	50.1*	58.8*	8.7	34.5

AIN457=secukinumab; DLQI=Dermatology Life Quality Index; IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index; PBO=placebo

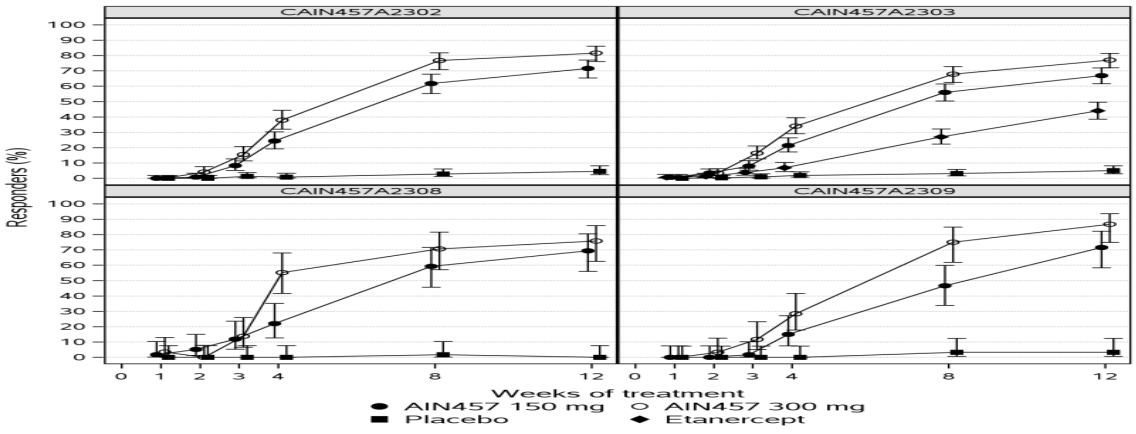
For IGA mod 2011 score of 0, Last Observation Carried Forward was used as the imputation method. For all other response criteria, the non-responder imputation method was used to deal with missing values. Statistical comparisons were not performed for IGA mod 2011 score of 0.

The pooled dataset comprised 12-week efficacy data from the 4 pivotal placebo-controlled trials (studies [A2302], [A2303], [A2308], [A2309])

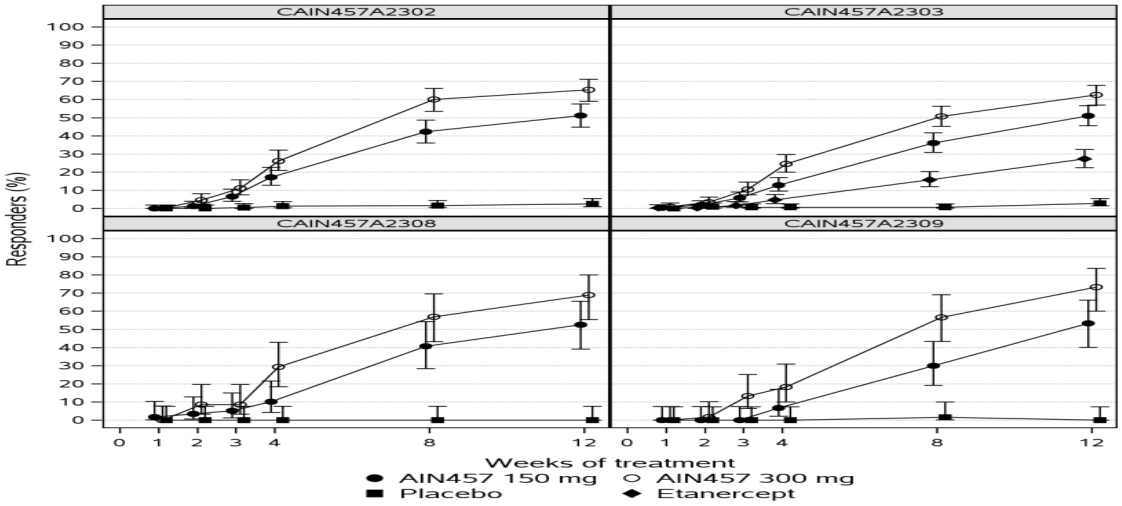
*statistically significant (at least $p<0.05$) comparison to placebo and etanercept (A2303 only)

# indicates a statistically significantly difference of 300 mg from 150 mg (pooled data only)

Figures 7 - PASI 75 response over 12 weeks of treatment (estimate + 95% CI) by study (non-responder imputation) (FAS) (A2302, A2303, A2308, A2309)



Figures 8 - IGA mod 2011 0 or 1 response over 12 weeks of treatment (estimate + 95% CI) by study (non -responder imputation) (FAS) (A2302, A2303, A2308, A2309)



Figures 9 - PASI 90 response over 12 weeks of treatment (estimate + 95% CI) by study (non-responder imputation) (FAS) (A2302, A2303, A2308, A2309)

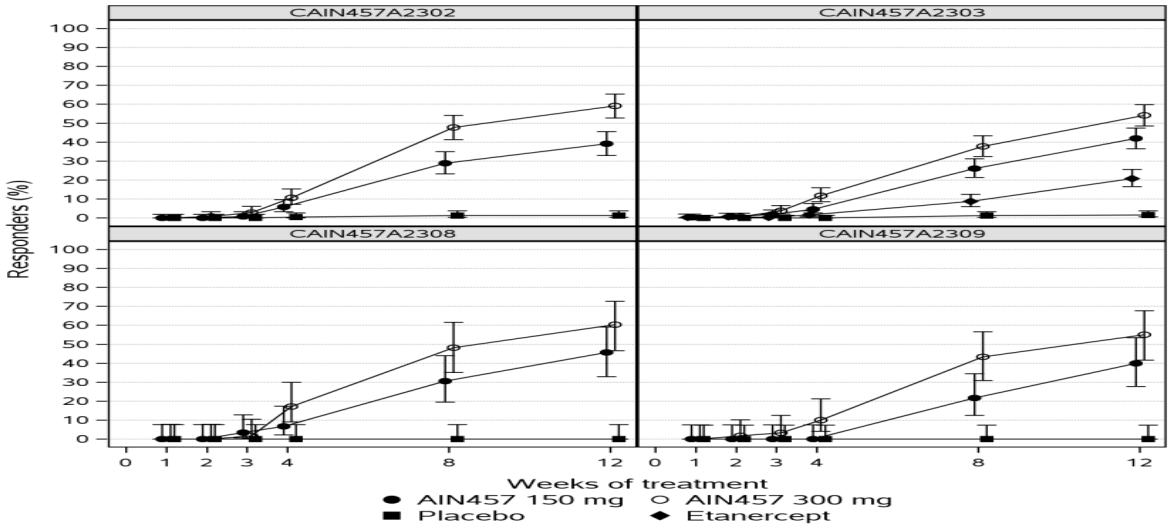


Table 44 PASI 75, PASI 90, PASI 100, and IGA mod 2011 0 or 1 response rates at Week 52 (non-responder imputation) – 52-week efficacy (pooled FAS)

	AIN457 150 mg		AIN457 300 mg		Etanercept	
Response Criterion	**n/m**	**(%)**	**n/m**	**(%)**	**n/m**	**(%)**
PASI 75	487/773	(63.0)	605/784	(77.2)	179/323	(55.4)
IGA mod 2011 0 or 1	365/774	(47.2)	495/784	(63.1)	120/323	(37.2)
PASI 90	328/773	(42.4)	486/784	(62.0)	108/323	(33.4)
PASI 100	157/773	(20.3)	292/784	(37.2)	32/323	(9.9)

	AIN457 150 mg		AIN457 300 mg		Etanercept	
Response Criterion	**n/m**	**(%)**	**n/m**	**(%)**	**n/m**	**(%)**

FAS=full analysis set; IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index

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

Figure 10 - PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response over 52 weeks of treatment (estimate + 95% CI) – Induction and Maintenance periods (non-responder imputation) (FAS) (Studies A2302 and A2303)

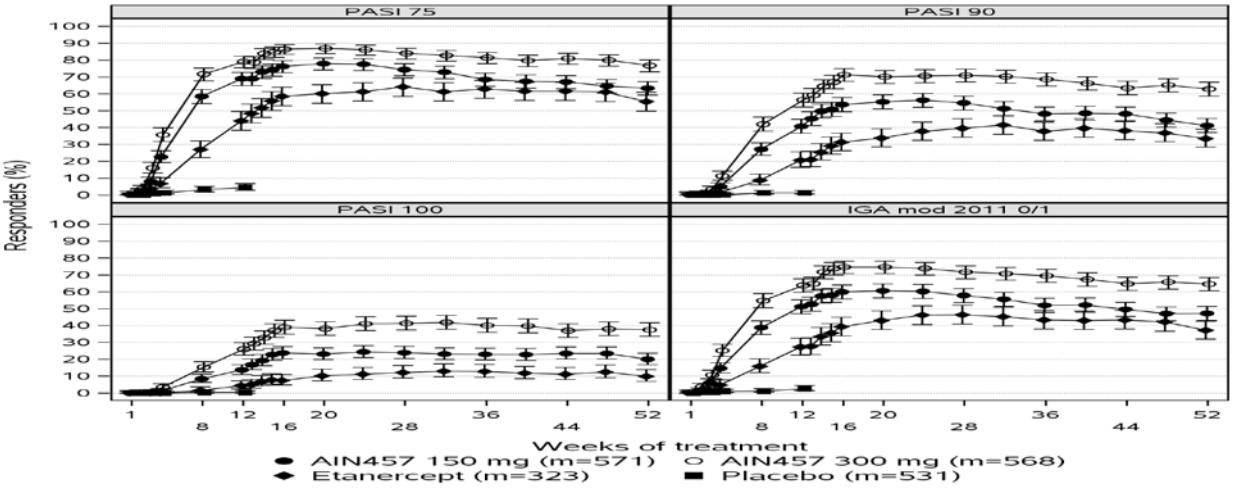


Table 45 Number (%) of subjects with PASI 50, PASI 75, PASI 90, PASI 100 and IGA 0/1 response by visit (non-responder imputation) by weight strata (short-term efficacy) (Full analysis set)

Weight stratum: < 90 kg

Visit	Criterion	AIN457 150 mg N=417 n/m	(%)	95% CI		AIN457 300 mg N=424 n/m	(%)	95% CI		Placebo N=423 n/m	(%)	95% CI	
Week 8	IGA 0/1	183/416	(44.0)	(39.2,	48.9)	256/421	(60.8)	(55.9,	65.5)	4/422	(0.9)	(0.3,	2.6)
	PASI 75	271/415	(65.3)	(60.5,	69.8)	325/421	(77.2)	(72.8,	81.1)	16/422	(3.8)	(2.3,	6.2)
	PASI 50	353/415	(85.1)	(81.2,	88.3)	385/421	(91.4)	(88.3,	93.9)	53/422	(12.6)	(9.6,	16.2)
	PASI 90	140/415	(33.7)	(29.2,	38.5)	211/421	(50.1)	(45.2,	55.0)	5/422	(1.2)	(0.4,	2.9)
	PASI 100	45/415	(10.8)	(8.1,	14.3)	92/421	(21.9)	(18.1,	26.2)	1/422	(0.2)	(0.0,	1.5)
Week 12	IGA 0/1	233/416	(56.0)	(51.1,	60.8)	296/421	(70.3)	(65.7,	74.6)	11/422	(2.6)	(1.4,	4.8)
	PASI 75	308/415	(74.2)	(69.7,	78.3)	352/421	(83.6)	(79.6,	86.9)	23/422	(5.5)	(3.6,	8.2)
	PASI 50	348/415	(83.9)	(79.9,	87.2)	392/421	(93.1)	(90.1,	95.3)	56/422	(13.3)	(10.3,	17.0)
	PASI 90	196/415	(47.2)	(42.4,	52.2)	272/421	(64.6)	(59.8,	69.1)	7/422	(1.7)	(0.7,	3.5)
	PASI 100	68/415	(16.4)	(13.0,	20.4)	143/421	(34.0)	(29.5,	38.7)	2/422	(0.5)	(0.1,	1.9)

Weight stratum: >= 90 kg

Visit	Criterion	AIN457 150 mg N=275 n/m	(%)	95% CI		AIN457 300 mg N=267 n/m	(%)	95% CI		Placebo N=269 n/m	(%)	95% CI	
Week 8	IGA 0/1	80/274	(29.2)	(24.0,	35.0)	122/265	(46.0)	(40.0,	52.2)	3/268	(1.1)	(0.3,	3.5)
	PASI 75	125/274	(45.6)	(39.6,	51.7)	168/265	(63.4)	(57.3,	69.1)	4/268	(1.5)	(0.5,	4.0)
	PASI 50	218/274	(79.6)	(74.2,	84.1)	233/265	(87.9)	(83.2,	91.5)	20/268	(7.5)	(4.7,	11.5)
	PASI 90	46/274	(16.8)	(12.7,	21.9)	82/265	(30.9)	(25.5,	36.9)	2/268	(0.7)	(0.1,	3.0)
	PASI 100	14/274	(5.1)	(2.9,	8.6)	19/265	(7.2)	(4.5,	11.1)	1/268	(0.4)	(0.0,	2.4)
Week 12	IGA 0/1	122/274	(44.5)	(38.6,	50.6)	150/265	(56.6)	(50.4,	62.6)	4/268	(1.5)	(0.5,	4.0)
	PASI 75	169/274	(61.7)	(55.6,	67.4)	193/265	(72.8)	(67.0,	78.0)	6/268	(2.2)	(0.9,	5.0)
	PASI 50	220/274	(80.3)	(75.0,	84.7)	235/265	(88.7)	(84.1,	92.1)	23/268	(8.6)	(5.6,	12.8)
	PASI 90	87/274	(31.8)	(26.4,	37.7)	116/265	(43.8)	(37.7,	50.0)	1/268	(0.4)	(0.0,	2.4)
	PASI 100	25/274	(9.1)	(6.1,	13.3)	46/265	(17.4)	(13.1,	22.6)	0/268	(0.0)	(0.0,	1.8)

Supportive studies

CAIN457A2202: a multicenter, randomized, double blind, placebo controlled, parallel-group proof-of-concept study A2202 and its 52-week open label extension study A2202E1 to assess the efficacy, safety and tolerability of two single i.v. infusions of secukinumab 10 mg/kg in patients with moderate to severe active Crohn's disease.

Results: The patient population was overall well balanced in demographics and baseline characteristics including CDAI. Prior bowel surgery and prior exposure to TNF blockers were more frequent in the AIN457 group. There were no differences in outcomes in patients with or without prior TNF exposure. AIN457 failed to reduce mean CDAI by ≥50 points more than placebo at week 6, missing the primary endpoint and fulfilling the pre-specified criterion for futility in the interim analysis. Consequently, the study was terminated prematurely. Key secondary endpoint AUC analysis (week4-10) showed a statistically significant difference in mean CDAI scores in favor of placebo (p = 0.043). Higher rates of discontinuations and adverse events, including worsening of disease and infections, occurred on secukinumab**.**

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

3430 patients with chronic plaque type psoriasis have been treated with secukinumab in 10 phase II/III studies providing efficacy data and covering 2725 patient-years of exposure. The clinical program included placebo and active (etanercept) controlled studies in patients with moderate to severe plaque psoriasis. Both short-term and long-term efficacy has been measured with standard efficacy variables, including but not limited to PASI, IGA, and DLQI.

Four phase II dose-finding studies were used to support dose selection for phase III. Studies A2102 (proof of concept) and A2212 evaluated i.v. administered secukinumab within a single dose range of 3 mg/kg to 10 mg/kg. Study A2220 aimed to identify the lowest effective dose of s.c. administered secukinumab with treatment doses of 25 mg, 75 mg and 150 mg administered every 4 weeks until week 12. The multi-dose regimen finding study A2211 aimed to identify the appropriate dosing regimen for the 150 mg s.c. secukinumab during the induction and maintenance periods, as well as assessed a fixed interval and start at relapse treatment approaches during the maintenance period.

There were six phase III studies to support the efficacy claims: Four placebo-controlled trials (A2302, A2308, A2309 and A2303) and two individualized maintenance regimen trials (Studies A2304 and A2307). All placebo-controlled studies had similar general design and A2303 also included an active control (TNF-α antagonist biologic etanercept). The primary objective of these studies was to demonstrate superiority of secukinumab with respect to both PASI 75 and IGA 0/1 response at Week 12, compared to placebo. Studies A2302 and A2303 were large pivotal trials with 738 and 1306 patients, respectively, while objectives of the smaller studies A2308 and A2309 included usability and satisfaction with the pre-filled syringe (PFS) and autoinjector (AI), respectively, in patients self-administering secukinumab. A2304 was a large phase III study that compared maintenance dosing with secukinumab 150 mg or 300 mg s.c. re-treatment at start of relapse (SoR) with fixed interval (FI) dosing every four weeks. A further small phase III study A2307 assessed the effect of dose escalation (secukinumab i.v. or s.c.) on response in partial responders after 12 weeks of active treatment in Study A2304. Only 43 patients were randomized into study A2307 and the efficacy data is only supportive. A phase II extension trial (Study A2211E1) was used to support treatment duration beyond 52 weeks. During the procedure the applicant provided A 16-week primary endpoint CSR for another extension Study A2302E1 (following Maintenance Periods of Studies A2302 and A2303 i.e. week 68 data).

The key inclusion criteria were adequate for the inclusion subjects with moderate to severe psoriasis, as defined by PASI score ≥12, IGA ≥3 and a total BSA of ≥10%. The study population was heterogeneous with respect to previous therapies and included both systemic treatment naïve as well as those previously exposed to systemic therapies including biologic therapies. No previous exposure to systemic therapy was reported in 37.0% and 36% of the patients in the large placebo-controlled studies A2302 and A2303, respectively. In the EMA Scientific Advice (EMEA/H/SA/2050/1/2011/III) the applicant was advised to stratify according to the history of previous treatments to ensure balanced randomization with respect to this clinically important issue. Stratification as proposed was not done, however, the randomization is considered by the CHMP well balanced with respect to previous treatments. Overall, there were no relevant differences in the demographics and baseline disease characteristics between the treatment groups.

The co-primary efficacy endpoint PASI 75 and IGA 0/1 response at Week 12 as well as the secondary efficacy endpoints were in principle adequate and in line with the EMA Psoriasis Guideline. It is acknowledged that the modified 5-point IGA scale (IGA mod 2011) used by the applicant is more stringent than the PGA scale as it corresponds to PASI 90 rather than to PASI75 response, as noted by the Applicant and as evidenced by the phase 3 efficacy results. The co-primary efficacy endpoint (PASI 75 and IGA (mod 2011) 0 or 1 response at Week 12) used in all placebo-controlled Phase III studies is very stringent and correlates to clinically highly relevant efficacy. The justification for the use of the IGA mod 2011 scale is considered acceptable to the CHMP. Psoriasis Symptom Diary has been developed by the Applicant and has been used in Studies A2302 and A2303.

Both short-term (up to 12 weeks) and long-term (up to 52 weeks) efficacy data with 150 mg and 300 mg s.c. secukinumab have been provided. In Studies A2308 and A2309 patients self-administered liquid

formulation of secukinumab in PFS or AI, respectively. In other phase III studies, lyophilisate in vial (LYO) formulation was used.

TNF-α antagonist etanercept was the active control in Study A2303, and the maximum allowed dose was used. Etanercept is a widely used biologic treatment for moderate to severe plaque psoriasis and, although there are some other more efficacious biologic therapies available for comparison, it is considered to be an adequate active control for secukinumab. Patients were self-administering etanercept at home while secukinumab was administered at scheduled site visits. During the procedure, this potential bias was discussed by the applicant and based on the compliance data provided, it was concluded by the CHMP that there was no relevant concern.

EMA clinical guidance (Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis CHMP/EWP/2454/02 corr) has been adhered to. EMA Scientific advice (EMEA/H/SA/2050/1/2011/III) has been sought at a late developmental phase in 2011 and concerned mainly confirmation of the design of the planned phase III studies. Overall, secukinumab clinical development program in chronic plaque psoriasis is considered adequate for the demonstration of efficacy in this indication.

Efficacy data and additional analyses

Dose finding

In phase II, the monthly 150 mg s.c. dose was shown to be superior to lower doses but was not shown to give the optimal response since higher s.c. doses were not tested. Studies with the i.v. administration suggested that a higher dose might be more appropriate which was further supported by PK modelling analysis with pooled data from the phase II studies. Therefore, both 150 mg and 300 mg s.c. doses were tested in phase III. In phase II, early induction dosing regimen was tested only with the 150 mg dose without statistically compelling superiority shown in comparison with the monthly dosing regimen. The selected maintenance dosing regimen with monthly injections was tested only in an open-label study and supported by PK modelling. In conclusion, based on the efficacy findings in phase II trials it remained unclear whether the induction and maintenance dose regimens were optimal. Therefore, the phase III continued to explore the optimal dose and dosing regimen.

The dosing regimen chosen for the phase III pivotal studies consisted of an initial 4-week induction period followed by maintenance dosing, with either 150 mg or 300 mg s.c. secukinumab. The proposed dose for clinical use includes only the 300 mg s.c. dose with the following posology in the product information is as follows: “The recommended dose is 300 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at week 4. Each 300 mg dose is given as two subcutaneous injections of 150 mg”.

In the pooled analysis of the placebo-controlled pivotal studies A2302, A2303, A2308 and A2309 at Week 12, both secukinumab 150 mg and 300 mg doses were superior to placebo with respect to the co-primary endpoints PASI 75 response (69.2% and 79.4%, respectively, vs. 4.2% for placebo) and IGA 0/1 response at Week 12 (51.4% and 65.0%, respectively, vs. 2.2% for placebo). The results were consistent across the studies with the p-values for each comparison vs. placebo <0.0001. Also PASI 90, PASI 100 and IGA 0 response rates were statistically significantly higher with both secukinumab doses compared to placebo (p-values for each comparison vs. placebo <0.0001). In exploratory testing, the 300 mg dose showed statistically significantly better results than the 150 mg dose in the larger studies A2302 and A2303. The responses with the 300 mg dose were particularly greater for variables indicative of clear/almost clear skin (PASI 90, PASI 100 and IGA 0/1). Both secukinumab doses were statistically significantly ($p<0.0001$) superior to etanercept. For etanercept treated patients, PASI 75 and IGA 0/1 response rates at Week 12 were 44.0% and 27.2%, respectively.

In the pooled analysis the onset of efficacy (estimated time to 50% reduction in mean PASI score) occurred at 3.0 weeks with secukinumab 300 mg and at 3.7 weeks with secukinumab 150 mg. At Week 2, around 40% reduction in symptoms was observed with the 300 mg dose in the larger studies A2302 and A2303. The improvements with secukinumab in clinical response were mirrored by the improvements in patient reported outcomes, including EQ-5D, DLQI, and Psoriasis symptom diary.

For items of the Psoriasis Symptom Diary, i.e. in itching, pain and scaling, statistically significant improvement in the secukinumab groups compared to placebo was observed at Week 12 in Studies A2302 and A2303. This information has been included in the product information. Self-administration of secukinumab with PFS or AI in studies A2308 and A2309 was found feasible and acceptable by the patients. The efficacy was consistent in studies using the lyophilisate and liquid formulations of secukinumab.

The response rates achieved at Week 12 in both secukinumab dose groups appeared to be well sustained up to Week 52 based on Studies A2302 and A2303, particularly in the 300 mg dose group. PASI 75 and IGA 0/1 responses reached their plateau at Week 16 and decline slightly thereafter. The cumulative probability (Kaplan-Meier estimates) of loss of PASI 75 response at Week 52 was lowest in 300 mg dose group (12.9%; 24.7% in the 150 mg dose group and 33.8% in the etanercept group). Relapse rates were also lower in the 300 mg group (7.4%) compared to the 150 mg (17.1%), etanercept (21.1%) and placebo (28.6%) groups.

In the overall population, the 300 mg secukinumab dose was more efficient than the 150 mg dose. The applicant considered that since psoriasis is a chronic disease and the mode of action of secukinumab is not curative, it is not expected that the responsiveness to secukinumab changes over time and that continuous treatment with secukinumab is necessary to maintain the treatment effect, and the 300 mg dose is superior to the 150 mg dose in the maintenance of efficacy up to Week 52. The CHMP agreed that continuous treatment with secukinumab is necessary to maintain the treatment effect, and the 300 mg dose is superior to the 150 mg dose in the maintenance of efficacy up to Week 52. There are also some data available to suggest that a 150 mg maintenance dose is not optimal even for the low-weight patients. Among patients in all weight categories including ≤50 kg, 50 - 60 kg and >60 - 70 kg, good initial response to the 150 mg dose was followed by gradually decreasing responses, while the efficacy was maintained in the 300 mg dose group up to Week 52. Following evaluation of these data the CHMP concluded that the 300 mg maintenance dose is recommended for all patient populations, including those with low body weight.

There is data available in subjects treated with secukinumab beyond 52 weeks. Patients in the open-label arm of Study A2211E1 were treated with the 150 mg s.c. dose for up to over three years (175 weeks). Most patients in the open-label arm were initially PASI 75 non-responders but over half of them turned responders during the 121-week extension. Efficacy was also maintained rather well with the 150 mg s.c. dose, however, the rate of discontinuations was high and mostly due to unsatisfactory therapeutic effect. During the procedure the applicant provided primary endpoint data of the first 16 weeks of Extension Study A2302E1 (Week 68 data). This is a randomized withdrawal two-year extension study of phase III core studies A2302 and A2303. In this study, both secukinumab doses were significantly superior to placebo groups in maintaining PASI 75 response up to Week 68.

Among the subpopulations based on age, gender, race and region, in the secukinumab 150 mg group slightly diminished (around -10%) PASI 75, PASI 90 and IGA 0/1 response rates were observed in males compared to females, and in the rest of the world compared to Europe. In the secukinumab 300 mg group, slightly diminished (around -10%) responses were observed in patients ≥65 years compared to those <65, and in Asian patients compared to Caucasians. These differences were not considered clinically meaningful by the CHMP.

The comparison of efficacy based on body weight is clinically relevant, as decreased efficacy was consistently observed in those in the higher weight subgroup (≥93 kg) and in the ≥ 90 kg randomization strata. The difference in response rates between the lowest and the highest weight groups in the secukinumab 300 mg group was around -10-15% for PASI 75 and IGA 0/1 responses, and up -20-30% for the higher PASI responses (PASI 90 and 100). During the procedure the applicant further explored the body weight – response relationship of secukinumab. The CHMP concluded that the benefit/risk of the 300 mg dose is positive also in patients weighing over 90 kg and there is no need for dose adjustment in this population.

Baseline disease characteristics did not have a clinically relevant effect on the efficacy of secukinumab. In 422 (out of 2401; 17.6%) patients with PsA at baseline, the response rates were slightly reduced compared with non-PsA patients. In variables related to PsA, there was improvement in HAQ-DI score in both secukinumab groups but no meaningful data on ACR responses was available. In patients with previous systemic psoriasis therapy including biologic therapy, efficacy was slightly diminished but yet clinically highly relevant. Higher response rates were consistently seen with the secukinumab 300 mg dose. In Study A2302 for those with previous exposure to systemic therapy compared to systemic treatment-naïve patients (37%), IGA 0/1 responses for secukinumab 300 mg dose at Week 12 were 63.2% vs. 69.5%, respectively, and PASI 75 responses were 77.9% vs. 89.0%, respectively. The corresponding figures in Study A2303 for IGA 0/1 responses were 61.0% vs. 65.0%, respectively, and for PASI 75 responses 77.1% vs. 76.9%, respectively.

Among the small number of patients available for initial evaluation, post-treatment relapse and rebound was observed less frequently in the 300 mg secukinumab group. During the procedure, the data was updated with the 8-week follow-up periods of pivotal studies. Based on these data, the CHMP concluded that the 300 mg secukinumab dose has superior efficacy compared to the 150 mg dose and continuous treatment with secukinumab is necessary to maintain the treatment effect. Further, there are no major differences in the rate of post-treatment relapses and rebounds between the two doses.

Study A2304 evaluating individualized maintenance regimen did not meet the primary endpoint, i.e. it could not be shown that re-treatment with secukinumab 150 mg or 300 mg s.c. at SoR regimen was non-inferior to the FI regimen with treatment every four weeks. Maintenance of response was in favor of the FI treatment regimen in all subgroup comparisons, with secukinumab 300 mg FI regimen being superior to the 150 mg FI regimen. In particular, higher efficacy levels (PASI 90 and 100, IGA 0/1) were well maintained the FI groups while reduction over time was seen in the SoR groups. In the analysis of time to relapse, the cumulative probability of having a relapse after Week 12 was low in the FI treatment groups but by study design, increased in the SoR groups. In the 300 mg and 150 mg SoR groups, the duration of treatment effect (after Week 12) was however relatively long as at >40 weeks, the cumulative probability of having a relapse was around 55% and 37%, respectively. Around 85% of patients in both SoR treatment groups met SoR criteria at least once. PASI 75 response was regained by 55% and 69% of patients in the 150 mg and 300 mg SoR groups, respectively. The response rate in subsequent SoR episodes was diminished. Taken together, it is concluded that secukinumab treatment with a fixed interval of 4 weeks is preferable to re-treatment at start of relapse.

Up-titration with 10 mg/kg i.v. secukinumab in Study A2307 was not statistically superior to the 300 mg s.c. dose in partial responders who had initial treatment up to 12 weeks with s.c. secukinumab, i.e. the primary objective of the study was not met. The initial response rates were however consistently higher in the secukinumab i.v. group. The dose of 10 mg/kg i.v. exceeds multiple-fold the s.c. doses of 150 mg and 300 mg used in the Phase III program for psoriasis. The limited number of patients available in Study A2307 (n=43 of which 22 were randomized to receive the i.v. treatment) does not allow any conclusions regarding the efficacy and safety of the i.v. up-titration regimen.

A multicentre, randomised, double blind, placebo controlled, parallel-group proof-of-concept (Study A2202) and its 52-week open label extension (study A2202E1) to assess the efficacy, safety and tolerability of two single i.v. infusions of secukinumab 10 mg/kg in patients with moderate to severe active Crohn's disease, were terminated prematurely as the primary study failed to reduce mean CDAI by ≥50 points more than placebo at week 6, thus missing the primary efficacy endpoint and fulfilling the pre-specified criterion for futility in the interim analysis and the study. Key secondary end-points showed statistically significant difference in favor of placebo. Higher rates of discontinuations and adverse events, including worsening of disease and infections occurred on secukinumab. Therefore, the inclusion in the product information of a warning and recommendation to close follow up of all patients with Crohn's disease was supported by the CHMP.

Based on the data from the submitted supportive studies in other indications, no firm conclusions can be made on the efficacy of secukinumab in indications other than psoriasis. The evidence for benefit from these studies in other indications is either preliminary or, if phase III results are available, mixed.

Taken together, clinically highly relevant efficacy has been shown in patients with moderate to severe plaque psoriasis, including systemic treatment naïve patients as well as those previously exposed to systemic therapies including biologic therapies. Therefore, the CHMP agreed to change the initially proposed indication: "Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA" to: "Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy". Note: 'Systemic therapy' within the context of indication wording includes both non-biologic (e.g. cyclosporine, MTX etc) systemic and biologic systemic agents.

2.5.4. Conclusions on the clinical efficacy

The efficacy data demonstrated superiority of secukinumab 150 mg and 300 mg s.c. compared to placebo and etanercept in the treatment of moderate to severe plaque psoriasis. The study population included both systemic treatment naïve patients as well as those previously exposed to systemic therapies including biologic therapies. Secukinumab 300 mg dose was consistently better than the 150 mg dose, and from the efficacy point of view it is the recommended dose. The efficacy of secukinumab 300 mg s.c. is considered clinically highly relevant, with fast onset of action and good sustainability. Therefore, the following indication is acceptable from the efficacy point of view: Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

All 6 core Phase 3 studies (CAIN457A2302, A2303, A2304, A2307, A2308, and A2309) have either been extended to a study duration of up to 4 years (A2308 and A2309) or have offered subjects on secukinumab in the core studies the opportunity to participate in long-term extension studies for up to a total treatment period of 5 years (for studies A2302 and A2303: A2302E1; for A2304 and A2307: A2304E1). The long term treatment is expected to last for an overall (core and extension) treatment duration of up to 5 years, or at least until the drug is commercially available (thus less than 5 years in some countries). Altogether, data from approximately 2000 subjects treated with secukinumab for more than 1 year and data up to 5 years will become available from these studies (as described in the RMP).

2.6. Clinical safety

The Applicant has addressed safety aspects in the safety summary using three defined safety sets:

- Pool A, n=2399, short-term safety up to12 weeks, 3 pivotal placebo-controlled and 1 pivotal placebo-and active-controlled (etanercept) phase II/III trials in psoriasis:
    - A2302, A2303, A2308, and A2309.

- Secukinumab 150 mg sc, n=692, 157 pt-years; secukinumab 300 mg sc, n=690, 158 pt-years; placebo, n=694, 155 pt-years, and etanercept, n=323, 73 pt-years.

- Pool B, n=3993, longer-term safety up to 52 weeks, 10 phase II/III studies in psoriasis indication:
  - A2211, A2211e1, A2212, A2220, A2302, A2303, A2304, A2307, A2308, and A2309.
  - 12 weeks: secukinumab 150 mg sc, n=1174, 268 pt-years, secukinumab 300 mg sc, n=1173, 268 pt-years, secukinumab any dose, n=2877, 655 pt-years, placebo, n=694, 155 pt-years, and etanercept, n=323, 73 pt-years.
  - 52 weeks: secukinumab 150 mg sc, n=1395, 1142 pt-years, secukinumab 300 mg sc, n=1410, 1178 pt-years, secukinumab any dose, n=3430, 2725 pt-years, placebo, n=793, 201 pt-years, and etanercept, n=323, 294 pt-years.
  - 75.9% of the total patient-year exposure to secukinumab in any indication (3588 pt-years).
  - 3430 patients exposed to secukinumab (1641 patients at least 1 year, 2751 at least 6 months)
  - iv-doses ranged from 3 to 30 mg/kg, sc-doses from 25 to 300 mg.
- Pool C, n= 5044 patients from 34 out of 39 phase I/II/III trials in dossier:
  - Only healthy volunteers in phase I studies were excluded.
  - N=4498, >3588 pt-years of exposure to secukinumab; n=1158, >339 pt-year exposure to placebo.

Deaths and overall AEs were examined for all three data pools (A, B and C). The severity of AEs, the relationship of AEs to study treatment, serious adverse events (SAEs), AEs causing permanent discontinuation of study treatment, laboratory values, vital signs, and ECG data were examined for patients in psoriasis studies (Pools A and B), but not for patients exposed to secukinumab in any indication (Pool C).

AEs of special interest corresponding to potential risks outlined in the Safety profiling plan for secukinumab and its class of drug were:

- potential risks of any immunomodulating biologic approved or assessed in psoriasis: infections, opportunistic infections, major adverse cardiovascular event (MACE), malignancies, neutropenia
- potential risks of foreign proteins: hypersensitivity, administration or immune reactions, and autoimmune disorders
- potential risk of compounds targeting the IL-17 pathway: Crohn's disease
- routine risks: hepatotoxicity, QTc prolongation

The ICH E1 safety exposure requirements of >1500 patients exposed, 300 to 600 for 6 months, >100 for 1 year are well exceeded. Regrouping of subjects to three pools described above has been done with rational considerations. In pool A the number of etanercept recipients was small compared to secukinumab and placebo recipients (n=327 out of 2399 patients). In pool B the number of placebo recipients after 12 weeks induction period was low due to intensive re-randomization of the non-responders or partial responders from the placebo-groups to active-treatment groups. Pool C appears valuable in assessing the largest obtainable secukinumab exposure and safety in special

situations, such as in patients with Crohn´s disease. It also includes higher dosages, number of other therapies (such as immunosuppressants for different comorbid states like rheumatoid arthritis or uveitis). In pool C no distinction of the study periods, either induction, maintenance, entire, or follow-up have been made.

Patient exposure

Exposure to secukinumab across Pools A, B and C is shown in Table 47

Table 47 Exposure to secukinumab across Pools A, B and C

	Pool A (12 weeks)			Pool B (52 weeks)			Pool C (52 weeks)
	150 mg N=692	300 mg N=690	Any dose N=1382	Any 150 mg N=1395	Any 300 mg N=1410	Any dose N=3430	Any dose N=4498
≥ 1 month	683	685	1368	1383	1397	3394	4433
≥ 3 months	15	16	31	1208	1236	2867	3462
≥ 6 months	1	0	1	1158	1189	2727	3139
≥ 12 months	n.a.	n.a.	n.a.	828	885	1947	2197
Total exposure (patient-years)	157.2	157.5	314.6	1142.0	1177.5	2724.6	3588.1

Exposure in month(s) is cumulative starting from first dose. Patient-years exposure was calculated as a sum of individual patient durations in days divided by 365.25. n.a.= not applicable

Demographic characteristics for Pool A and B are described in Tables 48, 49 and 50.

Table 48 Pool A: Pivotal placebo-controlled psoriasis trials – Safety set

Demographic variable	AIN457 150 mg N=692	AIN457 300 mg N=690	Placebo N=694	Etanercept N=323	Total N=2399
Age group in years, n (%)					
< 65	634 (91.6)	642 (93.0)	651 (93.8)	305 (94.4)	2232 (93.04)
≥ 65	58 (8.4)	48 (7.0)	43 (6.2)	18 (5.6)	167 (6.96)
≥ 75	10 (1.4)	6 (0.9)	10 (1.4)	3 (0.9)	29 (1.21)

Demographic variable	AIN457 150 mg N=692	AIN457 300 mg N=690	Placebo N=694	Etanercept N=323	Total N=2399
Age (years)					
n	692	690	694	323	2399
Mean	45.1	44.9	44.7	43.8	44.8
SD	13.38	13.32	12.79	12.99	13.14
Median	45.0	45.0	45.0	44.0	45.0
Min - Max	18 - 83	18 - 83	18 - 82	18 - 79	18 - 83
Sex, n (%)					
Female	207 (29.9)	214 (31.0)	208 (30.0)	94 (29.1)	723 (30.14)
Male	485 (70.1)	476 (69.0)	486 (70.0)	229 (70.9)	1676 (69.86)
Weight (kg)					
n	692	690	694	323	2399
Mean	86.60	86.56	86.05	84.45	86.14
SD	23.150	23.226	22.590	20.542	22.673
Median	84.00	83.91	83.25	81.60	83.30
Min - Max	43.1 - 215.0	45.0 - 219.1	42.0 - 191.9	42.0 - 175.6	42.0 - 219.1
BMI (kg/m^2)					
n	692	687	693	321	2393
Mean	29.38	29.40	29.08	28.71	29.21
SD	7.031	6.891	6.929	5.942	6.824
Median	28.32	28.10	27.83	27.64	28.03
Min - Max	16.5 - 79.7	17.4 - 67.4	16.2 - 71.2	15.4 - 58.3	15.4 - 79.7
Current smoker at baseline, n (%)					
No	442 (63.9)	441 (63.9)	462 (66.6)	214 (66.3)	1559 (64.99)
Yes	250 (36.1)	249 (36.1)	232 (33.4)	109 (33.7)	840 (35.01)
Race, n (%)					
Caucasian	499 (72.1)	504 (73.0)	511 (73.6)	216 (66.9)	1730 (72.11)
Black	13 (1.9)	9 (1.3)	13 (1.9)	0 (0.0)	35 (1.46)
Asian	129 (18.6)	129 (18.7)	121 (17.4)	74 (22.9)	453 (18.88)
Native American	33 (4.8)	29 (4.2)	28 (4.0)	27 (8.4)	117 (4.88)

Demographic variable	AIN457 150 mg N=692	AIN457 300 mg N=690	Placebo N=694	Etanercept N=323	Total N=2399
Pacific Islander	1 (0.1)	4 (0.6)	1 (0.1)	1 (0.3)	7 (0.29)
Unknown	1 (0.1)	2 (0.3)	2 (0.3)	1 (0.3)	6 (0.25)
Other	16 (2.3)	13 (1.9)	18 (2.6)	4 (1.2)	51 (2.13)

Table 49 Induction period (Pool B: All psoriasis trials – Safety set)

Demographic variable	AIN457 150 mg N=1174	AIN457 300 mg N=1173	Any AIN457 dose N=2877	Placebo N=793	Etanercept N=323	Total N=3993
Age group in years, n (%)						
< 65	1084 (92.33)	1090 (92.92)	2683 (93.26)	744 (93.8)	305 (94.4)	3732 (93.46)
≥ 65	90 (7.67)	83 (7.08)	194 (6.74)	49 (6.2)	18 (5.6)	261 (6.54)
≥ 75	12 (1.02)	10 (0.85)	24 (0.83)	10 (1.3)	3 (0.9)	37 (0.93)
Age (years)						
n	1174	1173	2877	793	323	3993
Mean	45.2	45.6	45.2	44.6	43.8	45.0
SD	13.15	13.13	12.96	12.74	12.99	12.92
Median	45.0	46.0	45.0	45.0	44.0	45.0
Min - Max	18 - 83	18 - 89	18 - 89	18 - 82	18 - 79	18 - 89
Sex, n (%)						
Female	384 (32.71)	365 (31.12)	868 (30.17)	241 (30.4)	94 (29.1)	1203 (30.13)
Male	790 (67.29)	808 (68.88)	2009 (69.83)	552 (69.6)	229 (70.9)	2790 (69.87)
Weight (kg)						
n	1174	1173	2877	793	323	3993
Mean	86.05	86.00	87.22	87.11	84.45	86.97
SD	22.985	23.209	23.099	23.608	20.542	23.012
Median	84.00	83.40	85.00	84.00	81.60	84.40
Min - Max	39.0 - 215.0	36.0 - 219.1	36.0 - 219.1	42.0 – 203.2	42.0 - 175.6	36.0 - 219.1
BMI (kg/m^2)						
n	1174	1168	2872	792	321	3985

Demographic variable	AIN457 150 mg N=1174	AIN457 300 mg N=1173	Any AIN457 dose N=2877	Placebo N=793	Etanercept N=323	Total N=3993
Mean	29.25	29.25	29.44	29.35	28.71	29.37
SD	6.914	6.884	6.885	7.274	5.942	6.895
Median	28.38	28.10	28.41	27.95	27.64	28.26
Min - Max	15.5 - 79.7	16.2 - 67.4	15.5 - 79.7	16.2 - 71.2	15.4 - 58.3	15.4 - 79.7
Current smoker at baseline, n (%)						
No	764(65.08)	756(64.45)	1786 (62.08)	512 (64.6)	214 (66.3)	2512 (62.91)
Yes	410(34.92)	417(35.55)	1001 (34.79)	271 (34.2)	109 (33.7)	1381 (34.59)
Race, n (%)						
Caucasian	848 (72.23)	847 (72.21)	2160 (75.08)	593 (74.8)	216 (66.9)	2969 (74.36)
Black	22 (1.87)	17 (1.45)	41 (1.43)	15 (1.9)	0 (0.0)	56 (1.40)
Asian	247 (21.04)	251 (21.40)	558 (19.40)	134 (16.9)	74 (22.9)	766 (19.18)
Native American	34 (2.90)	32 (2.73)	66 (2.29)	28 (3.5)	27 (8.4)	121 (3.03)
Pacific Islander	1 (0.09)	5 (0.43)	6 (0.21)	2 (0.3)	1 (0.3)	9 (0.23)
Unknown	3 (0.26)	3 (0.26)	6 (0.21)	2 (0.3)	1 (0.3)	9 (0.23)
Other	19 (1.62)	18 (1.53)	40 (1.39)	19 (2.4)	4 (1.2)	63 (1.58)

Table 50 Demographics and background characteristics – Maintenance period (Pool B: All psoriasis trials – Safety set)

Demographic variable	AIN457 150 mg N=748	AIN457 300 mg N=772	Any AIN457 dose N=2853	Placebo N=37	Etanercept N=303	Total N=3193
Age group in years, n (%)						
< 65	696 (93.0)	717 (92.9)	2669 (93.55)	36 (97.3)	287 (94.7)	2992 (93.70)
≥ 65	52 (7.0)	55 (7.1)	184 (6.45)	1 (2.7)	16 (5.3)	201 (6.30)
≥ 75	7 (0.9)	4 (0.5)	24 (0.84)	0 (0.0)	3 (1.0)	27 (0.85)
Age (years)						
n	748	772	2853	37	303	3193
Mean	44.8	45.4	45.0	46.3	43.6	44.8

Demographic variable	AIN457 150 mg N=748	AIN457 300 mg N=772	Any AIN457 dose N=2853	Placebo N=37	Etanercept N=303	Total N=3193
SD	12.92	13.07	12.81	12.29	13.04	12.83
Median	45.0	45.5	45.0	46.0	44.0	45.0
Min - Max	18 - 83	18 - 79	18 - 83	20 - 66	18 - 79	18 - 83
Sex, n (%)						
Female	240 (32.1)	232 (30.1)	852 (29.86)	14 (37.8)	90 (29.7)	956 (29.94)
Male	508 (67.9)	540 (69.9)	2001 (70.14)	23 (62.2)	213 (70.3)	2237 (70.06)
Weight (kg)						
n	748	772	2853	37	303	3193
Mean	85.01	84.96	86.21	83.25	84.85	86.05
SD	21.767	22.251	22.642	28.043	20.632	22.526
Median	83.55	82.53	84.00	76.10	81.74	83.60
Min - Max	40.5 - 162.9	40.0 - 219.1	36.0 - 219.1	53.0 - 191.9	42.0 - 175.6	36.0 - 219.1
BMI (kg/m^2)						
n	748	767	2847	37	301	3185
Mean	29.03	28.94	29.18	28.74	28.80	29.14
SD	6.482	6.586	6.814	6.865	5.991	6.740
Median	28.09	27.89	28.09	26.92	27.64	28.04
Min - Max	17.1 - 63.0	16.2 - 67.4	15.5 - 71.2	19.7 - 60.7	15.4 - 58.3	15.4 - 71.2
Current smoker at baseline, n (%)						
No	486 (65.0)	496 (64.2)	1831 (64.18)	19 (51.4)	199 (65.7)	2049 (64.17)
Yes	262 (35.0)	276 (35.8)	1022 (35.82)	18 (48.6)	104 (34.3)	1144 (35.83)
Race, n (%)						
Caucasian	519(69.4)	536 (69.4)	2056 (72.06)	17 (45.9)	204 (67.3)	2277 (71.31)
Black	13 (1.7)	8 (1.0)	41 (1.44)	1 (2.7)	0 (0.0)	42 (1.32)
Asian	170 (22.7)	179 (23.2)	611 (21.42)	11 (29.7)	68 (22.4)	690 (21.61)
Native American	32 (4.3)	31 (4.0)	90 (3.15)	2 (5.4)	25 (8.3)	117 (3.66)

Demographic variable	AIN457 150 mg N=748	AIN457 300 mg N=772	Any AIN457 dose N=2853	Placebo N=37	Etanercept N=303	Total N=3193
Pacific Islander	1 (0.1)	4 (0.5)	7 (0.25)	0 (0.0)	1 (0.3)	8 (0.25)
Unknown	0 (0.0)	2 (0.3)	7 (0.25)	0 (0.0)	1 (0.3)	8 (0.25)
Other	13 (1.7)	12 (1.6)	41 (1.44)	6 (16.2)	4 (1.3)	51 (1.60)

Adverse events

A general representation of the safety data from pool A and B is given in table 51. In pool A, the percentages are given. In pool B, exposure adjusted incidence rates (number of AEs/100 patient years) are given.

Table 51 Summary of AEs, SAEs and selected risks in the first 12 weeks and over 52 weeks of treatment:

	Pool A – First 12 weeks				Pool B – Entire 52 weeks			
	AIN457 150 mg N=692 n (%)	AIN457 300 mg N=690 n (%)	PBO N=694 n (%)	Etaner-cept N=323 n (%)	Any AIN457 150 mg N=1395 n (IR)	Any AIN457 300 mg N=1410 n (IR)	PBO N=793 n (IR)	Etaner-cept N=323 n (IR)
Total AEs	412 (59.5)	388 (56.2)	340 (49.0)	186 (57.6)	1066 (239.90)	1091 (236.10)	413 (351.79)	253 (243.44)
Total SAEs	14 (2.0)	14 (2.0)	12 (1.7)	3 (0.9)	76 (6.80)	85 (7.42)	15 (7.54)	20 (7.01)
Selected risks based on AEs								
Infections and infestations (SOC)	203 (29.3)	195 (28.3)	134 (19.3)	83 (25.7)	653 (85.29)	704 (91.06)	173 (101.89)	172 (93.68)
URTIs (HLT)	129 (18.6)	117 (17.0)	72 (10.4)	49 (15.2)	408 (45.02)	426 (45.39)	96 (52.03)	113 (50.50)
Candida infections (HLT)	3 (0.4)	8 (1.2)	2 (0.3)	1 (0.3)	21 (1.85)	41 (3.55)	2 (1.00)	4 (1.37)
MACE (NMQ)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	5 (0.44)	6 (0.51)	1 (0.50)	1 (0.34)
CCV-related events (NMQ)	7 (1.0)	3 (0.4)	11 (1.6)	6 (1.9)	30 (2.65)	82 (3.04)	13 (6.54)	14 (4.86)
Malignant or unspecified tumours (SMQ)	3 (0.4)	1 (0.1)	3 (0.4)	0 (0.0)	11 (0.97)	9 (0.77)	3 (1.49)	2 (0.68)
Hypersensitivity (narrow SMQ)	31 (4.5)	31 (4.5)	9 (1.3)	15 (4.6)	115 (10.70)	132 (11.94)	9 (4.50)	27 (9.73)

	Pool A – First 12 weeks				Pool B – Entire 52 weeks			
	AIN457 150 mg N=692 n (%)	AIN457 300 mg N=690 n (%)	PBO N=694 n (%)	Etaner-cept N=323 n (%)	Any AIN457 150 mg N=1395 n (IR)	Any AIN457 300 mg N=1410 n (IR)	PBO N=793 n (IR)	Etaner-cept N=323 n (IR)
Neutropenia (narrow NMQ)	2 (0.3)	4 (0.6)	0 (0.0)	2 (0.6)	15 (1.32)	16 (1.37)	0 (0.00)	5 (1.71)
Crohn's disease (PT)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.18)	0 (0.00)	0 (0.00)	0 (0.00)

IR=exposure-adjusted incidence rate per 100 patient-years. CCV=cardio-cerebrovascular; HLT=high level term; MACE=major adverse cardiovascular event; NMQ=Novartis MedDRA query; PBO=placebo; PT=preferred term; SMQ=standardized MedDRA query SOC=system organ class; URTIs=upper respiratory tract infections.

Induction period

Pool A – weeks 0 to 12

Table 52 Most frequent (>=2.0% in any group) AEs by preferred term – Induction period (Pool A: Pivotal placebo-controlled psoriasis trials – Safety set)

Preferred term	AIN457 150 mg N=692 n (%)	AIN457 300 mg N=690 n (%)	Any AIN457 dose N=1382 n (%)	Placebo N=694 n (%)	Etanercept N=323 n (%)
-Any AE	412 (59.5)	388 (56.2)	800 (57.89)	340 (49.0)	186 (57.6)
Nasopharyngitis	85 (12.3)	79 (11.4)	164 (11.87)	60 (8.6)	36 (11.1)
Headache	38 (5.5)	45 (6.5)	83 (6.01)	36 (5.2)	23 (7.1)
Diarrhea	18 (2.6)	28 (4.1)	46 (3.33)	10 (1.4)	11 (3.4)
Pruritus	21 (3.0)	23 (3.3)	44 (3.18)	18 (2.6)	8 (2.5)
Upper respiratory tract infection	22 (3.2)	17 (2.5)	39 (2.82)	5 (0.7)	7 (2.2)
Oropharyngeal pain	17 (2.5)	15 (2.2)	32 (2.32)	12 (1.7)	4 (1.2)
Arthralgia	20 (2.9)	9 (1.3)	29 (2.10)	17 (2.4)	12 (3.7)
Hypertension	22 (3.2)	7 (1.0)	29 (2.10)	12 (1.7)	5 (1.5)
Cough	9 (1.3)	19 (2.8)	28 (2.03)	9 (1.3)	4 (1.2)
Back pain	12 (1.7)	14 (2.0)	26 (1.88)	10 (1.4)	9 (2.8)
Nausea	12 (1.7)	14 (2.0)	26 (1.88)	14 (2.0)	4 (1.2)
Fatigue	14 (2.0)	10 (1.4)	24 (1.74)	7 (1.0)	5 (1.5)
Psoriasis	10 (1.4)	4 (0.6)	14 (1.01)	20 (2.9)	2 (0.6)
Pyrexia	4 (0.6)	10 (1.4)	14 (1.01)	6 (0.9)	7 (2.2)

Preferred term	AIN457 150 mg N=692 n (%)	AIN457 300 mg N=690 n (%)	Any AIN457 dose N=1382 n (%)	Placebo N=694 n (%)	Etanercept N=323 n (%)
Injection site erythema	0 (0.0)	1 (0.1)	1 (0.07)	0 (0.0)	16 (5.0)

Treatment-emergent AEs are summarized. Preferred terms are sorted in descending order of frequency in any AIN457 group.

Pool B induction – weeks 0 to 12

Table 53 Most frequent (>=2% in any group) AEs by preferred term – Induction period (Pool B: All psoriasis trials – Safety set)

Preferred term	AIN457 150 mg N=1174 n (%)	AIN457 300 mg N=1173 n (%)	Any AIN457 dose N=2877 n (%)	Placebo N=793 n (%)	Etanercept N=323 n (%)
-Any AE	661 (56.30)	636 (54.22)	1620 (56.31)	400 (50.4)	186 (57.6)
Nasopharyngitis	133 (11.33)	124 (10.57)	338 (11.75)	72 (9.1)	36 (11.1)
Headache	60 (5.11)	62 (5.29)	156 (5.42)	39 (4.9)	23 (7.1)
Upper respiratory tract infection	39 (3.32)	35 (2.98)	94 (3.27)	11 (1.4)	7 (2.2)
Pruritus	40 (3.41)	34 (2.90)	84 (2.92)	21 (2.6)	8 (2.5)
Diarrhea	25 (2.13)	36 (3.07)	68 (2.36)	11 (1.4)	11 (3.4)
Hypertension	33 (2.81)	18 (1.53)	62 (2.16)	13 (1.6)	5 (1.5)
Arthralgia	29 (2.47)	18 (1.53)	58 (2.02)	17 (2.1)	12 (3.7)
Cough	19 (1.62)	29 (2.47)	55 (1.91)	13 (1.6)	4 (1.2)
Back pain	22 (1.87)	18 (1.53)	48 (1.67)	11 (1.4)	9 (2.8)
Psoriasis	11 (0.94)	12 (1.02)	45 (1.56)	27 (3.4)	2 (0.6)
Pyrexia	7 (0.60)	10 (0.85)	21 (0.73)	7 (0.9)	7 (2.2)
Injection site erythema	2 (0.17)	2 (0.17)	5 (0.17)	0 (0.0)	16 (5.0)

Preferred terms are sorted in descending order of frequency in any AIN457 group.

Entire treatment period

Table 54 Exposure-adjusted incidence of AEs by primary system organ class – Entire treatment period (Pool B: All psoriasis trials – Safety set)

Primary system organ class	Any AIN457 150 mg N=1395 n (IR)	Any AIN457 300 mg N=1410 n (IR)	Any AIN457 dose N=3430 n (IR)	Placebo N=793 n (IR)	Etanercept N=323 n (IR)

Primary system organ class	Any AIN457 150 mg N=1395 n (IR)	Any AIN457 300 mg N=1410 n (IR)	Any AIN457 dose N=3430 n (IR)	Placebo N=793 n (IR)	Etanercept N=323 n (IR)
- Any AE	1066 (239.90)	1091 (236.10)	2637 (252.86)	413 (351.79)	253 (243.44)
Infections and infestations*	645 (83.85)	701 (90.47)	1628 (90.41)	170 (100.06)	170 (91.37)
Skin and subcutaneous tissue disorders	270 (27.53)	287 (28.39)	716 (30.75)	79 (42.20)	61 (24.11)
Gastrointestinal disorders	253 (25.36)	262 (25.58)	621 (26.11)	77 (41.39)	68 (27.18)
Musculoskeletal and connective tissue disorders	243 (24.11)	252 (24.20)	620 (25.83)	70 (36.96)	69 (27.43)
Nervous system disorders	178 (17.15)	182 (17.19)	447 (18.17)	62 (32.70)	54 (21.17)
Respiratory, thoracic and mediastinal disorders	147 (13.80)	197 (18.45)	412 (16.47)	47 (24.29)	35 (12.86)
Injury, poisoning and procedural complications	149 (14.02)	171 (15.70)	399 (15.82)	39 (20.21)	38 (14.03)
General disorders and administration site conditions	158 (15.00)	164 (15.06)	397 (15.82)	49 (25.61)	79 (33.21)
Metabolism and nutrition disorders	135 (12.75)	100 (8.95)	269 (10.49)	27 (13.95)	25 (9.02)
Investigations	90 (8.22)	94 (8.36)	238 (9.16)	16 (8.04)	23 (8.19)
Vascular disorders	91 (8.33)	88 (7.74)	219 (8.37)	19 (9.57)	17 (6.00)
Psychiatric disorders	68 (6.15)	48 (4.17)	139 (5.24)	20 (10.11)	16 (5.64)
Eye disorders	47 (4.22)	64 (5.58)	135 (5.09)	11 (5.53)	10 (3.46)
Blood and lymphatic system disorders	54 (4.85)	50 (4.36)	119 (4.47)	7 (3.50)	16 (5.65)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	47 (4.19)	42 (3.63)	113 (4.23)	8 (3.99)	10 (3.48)
Cardiac disorders	46 (4.10)	46 (3.98)	109 (4.07)	12 (6.02)	15 (5.25)
Renal and urinary disorders	38 (3.38)	36 (3.10)	89 (3.32)	3 (1.50)	9 (3.14)
Reproductive system and breast disorders	31 (2.75)	40 (3.46)	81 (3.02)	6 (2.99)	4 (1.37)
Ear and labyrinth disorders	22 (1.95)	33 (2.85)	69 (2.57)	6 (2.99)	3 (1.03)
Hepatobiliary disorders	23 (2.03)	20 (1.71)	52 (1.93)	7 (3.50)	5 (1.72)

Primary system organ class	Any AIN457 150 mg N=1395 n (IR)	Any AIN457 300 mg N=1410 n (IR)	Any AIN457 dose N=3430 n (IR)	Placebo N=793 n (IR)	Etanercept N=323 n (IR)
Immune system disorders	18 (1.59)	16 (1.37)	44 (1.63)	2 (1.00)	8 (2.78)
Endocrine disorders	6 (0.53)	7 (0.60)	14 (0.51)	1 (0.50)	1 (0.34)
Social circumstances	3 (0.26)	2 (0.17)	6 (0.22)	2 (0.99)	0 (0.00)
Congenital, familial and genetic disorders	1 (0.09)	4 (0.34)	5 (0.18)	0 (0.00)	0 (0.00)
Surgical and medical procedures	1 (0.09)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Pregnancy, puerperium and perinatal conditions	0 (0.00)	3 (0.25)	3 (0.11)	1 (0.50)	0 (0.00)

Primary system organ classes are sorted in descending order of IR in Any AIN457 dose column. * Primary infections and infestations SOC IR=incidence rate per 100 patient-years. For patients with event, exposure time is censored at time of first event.

Infections and Infestations

In pool B induction period, ear-infections, mostly *otitis externa*, were observed in 0.4% in secukinumab 150 mg group, 1.2% of secukinumab 300 mg group, 0% in etanercept group and 0.4% in placebo group. Herpes infections, mainly oral herpes, were observed in 1.0%, 1.2%, 0.3%, and 0.6% respectively.

3 cases of mycobacterial infections, all latent tuberculosis were observed. 1 case was present at baseline in secukinumab and etanercept groups, each. 1 new case was reported in the etanercept group. No further cases were found.

Infections requiring oral or parenteral antimicrobial concomitant treatment in Pool B induction period were more frequently reported in the 300 mg and 150 mg groups than in the placebo group, but there was no difference compared to the etanercept group (11.1% for 300 mg, 9.0% for 150 mg, and 9.9% for etanercept, vs. 7.4% for placebo).

Table 55 Exposure-adjusted incidence of candida infections – Entire treatment period (Pool B: All psoriasis trials – Safety set)

Level 1 Level 2 Preferred term	Any AIN457 150 mg N=1395 n (IR)	Any AIN457 300 mg N=1410 n (IR)	Any AIN457 dose N=3430 n (IR)	Placebo N=793 n (IR)	Etanercept N=323 n (IR)
Based on all AEs					
Infections and infestations (SOC)*	653 (85.29)	704 (91.06)	1640 (91.36)	173 (101.89)	172 (93.68)
Candida infections (HLT)	21 (1.85)	41 (3.55)	69 (2.56)	2 (1.00)	4 (1.37)
Oral candidiasis (PT)	8 (0.70)	22 (1.89)	32 (1.18)	1 (0.50)	0 (0.00)
Vulvovaginal candidiasis (PT)	4 (0.35)	10 (0.85)	14 (0.51)	1 (0.50)	0 (0.00)
Candidiasis (PT)	4 (0.35)	5 (0.43)	9 (0.33)	0 (0.00)	0 (0.00)
Skin candida (PT)	1 (0.09)	1 (0.08)	5 (0.18)	0 (0.00)	1 (0.34)
Intertrigo candida	2 (0.18)	1 (0.08)	4 (0.15)	0 (0.00)	1 (0.34)
Esophageal candidiasis (PT)	1 (0.09)	3 (0.26)	4 (0.15)	0 (0.00)	0 (0.00)
Axillary candidiasis (PT)	1 (0.09)	0 (0.00)	1 (0.04)	0 (0.00)	0 (0.00)
Balanitis candida (PT)	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	0 (0.00)
Genital candidiasis (PT)	0 (0.00)	0 (0.00)	1 (0.04)	0 (0.00)	1 (0.34)
Gastrointestinal candidiasis (PT)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Orophayngeal candidiasis (PT)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Based on SAEs					
Infections and infestations (SOC)*	12 (1.05)	16 (1.36)	40 (1.47)	2 (0.99)	4 (1.37)
Candida infections (HLT)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Risk levels are not mutually exclusive. HLT=high level term; PT=preferred term; SOC=system organ class. * Primary and secondary infections and infestations SOC. Preferred terms are sorted in descending order of frequency in the any AIN457 column. IR=incidence rate per 100 patient-years. For patients with event, exposure time is censored at time of first event.

Candida infections on secukinumab or placebo were mild or moderate in severity, while the gastrointestinal candidiasis reported for etanercept was severe. None were serious or led to study treatment discontinuation. The majority of the Candida infections in the any secukinumab dose group, and also in the any 300 mg group, consisted of oral candidiasis and vulvovaginal candidiasis.

Oesophageal candidiasis was reported in 4 patients, 3 on 300 mg and 1 on 150 mg. Two of these cases were mild and two were moderate in severity. All were managed successfully with antifungal treatment and did not result in any interruption or discontinuation of study treatment.

The overall incidence of opportunistic infections was low and comparable across the treatment groups (0.26, 0.09, 0.50 and 0.34 per 100 patient-years for any 300 mg, any 150 mg, placebo and etanercept). Cytomegaloviral infections were reported in 3 patients (1 on 300 mg, 1 on another secukinumab dose, 1 on placebo), with no difference in the exposure-adjusted rate between the any secukinumab dose group and placebo (0.07 vs. 0.50). None of these infections were serious.

There were no reports of hepatitis reactivation. Hepatitis B infection was reported during the active-treatment period in 2 patients on 150 mg secukinumab who tested negative for hepatitis B at screening.

Herpes viral infections were more frequent with etanercept compared with secukinumab and placebo over 52 weeks after adjusting for exposure (3.81 for etanercept vs. 3.28, 2.93 and 2.49, respectively, for any 300 mg, any 150 mg, and placebo). No cases of disseminated or CNS herpes were reported over 52 weeks. No meaningful difference was observed between the secukinumab doses. Ear infections occurred with a higher exposure-adjusted rate with any 300 mg relative to any 150 mg, which was comparable to placebo and etanercept (3.47 vs. 2.03, 2.00 and 1.71). Otitis externa was the predominant AE contributing to this imbalance (1.63 for any 300 mg vs. 0.97, 0.50 and 0.68 for any 150 mg, placebo and etanercept, respectively).

Major Adverse Cardiovascular Effects

Potential MACE cases in the induction period of Pool A studies were reported for 2 (0.3%) patients in the 300 mg group, and consisted of 1 acute myocardial infarction (in a 60 y male with dyslipidaemia, diabetes, and smoking habit at baseline), and 1 cerebrovascular accident (in a 49 y male with coronary heart disease, previous myocardial infarction and stent insertion, previous TIA, and sickle cell trait).

Potential MACE cases over the entire treatment period were reported for similar proportions of patients on secukinumab and etanercept, which were higher than placebo: 6 (0.4%) for any 300 mg, 5 (0.4%) for any 150 mg and 1 (0.3%) for etanercept vs. 1 (0.1%) for placebo. The MACE PTs were as follows:

- In the any 150 mg group, the 5 events were myocardial infarction, cerebrovascular accident, haemorrhagic stroke, ischemic stroke and moya-moya disease.
- In the any 300 mg group, the 6 events were myocardial infarction (n=2), acute myocardial infarction (n=2) and cerebrovascular accident (n=2).
- In the placebo group, one patient had brain stem haemorrhage.
- In the etanercept group, one patient experienced myocardial infarction.

After adjusting for exposure over the 52 weeks, the incidence per 100 patient-years of potential MACE AEs was similar across the treatment groups (0.51, 0.44, 0.50 and 0.34, respectively, for any 300 mg, any 150 mg, placebo, and etanercept).

Malignancies

The Applicant has summarised that patients with psoriasis may have an increased risk of non-melanoma skin cancers, in particular squamous cell carcinoma associated with psoralen-PUVA-therapy. Increased risk of lymphomas, in particular Hodgkin´s disease has also been observed in psoriasis-patients.

The exposure-adjusted rates of AEs related to malignant or unspecified tumours over the entire treatment period of Pool B revealed a higher incidence for the placebo group compared with the active treatment groups (1.49 for placebo vs. 0.96 for any secukinumab dose and 0.68 for etanercept) and no dose dependency (0.77 for any 300 mg vs. 0.97 for any 150 mg). There were no reports of lymphomas in any treatment group over 52 weeks of all psoriasis trials.

AEs related to skin tumours showed a similar pattern of higher incidence per 100-patient years in the placebo group compared with the secukinumab dose groups and the etanercept group (1.49 for placebo vs. 0.60, 0.70, and 0.34 for any 300 mg, any 150 mg, and etanercept). Both patients with malignant melanoma/malignant melanoma *in situ* were smokers and had prior exposure to phototherapy. Three uncomplicated cases of basal cell carcinoma were reported as resolved upon excision of the lesion. None of the cases led to discontinuation and none was suspected to be related to study treatment by the investigator.

For malignant or unspecific skin tumours, the incidence per 100 patient-years was lower with the any secukinumab dose group than with placebo (0.7 vs. 1.5). There were no reports of lymphoma over 52 weeks across all indications in Pool C trials.

Additional malignancies reported as SAEs were individual cases of colon cancer, renal cancer, pleomorphic adenoma, and testicular cancer.

Immune Reactions and Local tolerability

The incidence of hypersensitivity AEs were comparable between the secukinumab doses and etanercept and lower with placebo, with this difference driven by higher rates of urticaria and eczema. Analysis of 54 cases of urticaria reported across all psoriasis studies did not suggest a link with possible anaphylaxis. All 54 cases of urticaria were non-serious, and the reported symptoms were all mild to moderate in severity, except for 2 cases in which urticaria was reported as severe. The severe case on 300 mg also led to discontinuation of study treatment; no other cases of urticaria caused discontinuation. Only 15 of 54 patients developed urticaria within 2 days of study treatment dosing (13/50 on secukinumab and 2/3 on etanercept), suggesting that the majority of the urticaria cases were not drug-related immediate hypersensitivity events.

In 50 of 54 patients reporting urticaria, there were no associated AEs that suggested anaphylaxis. Whilst no cases of anaphylaxis related to study drug administration have been reported in the psoriasis program, one case was observed on first administration of study drug in Pool C (patient in a study of ankylosing spondylitis). Three cases were accompanied by concurrent angioedema, with a time-to-onset of urticaria from the most recent dose of study treatment of 1 day (A2211, on secukinumab), 5 days (A2309, on placebo) and 7 days (A2211, on secukinumab). A fourth patient (A2302, on secukinumab) who developed urticaria 4 days after the most recent dose of study treatment reported angioedema 249 days after the onset of urticaria. Of those patients on secukinumab, the latency of onset of urticaria in fourth patient indicates this was not an immediate hypersensitivity event, while no action was taken with study treatment in the other two patients, who both continued dosing throughout the maintenance period with no recurrence of urticaria or angioedema.

Immune/administration reactions were more frequent with etanercept than with the two secukinumab doses and placebo, mainly due to more injection site reactions following etanercept administration.

No different patterns of hypersensitivity and injection site reactions were observed for the PFS and AI forms of secukinumab.

There was no increase in hypersensitivity or immune/administration reactions in patients who received the Start of Relapse maintenance dosing regimens (in Study A2304, longer times between consequent injections) compared to patients on 4 week Fixed Interval dosing regimens.

No new events of CNS demyelination were identified, although an SAE of multiple sclerosis was reported for 1 patient in the 150 mg group with a long-standing history (16 years) of multiple sclerosis. The SAE of granulomatosis with polyangiitis was reported in a patient with no relevant medical history, diagnosed after more than 10 months of 300 mg secukinumab dosing on a fixed-interval. Study medication was

temporarily interrupted, but the patient eventually completed the study and continued to be dosed in the extension study. One SAE of pemphigus was reported in patient having received 2 doses of 300 mg secukinumab prior to the SAE (initially presenting on Day 8, with the diagnosis confirmed on Day 29) and then discontinued study treatment as a result of the event.

The incidence of Crohn's disease among psoriasis patients is about 4 times higher than that in control cohorts. The published data have been disappointing regarding the efficacy of targeting IL-17A for patients with Crohn's disease, and worsening of the symptoms of active Crohn's disease was observed in patients receiving either active treatment or placebo in two phase II studies.

Pre-filled syringes: The incidence of immune and administration reactions NMQ was highest in the secukinumab 300 mg group (9/59, 15.3%) compared with placebo (5/59, 8.5%) and secukinumab 150 mg group (6/59, 10.2%). Administration site reactions (HLGT) were rare and were reported by one patient in each treatment group (1 injection site pain in the 150 mg group, 1 injection site rash in the 300 mg group, and 1 injection site pain in the placebo group); all were mild, considered related to study drug, and did not lead to study treatment discontinuation.

Auto-injector pen: A broad search for immune and administration reactions NMQ yielded the highest incidence in the 300 mg group (21.7%, 13/60), with a rate of 4.9% (3/61) in the 150 mg group and 16.4% (10/61) in the placebo group. A search for administration site reactions (high-level group term) yielded 3 cases each in the 300 mg and placebo groups: injection site bruising, injection site pain, and injection site erythema in the 300 mg group; injection site warmth and injection site hematoma (2 cases) in the placebo group. All cases were mild or moderate and non-serious, and did not lead to treatment discontinuation.

Vital Signs and ECGs

Secukinumab did not appear to have any clinically significant effects on the cardiovascular functions (blood pressure, heart rate, QT-interval).

Hepatotoxicity

The available safety data do not suggest the potential for severe drug-induced liver injury (DILI) from secukinumab treatment. Despite small imbalances in the incidence of mild hepatic transaminase elevations vs. placebo, secukinumab at both doses was not associated with a higher rate of combined elevations in hepatic transaminases and serum bilirubin. Rather, incidence rates of AEs related to liver enzyme abnormalities and hepatic disorders were comparable between secukinumab and etanercept. Although liver-related SAEs were only observed with secukinumab, the rates were low and clinical review of these cases indicates that they were not reflective of severe or serious DILI attributable to secukinumab and without other identified causes. Thus, in the absence of severe DILI cases in a premarketing safety database that included 3430 patients exposed to secukinumab, the rate of potential Hy's Law cases is estimated to be less than 1/1000 patients by the binomial distribution "Rule of 3," which correlates to an expected rate of severe DILI of less than 1/10,000 in the post-marketing setting.

Renal Effects

Across the pool B studies, the incidence rate of AE SOC "renal and urinary disorders" in the pooled secukinumab patients was of the same magnitude during the entire treatment period than in etanercept patients (3.32 per 100 patient-years and 3.14 per 100 patient-years, respectively), but higher than in patients on placebo (1.50 per 100 patient-years). Similarly, the incidence rate of SAEs in this SOC category were 0.33, 0.34 and 0 per 100-patient years in secukinumab, etanercept and placebo-groups, respectively.

Adverse Events and SmPC

ADRs pertaining to pre-specified terms were identified in Pool A in the target indication. Exposure-adjusted data from Pool B were also used to evaluate the consistency of the data with Pool A. Rare events such as malignancies, MACE, Crohn's disease and deaths were evaluated in Pool C across all indications.

Table 56 Percentage of patients with adverse drug reactions (Pool A: pivotal placebo-controlled psoriasis studies – Safety set)

System Organ Class		Cosentyx		Placebo (N=694) n (%)
		300 mg (N=690) n (%)	150 mg (N=692) n (%)	
Infections and infestations				
Very common	Upper respiratory tract infections	117 (17.0)	129 (18.6)	72 (10.4)
Common	Oral herpes	9 (1.3)	1 (0.1)	2 (0.3)
Uncommon	Oral candidiasis	4 (0.6)	1 (0.1)	1 (0.1)
Uncommon	Tinea pedis	5 (0.7)	5 (0.7)	0 (0)
Uncommon	Otitis externa	5 (0.7)	3 (0.4)	0 (0)
Blood and lymphatic system disorders				
Uncommon	Neutropenia	2 (0.3)	1 (0.1)	0 (0)
Eye disorders				
Uncommon	Conjunctivitis	5 (0.7)	2 (0.3)	1 (0.1)
Respiratory, thoracic and mediastinal disorders				
Common	Rhinorrhoea	8 (1.2)	2 (0.3)	1 (0.1)
Gastrointestinal disorders				
Common	Diarrhoea	28 (4.1)	18 (2.6)	10 (1.4)
Skin and subcutaneous tissue disorders				
Common	Urticaria	4 (0.6)	8 (1.2)	1 (0.1)

[1)] Placebo-controlled clinical studies (phase III) in plaque psoriasis patients exposed to 300 mg, 150 mg or placebo up to 12 weeks treatment duration

Note: A single case of anaphylactic reaction was observed in a non-psoriasis study as outlined below.

ADR frequencies are based upon the highest percentage rate seen in any of the secukinumab groups. Very common = ≥1/10; common = ≥1/100 to <1/10; uncommon = ≥1/1000 to <1/100.

Serious adverse event and deaths

Deaths

In psoriasis there were a total of 6 deaths occurred in patients participating in psoriasis clinical studies. Five deaths were reported in the post-induction period, 2 off-treatment deaths for 150 mg secukinumab, 1 patient who switched from placebo to secukinumab 300 mg maintenance treatment, 1 off-treatment death for a placebo patient. In addition, one patient died during the screening phase. Causes of these deaths could be attributed to concomitant morbidity and seemed not be related to use of secukinumab.

Serious Adverse Events

Induction period

Most frequent SAEs (>=0.10% in any group) by preferred term – Induction period (Pool B: All psoriasis trials – Safety set) are described in Table 57.

Table 57 SAEs by primary system organ class – Induction period (Pool B: All psoriasis trials – Safety set)

Primary system organ class	AIN457 150 mg N=1174 n (%)	AIN457 300 mg N=1173 n (%)	Any AIN457 dose N=2877 n (%)	Placebo N=793 n (%)	Etanercept N=323 n (%)
-Any SAE	22 (1.87)	23 (1.96)	62 (2.16)	13 (1.6)	3 (0.9)
Injury, poisoning and procedural complications	3 (0.26)	5 (0.43)	11 (0.38)	3 (0.4)	0 (0.0)
Cardiac disorders	4 (0.34)	2 (0.17)	10 (0.35)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	4 (0.34)	2 (0.17)	8 (0.28)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant…	3 (0.26)	3 (0.26)	7 (0.24)	0 (0.0)	0 (0.0)
Infections and infestations	2 (0.17)	1 (0.09)	6 (0.21)	2 (0.3)	0 (0.0)
Nervous system disorders	1 (0.09)	3 (0.26)	5 (0.17)	0 (0.0)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	4 (0.34)	0 (0.00)	5 (0.17)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	2 (0.17)	1 (0.09)	5 (0.17)	5 (0.6)	0 (0.0)
Hepatobiliary disorders	1 (0.09)	2 (0.17)	3 (0.10)	0 (0.0)	1 (0.3)
Psychiatric disorders	3 (0.26)	0 (0.00)	3 (0.10)	2 (0.3)	0 (0.0)
Vascular disorders	2 (0.17)	0 (0.00)	3 (0.10)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	2 (0.17)	0 (0.00)	2 (0.07)	1 (0.1)	0 (0.0)
Metabolism and nutrition disorders	1 (0.09)	1 (0.09)	2 (0.07)	0 (0.0)	0 (0.0)
Renal and urinary disorders	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.0)	1 (0.3)

Primary system organ class	AIN457 150 mg N=1174 n (%)	AIN457 300 mg N=1173 n (%)	Any AIN457 dose N=2877 n (%)	Placebo N=793 n (%)	Etanercept N=323 n (%)
Investigations	1 (0.09)	0 (0.00)	1 (0.03)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.00)	1 (0.09)	1 (0.03)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	0 (0.00)	1 (0.09)	1 (0.03)	0 (0.0)	0 (0.0)
Social circumstances	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.1)	0 (0.0)

Treatment-emergent SAEs are summarized in this table. Primary SOCs are sorted in descending order of frequency in any AIN457 group.

Entire treatment period

Exposure adjusted incidence of the most frequent (>=0.10 per 100 patient years in any group) SAEs by preferred term – Entire treatment period (Pool B: All psoriasis trials – Safety set) are described in Table 58.

Table 58 Exposure adjusted incidence of the most frequent (>=0.10 per 100 patient years in any group) SAEs by preferred term – Entire treatment period (Pool B: All psoriasis trials – Safety set)

Preferred Term	Any AIN457 150 mg N=1395 n (IR)	Any AIN457 300 mg N=1410 n (IR)	Any AIN457 dose N=3430 n (IR)	Placebo N=793 n (IR)	Etanercept N=323 n (IR)
-Any SAE	76 (6.80)	85 (7.42)	207 (7.80)	15 (7.54)	20 (7.01)
Pneumonia	3 (0.26)	3 (0.25)	6 (0.22)	0 (0.00)	0 (0.00)
Angina pectoris	2 (0.18)	1 (0.08)	5 (0.18)	0 (0.00)	0 (0.00)
Cellulitis	2 (0.18)	1 (0.08)	5 (0.18)	2 (0.99)	1 (0.34)
Abscess bacterial	3 (0.26)	0 (0.00)	4 (0.15)	0 (0.00)	0 (0.00)
Appendicitis	1 (0.09)	2 (0.17)	4 (0.15)	0 (0.00)	0 (0.00)
Coronary artery disease	1 (0.09)	1 (0.08)	4 (0.15)	0 (0.00)	0 (0.00)
Hypertensive crisis	1 (0.09)	2 (0.17)	4 (0.15)	0 (0.00)	0 (0.00)
Psoriasis	1 (0.09)	1 (0.08)	4 (0.15)	4 (1.99)	1 (0.34)
Sciatica	2 (0.18)	2 (0.17)	4 (0.15)	0 (0.00)	0 (0.00)
Angina unstable	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Arthralgia	0 (0.00)	2 (0.17)	3 (0.11)	0 (0.00)	1 (0.34)
Back pain	1 (0.09)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)

Preferred Term	Any AIN457 150 mg N=1395 n (IR)	Any AIN457 300 mg N=1410 n (IR)	Any AIN457 dose N=3430 n (IR)	Placebo N=793 n (IR)	Etanercept N=323 n (IR)
Basal cell carcinoma	1 (0.09)	2 (0.17)	3 (0.11)	0 (0.00)	0 (0.00)
Cerebrovascular accident	1 (0.09)	2 (0.17)	3 (0.11)	0 (0.00)	0 (0.00)
Cholelithiasis	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Colitis ulcerative	1 (0.09)	2 (0.17)	3 (0.11)	0 (0.00)	0 (0.00)
Crohn's disease	2 (0.18)	0 (0.00)	3 (0.11)	0 (0.00)	0 (0.00)
Headache	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Nephrolithiasis	0 (0.00)	2 (0.17)	3 (0.11)	0 (0.00)	0 (0.00)
Osteoarthritis	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Pancreatitis	1 (0.09)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Syncope	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Acute myocardial infarction	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.00)	0 (0.00)
Cholecystitis	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Concussion	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.00)	0 (0.00)
Hypoaesthesia	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Myocardial infarction	1 (0.09)	1 (0.08)	2 (0.07)	0 (0.00)	1 (0.34)
Overdose	1 (0.09)	1 (0.08)	2 (0.07)	1 (0.50)	0 (0.00)
Palpitations	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Pulmonary edema	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Rib fracture	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.00)	0 (0.00)
Tendon rupture	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.00)	0 (0.00)
Vomiting	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Acute tonsillitis	0 (0.00)	0 (0.00)	1 (0.04)	0 (0.00)	1 (0.34)
Alcohol withdrawal syndrome	0 (0.00)	1 (0.08)	1 (0.04)	1 (0.50)	0 (0.00)
Arteriosclerosis coronary artery	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	1 (0.34)
Bursitis	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	1 (0.34)
Cholecystitis acute	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	1 (0.34)
Ligament rupture	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	1 (0.34)
Non-cardiac chest pain	1 (0.09)	0 (0.00)	1 (0.04)	1 (0.50)	0 (0.00)
Panic attack	1 (0.09)	0 (0.00)	1 (0.04)	1 (0.50)	0 (0.00)

Preferred Term	Any AIN457 150 mg N=1395 n (IR)	Any AIN457 300 mg N=1410 n (IR)	Any AIN457 dose N=3430 n (IR)	Placebo N=793 n (IR)	Etanercept N=323 n (IR)
Radius fracture	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	1 (0.34)
Transient ischemic attack	0 (0.00)	0 (0.00)	1 (0.04)	1 (0.50)	2 (0.68)
Abstains from alcohol	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Alcohol poisoning	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Benign neoplasm of skin	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Calculus urethral	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Cardiac arrest	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Clavicle fracture	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Dermatitis exfoliative	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Diverticulitis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Interstitial lung disease	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Major depression	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Mitral valve incompetence	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Osteonecrosis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Psoriatic arthropathy	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Rotator cuff syndrome	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Tendon injury	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Thyrotoxic crisis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Urinary tract infection	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
VII nerve paralysis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)

Treatment-emergent SAEs are summarized in this table. Preferred terms are sorted in descending order of frequency in the any AIN457 dose. IR=incidence rate per 100 patient years. For patients with event, exposure time is censored at time of first event.

During the Induction period in Pool B, there were 10 cardiac disorders reported as SAEs in the “Any secukinumab dose” group, compared to none in the placebo- and etanercept-groups. MACEs can occur early in treatment following change in cytokine balance. However, only two MACEs were reported from pool A induction period, see section 4.3.5., which is reassuring.

Laboratory findings

Placebo-controlled pivotal studies (A2302, A2303, A2308 and A2309)

There was a significant decrease in total leukocytes and neutrophils in the pooled secukinumab group during all pivotal studies. This effect was probably due to the pharmacodynamic effects of the drug. There was also a modest decrease observed in platelet level in the secukinumab groups. The decreases observed in mean leukocyte, neutrophil and platelet levels were somewhat more prominent in the

etanercept group compared to secukinumab patients (study A2303). The proportion of grade 2 or more severe leukopenias or neutropenias was somewhat lower in the pooled secukinumab group compared to etanercept in study A2303 (3.9%vs. 6.3%). Within the placebo-controlled pivotal studies, there were altogether five hematology abnormality cases of SAEs or AEs leading to permanent study drug discontinuation associated with secukinumab use (one grade 1 leukopenia, one grade 3 neutropenia, three cases of thrombocytopenia), and 2 cases associated with etanercept use (two cases of neutropenia). Taking into account the exposure rates to secukinumab and etanercept in these studies, the proportion of the cases in the secukinumab group is not essentially different from the etanercept group.

The impact of the other trials from safety pool B on laboratory findings

On the whole, the laboratory findings of the other pool B studies were in accordance with the placebo-controlled pivotal studies and do not change the safety profile of secukinumab.

Within all phase II and III psoriasis trials included in the safety pool B, there were 2 cases of neutropenia (severity: grade 2 and grade 3) leading to permanent discontinuation of study drug in secukinumab patients. There were 2 corresponding neutropenia cases in etanercept group and none in the placebo group.

Safety in special populations

Age

No meaningful differences can be observed in patient groups <65 and ≥65 years regarding the AEs or SAEs (see Table 59).

Table 59 Exposure-adjusted incidence of AEs by age – Entire treatment period (Pool B: All psoriasis trials – Safety set)

Table 2-9 Absolute and relative frequencies for secukinumab ADRs and selected adverse events, by treatment group and age category (pivotal psoriasis placebo-controlled studies – Induction period)[1]

	AIN457 150 mg			AIN457 300 mg		
MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)
Total ADRs	148/634 (23.3)	4/ 48 (8.3)	2/ 10 (20.0)	160/642 (24.9)	5/ 42 (11.9)	1/ 6 (16.7)
Serious ADRs – Total	0/634 (0.0)	0/ 48 (0.0)	0/ 10 (0.0)	0/642 (0.0)	0/ 42 (0.0)	0/ 6 (0.0)
- Fatal	0/634 (0.0)	0/ 48 (0.0)	0/ 10 (0.0)	0/642 (0.0)	0/ 42 (0.0)	0/ 6 (0.0)
- Hospitalization/prolong existing hospitalization	0/634 (0.0)	0/ 48 (0.0)	0/ 10 (0.0)	0/642 (0.0)	0/ 42 (0.0)	0/ 6 (0.0)
- Life-threatening	0/634 (0.0)	0/ 48 (0.0)	0/ 10 (0.0)	0/642 (0.0)	0/ 42 (0.0)	0/ 6 (0.0)
- Disability/incapacity	0/634 (0.0)	0/ 48 (0.0)	0/ 10 (0.0)	0/642 (0.0)	0/ 42 (0.0)	0/ 6 (0.0)
- Other (medically significant)	0/634 (0.0)	0/ 48 (0.0)	0/ 10 (0.0)	0/642 (0.0)	0/ 42 (0.0)	0/ 6 (0.0)
AE leading to drop-out	6/634 (0.9)	2/ 48 (4.2)	0/ 10 (0.0)	6/642 (0.9)	3/ 42 (7.1)	0/ 6 (0.0)
Psychiatric disorders (SOC)	11/634 (1.7)	1/ 48 (2.1)	0/ 10 (0.0)	15/642 (2.3)	0/ 42 (0.0)	0/ 6 (0.0)
Nervous system disorders (SOC)	54/634 (8.5)	4/ 48 (8.3)	1/ 10 (10.0)	65/642 (10.1)	3/ 42 (7.1)	0/ 6 (0.0)
Accidents and injuries (SMQ)	23/634 (3.6)	4/ 48 (8.3)	1/ 10 (10.0)	30/642 (4.7)	1/ 42 (2.4)	0/ 6 (0.0)
Cardiac disorders (SOC)	5/634 (0.8)	3/ 48 (6.3)	0/ 10 (0.0)	4/642 (0.6)	0/ 42 (0.0)	0/ 6 (0.0)
Vascular disorders (SOC)	24/634 (3.8)	4/ 48 (8.3)	0/ 10 (0.0)	7/642 (1.1)	2/ 42 (4.8)	0/ 6 (0.0)
Cerebrovascular disorders (SMQ)	1/634 (0.2)	0/ 48 (0.0)	0/ 10 (0.0)	1/642 (0.2)	0/ 42 (0.0)	0/ 6 (0.0)
Infections and infestations (SOC)	194/634 (30.6)	7/ 48 (14.6)	2/ 10 (20.0)	186/642 (29.0)	7/ 42 (16.7)	1/ 6 (16.7)
Quality of life decreased (PT)	0/634 (0.0)	0/ 48 (0.0)	0/ 10 (0.0)	0/642 (0.0)	0/ 42 (0.0)	0/ 6 (0.0)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	4/634 (0.6)	0/ 48 (0.0)	0/ 10 (0.0)	7/642 (1.1)	0/ 42 (0.0)	0/ 6 (0.0)

	Placebo			Etanercept		
MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)
Total ADRs	81/651 (12.4)	2/ 33 (6.1)	1/ 10 (10.0)	59/305 (19.3)	3/ 15 (20.0)	1/ 3 (33.3)
Serious ADRs – Total	0/651 (0.0)	0/ 33 (0.0)	0/ 10 (0.0)	0/305 (0.0)	0/ 15 (0.0)	0/ 3 (0.0)
- Fatal	0/651 (0.0)	0/ 33 (0.0)	0/ 10 (0.0)	0/305 (0.0)	0/ 15 (0.0)	0/ 3 (0.0)
- Hospitalization/prolong existing hospitalization	0/651 (0.0)	0/ 33 (0.0)	0/ 10 (0.0)	0/305 (0.0)	0/ 15 (0.0)	0/ 3 (0.0)
- Life-threatening	0/651 (0.0)	0/ 33 (0.0)	0/ 10 (0.0)	0/305 (0.0)	0/ 15 (0.0)	0/ 3 (0.0)
- Disability/incapacity	0/651 (0.0)	0/ 33 (0.0)	0/ 10 (0.0)	0/305 (0.0)	0/ 15 (0.0)	0/ 3 (0.0)
- Other (medically significant)	0/651 (0.0)	0/ 33 (0.0)	0/ 10 (0.0)	0/305 (0.0)	0/ 15 (0.0)	0/ 3 (0.0)
AE leading to drop-out	9/651 (1.4)	0/ 33 (0.0)	0/ 10 (0.0)	5/305 (1.6)	1/ 15 (6.7)	0/ 3 (0.0)
Psychiatric disorders (SOC)	15/651 (2.3)	0/ 33 (0.0)	0/ 10 (0.0)	5/305 (1.6)	1/ 15 (6.7)	0/ 3 (0.0)
Nervous system disorders (SOC)	50/651 (7.7)	0/ 33 (0.0)	0/ 10 (0.0)	26/305 (8.5)	3/ 15 (20.0)	0/ 3 (0.0)
Accidents and injuries (SMQ)	20/651 (3.1)	2/ 33 (6.1)	0/ 10 (0.0)	9/305 (3.0)	1/ 15 (6.7)	0/ 3 (0.0)
Cardiac disorders (SOC)	11/651 (1.7)	1/ 33 (3.0)	0/ 10 (0.0)	5/305 (1.6)	2/ 15 (13.3)	0/ 3 (0.0)
Vascular disorders (SOC)	15/651 (2.3)	1/ 33 (3.0)	0/ 10 (0.0)	6/305 (2.0)	1/ 15 (6.7)	0/ 3 (0.0)
Cerebrovascular disorders (SMQ)	0/651 (0.0)	0/ 33 (0.0)	0/ 10 (0.0)	1/305 (0.3)	1/ 15 (6.7)	0/ 3 (0.0)
Infections and infestations (SOC)	127/651 (19.5)	3/ 33 (9.1)	1/ 10 (10.0)	73/305 (23.9)	4/ 15 (26.7)	2/ 3 (66.7)
Quality of life decreased (PT)	0/651 (0.0)	0/ 33 (0.0)	0/ 10 (0.0)	0/305 (0.0)	0/ 15 (0.0)	0/ 3 (0.0)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	5/651 (0.8)	0/ 33 (0.0)	0/ 10 (0.0)	2/305 (0.7)	0/ 15 (0.0)	0/ 3 (0.0)

[1] Cumulative number over all indications in the clinical trial programme and percentage over the age group.
Source: Table A75 1-3

Caucasians and Asians constituted more than 90% of the population and the AE profile in the induction period by race was similar to that observed in the overall population. No black patients received etanercept. There were no race-related trends overall or in the most frequently affected SOC of infections and infestations compared to the overall population.

No clinically significant differences in the AE- or SAE-profiles or -rates were observed between those secukinumab patients who had received previous systemic or biologic psoriasis treatment and those who had not.

The subgroup analyses according to renal or hepatic function/condition are not needed since clinically significant renal and hepatic conditions were excluded from psoriasis trials. In addition, according to the PK data, secukinumab is not metabolised by the liver or excreted by the kidneys.

Immunological events

Collectively, among the 3627 patients evaluated for ADA across the specified phase II and III trials (263 in A2211E1 and 3364 across all phase III trials), a total of 27 (0.7%) showed treatment-emergent ADA, with neutralizing antibodies detected in one-third of these cases (9/27).

Non-treatment emergent ADA was also observed in phase III trials. A total of 56/3364 (1.7%) secukinumab naive patients were ADA positive at baseline (n=47) or at a post-baseline time point without secukinumab exposure in the placebo (n=5) or etanercept (n=4) groups. In addition, 7/2842 (0.2%) patients tested positive for ADA at baseline and had at least one positive ADA sample following treatment with secukinumab (see Table 60).

Table 60 Overview of patients with treatment-emergent anti-drug antibodies (ADA) in phase II long-term study AIN457A2211E1

Treatment arm	Prior biologics	ADA[1] (titer) / N-Ab	AEs possibly IG-related[2] (Day of onset)	PK[3]
150 mg SoR	none	W61 (2.51) / Yes	none	n.a.
150 mg SoR	none	W13 (1.43) / Yes	seasonal allergy, nausea post injection	n.a.
150 mg FI q12w	efalizumab	W13 (1.40) / No W25 (1.29) / No W37 (1.95) / Yes	dermatitis	normal
150 mg OL q4w	adalimumab	W49 (none)[4] / No	none	normal
150 mg OL q4w	none	W49 (2.22) / Yes W61 (none) / Yes	none	normal
150 mg OL q4w	etanercept	EoS (2.93) / Yes	none	n.a.
150 mg OL q4w	adalimumab efalizumab etanercept	EoS (3.12) / Yes	none	normal
150 mg FI q12w	none	EoS (76.7) / No	none	normal

ADA=anti-drug antibodies; EoS =end of study; FI=fixed interval dosing; IG=immunogenicity; N-Ab=neutralizing antibodies; n.a.=not applicable; OL =open label; PK=pharmacokinetics; SoR=start of relapse; W=Week;[1] Only positive ADA results at the respective study week are shown;[2] IG-related AEs refers to preferred terms in the Hypersensitivity SMQ;[3] Normal PK was defined as: concentrations at various time points for individual patients that fit into the observed range for all patients without ADA formation for the given dosing regimen;[4] Test was positive in the screening and confirmatory assay but was negative in the titer assay

The presence of anti-secukinumab antibodies was scarce with the analytical method used, suggesting that the potential risk of immunogenicity is low.

Non-treatment emergent ADA was also observed in phase III trials. A total of 56/3364 (1.7%) secukinumab naive patients were ADA positive at baseline (n=47) or at a post-baseline time point without secukinumab exposure in the placebo (n=5) or etanercept (n=4) groups. Of the 74 patients who tested positive for ADA at any time point in either phase II or III trials, 52 (70.3%) reverted to a seronegative state at a later time point with no detectable ADA, with 50 of these patients reverting while on treatment.

Loss of efficacy was systematically assessed in phase III studies. The development of treatment-emergent ADA was not associated with a loss of PASI 75 response or a loss of efficacy. Although not systematically assessed for loss of efficacy, of the 8 patients with treatment-emergent ADA in the phase II extension study, there was no discernible pattern of changes in PASI score in these patients.

Safety related to drug-drug interactions and other interactions

The drug-drug interactions between monoclonal antibodies and low molecular weight drugs were not investigated in vitro.

Interactions *In vivo* were not investigated in a systematic manner*:*

Effect of co-medications on secukinumab:

- The drug-drug interactions between secukinumab and low molecular weight drugs were not investigated, because hepatic metabolizing enzymes (e.g. CYPs and UGTs) are not presumed to be involved in secukinumab elimination.
- In a dose-finding study in RA patients with secukinumab on the basis of the PK results methotrexate does not seem to have an impact on the disposition of secukinumab, however, no clear data has been presented. CYP inhibitors and inducers are unlikely to affect secukinumab exposure-response relationship.

Effect of secukinumab on other drugs:

- Potential DDI between secukinumab, a monoclonal IgG1 Ab, and small drug molecules is expected to be low but treatment with cytokines or cytokine modulators can interfere with CYP regulation although difficult to predict from in vitro.

Vaccines

Study A2224 was designed to explore a possible interference of the drug with the effectiveness of 2 widely used vaccines – influenza and meningitis. Vaccinations were given after 2 weeks of secukinumab 150 mg administration. Responses in antibody titer ($\geq$4-fold increase) to influenza and meningococcal vaccination were similar in secukinumab exposed and control healthy volunteers at 4 weeks post-vaccination; response rates of ~80% in both groups were consistent with results of previous published studies. These results suggest that secukinumab as a single 150 mg s.c. dose does not significantly impair the generation of protective antibody levels with influenza and *meningococcus* vaccines (refer also to section *Pharmacodynamics*).

No study has been performed to evaluate the concurrent use of live vaccines with secukinumab.

Discontinuation due to adverse events

Table 61 The most frequent (>=0.20% in any group) AEs causing discontinuation by preferred term – Entire treatment period (Pool B: All psoriasis trials – Safety set) are described in Table 61

Preferred term	Any AIN457 150 mg N=1395 n (%)	Any AIN457 300 mg N=1410 n (%)	Any AIN457 dose N=3430 n (%)	Placebo N=793 n (%)	Etanercept N=323 n (%)
-Any AE causing discontinuation	43 (3.08)	46 (3.26)	118 (3.44)	11 (1.4)	12 (3.7)
Psoriasis	2 (0.14)	2 (0.14)	8 (0.23)	6 (0.8)	2 (0.6)
Psoriatic arthropathy	4 (0.29)	0 (0.00)	6 (0.17)	0 (0.0)	0 (0.0)
Thrombocytopenia	3 (0.22)	1 (0.07)	4 (0.12)	0 (0.0)	0 (0.0)
Colitis ulcerative	2 (0.14)	1 (0.07)	3 (0.09)	0 (0.0)	1 (0.3)
Gamma-glutamyltransferase increased	3 (0.22)	0 (0.00)	3 (0.09)	0 (0.0)	0 (0.0)
Hepatic enzyme increased	1 (0.07)	2 (0.14)	3 (0.09)	0 (0.0)	1 (0.3)
Neutropenia	1 (0.07)	1 (0.07)	2 (0.06)	0 (0.0)	2 (0.6)
Interstitial lung disease	0 (0.00)	1 (0.07)	1 (0.03)	0 (0.0)	1 (0.3)
Arteriosclerosis coronary artery	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.0)	1 (0.3)
Injection site edema	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.0)	1 (0.3)
Injection site rash	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.0)	1 (0.3)
Myocardial infarction	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.0)	1 (0.3)
Transient ischemic attack	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.0)	1 (0.3)
VIIth nerve paralysis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.0)	1 (0.3)

Preferred terms are sorted in descending order of frequency in any AIN457 group.

2.6.1. Discussion on clinical safety

For analyses of safety data, the applicant has created three pooled safety datasets. Pool A (n=2399) contains the induction period (12-week) safety data from the pivotal efficacy studies A2302 (secukinumab 150 mg and 300 mg sc, or placebo), A2303 (secukinumab 150 mg and 300 mg sc, etanercept sc, or placebo), A2308 (secukinumab 150 mg and 300 mg sc, placebo in pre-filled syringe), and A2309 (secukinumab 150 mg and 300 mg sc, placebo in auto-injector pen). Pool B (n=3993) contains the safety data from 10 phase II/III trials in psoriasis divided to induction period (12 weeks) and entire treatment period (up to 52 weeks). Pool C (n=5044) contains the safety data from 34 out of 39 phase I/II/III trials in psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, Crohn´s disease, different forms of uveitis, and in dry-eye syndrome.

These datasets have a rational basis and the pooled reporting is consistent with that from the separate studies. The ICH E1 safety exposure requirements of >1500 patients exposed, 300 to 600 for 6 months, >100 for 1 year are well exceeded. Regrouping of subjects to three pools described above has been done with rational considerations to the most part. In pool A the number of etanercept recipients was small compared to secukinumab and placebo recipients (n=327 out of 2399 patients). In pool B the number of placebo recipients after 12 weeks induction period was low due to intensive re-randomization of the non-responders or partial responders from the placebo-groups to active-treatment groups.

Pool B contains the most relevant populations (and demographics of the patients), investigated for the psoriasis-indication. Caucasians are the largest population in the study groups. Mean age of patients was around 45 years, 6 to 7% of the patients were >65 years and around 1% >75 years. 2/3 of the patients were males. Pool A and Pool B induction period patients were balanced for the demographic factors in the secukinumab 150 mg and 300 mg, etanercept, and placebo groups. In pool B maintenance period, representation of patients over 65 years of age in the placebo groups was small, due to small number of patients receiving placebo (n=37) after re-randomization of patients receiving placebo to active medications on week 13 of the trials.

For the induction periods, the absolute numbers and percentages of the AEs were reported. For the entire treatment periods, exposure adjusted incidence rates were calculated as well. This is important, because number of patients in the secukinumab groups exceeded significantly the number of patients receiving etanercept, and similarly the number of patients receiving placebo after 12 weeks. Estimates of the adverse drug reactions can be performed in the most reliable way from the induction period safety data, complementing it with findings of significant adverse reactions observed throughout the studies and over the entire time course.

In the psoriasis indication the phase II and III studies involve subjects of male and female patients > 18 years of age with moderate to severe plaque psoriasis, poorly controlled by topical treatments, systemic treatments (either non-biologic or biologic), or phototherapy. 20% of the subjects had concurrent psoriatic arthritis. The inclusion and exclusion criteria did not restrict the upper age limit, and allowed inclusion of patients with latent tuberculosis, active ongoing cardiovascular or cerebrovascular disease (unless severely progressive or uncontrolled like significant hypertension or congestive heart failure; heart attacks more than 26 weeks prior to inclusion allowed), history of basal cell carcinoma or actinic keratosis (treated and no recurrence in 12 weeks before trial), carcinoma in situ of cervix or colon polyps (must have been removed), and all other previous malignancies (with 5 years period remission free), or Crohn´s disease.

Demographic characteristics, baseline morbidity and co-morbidity, as well as use of concomitant medications were well balanced to the most part between the study groups, throughout the studies. Higher baseline rates of hypertension in the secukinumab 150 mg and 300 mg patients were observed. Higher baseline rates of diabetes, stable coronary heart disease/myocardial infarctions and uncomplicated diabetes were observed in secukinumab-patients. Despite the bias against secukinumab in some background medical conditions, the occurrence of MACE was low and the exposure adjusted incidence was comparable for secukinumab and placebo over the entire treatment period which suggests secukinumab does not confer a risk for MACE.

In pool A, representing the first 12 weeks of treatment in the pivotal efficacy studies, AEs mainly infections and infestations, were more common in the secukinumab-patients compared to placebo-patients, but occurred at similar rate compared to etanercept-patients. A slightly elevated incidence of GI-disorders, eye-disorders, and respiratory system disorders was seen in the secukinumab 300 mg -treated patients compared to rest of the patients. Reproductive system disorders (dysmenorrhea, menorrhagia, and metrorrhagia) were more common in secukinumab-treated patients in

the pivotal trials (pool A). Blood and lymphatic system -disorders as well as renal and urinary disorders (apart from nephrolithiasis, see below) occurred at similar rates in all secukinumab- and etanercept-groups, slightly more than in placebo-group. Administration site conditions were more common in patients receiving etanercept. Immune system disorders including seasonal allergy and hypersensitivity were also more common in etanercept-patients, but were also more frequently reported in secukinumab-treated patients compared to placebo-patients. Looking at PTs, there is no clear dose-dependence for most of the AEs related to secukinumab-doses. The upper respiratory tract infections were more common in secukinumab patients, similarly to candida-infections, oral herpes infections, external otitis, and conjunctivitis, of which the last four PTs also displayed some dose-dependence.

The AE profiles of pool A and pool B induction period closely resembled each other. The major finding in the entire pool B dataset is the disappearance of the difference in the exposure adjusted incidence rate of infections and infestations between all active treatment and placebo group seen during the induction period. Incidences of oral herpes, oral candidiasis, and otitis externa were slightly higher in secukinumab 300 mg patients compared to 150 mg patients. Oral herpes and urinary tract infections were more common in the etanercept-patients. Blood and lymphatic system disorders were more common in the etanercept-patients compared to secukinumab-patients. Administration site conditions (injection site erythema) and immune system disorders (seasonal allergy, hypersensitivity including pyrexia) were also more common in the etanercept-patients.

Comparison of the two maintenance regimens (4 week fixed intervals vs. start of relapse, study A2304) show that there were fewer AEs related to GI-system, blood and lymphatics, and eye SOCs, as well as PTs pharyngitis and bronchitis, in the Start of Relapse -group with smaller secukinumab exposure. The smaller exposure, however, was adversely reflected in the efficacy.

Nine (9) pregnancies were reported from secukinumab psoriasis studies that led to discontinuation from the study. 6 abortions were carried out and 3 babies were delivered normally. None of the congenital defects reported were associated with these pregnancies as they consisted of findings and diagnoses in the adult study patients. A close follow-up of the three babies born is of uttermost importance. Although the preclinical data is reassuring, the currently available human data is inadequate and therefore as a precautionary measure, it is preferable to avoid the use of Cosentyx in pregnancy (as described in the product information and the RMP).

According to the Applicant and the scientific literature, the Candida infections could be expected as a “pharmacodynamic” consequence related to IL-17 blockade. Similarly, concern about an increased risk of staphylococcal skin infections and mycobacterial infections has been raised. A significant cluster of oral, vulvovaginal, and skin candidiasis were reported from the patients having received secukinumab. Four cases of esophageal candidiasis were observed as well. All of these were treatable and did not result in discontinuations in the studies. It is reassuring to observe that there have not been cases of serious, systemic fungal infections in the studies, attributable to use of secukinumab (no differences in the rates between the study treatments).

No increase was observed in the rate of mycobacterial or serious opportunistic infections. Regarding tuberculosis, the inclusion criteria specified that patients with latent tuberculosis could be included in the clinical studies with secukinumab (if adequately treated for their TB infection). Prior to study start, 27 patients on secukinumab had a past history of either pulmonary tuberculosis, latent tuberculosis infection or a positive tuberculosis test. Additionally, during screening in Phase 3 trials 105 patients were diagnosed with latent TB and received treatment with secukinumab for approximately one year. None of these patients experienced a reactivation of the tuberculosis infection. The applicant has included a

contra-indication and warning in the product information regarding active infection (e.g. active tuberculosis) which was agreed by the CHMP.

The incidences of MACEs were similar in the etanercept group and both dose level groups of secukinumab. Slightly elevated rates were observed compared to placebo group (see discussion about SAEs below). There is no implication that secukinumab would predispose the patients to serious cardiovascular complications during the induction phase. Secukinumab did not appear to have any clinically significant effects on the cardiovascular functions (heart rate, or QT-interval). No cases of Torsade de pointes/QT prolongation were reported as an AE in the induction period of either Pool A or Pool B, or in the entire treatment period of Pool B. Hypertension was more frequent in patients exposed to 150 mg group than 300 mg, in both safety pools investigated, refer also above to discussion about baseline morbidity. The available evidence presented by the Applicant did not show that treatment with secukinumab increases the risk of hypertension. Furthermore, cardiovascular events including hypertension will continue to be monitored as part of the pharmacovigilance monitoring.

The incidence of malignant tumors was not elevated in either of the secukinumab groups or etanercept group in pool B. There were no additional findings in pool C. Two cases of melanoma were observed in these studies and there were predisposing factors present. Lymphomas were not reported. A higher rate of malignancies per 100 patient-years for the placebo group compared with the active treatment groups (1.49 for placebo vs. 0.96 for any secukinumab dose and 0.68 for etanercept) and no dose dependency (0.77 for any 300 mg vs. 0.97 for any 150 mg) was seen for Pool B exposure-adjusted at 52 weeks.

The incidence rates of eczema, urticaria, and conjunctivitis were slightly higher in the secukinumab groups compared to etanercept and placebo groups. Injection site reactions were more common in the etanercept group. Anaphylaxis after use of secukinumab (n=1, in pool C) or angioedema (n=3, with latency of several days) were rare.

Other autoimmune disorders were reported as single cases in three patients having received secukinumab: 1 granulomatous polyangiitis (after 10 months use of secukinumab 300 mg sc doses), 1 multiple sclerosis (worsening of an existing condition), and 1 pemphigus (after 2 doses of secukinumab, discontinued).

A search for autoimmune disorders showed a higher incidence for placebo vs. secukinumab and etanercept in Pools A and B, primarily due to psoriasis reported as an AE/SAE. No new events of central nervous system (CNS) demyelination were identified.

Fixed dose regimen at 4 week intervals (65 patients) and start of relapse regimen (67 patients) for 32 weeks in study A2211 did not display different AE profile – particularly regarding the immune reactions or administration site conditions.

Tolerability data were provided across the lyophilisate (LYO) studies (A2302, A2303 and 2304) (not pooled) as well as for the studies with the liquid formulation using pre-filled syringe (A2308) and auto-injector (A2309). The patient exposure to lyophilisate in the finished studies has been significantly larger than the exposure to the prefilled syringes or autoinjectors. Administration site reactions occurring with prefilled syringes or autoinjectors have been observed mostly as single cases, which does not imply to a worse local tolerability profile compared to the lyophilisate.

Study A2202 in patients with moderate to severe active Crohn's disease was terminated prematurely due to lack of efficacy. In addition, higher rates of discontinuations and adverse events including worsening of disease and infections occurred on secukinumab compared to placebo. From the large patient pool of psoriasis studies, 3 cases of Crohn´s disease were identified, 2 with pre-existing Crohn´s disease and 1 new case. The Applicant has provided a review of the relevant data from several different sources and the

CHMP concluded that they do not support a need for a contraindication. A warning and recommendation for close follow up of all patients with Crohn's disease has been included in the product information and this was agreed by the CHMP.

The number of cases of *colitis ulcerosa* in psoriasis studies was small, 4 cases, and in 3 out of these, an underlying condition could be pointed out. Exclusion criterion of active inflammatory bowel disease at baseline was not met in one patient. The current evidence from all sources does not indicate a causal relationship between secukinumab and ulcerative colitis.

The overall safety profile (adverse events, SAEs, AE leading to discontinuation) in SOC Hepatobiliary Disorders is comparable between secukinumab, placebo and etanercept. The observed small numerical imbalance in the exposure adjusted incidence rate of SAE and AE leading to discontinuation with secukinumab is not considered clinically meaningful based on the medical review of cases confounded by other risk factors. The CHMP agreed that the majority of the patients with this SOC had other contributing risk factors for the reported events.

The available safety data do not raise any special safety concern related to renal function or urinary findings in secukinumab patients.

Six deaths were reported from the psoriasis-trials and three additional deaths from other trials of patients exposed to secukinumab. Causes of these deaths could be attributed to concomitant morbidity and seemed not be related to use of secukinumab. 16 deaths altogether have been reported up to 31 July, 2013 across all secukinumab trials. During the procedure the applicant reported three deaths not related to study medications.

Although the incidence rate of SAEs was higher during the induction period in both secukinumab dose groups compared to placebo and etanercept groups, the single occurrences of SAEs with no trends of dose-dependency does not raise additional safety concerns. The heavy co-morbidity at baseline seems to be the likely cause for most of the SAEs. The higher SAE-rates in secukinumab-groups were reduced when adjusted for the exposure from the entire treatment period.

Cardiovascular co-morbidity was over-presented in the baseline in the secukinumab groups, as discussed above. During the Induction period in Pool B, there were 10 cardiac disorders reported as SAEs in the "Any secukinumab dose" group, compared to none in the placebo- and etanercept-groups. Number of patients experiencing a serious cardiovascular adverse event (and the incidence rate per 100 patient years) for Placebo 0 (0.00), AIN457 150 mg 13 (1.14), AIN 457 300 mg 7 (0.60), and etanercept 3 (1.03) would suggest a slightly increased risk for users of secukinumab. However, taking into account the larger and - in particular - longer exposure to secukinumab and that most of the SAE occurred weeks or months after continuous secukinumab use in patients with predisposing factors and cardiovascular morbidity, there no implication that secukinumab would predispose patients to serious cardiovascular complications.

There was a significant decrease in total leukocytes and neutrophils in the pooled secukinumab group during all pivotal studies. This decrease was probably due to the pharmacodynamic effects of the drug and it was somewhat more prominent in the etanercept group compared to secukinumab patients. In general, the neutropenia cases were not associated with SAEs or treatment discontinuation (as described in the product information).

There were no clinically significant differences in the distribution of hepatic enzymes, blood lipids and other chemistry parameters during the pivotal studies between secukinumab, etanercept and placebo groups.

No meaningful differences could be observed in patient groups <65 and >65 years or between genders regarding the AEs or SAEs. The AE rates in patients weighing <90 kg and >90 kg did display differences

but inconsistently from SOC to another. Infections and infestations were more common in patients weighing >90 kg. Overall, based on the data available, the increased exposure and efficacy observed in patients weighing less than 90 kg was not associated with worse safety profile. It appears that the increased weight as such correlates with an increased rate of non-treatment related AEs, as seen also in the placebo group.

No clinically significant differences in the AE- or SAE-profiles or -rates were observed in secukinumab patients who had received systemic or systemic biologic psoriasis treatment before and who had not.

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

Safety results requested for the 8-week off-treatment follow-up periods of studies CAIN457A2302/A2303/A2304 and for the 16-week period covering the PEA in study A2302E1 were consistent with the overall safety profile of secukinumab. Following the submission of the original MAA, approximately 1900 patient-years of additional exposure including 800 patient-years in plaque psoriasis is available. No new safety signals could be identified.

The overall safety profile of secukinumab is favourable. The safety profile of the 300 mg dose did not significantly differ from that of the 150 mg dose. Unfavourable effects typical for biologic psoriasis therapies have been observed, including infections, neutropenia and hypersensitivity, but no increase was observed in the rate of mycobacterial or serious opportunistic infections. In relation to other systemic treatments available for the treatment of psoriasis, no particular additional safety concerns have been raised. Therefore, the CHMP agreed to change the initially proposed indication: “Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA” to: “Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy”.

2.6.2. Conclusions on the clinical safety

Secukinumab appears to have a favourable safety profile. Data from 5044 patients in the clinical trials extends up to 52 weeks. During the procedure, further treatment free follow up data for 8 to 12 weeks has been supplemented together with an interim update from all ongoing studies.

Secukinumab increased the incidence of upper respiratory tract infections compared to placebo but only negligibly compared to etanercept. Mucocutaneous candida infections (treatable, not leading to discontinuations of secukinumab treatment), mild ear canal infections, as well as *Herpes simplex* -infections also have a slightly elevated incidence. Conjunctivitis and GI-symptoms, mainly diarrhoea, were reported more frequently. The incidence of neutropenia was lower and the local tolerability better compared to etanercept. The safety profile of 150 mg and 300 mg s.c. doses did not differ significantly. Slight dose dependence could be observed in the rate of candida infections, oral herpes infections, ear infections, and conjunctivitis, but not in the rate of serious adverse effects.

Currently available data does not suggest that secukinumab would increase the risk of MACE/cardiovascular disease and malignancies. However, long-term safety data is still limited and a potential association between secukinumab and these events cannot be completely excluded based on its mechanism of action (malignancies and MACE have been included in the RMP as potential risks) and further information needs to be collected post-approval, e.g. in a registry and in the extension studies (as described in the RMP). Several patients with latent tuberculosis received secukinumab in clinical trials

after treatment with anti-tuberculosis medication. None of these patients had a reactivation of the tuberculosis. The effects of secukinumab in patients with clinically important and active infection (e.g. active tuberculosis), however, are unknown and due to the potential immunosuppressive effects secukinumab is contraindicated in these patients.

Exacerbations of Crohn's disease, some of which were serious, have been reported in patients receiving secukinumab. A warning and a recommendation for close follow up of all patients with Crohn's disease is included in the product information.

Although the preclinical data is reassuring, the currently available human data is inadequate and therefore as a precautionary measure, it is preferable to avoid the use of Cosentyx in pregnancy.

There is no data on the use of live vaccines in patients receiving secukinumab treatment. Live vaccines should not be given concurrently with Cosentyx (as described in the product information).

Based on the data available, immunogenicity of secukinumab is low and does not appear to have an effect on the safety, efficacy, or pharmacokinetics of secukinumab.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. 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 1.2 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 1.3 with the following content:

Safety concerns

Table 62 Summary of the Safety Concerns

Important identified risks	Infections and infestations
	Neutropenia
	Hypersensitivity
Important potential risks	Malignant or unspecified tumors
	Major Adverse Cardiovascular Events (MACE)
	Immunogenicity
	Crohn's disease
	Hepatitis B reactivation
	Interaction with live vaccines
Missing information	Fetal exposure in utero

Important identified risks	Infections and infestations Neutropenia Hypersensitivity Long-term safety data Long-term efficacy data Use in pediatric patients Patients with severe hepatic impairment Patients with severe renal impairment Patients with severe cardiac disease or uncontrolled hypertension

Pharmacovigilance plan

Table 63 Table of on-going and planned additional PhV studies / activities in the PhV Plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final Reports** (planned or actual)
Psoriasis Registry Category 3	1- The primary goal of the registry is to assess the incidence and nature of malignancies in a real-world population of moderate-to-severe psoriasis patients on secukinumab therapy 2- It will also systematically collect and analyze longitudinal outcomes associated with psoriasis treatments (biologics and nonbiologics) in a cohort of patients with psoriasis, allowing a better understanding of the epidemiology and natural history of the disease, comorbidities,	Malignant or unspecified tumors	Planned (Protocol under development To be finalized Q4 2014)	Progress reports including data presentation to be included in DSUR/PSUR according to the regulated timelines No additional interim reports planned Final study report in Q1 2024.

	current treatment practices, comparative effectiveness and safety outcomes related to medication therapy including capturing rare AEs with secukinumab in real world medical population			

Risk minimisation measures

Table 64 Summary table of Risk Minimization Measures

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

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	SmPC section 4.4 (Special warnings and precautions for use)	
Hepatitis B reactivation	No risk minimization measure is considered necessary at this time.	None
Interaction with live vaccines	Labeling	None
	SmPC section 4.4 (Special warnings and precautions for use) and section 4.5 (Interaction with other medicinal products and other forms of interaction)	
Missing Information		
Fetal exposure in utero	Labeling	None
	SmPC section 4.6 (Fertility, pregnancy and lactation)	
Long-term safety data	No risk minimization measure is considered necessary at this time. Routine risk minimization (standard of care for the target population) is considered sufficient.	None
Long-term efficacy data	No risk minimization measure is considered necessary at this time. Routine risk minimization (standard of care for the target population) is considered sufficient.	None
Use in pediatric patients	Labeling	None
	SmPC section 4.1 (Therapeutic indications)	
Patients with severe hepatic impairment	No risk minimization measure is considered necessary at this time.	None
Patients with severe renal impairment	No risk minimization measure is considered necessary at this time.	None
Patients with severe cardiac disease or uncontrolled hypertension	No risk minimization measure is considered necessary at this time.	None

2.9. Product information

2.9.1. User consultation

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

3. Benefit-Risk Balance

Benefits

Beneficial effects

Short-term and long-term efficacy of secukinumab has been robustly shown in comparison to placebo and etanercept. In a pooled analysis from four phase III trials, Secukinumab 150 mg and 300 mg doses were superior to placebo with respect to the co-primary endpoints PASI 75 (69.2% and 79.4%, respectively, vs. 4.2% for placebo) and IGA 0/1 (51.4% and 65.0%, respectively, vs. 2.2% for placebo) response at Week 12. The results were consistent across the studies (A2302, A2303, A2308 and A2309) with the p-values for each comparison vs. placebo <0.0001. In the pooled analysis, PASI 90, PASI 100 and IGA 0 response rates indicating nearly complete/complete clearance were also statistically significantly better with both secukinumab doses compared to placebo (p-values for each comparison vs. placebo <0.0001). This level of efficacy is considered clinically highly relevant and meets the expectations for a new biologic treatment. Other secondary endpoints were also consistently in favour of secukinumab.

The study population was heterogeneous with respect to previous therapies and included both systemic treatment naïve as well as those previously exposed to systemic therapies including biologic therapies. Response rates were generally higher in those with no previous exposure to systemic psoriasis therapies.

Both 150 mg and 300 mg secukinumab doses were statistically significantly (p=0.0250) superior to etanercept at Week 12 in achieving PASI 75 (67.0% and 77.1%, respectively, vs. 44.0% for etanercept) and IGA 0/1 (51.1% and 62.5%, respectively, vs. 27.2% for etanercept) response based on Study A2303. In patients with previous systemic psoriasis therapy, including biologic therapy, efficacy was slightly diminished but yet clinically highly relevant. Thus, secukinumab provides a relevant alternative to biologic treatments currently available, also for difficult-to-treat patients who have failed previous biologic therapies.

The onset of efficacy of secukinumab was rapid as the estimated time to 50% reduction in mean PASI score occurred at 3.0 weeks with secukinumab 300 mg dose and at 3.7 weeks with secukinumab 150 mg dose.

The response rates achieved at Week 12 in both secukinumab dose groups were mainly sustained up to Week 52 (based on Studies A2302 and A2303), particularly in the 300 mg dose group. Considering that non-responder imputation was used in the analyses, the rate of maintenance of efficacy was at a good level. Relapses (on-treatment and post-treatment) were least common in the secukinumab 300 mg dose group based on both 12-week and 52-week pooled analyses.

The improvements with secukinumab in clinical response were mirrored by the improvements in patient reported outcomes, including EQ-5D, DLQI, and items of the Psoriasis symptom diary.

Secukinumab 300 mg dose showed clinically and statistically significantly better results than the 150 mg dose in the larger studies A2302 and A2303. From the efficacy point of view 300 mg is the recommended dose. The maintenance dosing every 4 weeks is feasible for the patients.

The body weight – response relationship of secukinumab was explored by the applicant. It was concluded that the benefit/risk of the 300 mg dose is positive also in patients weighing over 90 kg and there is no need for dose adjustment in this population. It was also concluded that the 300 mg maintenance dose is recommended for all patient populations, including those with low body weight.

Uncertainty in the knowledge about the beneficial effects.

Long-term efficacy data beyond 52 weeks are limited. All 6 core Phase 3 studies (CAIN457A2302, A2303, A2304, A2307, A2308, and A2309) have either been extended to a study duration of up to 4 years (A2308 and A2309) or have offered subjects on secukinumab in the core studies the opportunity to participate in long-term extension studies for up to a total treatment period of 5 years (for studies A2302 and A2303: A2302E1; for A2304 and A2307: A2304E1). The long term treatment is expected to last for an overall (core and extension) treatment duration of up to 5 years, or at least until the drug is commercially available (thus less than 5 years in some countries). Altogether, it is expected that data from approximately 2000 subjects treated with secukinumab for more than 1 year and data up to 5 years will become available from these studies (as described in the RMP).

Risks

Unfavourable effects

Infections were more commonly reported in secukinumab-patients compared to placebo (28.7% vs.18.9% at 12 weeks), but occurred at a similar rate compared to etanercept. The imbalance with secukinumab vs. placebo was mainly due to upper respiratory tract infections. Also candida infections, oral herpes infections and ear infections, mainly otitis externa, were more commonly reported compared to placebo and slightly more often with secukinumab 300 mg group compared to 150 mg group. No increase was observed in the rate of mycobacterial or serious opportunistic infections.

The increased incidence of candida infections (3.55 per 100 patient years for secukinumab 300 mg versus 1.00 per 100 patient years for placebo) was mainly due oral candidiasis and vulvovaginal candidiasis and consistent with the mechanism of action of secukinumab and knowledge on the IL-17 biology. Also individual cases of oesophageal candidiasis were reported. All candida infections were mild to moderate in severity and none led to treatment discontinuation.

A slightly elevated incidence of GI-disorders (diarrhoea), eye-disorders (conjunctivitis), and respiratory system disorders was seen in secukinumab 300 mg -treated patients compared to rest of the patients.

Neutropenia was more common in secukinumab 150 mg and 300 mg doses treated patients compare to placebo (0.1, 0.3 and 0.0%, respectively, at 12 weeks), but the incidence was lower compared to etanercept. In general, the neutropenia cases were not associated with SAEs or discontinuations, and only 2 patients in the phase II/III studies with secukinumab discontinued the treatment due to neutropenia. At 52 weeks, Grade 2 neutropenia was reported in 2.8% and 2.4 %, and Grade 3 neutropenia in 0.6% and 0.7% of patients receiving 150 mg and 300 mg secukinumab, respectively. None of the Grade 3 neutropenias were associated with severe or serious infections.

The incidence of hypersensitivity AEs in secukinumab treated patients was comparable to etanercept, but higher than with placebo, driven by higher rates of urticaria and eczema. A single case of anaphylaxis has been reported. Injection site reactions, including erythema, swelling, pruritus and pain, were slightly more common than with placebo, but less common than with etanercept.

Uncertainty in the knowledge about the unfavourable effects

Currently available data does not suggest that secukinumab would increase the risk of MACE/cardiovascular disease and malignancies. However, long-term safety data is still limited and

further information will be collected post-approval (as described in the RMP e.g. in a registry and in the extension studies). Malignancies and MACE have been addressed in the RMP as potential risks.

Several patients with latent tuberculosis received secukinumab in clinical trials after treatment with anti-tuberculosis medication. None of these patients had a reactivation of the tuberculosis. The effects of secukinumab in patients with clinically important and active infection (e.g. active tuberculosis), however, are unknown and due to the potential immunosuppressive effects secukinumab is contraindicated in these patients.

There is no data on the use of live vaccines in patients receiving secukinumab treatment. Live vaccines should not be given concurrently with Cosentyx (as described in the product information).

Benefit-risk balance

Importance of favourable and unfavourable effects

Statistically significant and clinically highly relevant short-term and long-term efficacy of secukinumab has been shown. There is a need for additional therapies in moderate to severe psoriasis, particularly for those with hard-to-treat disease.

The most relevant safety concerns of secukinumab identified so far are related to infections, which are mostly mild to moderate in severity.

Benefit-risk balance

Efficacy of secukinumab in the treatment of moderate to severe psoriasis has been demonstrated in all patient populations studied, including systemic treatment naïve and those with previous systemic psoriasis therapies including biologic therapies. In the systemic treatment naïve population, the response rates were generally higher. Based on the large safety database currently available, the short term safety profile of secukinumab is reassuring and no particular additional safety concerns have been raised compared to other systemic treatments available for the treatment of psoriasis. Further data on long term safety will be captured in the extension studies and planned registry study (as described in the RMP). The potential risk associated with lack of long term safety data is considered as out balanced by the high level of efficacy and therefore, the benefit-risk balance is considered positive in all patients with moderate to severe plaque psoriasis who are candidates for systemic therapy.

Discussion on the benefit-risk balance

Robust and clinically relevant efficacy has been shown for secukinumab in the treatment of moderate to severe psoriasis. The 300 mg dose was consistently superior to the 150 mg dose. The overall safety profile of secukinumab is favourable. The safety profile of the 300 mg dose did not significantly differ from that of the 150 mg dose. Unfavourable effects typical for biologic psoriasis therapies have been observed, including infections, neutropenia and hypersensitivity, but no increase was observed in the rate of mycobacterial or serious opportunistic infections. In relation to other systemic treatments available for the treatment of psoriasis, no particular additional safety concerns have been raised. In addition, the magnitude of the beneficial effect was pronounced and superior to the effect of etanercept. The benefit-risk balance can be considered positive in all patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and therefore, the initially proposed indication: “Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA” was changed to “treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy”.

Note: ‘Systemic therapy’ within the context of indication wording, i.e. this includes both non-biologic (e.g. cyclosporine, MTX etc) systemic and biologic systemic agents.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Cosentyx in the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

The 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.

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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that secukinumab is qualified as a new active substance.