Report on the Deliberation Results

December 3, 2014

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Cosentyx for Subcutaneous Injection 150 mg Syringe Cosentyx for Subcutaneous Injection 150 mg
[Non-proprietary name]	Secukinumab (Genetical Recombination) (JAN*)
[Name of applicant]	Novartis Pharma K.K.
[Date of application]	December 26, 2013

[Results of deliberation]
In the meeting held on November 28, 2014, the Second Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 8 years. The drug substance and the drug product are both classified as powerful drugs, and the product is classified as a biological product.

[Conditions for approval]
The applicant is required to:
1. Develop a risk management plan for the product and implement it appropriately.
2. Conduct an appropriate post-marketing surveillance study to fully evaluate the long-term safety and efficacy of the product, including the occurrence of infections, etc.

**Japanese Accepted Name (modified INN)*

-

Review Report

November 14, 2014
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	(a) Cosentyx for Subcutaneous Injection 150 mg Syringe (b) Cosentyx for Subcutaneous Injection 150 mg
[Non-proprietary name]	Secukinumab (Genetical Recombination)
[Name of applicant]	Novartis Pharma K.K.
[Date of application]	December 26, 2013
[Dosage form/Strength]	(a) Solution for injection in a pre-filled syringe: Each syringe contains150 mg of Secukinumab (Genetical Recombination) in 1mL. (b) Powder for injection in a vial for reconstitution before use:[1] Each vial contains 180 mg of Secukinumab (Genetical Recombination).
[Application classification]	Prescription drug, (1) Drug with a new active ingredient
[Chemical structure]	See Figure 1 and Figure 2 below. Molecular formula: L-chain molecule: $C_{1024}H_{1594}N_{280}O_{335}S_6$ H-chain molecule: $C_{2268}H_{3477}N_{597}O_{686}S_{16}$ Molecular weight: 147,942.30 (the protein)
[Definition]	Secukinumab is a recombinant human IgG1 monoclonal antibody against human interleukin-17A. Secukinumab is produced in Chinese hamster ovary cells. Secukinumab is a glycoprotein (molecular weight, ca. 151,000) consisting of two molecules of H-chain (γ1-chain) containing 457 amino acid residues and two molecules of L-chain (κ-chain) containing 215 amino acid residues.
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug IV

[1] The product is designed to ensure an extractable volume of 1.0 mL of solution for injection containing 150 mg of Secukinumab (Genetical Recombination) after the lyophilized powder is reconstituted with 1.0 mL of Water for Injection (Japanese Pharmacopoeia [JP]), and contains a 20% overage to compensate for loss during reconstitution. Doses of the product in this report are expressed in terms of Secukinumab (Genetical Recombination).

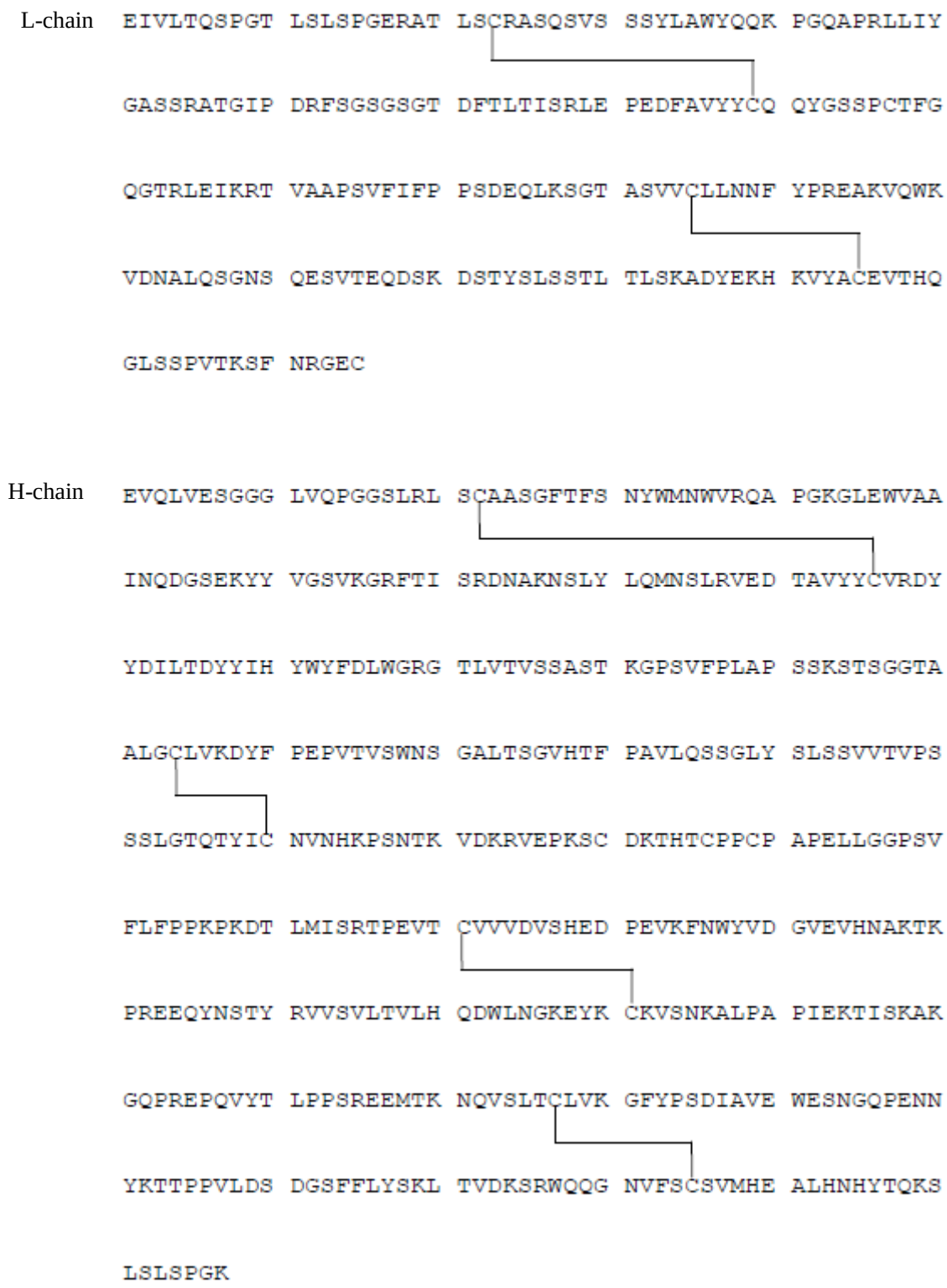


Figure 1. H- and L-chains of Secukinumab (Genetical Recombination)
H-chain E1: partial formation of pyroglutamic acid, H-chain N307: glycosylation, H-chain K457: partial processing
L-chain C215-H-chain C230, H-chain C236-H-chain C236, and H-chain C239-H-chain C239: inter-chain disulfide bonds
Solid line: intra-chain disulfide bonds

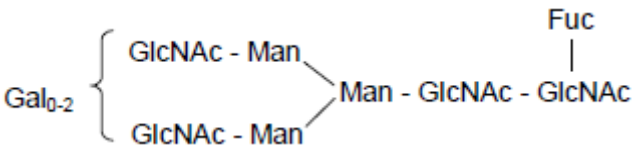


Figure 2. Main proposed glycosylation structures
Gal: Galactose, GlcNAc: *N*-acetylglucosamine, Man: Mannose, Fuc: Fucose

Review Results

November 14, 2014

[Brand name]	(a) Cosentyx for Subcutaneous Injection 150 mg Syringe
	(b) Cosentyx for Subcutaneous Injection 150 mg
[Non-proprietary name]	Secukinumab (Genetical Recombination)
[Name of applicant]	Novartis Pharma K.K.
[Date of application]	December 26, 2013

[Results of review]

Based on the submitted data, the efficacy of the product has been demonstrated in the treatment of psoriasis vulgaris and psoriatic arthritis in patients who have had an inadequate response to conventional therapy, and its safety is acceptable in view of its observed benefits. Serious adverse drug reactions such as infections may occur following administration of the product. Therefore, prior to the use of the product, the patient's symptoms, etc. should be monitored closely and the risks and benefits of the product should be weighed. A post-marketing surveillance study, etc. to follow the patients for the occurrence of serious infections and malignancy, etc. should be conducted and the obtained information etc. should be provided accordingly to physicians and patients, etc.

As a result of its review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for "Indications" and "Dosage and administration" as shown below, with the following conditions.

[Indications] Treatment of the following diseases in patients who have had an inadequate response to conventional therapy:
Psoriasis vulgaris and psoriatic arthritis

[Dosage and administration] The usual adult dosage is 300 mg of Secukinumab (Genetical Recombination) by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. A dose of 150 mg may be acceptable for some patients, depending on their body weight.

[Conditions for approval] The applicant is required to:

1. Develop a risk management plan for the product and implement it appropriately.
2. Conduct an appropriate post-marketing surveillance study to fully evaluate the long-term safety and efficacy of the product, including the occurrence of infections, etc.

Review Report (1)

October 23, 2014

I. Product Submitted for Registration

[Brand name]	(a) Cosentyx for Subcutaneous Injection 150 mg Syringe (b) Cosentyx for Subcutaneous Injection 150 mg
[Non-proprietary name]	Secukinumab (Genetical Recombination)
[Name of applicant]	Novartis Pharma K.K.
[Date of application]	December 26, 2013
[Dosage form/Strength]	(a) Solution for injection in a pre-filled syringe: Each syringe contains 150 mg of Secukinumab (Genetical Recombination) in 1mL. (b) Powder for injection in a vial for reconstitution before use:[2] Each vial contains 180 mg of Secukinumab (Genetical Recombination).
[Proposed indications]	Treatment of the following diseases in patients who have had an inadequate response to conventional therapy: Psoriasis vulgaris and psoriatic arthritis
[Proposed dosage and administration]	The usual adult dosage is 300 mg of Secukinumab (Genetical Recombination) by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3, followed by dosing every 4 weeks, starting at Week 4. A dose of 150 mg may be acceptable for some patients, depending on their symptoms.

II. Summary of the Submitted Data and Outline of the Review by the Pharmaceuticals and Medical Devices Agency

A summary of the submitted data in the application and the outline of a review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

The active substance of Cosentyx for Subcutaneous Injection 150 mg Syringe and Cosentyx for Subcutaneous Injection 150 mg (hereinafter collectively referred to as Cosentyx) is Secukinumab (Genetical Recombination) (hereinafter referred to as secukinumab), which is a human immunoglobulin G (IgG) 1/κ monoclonal antibody against human interleukin-17 (IL-17) A developed by Novartis Pharma AG (Switzerland).

Psoriasis is an inflammatory disease of the skin characterized by erythema from capillary dilatation, increase in epidermal thickness and excessive scaling (hyperkeratosis), and well-defined edges (plaques), etc. Psoriasis has five types, each having unique signs and symptoms: psoriasis vulgaris, psoriatic arthritis, guttate psoriasis,

[2] The product is designed to ensure an extractable volume of 1.0 mL of solution for injection containing 150 mg of Secukinumab (Genetical Recombination) after the lyophilized powder is reconstituted with 1.0 mL of Water for Injection (JP), and contains a 20% overage to compensate for loss during reconstitution. Doses of the product in this report are expressed in terms of Secukinumab (Genetical Recombination).

erythrodermic psoriasis, and pustular psoriasis. Psoriasis vulgaris is characterized by skin plaques only while psoriatic arthritis is an inflammatory arthritis associated with skin plaques. In general, patients with mild to moderate disease are treated with topical corticosteroids, topical vitamin D_3 derivatives, and the combination of these agents. Patients with moderate to severe disease undergo phototherapy, photochemotherapy, and systemic therapies (e.g., cyclosporine and etretinate). Anti-TNFα agents, namely Infliximab (Genetical Recombination) (hereinafter referred to as infliximab) and Adalimumab (Genetical Recombination) (hereinafter referred to as adalimumab) and an anti-IL-12/23 agent, namely Ustekinumab (Genetical Recombination) (hereinafter referred to as ustekinumab) have been approved to treat patients who have had an inadequate response to these conventional therapies.

A pro-inflammatory cytokine, IL-17A is considered to play a key role in the pathogenesis of psoriasis and the retention and amplification of local inflammation (Di Cesare A, et al. *J Invest Dermatol*. 2009;129:1339-1350, Weaver CT, et al. *Annu Rev Pathol Mech Dis*. 2013;8:477-512, Iwakura Y, et al. *Immunity.* 2011;34:149-162). Secukinumab binds with high affinity to IL-17A in the human IL-17 family and inhibits the binding of IL-17A to the IL-17 receptor, thereby neutralizing its bioactivity. Therefore, Secukinumab was developed as a treatment option for psoriasis.

The clinical development of secukinumab for the treatment of psoriasis began in 2007 overseas. Regulatory applications were filed in October 2013 in Europe and the US, and the review of the applications is currently in progress.

In Japan, the clinical development of secukinumab for the treatment of psoriasis began in July 2009. The marketing application for secukinumab has been filed based on the results from multinational clinical studies (including Japan), etc.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Generation and control of the cell substrate

[redacted] This gene expression construct was transfected into a Chinese hamster ovary (CHO) cell line adapted to suspension culture in serum-free medium. Among the cloned cell lines, a clone producing a sufficient amount of the antibody was selected. A master cell bank (MCB) was prepared from the selected cell clone and a working cell bank (WCB) was derived from the MCB.

Tests for identity (isoenzyme analysis, cDNA sequence, Northern blot, Southern blot, or the number of copies) were performed for the MCB, WCB, and an Extended Cell Bank (ECB), which demonstrated genetic stability during the production of secukinumab.

Tests for purity (sterility testing, mycoplasma testing, extended S^+L^- assay, extended XC plaque assay, transmission electron microscopy, reverse transcriptase activity, *in vitro* assays, *in vivo* assays, mouse antibody production test, hamster antibody production test, extensive testing for bovine viruses, test for bovine polyomavirus or porcine viruses) were performed for the MCB, WCB, and ECB. As a result, no viral or non-viral adventitious agents were detected other than endogenous retroviruses and retrovirus-like particles, which are generally observed in rodent cell lines, within the scope of the tests performed.

The MCB and WCB are stored in the vapor phase of liquid nitrogen. There is no plan for generating a new MCB or WCB at present.

2.A.(1).2) Manufacturing process

[redacted]

Validation of the commercial-scale drug substance manufacturing process has been performed.

2.A.(1).3) Adventitious agents safety evaluation

Except for the host CHO cell line, no animal- or human-derived raw materials are used in the drug substance manufacturing process.

Tests for purity were performed on the MCB, WCB, and ECB [see "2.A.(1).1) Generation and control of the cell substrate"]. Tests for bioburden, mycoplasma (culture method and indicator cell culture method), and adventitious viruses (*in vitro*) and transmission electron microscopy were performed for unprocessed bulk at commercial scale. As a result, the unprocessed bulk was shown to be free of contamination with viral and non-viral adventitious agents, within the scope of the tests performed. Tests for bioburden, mycoplasma, and adventitious viruses (*in vitro*) are included as in-process controls for unprocessed bulk.

Viral clearance studies of the purification process were performed with model viruses, which demonstrated a certain robustness of the purification process, as shown in Table 1.

Table 1. Results of viral clearance studies

Process step	Virus reduction factor (log_{10})			
	Xenotropic murine leukemia virus	Pseudorabies virus	Reovirus type 3	Minute virus of mice
[redacted]	[redacted]a)	[redacted]	[redacted]	[redacted]
Virus inactivation	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	≥[redacted]	≥[redacted]	≥[redacted]	≥[redacted]
Nanofiltration	≥[redacted]	≥[redacted]	≥[redacted]	≥[redacted]
Overall reduction factor	≥20.36	≥18.81	≥17.51	≥14.19

a) Result of quantitative PCR

2.A.(1).4) Manufacturing process development (Comparability)

Major changes made to the drug substance manufacturing process during development were as shown below (Processes A, B, C, and D [the intended commercial production process]).

- Process A → Process B: [redacted]
- Process B → Process C: [redacted]
- Process C → Process D: [redacted]

When changes were made in the manufacturing process, comparability studies on quality attributes were performed, which demonstrated comparability between pre-change and post-change drug substances. [redacted]

2.A.(1).5) Characterization

2.A.(1).5).(a) Structure and composition

Primary structure

- The amino acid sequence of secukinumab, as determined by mRNA sequencing, N-terminal amino acid sequencing by Edman degradation, and peptide mapping of a reduced Lys-C digest and a reduced Asp-N digest and tandem mass spectrometry (MS/MS), agreed with the one estimated from the nucleotide sequence of the gene expression construct for the production of secukinumab.
- N-terminal pyroglutamate formation was observed on a heavy chain and a light chain by N-terminal and C-terminal amino acid sequence analyses. Variants were found also through the loss of C-terminal Lys residues or Lys and Gly residues of the heavy chains.

Higher order structure

- A total of 2 intra-chain disulfide bonds in each light chain and 4 intra-chain disulfide bonds in each heavy chain, 2 inter-heavy chain disulfide bonds, and 1 inter-light-heavy chain disulfide bond were identified by peptide mapping of a non-reduced Lys-C digest.
- [redacted] The Ellman's assay indicated that there are [redacted] to [redacted] mol of free thiol per mol of secukinumab.

- The antigen-binding site of secukinumab was identified and the molecular details of the complementarity-determining regions (CDRs) were revealed by X-ray crystallography. [redacted]
- The far-ultraviolet circular dichroism (CD) spectrum showed a peak at [redacted] nm corresponding to β sheet structure, which is characteristic of IgG. The near-ultraviolet CD spectrum above [redacted] nm specific to secukinumab was obtained.
- The fluorescence spectrum showed a peak near [redacted] nm.
- The thermal transition temperatures as determined by differential scanning calorimetry were at approximately [redacted]°C, [redacted]°C, and [redacted]°C.

Carbohydrate structure

- Peptide mapping of a Lys-C digest and a Asp-N digest, reverse-phase chromatography (RP-HPLC)/mass spectrometry (MS), and capillary gel electrophoresis under reducing conditions (CE-SDS) showed that [redacted]% of secukinumab heavy chains are *N*-glycosylated at Asn307 and that there are no *O*-linked glycosylation sites in secukinumab.
- Peptide mapping and normal-phase liquid chromatography/MS after PNGase F treatment showed that the predominant oligosaccharide is a fucosylated structure having zero terminal galactose residue (G0F) and that other main oligosaccharides are a fucosylated structure having one terminal galactose residue (G1F) and a non-fucosylated structure (G0).

2.A.(1).5).(b) Physicochemical properties

Molecular mass

- The molecular mass of secukinumab obtained by analysis of non-reduced or reduced-alkylated samples using RP-HPLC/electrospray ionization MS nearly matched the theoretical mass.

Electrophoresis

- [redacted]
- [redacted]
- [redacted]
- The isoelectric points of the main peak and two basic peaks, as determined by capillary isoelectric focusing (cIEF), were [redacted], [redacted], and [redacted], respectively.

Liquid chromatography

- [redacted]
- [redacted]
- [redacted]
- The percentage of glycated secukinumab separated from total secukinumab by boronate affinity chromatography was approximately [redacted]%.

Others

- The extinction coefficient (280 nm) was [redacted] mL/(mg·cm).
- [redacted]

2.A.(1).5).(c) Immunochemical properties

- A band corresponding to the theoretical molecular mass was detected by immunoblotting with anti-human IgG antibody and anti-human IgGκ light chain antibody (reducing SDS-PAGE). No bands were detected by immunoblotting with anti-host cell protein (HCP) antibody.

2.A.(1).5).(d) Biological properties

- [redacted]
- [redacted]
- The equilibrium dissociation constant (K_d) for the interaction between secukinumab and recombinant human IL-17A, as determined by surface plasmon resonance (SPR), was approximately [redacted] pmol/L.
- The binding affinities of secukinumab to FcγIa, FcγIIa, FcγIIIa, FcγIIIb, and neonatal Fc receptors were evaluated using SPR. Secukinumab was oligomerized in the presence of IL-17A, which showed higher binding affinity to FcγIa and FcγIIIb receptors.

2.A.(1).5).(e) Product-related substances

Deamidated, oxidized, and amidated forms were considered to be product-related substances.

2.A.(1).5).(f) Impurities

Process-related impurities

[redacted] All of the process-related impurities have been demonstrated to be adequately removed in the manufacturing process. HCP content is controlled by the drug substance specification.

Product-related impurities

[redacted]

2.A.(1).6) Control of drug substance

[redacted]

2.A.(1).7) Stability of drug substance

Stability studies on the drug substance were as shown in Table 2.

Table 2. Overview of stability studies on drug substance

	No. of batches[a)]	Storage conditions	Testing period	Storage package
Long-term testing	3	-60 ± [redacted]°C	36 months[b)]	Plastic bag
Accelerated testing		[redacted] ± [redacted]°C	[redacted] months	

a) Drug substance produced with Process D, b) The stability study is ongoing.

There were no significant changes in quality attributes at the long-term and accelerated conditions throughout the testing period.

Based on the above, a shelf life of 36 months was proposed for the drug substance when stored in a plastic bag at ≤ -60°C. The long-term stability study on the drug substance will be continued up to [redacted] months.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product and formulation development

The drug product is presented as a solution in a pre-filled glass syringe (PFS) with a stainless steel needle (1 mL) containing 150 mg of secukinumab (PFS formulation) (Cosentyx for Subcutaneous Injection 150 mg Syringe) and as lyophilized powder in a glass vial (6 mL) containing 180 mg of secukinumab (the vial formulation) (Cosentyx for Subcutaneous Injection 150 mg). Each pre-filled syringe is equipped with a needle safety guard (UltraSafe Passive Needle Guard).

The PFS formulation contains trehalose dihydrate, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, and polysorbate 80 as excipients. The primary packaging is a glass syringe with a rubber plunger stopper and a blister pack is used as the secondary packaging.

The vial formulation contains sucrose, L-histidine, L-histidine hydrochloride monohydrate, and polysorbate 80 as excipients. The lyophilized product contains a 20% overage of the labeled amount of secukinumab to ensure an extractable volume of 1 mL of solution for injection containing 150 mg of secukinumab after the lyophilized powder is reconstituted with 1 mL of Water for Injection. The primary packaging is a glass vial with a rubber stopper and a carton is used as the secondary packaging.

2.A.(2).2) Manufacturing process

[redacted]

Validation of the commercial-scale drug product manufacturing process has been performed.

2.A.(2).3) Manufacturing process development (Comparability)

There was a change in manufacturing scale during the development of the PFS formulation.

Major changes made to the manufacturing process during the development of the vial formulation were as shown below (Processes A, B, C and D [the intended commercial production process] in line with changes to the drug substance manufacturing process). No changes were made to the manufacturing process for the vial formulation when the drug substance manufacturing process was changed from Process C to Process D.

- Process A → Process B: [redacted]
- Process B → Process C: [redacted]

For both formulations, when changes were made in the manufacturing process, comparability studies on quality attributes were performed, which demonstrated comparability between pre-change and post-change drug products.

The comparability between the PFS and vial formulations has been demonstrated.

2.A.(2).4) Control of drug product

[redacted]

2.A.(2).5) Stability of drug product

Primary stability studies on the drug product were as shown in Table 3.

Table 3. Overview of primary stability studies on drug product

		No. of batches[a)]	Storage conditions	Testing period	Storage package
PFS formulation	Long-term testing	3	5 ± 3°C	24 months[b)]	A glass syringe (equipped with a needle guard) in a blister pack
	Accelerated testing		25 ± 2°C /60 ± 5%RH	[redacted] months	
	Stress testing		[redacted] ± [redacted]°C [redacted] ± [redacted]%RH		
	Photostability testing	1	An overall illumination of 1.2 million lux·h and an integrated near ultraviolet energy of 200 W·h/m^2		A glass syringe (equipped with a needle guard) in a blister pack and a glass syringe (equipped with a needle guard) in a blister pack kept in a carton in order to protect from light
Vial formulation	Long-term testing	3	5 ± 3°C	36 months	A glass vial
	Accelerated testing		25 ± 2°C/60 ± 5%RH	[redacted] months	
	Stress testing		[redacted] ± [redacted]°C [redacted] ± [redacted]%RH		
	Photostability testing	1	An overall illumination of 1.2 million lux·h and an integrated near ultraviolet energy of not less than 200 W·h/m^2		

a) Drug product produced with Process D, b) The stability study is ongoing.

[redacted]

In stability studies with the vial formulation, there were no significant changes in quality attributes at the long-term condition throughout the testing period.

[redacted]

[redacted]

Based on the above stability data, a shelf life of 24 months was proposed for the PFS formulation when stored in a glass syringe at 2°C to 8°C and protected from light. A shelf life of 36 months was proposed for the vial formulation when stored in a glass vial at 2°C to 8°C. The long-term stability study with the PFS formulation will be continued up to [redacted] months.

2.A.(3) Reference materials

A reference material is prepared from drug substance batches and stored at ≤[redacted]°C. The stability of the reference material for up to [redacted] months has been demonstrated at present. [redacted]

[redacted]

2.B Outline of the review

Based on the submitted data and the following considerations, PMDA concluded that the quality of the drug substance and drug products is adequately controlled.

Novel excipients

The novel excipients contained in the drug products are trehalose dihydrate, which is a new ingredient used in the development of subcutaneous formulations, and/or L-histidine hydrochloride monohydrate whose content is higher in secukinumab than in existing subcutaneous formulations.

2.B.1) Specification and stability

PMDA concluded that since trehalose dihydrate and L-histidine hydrochloride monohydrate comply with their respective Japanese Pharmacopoeia monographs, there are no problems with the specifications or stability.

2.B.2) Safety

PMDA concluded as follows:

Both trehalose dihydrate and L-histidine hydrochloride monohydrate have been used in an intravenous formulation, which was administered at a dose exceeding the maximum daily dose of secukinumab. No local irritation was observed after the subcutaneous administration of secukinumab in toxicity studies submitted. Thus, there is no particular safety concern.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

Primary pharmacodynamic studies of Secukinumab (Genetical Recombination) (hereinafter referred to as secukinumab) assessed binding to the IL-17 family members (IL-17A, IL-17AF, IL-17F), inhibition of IL-17A binding to the receptor, inhibition of the bioactivity of IL-17A, and interspecies differences in binding affinity and neutralizing activity. A secondary pharmacodynamic study evaluated interaction with Fcγ receptors. A safety pharmacology study evaluated the effects of secukinumab on the central nervous, cardiovascular, and respiratory systems in cynomolgus monkeys. [redacted][3] [redacted] No pharmacodynamic drug interaction studies have been performed. Unless otherwise specified, pharmacologic parameters are expressed as the mean.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) Binding affinities and selectivity for human IL-17A, IL-17AF, and IL-17F

3.(i).A.(1).1).(a) Analysis of binding affinity (4.2.1.1-3 to 4.2.1.1-6, 3.2.S.3.1)

The binding affinities of secukinumab to IL-17A, IL-17AF, and IL-17F (among the IL-17 family members, IL-17A shares the highest similarity with IL-17F) were determined by surface plasmon resonance. The dissociation constant (K_d) of secukinumab for recombinant human IL-17A was 122 pmol/L for secukinumab derived from hybridoma cells, 227 to 370 pmol/L for secukinumab derived from [redacted] cells, and 60 to 204 pmol/L for secukinumab derived from CHO cells. The K_d values were similar for all production cell lines. The K_d value of secukinumab derived from CHO cells for recombinant human IL-17AF was 2400 pmol/L. The binding of secukinumab to recombinant human IL-17F was weak and no K_d could be determined.

3.(i).A.(1).1).(b) Binding to other human IL-17 family members and cytokines (4.2.1.1-3, 4.2.1.1-4, 4.2.1.1-8)

The binding affinities of secukinumab to other human IL-17 family members and human cytokines were determined by surface plasmon resonance. Secukinumab did not bind to IL-17B, IL-17C, IL-17D, IL-17E, interferon-γ (IFNγ), IL-1β, IL-2, IL-6, IL-8, IL-13, IL-18, IL-19, IL-20, IL-22, IL-23, TGFβ1, TGFβ2, or TNFα.

[3] It is produced by different cells, but has an identical amino acid sequence to secukinumab and is referred to as secukinumab in this section.

3.(i).A.(1).2) Inhibition of human IL-17A binding to IL-17 receptor (4.2.1.1-7)

The effect of secukinumab on human IL-17A binding to the human IL-17 receptor (IL-17RA) was analyzed by enzyme-linked immunosorbent assay (ELISA). Secukinumab inhibited human IL-17A binding to IL-17RA concentration-dependently, and the 50% inhibitory concentration (IC_{50}) was 0.51 nmol/L.

3.(i).A.(1).3) Binding affinities to IL-17A, IL-17AF, and IL-17F from different species (4.2.1.1-3 to 4.2.1.1-5)

The binding affinities of secukinumab to IL-17A, IL-17AF, and IL-17F from cynomolgus monkeys, rhesus monkeys, marmosets, mice, and rats were determined by surface plasmon resonance. Secukinumab did not bind to mouse or rat IL-17A. On the other hand, secukinumab bound to cynomolgus monkey, rhesus monkey, and marmoset IL-17A, and the K_d values of secukinumab derived from [redacted] cells for human, cynomolgus monkey, rhesus monkey, and marmoset IL-17A were 0.23 to 0.37 nmol/L, 4.0 to 6.0 nmol/L, 8.8 to 9 nmol/L, and 1.2 to 1.9 nmol/L, respectively. The K_d values of secukinumab for human and cynomolgus monkey IL-17AF were 2.4 and 4.3 nmol/L, respectively. The binding of secukinumab to human and cynomolgus monkey IL-17F was weak and no K_d could be determined.

3.(i).A.(1).4) Effect on IL-6 production induced by TNFα and IL-17A costimulation in human fibroblast-like synoviocytes (4.2.1.1-9)

The effect of secukinumab on IL-6 production induced by human IL-17A (30 pmol/L), IL-17AF (1 nmol/L), or IL-17F (33 nmol/L) and TNFα (60 pmol/L) costimulation was assessed in primary human fibroblast-like synoviocytes. Secukinumab inhibited the production of IL-6 in a concentration-dependent manner. IC_{50} values for the inhibition of IL-17A-, IL-17AF-, and IL-17F-costimulated effects were 0.14 nmol/L, 3.30 nmol/L, and 1.80 μmol/L, respectively, and the neutralization by secukinumab was weaker for IL-17F than for IL-17A- or IL-17AF-costimualted effects.

3.(i).A.(1).5) Effect on IL-6 production induced by IL-17A in cynomolgus monkey synoviocytes (4.2.1.1-10)

The effect of secukinumab on IL-6 production induced by cynomolgus monkey IL-17A and IL-17F (0.5 and 5 nmol/L, respectively) was assessed in primary cynomolgus monkey synoviocytes. Secukinumab inhibited cynomolgus monkey IL-17A- and IL-17F-induced IL-6 production in a concentration-dependent manner and secukinumab at 10 μmol/L blocked the release of IL-6 completely.

3.(i).A.(1).6) Effect on IL-6 production induced by IL-17A from different species in human dermal fibroblasts (4.2.1.1-11)

The effect of secukinumab on IL-6 production induced by human, cynomolgus monkey, or rhesus monkey IL-17A (all 0.67 nmol/L) was assessed in primary human dermal fibroblasts. Concentration-dependent inhibition of IL-6 production was observed. The IC_{50} values of secukinumab derived from hybridoma cells for human, cynomolgus monkey, and rhesus monkey IL-17A-induced effects were 0.372 nmol/L, 68.7 nmol/L, and 44.8 nmol/L, respectively.

3.(i).A.(1).7) Effects in animal models of disease

3.(i).A.(1).7).(a) Effect on mouse arthritis induced by injection of human IL-17A-producing cells (4.2.1.1-12)

A mouse model of arthritis was generated by the injection of 3T3-NIH cells secreting human IL-17A into a knee joint of the mouse. Using this model, the effect of secukinumab on knee joint inflammation and swelling was evaluated by measuring ^{99m}Tc uptake in the inflamed knee joint. Secukinumab 20 mg/kg was injected intraperitoneally 2 and 24 hours before the injection of 3T3-NIH cells into the right knee joint of the mouse, and knee joint swelling was measured 3 days after the injection of the cells. Secukinumab inhibited knee joint swelling, prevented reduction of knee chondrocyte proteoglycan synthesis, and reduced inflammatory cellular infiltration into the synovial lining of the inflamed knee joint, as compared with the negative control antibody (anti-human CD25 antibody).

3.(i).A.(1).7).(b) Effect on mouse neutrophil migration induced by injection of human IL-17A-producing cells (4.2.1.1-13)

An inflammatory mouse model was generated by the injection of 3T3-NIH cells into the mouse air pouch. Using this model, the effect of secukinumab on the migration of polymorphonuclear leucocytes to the inflammation site was evaluated. Secukinumab (1, 3, 10, or 30 mg/kg) was injected intraperitoneally 24 hours before the injection of 3T3-NIH cells into the mouse air pouch, and the migration of polymorphonuclear leucocytes to the air pouch was measured 48 hours after the injection of the cells. Secukinumab inhibited polymorphonuclear leucocyte migration dose-dependently as compared to saline, with ED_{50} of 5.4 mg/kg.

3.(i).A.(1).8) Other pharmacology studies

3.(i).A.(1).8).(a) Binding affinity and neutralizing activity of mouse surrogate antibody and inhibition of knee joint swelling in a mouse antigen-induced arthritis model (4.2.1.1-14, 4.2.1.1-15)

Due to lack of cross-reactivity of secukinumab with mouse IL-17A, an anti-mouse IL-17A monoclonal antibody (BZN035) was used as a murine surrogate antibody for secukinumab in a study with an arthritis mouse model. The K_d value of BZN035 for mouse IL-17A was 0.067 pmol/L. BZN035 neutralized chemokine (CXCL1/KC) secretion from murine rectal carcinoma cells stimulated with mouse IL-17A (IC_{50}, 0.04 nmol/L), and this neutralization by BZN035 was comparable to the neutralization of the bioactivity of human IL-17A with secukinumab in human cells (IC_{50}, 0.14 nmol/L). BZN035 did not bind to mouse IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, IL-18, IL-23, TNFα, IFNγ, or CXCL1/KC.

Mice were sensitized with methylated bovine serum albumin to induce arthritis, and a single subcutaneous dose of BZN035 (0.015, 0.15, 1.5, or 15 mg/kg) were administered 2 days prior to the induction of arthritis. BZN035 reduced knee joint swelling in a dose-dependent manner, as compared to the negative control antibody (murine IgG2aκ), with an ED_{50} of 2.11 mg/kg.

3.(i).A.(2) Secondary pharmacodynamics

3.(i).A.(2).1) Binding to recombinant human Fcγ receptors (3.2.S.3.1)

Secukinumab is a human IgG1 antibody and thus is able to interact with Fcγ receptors. The binding affinities of secukinumab to various recombinant human Fcγ receptors were determined by surface plasmon resonance. Secukinumab showed high affinity to FcγRIa (K_d value, 18.7-20.0 nmol/L) and low affinity to FcγRIIa, FcγRIIIa, and FcγRIIIb.

3.(i).A.(2).2) Binding to human and cynomolgus monkey neonatal Fc receptors (FcRn) (4.2.1.1-16)

The binding affinities of secukinumab to human and cynomolgus monkey FcRn were determined by surface plasmon resonance. Secukinumab bound to human and cynomolgus monkey FcRn at pH 6.0, with K_d values of 3.1 μmol/L to human FcRn and 4.2 μmol/L to cynomolgus monkey FcRn. Secukinumab did not bind to either FcRn at pH 7.4.

3.(i).A.(3) Safety pharmacology (4.2.1.3-1)

A single intravenous dose of 10, 30, or 100 mg/kg of secukinumab was administered to cynomolgus monkeys. No treatment-related effects on any of central nervous system (clinical signs and behavior, changes in posture, eye and muscle reflexes), cardiovascular parameters (hemodynamics, heart rate, systolic blood pressure, diastolic blood pressure, and ECG waveforms by telemetry) or respiratory parameters (respiratory rate, blood gases [partial pressure of carbon dioxide, partial pressure of arterial oxygen, pH, hemoglobin oxygen saturation]) were noted.

3.(i).B Outline of the review

The applicant discussed the role of IL-17A in the pathogenesis of psoriasis and the mode of action of secukinumab as follows:

IL-23 is known to be involved in the survival of T-helper (Th) 17 cells (the major IL-17A-producing cells) and the production of IL-17A (Weaver CT, et al. *Annu Rev Immunol*. 2007;25:821-852). Reports suggest that the Th17/IL-23/IL-17A pathway plays an important role in the pathogenesis of psoriasis (Di Cesare A, et al. *J Invest Dermatol*. 2009;129:1339-1350, Weaver CT, et al. *Annu Rev Pathol Mech Dis*. 2013;8:477-512). The produced IL-17A works synergistically with other pro-inflammatory cytokines, e.g. TNFα (Chiricozzi A, et al. *J Invest Dermatol*. 2011;131:677-687), IFNγ (Teunissen MBM, et al. *J Invest Dermatol*. 1998;111:645-649), or IL-22 (Tohyama M, et al. *Eur J Immunol*. 2009;39:2779-2788) in directly activating keratinocytes and dermal fibroblasts to increase the production of pro-inflammatory cytokines (IL-6, TNFα, IL-1β, IL-20 family, GM-CSF), pro-inflammatory chemokines (CXCL1, CXCL2, CCL20, CXCL8/IL-8), and anti-microbial peptides (β-defensin 2, lipocalin 2, S100 proteins such as S100A7/Psoriasin) (Iwakura Y, et al. *Immunity*. 2011;34:149-162), etc. This leads to the recruitment of neutrophils and lymphocytes into the psoriatic lesion thereby maintaining and amplifying local inflammation. Secukinumab is considered to show efficacy in psoriasis by inhibiting the binding of IL-17A to IL-17RA and the subsequent inflammatory cascade as described above.

According to published literature, the number of circulating Th17 cells in the peripheral blood of patients with psoriatic arthritis (Jandus C, et al. *Arthritis Rheum*. 2008;58:2307-2317) increased, and IL-17A levels also increased in synovial tissue lysates in patients with rheumatoid arthritis (Moran EM, et al. *Arthritis Res Ther*. 2009;11:R113). Given these findings, etc., secukinumab is expected to be effective also in reducing the joint symptoms of psoriatic arthritis.

Based on the submitted data, PMDA concluded that the pharmacological effects of secukinumab via IL-17A were demonstrated and that the effectiveness of secukinumab in the treatment of psoriasis is accountable.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

Absorption and distribution data from the studies on secukinumab administered subcutaneously and intravenously to cynomolgus monkeys and mice were submitted. Pharmacokinetic studies were conducted with secukinumab derived from CHO cells or [redacted] cells. An anti-mouse IL-17A antibody (BZN035) was also used as murine surrogate antibody for secukinumab. Serum concentrations of secukinumab derived from CHO cells or [redacted] cells were determined by enzyme-linked immunosorbent assay (ELISA) using an anti-idiotypic anti-secukinumab antibody coated on a plate (lower limit of quantification, 80 ng/mL) or ELISA using IL-17A coated on a plate (lower limit of quantification, 1.2 μg/mL). Serum BZN035 concentrations were determined by ELISA (lower limit of quantification, 7.00 μg/mL). Anti-secukinumab antibodies were measured by an assay using surface plasmon resonance, and anti-BZN035 antibodies were measured by bridging ELISA (lower limit of quantification, 1 μg/mL). Serum IL-17A concentrations were determined by sandwich ELISA (lower limit of quantification, 81.9 pg/mL).

Unless otherwise specified, pharmacokinetic parameters are expressed as the mean or the mean ± SD.

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single-dose studies (4.2.2.2-1 to 4.2.2.2-3, Toxicokinetics 4.2.3.1-1)

The pharmacokinetic parameters of secukinumab derived from CHO cells or [redacted] cells in male and female cynomolgus monkeys (n = 2-6/sex/group) after a single subcutaneous or intravenous dose were as shown in Table 4.

Table 4. Pharmacokinetic parameters of secukinumab derived from CHO cells or [redacted] cells in cynomolgus monkeys after a single dose

Dose (mg/kg)	Route of administration	n	C_{max} (μg/mL)	AUC_{inf} (μg·day/mL)	t_{max} (day)	$t_{1/2}$ (day)	CL (mL/day/kg)	V_{ss} (mL/kg)	CTD location
Secukinumab derived from CHO cells									
15 [a)]	s.c.	2M	243	5370	2	18	—	—	4.2.2.2-2
10 [a)]	i.v.	2M	319	5730	—	25	1.8	59.0	
10 [a)]	i.v.	2M	275	2680	—	16	3.8	73	4.2.2.2-3
10 [b)]	i.v.	2M	241	2170	—	12	4.8	76	
15 [a)]	s.c.	2M	76.6	471 [c) d)]	2	—	—	—	4.2.3.1-1
		3F	150	896 [c) d)]	4	—	—	—	
150 [a)]	s.c.	6M	1470	8000 [c) d)]	2.5	11.8 [d)]	—	—	
		6F	1570	8500 [c) d)]	3	16.1 [d)]	—	—	
Secukinumab derived from [redacted] cells									
15 [b)]	s.c.	3M	196 ± 10.6	5640 [f)]	3 (2-3) [e)]	—	—	—	4.2.2.2-1
10 [b)]	i.v.	3M	253 ± 12.3	4020 ±703	—	20.1 ± 6.1	2.8 ± 0.6	74.5 ± 7.6	
10 [a)]	i.v.	2M	—	4090	—	15	2.6	48	4.2.2.2-3
10 [b)]	i.v.	2M	301	3780	—	16	2.7	59	

Mean or Mean ± SD
C_{max}: maximum serum concentration
t_{max}: time to the maximum observed serum concentration
AUC_{inf}: area under the serum concentration-time curve from time 0 to infinity
CL: systemic clearance
V_{ss}: steady state volume of distribution
$t_{1/2}$: elimination half-life
s.c.: subcutaneous administration
i.v.: intravenous administration
a) Determined by an ELISA using an anti-idiotypic antibody coated on a plate.
b) Determined by an ELISA using IL-17A coated on a plate.
c) $AUC_{0\text{-}168h}$, d) n = 3, e) Median (range), f) n = 2

Immunogenicity evaluations were performed in all single-dose studies except for 4.2.3.1-1. Anti-secukinumab antibodies were detected in 1 out of 3 animals after a single subcutaneous dose of 15 mg/kg of secukinumab derived from [redacted] cells and in 1 out of 3 animals after a single intravenous dose of 10 mg/kg of secukinumab derived from [redacted] cells.

In Studies 4.2.3.1-1 and 4.2.2.2-1, serum IL-17A concentrations were determined. Serum IL-17A concentrations reached maximal levels 3 to 10 days post-dose then decreased gradually.

3.(ii).A.(1).2) Repeat-dose studies (Toxicokinetics) (4.2.3.2-1 to 4.2.3.2-4, 4.2.3.5.1-1)

The toxicokinetics of secukinumab derived from CHO cells or [redacted] cells in male and female cynomolgus monkeys (n = 3-6/sex/group) were investigated after weekly subcutaneous or intravenous administration. The pharmacokinetic parameters of secukinumab were as shown in Table 5. C_{max} and $AUC_{0\text{-}168h}$ increased dose-proportionally and no obvious sex differences were observed. After subcutaneous administration of secukinumab, steady-state serum concentrations of secukinumab were nearly achieved by Week 5.

Table 5. Pharmacokinetic parameters of secukinumab derived from CHO cells or [redacted] cells in cynomolgus monkeys after weekly administration

Duration of dosing	Dose (mg/kg/week)	Route of administration	n	Time point	Male		Female	
					C_{max} (μg/mL)	$AUC_{0\text{-}168h}$ (μg·day/mL)	C_{max} (μg/mL)	$AUC_{0\text{-}168h}$ (μg·day/mL)
Secukinumab derived from CHO cells								
13 weeks [a)]	15	s.c.	3	Day 1	136	746	196	1013
				Day 36	360	2267	564	3233
				Day 85	494	3146	618	3896
	50		3	Day 1	492	2763	467 [c)]	2696 [c)]
				Day 36	1710	10542	1640	9625
				Day 85	1990	12042	2040	12708
	150		5	Day 1	1820	9750	1700	9042
				Day 36	4630	25958	5360	30958
				Day 85	5310	32792	5600	34750
4 weeks [b)]	15	i.v.	3	Day 1	411	1375 [d)]	520	1783 [d)]
				Day 22	711	2921 [d)]	573	3125 [d)]
	50		3	Day 1	1630	4458 [d)]	1830	4833 [d)]
				Day 22	2110	9292 [d)]	2960	12583 [d)]
	150		5	Day 1	5060	14542 [d)]	3970	12708 [d)]
				Day 22	7660	32750 [d)]	6260	27542 [d)]
26 weeks [a)]	15	i.v.	4	Day 1	370	1229 [d)]	398	1358 [d)]
				Day 176	785	3804	982	4625
	50		4	Day 1	1530	4250	1500	3904
				Day 176	3210	13250	3140	13125
	150		6	Day 1	4010	13292	3860	11417
				Day 176	8460	38417	8770	34542
Secukinumab derived from [redacted] cells								
4 weeks [b)]	10	i.v.	3	Day 1	275	881 [d)]	295	961 [d)]
				Day 22	443	2050 [d)]	509	2103 [d)]
	30		3	Day 1	772	2519 [d)]	743	2511 [d)]
				Day 22	1395	5792 [d)]	1309	5403 [d)]
	100		5	Day 1	2873	8492 [d)]	3159	9042 [d)]
				Day 22	4763	19317 [d)]	4814	21575 [d)]

Mean
a) Determined by an ELISA using an anti-idiotypic antibody coated on a plate.
b) Determined by an ELISA using IL-17A coated on a plate.
c) n = 2, d) $AUC_{0.083\text{-}168h}$

Immunogenicity evaluations were performed in all repeat-dose studies. Although anti-secukinumab antibodies were detected in 1 out of 5 females in the 150 mg/kg group in a 13-week subcutaneous administration study, serum secukinumab concentrations in this animal were not substantially different from those in the animals without anti-secukinumab antibodies.

Serum IL-17A concentrations were determined in all repeat-dose studies. Although highly variable among animals, serum IL-17A concentrations started to increase on Day 2 and peaked by Week 4 and fell below the lower limit of quantification after a recovery period in all studies. The applicant discussed that secukinumab dosing increased serum IL-17A concentrations due to slow elimination of the secukinumab-IL-17A complexes as compared to free IL-17A.

3.(ii).A.(2) Distribution

Since secukinumab is a human IgG monoclonal antibody, its antigen-nonspecific distribution should be consistent with endogenous IgG. According to a report, the radioactivity concentration-time profiles in normal tissues were consistent with human IgG as control and no specific uptake was seen in any tissue in a tissue distribution study with a radiolabeled form of an IgG antibody drug (Fox JA, et al. *J Pharmacol Exp Ther.* 1996;279:1000-1008, Kamath AV, et al. *PLoS One.* 2012;7:e45116). Therefore, no distribution studies of secukinumab were performed. The placental transfer of secukinumab was studied.

3.(ii).A.(2).1) Placental transfer to fetus (4.2.2.2-4, 4.2.3.5.2-1, 4.2.3.5.3-1)

Following the administration of a single intravenous dose of 100 mg/kg of secukinumab derived from [redacted] cells to pregnant cynomolgus monkeys (n = 5) from gestation day 98 to gestation day 101, serum secukinumab concentrations in dams and fetuses[4] from gestation day 99 to gestation day 102 were 2320 ± 248 and 52 ± 15 μg/mL, respectively, and the fetal to maternal ratio was 0.022.

Following the weekly subcutaneous administration of 15, 50, or 150 mg/kg secukinumab derived from CHO cells to pregnant cynomolgus monkeys (n = 13 or 14/group) from gestation day 20 to gestation day 90, the serum secukinumab concentrations[3] on gestation day 100 were 312, 1020, and 2890 μg/mL, respectively, in the dams and 91.4, 201, and 562 μg/mL, respectively, in the fetuses and the fetal to maternal ratio was 0.194 to 0.293. The secukinumab concentrations in amniotic fluid[3] were 10.7, 27.9, and 85.8 μg/mL, respectively, and the amniotic fluid to maternal serum ratio was 0.030 to 0.034.

Following the subcutaneous administration of 15, 50, or 150 mg/kg of BZN035 to pregnant mice (n = 3/group) on gestation days 6, 11, and 17 and on postpartum days 4, 10, and 16, the $AUC_{0\text{-}72h}$ values on postpartum day 16 were 96, 328, and 925 μg·day/mL, respectively, in the dams and 148, 442, and 1675 μg·day/mL, respectively, in the pups and the pup to maternal ratio was 1.3 to 1.8.

3.(ii).A.(3) Metabolism and excretion

Since secukinumab is an IgG1 antibody, and IgG is thought to be eliminated through intracellular catabolism following endocytosis, no metabolism or excretion studies of secukinumab have been performed.

3.(ii).B Outline of the review

PMDA concluded that there are no particular problems with the submitted non-clinical pharmacokinetic data.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

Toxicity studies of secukinumab conducted were single-dose toxicity, repeat-dose toxicity, reproductive and developmental toxicity, and other toxicity studies (a blood compatibility study, an antibody-dependent cellular cytotoxicity [ADCC] study, tissue cross-reactivity studies). The cynomolgus monkey was selected as relevant species for the evaluation of toxicity since secukinumab cross-reacts with cynomolgus monkey IL-17A but not with rodent IL-17A [see "3.(i) Summary of pharmacology studies"]. Reproductive and developmental toxicity studies (a study of fertility and early embryonic development to implantation, a study for effects on pre- and postnatal development, including maternal function) were conducted in mice using an anti-mouse IL-17A antibody (BZN035) as a murine surrogate antibody for secukinumab.

3.(iii).A.(1) Single-dose toxicity

3.(iii).A.(1).1) Single dose subcutaneous injection toxicity study in monkeys (4.2.3-1)

A single subcutaneous dose of 0 (vehicle: sterile water for injection), 15, or 150 mg/kg of secukinumab derived

[4] Determined by an ELISA using an anti-idiotypic antibody coated on a plate.

from CHO cells was administered to male and female cynomolgus monkeys. There were no deaths or secukinumab-related effects on clinical signs and no local irritation or immunogenicity was observed. Based on the above, the no observed adverse effect level (NOAEL) was determined to be 150 mg/kg.

3.(iii).A.(2) Repeat-dose toxicity

Repeat-dose toxicity was investigated in a 3-month subcutaneous administration study and 1-month and 6-month intravenous administration studies in monkeys. There were no deaths, secukinumab-related effects on clinical signs, or local irritation in any of the studies. The NOAEL in the 3-month subcutaneous injection toxicity study was determined to be 150 mg/kg, and the corresponding C_{max} (5455 μg/mL) was approximately 53 and 100 times the predicted C_{max} values in patients with psoriasis treated with 300 mg of subcutaneous secukinumab during the induction period and during the maintenance period, respectively (103 μg/mL during the induction period, 54.8 μg/mL during the maintenance period)[5]. Secukinumab derived from [redacted] cells and secukinumab derived from CHO cells were used in the 1-month intravenous administration studies and there were no differences in the toxicological profile of secukinumab according to the host cell line.

3.(iii).A.(2).1) Three-month subcutaneous injection toxicity study in monkeys (4.2.3.2-1)

Secukinumab derived from CHO cells was subcutaneously administered once weekly to male and female cynomolgus monkeys at 0 (vehicle: sterile water for injection), 15, 50, or 150 mg/kg for 13 weeks. There were no deaths or secukinumab-related effects on clinical signs. Immunophenotyping revealed moderately lower total lymphocyte counts, T cell populations, and B cell counts in females at ≥50 mg/kg. In the T-cell dependent antibody response (TDAR) study, an immunoglobulin class switch from IgM to IgG was detected in all animals and mild to moderate decreases in anti-keyhole-limpet hemocyanin (KLH) IgG antibody levels were observed in males at ≥15 mg/kg and females at ≥50 mg/kg. The immunophenotyping and TDAR findings were considered of no toxicological significance because the observed changes were reversible and variable among animals and were not associated with clinical signs or histopathological changes in immune tissues. While anti-secukinumab antibodies were detected in 1 out of 5 females in the 150 mg/kg group, the exposure to secukinumab in this animal was not substantially different from that in the animals without anti-secukinumab antibodies. Accordingly, the NOAEL was determined to be 150 mg/kg.

3.(iii).A.(2).2) One-month intravenous bolus toxicity study in monkeys (4.2.3.2-2)

Secukinumab derived from [redacted] cells was administered intravenously once weekly to male and female cynomolgus monkeys at 0 (vehicle: sterile water for injection), 10, 30, and 100 mg/kg for 4 weeks. There were no deaths or secukinumab-related effects on clinical signs, and no immunogenicity was observed. Immunophenotyping revealed decreases in B cell counts in females at 10 and 30 mg/kg and males at 30 mg/kg, decreases in total lymphocyte counts and T cell counts in females at ≥30 mg/kg, and a decrease in the percentage of cytotoxic T cells in females at 100 mg/kg. Although increases in NK cell counts in males at ≥10 mg/kg, increases in activated NK cell counts in males at 10 and 30 mg/kg, and decreases in activated NK cell counts in females at 100 mg/kg were observed, there were no changes in NK cell activity in any group. These

[5] The C_{max} values in psoriatic patients treated with subcutaneous doses of 300 mg of secukinumab administered at Weeks 0, 1, 2, 3, and 4 followed by every 4 weeks were predicted by a population pharmacokinetic model based on pharmacokinetic data from clinical studies.

changes were reversible in females and were not associated with clinical signs or histopathological changes in immune tissues, and were considered of no toxicological significance. Accordingly, the NOAEL was determined to be 100 mg/kg.

3.(iii).A.(2).3) One-month intravenous injection toxicity study in monkeys (4.2.3.2-3)

Secukinumab derived from CHO cells was administered intravenously once weekly to male and female cynomolgus monkeys at 0 (vehicle: sterile water for injection), 15, 50, and 150 mg/kg for 4 weeks. There were no deaths or secukinumab-related effects on clinical signs, and no immunogenicity or immunotoxicity was observed. The NOAEL was determined to be 150 mg/kg.

3.(iii).A.(2).4) Six-month intravenous injection toxicity study in monkeys (4.2.3.2-4)

Secukinumab derived from CHO cells was administered intravenously once weekly to male and female cynomolgus monkeys at 0 (vehicle: sterile water for injection), 15, 50, and 150 mg/kg for 26 weeks. There were no deaths and no immunogenicity was observed. Rash, a decrease in NK cell activity, and minimal splenic lymphoid atrophy were observed in 1 out of 4 females in the 150 mg/kg group, which resolved during continued treatment, and serological and immunological test results (lymphocyte counts and immunophenotyping) were not suggestive of infections, and no changes in body weight or food consumption were observed. Thus, these findings were considered of little toxicological significance. In the TDAR study, anti-KLH IgM and anti-KLH IgG titers decreased at ≥10 mg/kg. These TDAR findings were not associated with clinical signs or histopathological changes in immune tissues and were considered of no toxicological significance. Hematological examination revealed decreases in neutrophil counts in males at 150 mg/kg, which did not resolve completely even after the recovery period. However, it was considered of no toxicological significance because decreased neutrophil counts was not observed in females and was highly variable among animals. Decreases in red blood cell parameters were seen in females at 150 mg/kg, which were minimal changes and resolved after the recovery period. Clinical chemistry examination showed mild increases in globulin concentration at ≥15 mg/kg, which were caused by administration of a large amount of exogenous IgG (secukinumab), and were considered of no toxicological significance. Accordingly, the NOAEL was determined to be 150 mg/kg.

3.(iii).A.(3) Genotoxicity

Since secukinumab is an antibody drug and there is little concern about its genotoxic potential, no genotoxicity studies have been conducted.

3.(iii).A.(4) Carcinogenicity

No carcinogenicity studies have been conducted for the following reasons:

- Secukinumab is an IgG1 antibody and its molecular structure itself does not have a carcinogenic risk.
- Secukinumab is not pharmacologically active in rodents. Carcinogenicity studies are not feasible in the cynomolgus monkey.
- Based on the literature available to date in pre-clinical models (Langowski JL, et al. *Nature.* 2006;442:461–465, Langowski JL, et al. *Trends Immunol.* 2007;28:207-212, Xiao, et al. *Cancer Res.* 2009;69:2010-2017,

etc.), the neutralization of IL-17A is unlikely to increase the carcinogenic risk.

3.(iii).A.(5) Reproductive and developmental toxicity

As reproductive and developmental toxicity studies, an embryo-fetal development study with secukinumab was conducted in monkeys. A study on fertility and early embryonic development to implantation and a study on the effects of secukinumab on pre- and postnatal development, including maternal function, were conducted in mice with an anti-mouse IL-17A antibody (BZN035) as murine surrogate antibody for secukinumab.

3.(iii).A.(5).1) Study on fertility and early embryonic development to implantation in mice (4.2.3.5.1-1)

BZN035 was subcutaneously administered at the dose of 0 (vehicle: sterile water for injection), 15, 50 or 150 mg/kg to male CD-1 mice weekly for 4 weeks before mating, during the mating period, and until necropsy (within 3 weeks after the mating period) and to female CD-1 mice for 2 weeks before mating, during the mating period, and until gestation day 6. There were no deaths or BZN035-related effects on clinical signs, mating, estrous cyclicity, or fertility, and no immunogenicity was observed. Accordingly, the NOAEL for reproductive function, fertility, and early embryonic development was determined to be 150 mg/kg.

3.(iii).A.(5).2) Embryo-fetal development study in monkeys (4.2.3.5.2-1)

CHO cell-derived secukinumab was administered subcutaneously to pregnant cynomolgus monkeys at the dose of 0 (vehicle: sterile water for injection), 15, 50, or 150 mg/kg weekly, from day 20 to 50 of gestation or from day 20 to 90 of gestation. In the dams, there were no deaths, secukinumab-related effects on clinical signs, or immunogenicity. No embryo-fetal toxicity or teratogenicity was observed. A fetal skeletal examination revealed a dose-related increase in the incidence of misaligned vertebrae in the tail region (1 of 16 fetuses in the 15 mg/kg group [6.3%], 2 of 16 fetuses in the 50 mg/kg group [12.5%], 6 of 16 fetuses in the 150 mg/kg group [37.5%]). However, since this skeletal finding is a commonly observed spontaneous variation in cynomolgus monkeys and its incidence did not far exceed the incidence of misaligned vertebrae in studies performed at the same contract research organization (31.3%), the condition was not considered secukinumab-related. Accordingly, the NOAEL was determined to be 150 mg/kg for both maternal toxicity and embryo-fetal toxicity. The corresponding C_{max} (5070 μg/mL) was 49 times greater during the induction period and was 93 times greater during the maintenance period than the predicted C_{max} values in patients with psoriasis treated with 300 mg of subcutaneous secukinumab.

3.(iii).A.(5).3) Study on effects on pre- and postnatal development, including maternal function in mice (4.2.3.5.3-1)

BZN035 were administered subcutaneously to pregnant CD-1 mice at the dose of 0 (vehicle: sterile water for injection), 15, 50, or 150 mg/kg on gestation days 6, 11, and 17, and on postpartum days 4, 10, and 16. In the dams, there were no deaths, BZN035-related effects on clinical signs or reproductive parameters (gestation index, duration of gestation, live birth index, implantation sites), or immunogenicity. In the F1 pups, there were no BZN035-related effects on survival, sex ratio, clinical signs, physical development, or reflex development, and no immunogenicity was observed. In the F1 adult animals, there were no effects on clinical signs or reproductive parameters. Immunophenotyping revealed increases in T cell counts in the thymus at ≥50

mg/kg, increases in total lymphocyte counts in the spleen in males at ≥50 mg/kg, and mild decreases in total lymphocyte counts in blood in males at 50 mg/kg. All of these were changes in absolute number, and differential white blood cell count and differential T cell count were unaffected. There were no treatment-related effects on anti-KLH IgM or anti-KLH IgG response in the TDAR study and no changes in lymphoid tissue weight or no histopathological changes. Therefore these findings were considered of no toxicological significance. In the F2 pups, there were no BZN035-related effects on survival, sex ratio, or clinical signs. Accordingly, the NOAEL was determined to be 150 mg/kg for both the F0 and F1 generations.

3.(iii).A.(6) Other toxicity studies

3.(iii).A.(6).1) Blood compatibility study (4.2.3.7.7-1)

Secukinumab derived from [redacted] cells at 0 (vehicle: 5 mmol/L histidine buffer), 0.62, 1.25, or 2.5 mg/mL was mixed with human or cynomolgus monkey whole blood, serum, or plasma. Secukinumab did not cause hemolysis of human or cynomolgus monkey erythrocytes and proved to be compatible with human and cynomolgus monkey serum and plasma.

3.(iii).A.(6).2) ADCC study (4.2.3.7.7-2)

The potential of secukinumab derived from [redacted] cells to elicit ADCC was evaluated using human B21 T cells (memory T cells capable of producing IL-17A). Secukinumab (10 μg/mL) did not elicit NK cell-mediated ADCC.

3.(iii).A.(6).3) Cross-reactivity study of secukinumab with normal human and cynomolgus monkey tissues (4.2.3.7.7-3)

A cross-reactivity study of secukinumab derived from [redacted] cells (1, 20, 50, or 230 μg/mL) with normal human and cynomolgus monkey tissues was conducted. In human tissues, secukinumab-specific staining of mononuclear cells/lymphocytes in the kidney, lymph node, tonsil, and urinary bladder was observed. Since the molecular target of secukinumab, IL-17A is expressed by activated T-lymphocytes (Kennedy J, et al. *J Interferon Cytokine Res*. 1996;16:611-617, Shin HC, et al. *Cytokine*. 1999;11:257-266, Albanesi C, et al. *J Invest Dermatol*. 2000;115:81-87), lymphocytes in these tissues may have been partially activated. In cynomolgus monkey tissues, secukinumab cross-reacted with mononuclear cells in the lymph node and the basal lamina of epithelium in the colon, esophagus, small intestine, pituitary, prostate, salivary gland, skin, tonsil, ureter, urinary bladder, uterus, and cervix. However, as no relevant histopathological findings were observed in a repeat-dose toxicity study, the reactivity seen in the tissue cross-reactivity study is considered of negligible toxicological significance. It has been concluded that there are no toxicologically significant differences in the cross-reactivity of secukinumab between human and cynomolgus monkey tissues.

3.(iii).A.(6).4) Cross-reactivity study of secukinumab with normal human and cynomolgus monkey tissues (4.2.3.7.7-4)

A cross-reactivity study of CHO cell-derived secukinumab (1, 20, 50, or 230 μg/mL) with normal human and cynomolgus monkey tissues was conducted. In human tissues, secukinumab-specific staining of mononuclear cells/lymphocytes in the esophagus, small intestine, stomach, heart, kidney, liver, ovary, fallopian tube, pancreas, placenta, salivary gland, skin, spinal cord, spleen, thymus, tonsil, uterus, and cervix was observed. In addition, the binding of secukinumab to hematopoietic precursor cells was observed in the bone marrow. However, since the expression of IL-17A in these cells has not been identified, CHO cells may have bound to or cross-reacted with these cells. In cynomolgus monkey tissue, secukinumab-specific staining of mononuclear cells/lymphocytes was observed in the small intestine, liver, lung, lymph node, spleen, tonsil, uterus, and cervix. In the liver and spleen (splenic red pulp), the binding of secukinumab to mononuclear cells morphologically consistent with macrophages, as well as mononuclear cells/lymphocytes, was observed. However, this finding is considered of little toxicological significance because IL-17 expression in macrophages in inflammatory disease has been reported (Fujino S, et al. *Gut.* 2003;5:65-70) and no relevant toxicological findings were observed in repeat-dose toxicity studies. Lower binding of secukinumab to cynomolgus monkey tissue than to human tissue was possibly due to the difference in the number of activated lymphocytes between cynomolgus monkey and human tissues (due to the difference in the tissue collection method [cynomolgus monkey tissue was taken promptly after euthanasia of healthy, young cynomolgus monkeys.]) or the species difference in binding affinity (lower binding affinity of secukinumab to cynomolgus monkey IL-17A than to human IL-17A) [see "3.(i) Summary of pharmacology studies"]. Accordingly, it has been concluded that there are no toxicologically significant differences in the cross-reactivity of secukinumab between human and cynomolgus monkey tissues and that there are also no toxicologically significant differences in the binding or cross-reactivity of secukinumab according to the host cell line (CHO cells or [redacted] cells).

3.(iii).B Outline of the review

3.(iii).B.(1) Effects on the immune system

The applicant explained the effects of secukinumab on the immune system as follows:

IL-17A is primarily associated with the clearance of extracellular bacteria and fungi, and the Th17/IL-17A pathway plays an important role in the immune surveillance of mucocutaneous barrier tissues (gastrointestinal and respiratory tracts, and skin). Reports on human primary immunodeficiency in the Th17/IL-17 pathway have revealed that IL-17A is involved in host defense against mucocutaneous infections with *Candida albicans* and with *Staphylococcus aureus* (Notarangelo LD, et al. *J Allergy Clin Immunol.* 2009;124:1161-1178, Maródi L and Casanova JL. *J Allergy Clin Immunol.* 2010;126:910-917, Puel A, et al. *Curr Opin Allergy Clin Immunol.* 2012;12:616-622, Bousfiha AA, et al. *J Clin Immunol.* 2013;33:1-7), and studies in the IL-17 pathway deficient mice or mice treated with anti-IL-17A antibody or anti-IL-17F antibody also indicated that the IL-17 pathway is involved in host defense against infection by *Candida albicans* or *Staphylococcus aureus* infection (Gladiator A, et al. *J Immunol.* 2013;190:521-525, Ishigame H, et al. *Immunity.* 2009;*30*:108-119, Cho JS, et al. *J Clin Invest.* 2010;120:1762-1773). Taking account of these findings, etc., the neutralization of IL-17A by secukinumab may impair the immune function, which may result in increased risk of mucocutaneous infections, especially with *Candida albicans* and with *Staphylococcus aureus*.

Immunophenotyping and the T-cell dependent antibody response (TDAR) assay were performed in repeat-dose toxicity studies in monkeys. Decreases in total lymphocyte counts, T cell populations, B cell counts, and anti-KLH IgG titers, etc. were found sporadically. There was a persistent decrease in neutrophil count in a 6-month intravenous injection toxicity study in monkeys. PMDA asked the applicant to explain the possible relationship of these findings to secukinumab in more details.

The applicant explained as follows:
No dose-response relationship was observed for any of the immunophenotyping and TDAR findings in monkey repeat-dose toxicity studies, and these findings are unlikely to be related to secukinumab. These findings were not associated with secukinumab-related effects on clinical signs or histopathological changes in immune tissues suggestive of decreased host defense, and are therefore considered of no toxicological significance. Moreover, the effect of secukinumab on human peripheral T cell subpopulations ($CD3^+CD8^+$ T cell fraction and $CD4^+$ T cell fraction) was investigated in a psoriasis clinical study (A2212[6]). The result revealed no major changes, and secukinumab was well tolerated. While secukinumab inhibits IL-17A- and IL-17F-induced IL-6 production in cynomolgus monkeys, secukinumab is selective for IL-17A or IL-17AF in humans [see "3.(i) Summary of pharmacology studies"]. The effects of secukinumab seem to be more limited in the human as compared to the monkey. Taking account of these points, the immunophenotyping and TDAR findings are considered of little relevance to humans. In the 6-month intravenous injection repeat-dose toxicity study in monkeys, decreases in neutrophil counts were observed in males in the 150 mg/kg group. The decreases in neutrophil counts greatly varied among the animals, and only 2 of 6 animals had values lower than the variation range in the control group. No changes in neutrophil counts in females, no sex differences in the differentiation and proliferation of neutrophils were reported. No sex differences for secukinumab-related effects including the exposure to secukinumab were observed. Therefore, the decreased neutrophil counts were also considered unrelated to secukinumab

PMDA considers as follows:
The number of animals assessed for each parameter was limited and there was a high inter-animal variability. It is therefore difficult to determine whether or not decreased total lymphocyte counts, T cell populations, and B cell counts and decreases in anti-KLH IgG and anti-KLH IgM levels observed in repeat-dose toxicity studies were related to secukinumab. However, given the pharmacological effects of secukinumab, the possibility that these findings were related to secukinumab cannot be ruled out. Decreases in neutrophil counts observed in a 6-month intravenous injection toxicity study in monkeys should also be considered related to secukinumab because IL-17A inhibition may suppress neutrophil production and migration and reduce peripheral neutrophil counts (Stark MA, et al. *Immunity*. 2005;22:285-294, Weaver CT, et al. *Annu Rev Immunol*. 2007;25:821-852), and the finding was not reversible. Given the pharmacological effects of secukinumab, there is a concern about the risk of infections associated with immunosuppression also in clinical use. Therefore, the risk of serious infections caused by *Candida albicans* and *Staphylococcus aureus*, etc. needs to be assessed based on clinical

[6] A clinical study in foreign patients with psoriasis who received a single intravenous dose of 3 mg/kg or 10 mg/kg of secukinumab or three intravenous doses of secukinumab 10 mg/kg or placebo administered every 2 weeks (5.3.5.1-3).

study data [see “4.(iii).B.(2) Safety”].

3.(iii).B.(2) Carcinogenicity

PMDA asked the applicant to discuss the oncogenic risk of secukinumab and the risk of progression of malignancies.

The applicant explained as follows:

Increased IL-17A expression has been reported for various tumors, and IL-17A increases the production of a variety of inflammatory cytokines and angiogenic factors (Kolls JK and Linden A. *Immunity.* 2004;21:467-476, Takahashi H, et al. *Immunol Lett.* 2005;98:189-193) to promote tumor development (Numasaki M, et al. *Blood.* 2003;101:2620-2627, Numasaki M, et al. *J Immunol.* 2005;175:6177-6189). In IL-23 knockout mice in which low or no IL-17A is detected (Langowski JL, et al. *Nature.* 2006;442:461-465), tumor development and the growth of transplanted tumors were suppressed. An anti-mouse IL-17A antibody decreased chemically-induced nascent papilloma development in mice (Xiao M, et al. *Cancer Res.* 2009;69:2010-2017). Therefore, an anti-IL-17A antibody, secukinumab, may have an anti-tumorigenic effect.

On the other hand, IL-17A has a role in tumor immuno-surveillance (Hirahara N, et al. *Oncology.* 2001;61:79-89, Benchetrit F, et al. *Blood.* 2002;99:2114-2121, Honorati MC, et al. *Clin Exp Immunol.* 2003;133:344-349). Tumor-infiltrating T cells and NK cells producing IFNγ are reduced in IL-17 knockout mice and when a murine colon cancer cell line (MC38) was inoculated into wild-type and IL-17 knockout mice, the IL-17 knockout mice exhibited an accelerated tumor growth and more metastatic foci of tumors as compared with the wild-type mice (Kryczek I, et al. *Blood.* 2009;114:857-859). IL-17 production by γδT cells is important for the antitumor effect of *Mycobacterium bovis bacillus Calmette–Guerin* (BCG) treatment against bladder cancer (Takeuchi A, et al. *Eur J Immunol.* 2011;41:246-251). Given that an anti-tumor effect of IL-17A has been suggested, an anti-IL-17A antibody, secukinumab, may have a pro-tumor growth effect as well. In summary, both protection from cancer and promotion of cancer have been reported as carcinogenicity modulation by IL-17A and IL-17A-mediated signaling.

Secukinumab did not induce proliferative changes or atypia suggestive of carcinogenicity at dose levels of up to 150 mg/kg/week in the repeat-dose toxicity study in monkeys. The incidence of malignancies was low in clinical studies, and the incidence in the secukinumab group was similar to that in the placebo group or the Etanercept (Genetical Recombination) (hereinafter referred to as etanercept) group [see “4.(iii).B.(2) Safety”]. Thus, no carcinogenic potential of secukinumab has been indicated to date.

PMDA accepts the applicant’s explanation from a toxicological standpoint. However, the incidence of malignancies resulting from secukinumab in clinical use should be carefully studied, given that immunotoxicity findings such as decreased T-cell dependent antibody response were sporadically observed in repeat-dose toxicity studies, that inhibition of IL-17A or IL-17A-mediated signaling promotes tumor growth, and that, as with the approved immunosuppressive biological products and immunosuppressants, the possibility that secukinumab affects the anti-tumor immune defense mechanisms cannot be ruled out [see

"4.(iii).B.(2) Safety"].

4. Clinical data

4.(i) Summary of biopharmaceutical studies and associated analytical methods

4.(i).A Summary of the submitted data

The results from an absolute bioavailability study in foreign patients with psoriasis (5.3.1.1-1, A2103) and a bioequivalence study in foreign healthy adult subjects (5.3.1.2-1, A2106) were submitted as reference data. The drug product manufactured from the drug substance derived from Chinese hamster ovary (CHO) cells was used in both studies. Secukinumab concentrations in serum (lower limit of quantification, 80 ng/mL) and in dermal interstitial fluid (lower limit of quantification, 76 ng/mL) were determined by ELISA using an anti-idiotypic anti-secukinumab antibody coated on a plate. Serum IL-17A concentrations were determined using a Meso Scale Discovery assay (MSD assay; lower limit of quantification, 20 pg/mL) and IL-17A concentrations in dermal interstitial fluid were determined by sandwich ELISA (lower limit of quantification, 0.02 pg/mL). Anti-secukinumab antibodies were measured by an assay using surface plasmon resonance or the MSD assay (lower limit of quantification, 4 ng/mL) and the neutralizing activity of anti-secukinumab antibodies was determined by ELISA (threshold concentration, 2.5 μg/mL).

Unless otherwise specified, pharmacokinetic parameters are expressed as the mean ± SD.

4.(i).A.1) Bioavailability study (Reference data 5.3.1.1-1, Study A2103 [January to May 2009])

A foreign, randomized, open-label, two-treatment, two-period, crossover study was conducted in patients with psoriasis (N = 14) to determine the absolute bioavailability of subcutaneous secukinumab. The pharmacokinetic parameters of secukinumab following a single subcutaneous dose of 150 mg or a single intravenous dose of 1 mg/kg were as shown in Table 6. The absolute bioavailability of secukinumab following subcutaneous administration (the geometric mean ratio of dose-normalized AUC_{inf}) was 55%.

None of the subjects tested positive for anti-secukinumab antibodies.

Table 6. Pharmacokinetic parameters of secukinumab following a single subcutaneous or intravenous dose in foreign patients with psoriasis

Route of administration	Dose	N	C_{max} (μg/mL)	AUC_{last} (μg·day/mL)	AUC_{inf} (μg·day/mL)	t_{max} (day)	$t_{1/2}$ (day)	CL (L/day)	V_z (L)
s.c.	150 mg	14	11.8 ± 3.8	364 ± 134	421 ± 164	8.50 (1.00-14.0)	22.2 ± 7.8	—	—
i.v.	1 mg/kg	14	24.1 ± 3.2	376 ± 70.5	441 ± 103	0.09 (0.08-0.33)	27.1 ± 6.3	0.22 ± 0.07	7.1 ± 2.4

Mean ± SD, Median (range) for t_{max}
C_{max}, maximal drug serum concentration
AUC_{last}: area under the drug serum concentration-time curve from time 0 to the last measurable concentration sampling time
AUC_{inf}: area under the drug serum concentration-time curve from time 0 to infinity
t_{max}: time to reach the maximum drug serum concentration following drug administration
$t_{1/2}$: elimination half lif
CL: systemic clearance
V_z: distribution volume during terminal elimination phase
s.c.: subcutaneous administration
i.v.: intravenous administration

4.(i).A.2) Bioequivalence study (Reference data 5.3.1.2-1, Study A2106 [May to November 2011])

A foreign, randomized, open-label, parallel-group study was conducted in healthy adult subjects (N = 150) to

determine the bioequivalence of the vial and PFS formulations. The pharmacokinetic parameters of secukinumab following a single subcutaneous dose of 300 mg presented in the vial or PFS formulation were as shown in Table 7. The ratios of the pharmacokinetic parameters for the PFS formulation vs. the vial formulation [90% CI] were 1.04 [0.96, 1.12] for C_{max} and 1.01 [0.93, 1.08] for AUC_{last}, demonstrating the pharmacokinetic comparability between the two formulations.

Anti-secukinumab antibodies were detected in 1 of 68 subjects in the vial formulation group.

Table 7. Pharmacokinetic parameters following a single subcutaneous dose of secukinumab presented in the vial or PFS formulation in foreign healthy adult subjects

	Route of administration	Dose	N	C_{max} (μg/mL)	AUC_{last} (μg·day/mL)	AUC_{inf} (μg·day/mL)	t_{max} (day)	$t_{1/2}$ (day)	CL (L/day)	V_z (L)
Vial formulation	s.c.	300 mg	68	42.0 ± 11.2	1680 ± 432	1800 ± 498	5.00 (2.00-14.0)	26.6 ± 5.1	0.18 ± 0.06	6.7 ± 1.5
PFS formulation	s.c.	300 mg	70	43.2 ± 10.4	1680 ± 411	1790 ± 461	5.00 (2.00-14.0)	25.9 ± 4.6	0.18 ± 0.05	6.6 ± 1.7

Mean ± SD, Median (range) for t_{max}

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

As evaluation data on the pharmacokinetics of secukinumab, the results from a Japanese phase I study in healthy adult subjects (5.3.3.1-1, A1101), multinational phase II studies in patients with psoriasis (including Japan) (5.3.5.1-4, A2220; 5.3.5.1-1, A2211; 5.3.5.1-2, A2211E1; 5.3.5.1-3, A2212; 5.3.3.2-2, A2225), multinational phase III studies in patients with psoriasis (including Japan) (5.3.5.1-5, A2302; 5.3.5.2-1, A2304), a population pharmacokinetic analysis (5.3.3.5-1), and a population PK-PASI analysis (5.3.5.3-8) were submitted. As reference data, the results from a foreign phase II study in healthy adult subjects (5.3.4.1-2, A2104) and a foreign phase II study in patients with psoriasis (5.3.3.2-1, A2102), etc. were submitted. [redacted]

Unless otherwise specified, pharmacokinetic parameters and measurements are expressed as the mean ± SD.

4.(ii).A.(1) Healthy adult subject studies

4.(ii).A.(1).1) Japanese single intravenous/subcutaneous dose study (5.3.3.1-1, Study A1101 [February to September 2009])

A placebo-controlled, randomized, double-blind, single dose-escalation study was conducted in healthy adult subjects (N = 42) and the pharmacokinetics of a single intravenous or subcutaneous dose of secukinumab was evaluated. The pharmacokinetic parameters of secukinumab following a single intravenous dose of 1, 3, or 10 mg/kg (a 2-hour intravenous infusion) or a single subcutaneous dose of 150 or 300 mg were as shown in Table 8. C_{max} and AUC increased dose-proportionally. The absolute bioavailability of secukinumab following subcutaneous administration (the ratio of dose-normalized AUC_{inf}) was 77%. Serum IL-17A concentrations

[7] It is produced by different cells but has an identical amino acid sequence to secukinumab. Thus it is referred to as secukinumab in this section.

following a single intravenous dose of 10 mg/kg of secukinumab or a single subcutaneous dose of 150 mg of secukinumab were determined. Serum IL-17A concentrations increased following the administration of secukinumab in both treatment groups and the serum levels of IL-17A were higher following intravenous administration as compared to subcutaneous administration.

None of the subjects tested positive for anti-secukinumab antibodies.

Table 8. Pharmacokinetic parameters of secukinumab following a single intravenous or subcutaneous dose in Japanese healthy adult subjects

Route of administration	Dose	N	C_{max} (μg/mL)	AUC_{last} (μg·day/mL)	AUC_{inf} (μg·day/mL)	t_{max} (day)	$t_{1/2}$ (day)	CL (L/day)	V_z (L)
i.v.	1 mg/kg	6	24.0 ± 2.5	475 ± 67.7	520 ± 94.7	0.08 (0.08-0.17)	31.2 ± 5.1	0.12 ± 0.03	5.3 ± 1.0
	3 mg/kg	6	70.4 ± 5.9	1500 ± 120	1590 ± 154	0.17 (0.08-0.17)	26.4 ± 5.8	0.11 ± 0.01	4.3 ± 0.6
	10 mg/kg	6	264 ± 43.9	5670 ± 580	5990 ± 569	0.08 (0.08-0.17)	25.9 ± 3.3	0.11 ± 0.01	4.2 ± 0.4
s.c.	150 mg	6	21.1 ± 2.9	999 ± 132	1070 ± 153	8.01 (4.00-21.0)	30.0 ± 6.9	—	—
	300 mg	6	46.3 ± 7.6	1800 ± 353	1930 ± 408	8.01 (7.00-14.0)	25.9 ± 5.1	—	—

Mean ± SD, Median (range) for t_{max}

4.(ii).A.(1).2) Foreign single intravenous dose study (Reference data 5.3.4.1-2, Study A2104 [March to November 2009])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in healthy adult subjects (N = 24) and the pharmacokinetics of a single intravenous dose of secukinumab was evaluated. The pharmacokinetic parameters of secukinumab following a single intravenous administration of 10 mg/kg (a 2-hour intravenous infusion) were as shown in Table 9.

None of the subjects tested positive for anti-secukinumab antibodies.

Table 9. Pharmacokinetic parameters of secukinumab following a single intravenous administration in foreign healthy adult subjects

Route of administration	Dose	N	C_{max} (μg/mL)	AUC_{last} (μg·day/mL)	AUC_{inf} (μg·day/mL)	t_{max} (day)	$t_{1/2}$ (day)	CL (L/day)	V_z (L)
i.v.	10 mg/kg	12	255 ± 31.9	5944 ± 795	6414 ± 986	0.09 (0.09-0.17)	29.8 ± 4.6	0.12 ± 0.03	5.1 ± 0.7

Mean ± SD, Median (range) for t_{max}

4.(ii).A.(2) Patient studies

4.(ii).A.(2).1) Single and multiple subcutaneous dose study in Japanese and foreign patients with psoriasis (5.3.5.1-4, Study A2220 [March 2010 to February 2011])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in Japanese and foreign patients with psoriasis (N = 125) and the pharmacokinetics of secukinumab was evaluated. Secukinumab was subcutaneously administered as a single dose of 25 mg or as multiple doses (3 × 25 mg, 3 × 75 mg, or 3 × 150 mg) every 4 weeks. The serum secukinumab concentrations in the 25 mg, 3 × 25 mg, 3 × 75 mg, and 3 × 150 mg groups at Week 12 were 0.67 ± 0.43 μg/mL (N = 3), 2.82 ± 1.29 μg/mL (N = 6), 12.08 ± 1.27 μg/mL (N = 4), and 19.94 ± 6.40 μg/mL (N = 5), respectively, in Japanese subjects; and 0.48 ± 0.29 μg/mL (N = 21), 3.62 ± 2.03 μg/mL (N = 17), 7.86 ± 2.76 μg/mL (N = 14), and 16.49 ± 7.38 μg/mL (N = 18), respectively, in foreign

subjects.

None of the subjects tested positive for anti-secukinumab antibodies.

4.(ii).A.(2).2) Single and multiple subcutaneous dose study in Japanese and foreign patients with psoriasis (5.3.5.1-1, Study A2211 [July 2009 to December 2010])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in Japanese and foreign patients with psoriasis (N = 404) and the pharmacokinetics of secukinumab was evaluated. During the induction period, secukinumab 150 mg was administered subcutaneously as a single injection, as monthly injections (at Day 1, Week 4, and Week 8), or as early loading injections (at Day 1, Week 1, Week 2, and Week 4); and the serum secukinumab concentrations were as follows: in Japanese subjects, 8.45 ± 4.72 μg/mL (N = 6), 8.71 ± 4.09 μg/mL (N = 15), and 30.41 ± 8.35 μg/mL (N = 12), respectively, at Week 4; 3.45 ± 2.32 μg/mL (N = 6), 12.28 ± 5.85 μg/mL (N = 15), and 22.73 ± 6.07 μg/mL (N = 12), respectively, at Week 8; and 1.67 ± 1.60 μg/mL (N = 6), 14.91 ± 7.76 μg/mL (N = 15), and 10.50 ± 4.67 μg/mL (N = 12), respectively, at Week 12; while in foreign subjects, 8.89 ± 3.20 μg/mL (N = 51), 7.84 ± 2.92 μg/mL (N = 104), and 29.29 ± 10.65 (N = 108), respectively, at Week 4; 4.40 ± 2.03 μg/mL (N = 52), 11.09 ± 4.22 μg/mL (N = 109), and 21.97 ± 8.57 μg/mL (N = 103), respectively, at Week 8; and 2.14 ± 1.30 μg/mL (N = 45), 13.08 ± 5.41 μg/mL (N = 108), and 11.94 ± 6.36 μg/mL (N = 99), respectively, at Week 12.

None of the subjects tested positive for anti-secukinumab antibodies.

4.(ii).A.(2).3) Multiple subcutaneous dose study in Japanese and foreign patients with psoriasis (5.3.5.1-2, Study A2211E1 [May 2010 to ongoing (data cut-off date of January 21, 2013])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in Japanese and foreign patients with psoriasis who had completed Study A2211 (N = 275) and the pharmacokinetics of secukinumab was evaluated. Secukinumab 150 mg was administered subcutaneously every 12 weeks or every 4 weeks. The trough serum secukinumab concentrations in Japanese subjects were 3.55 ± 2.01 μg/mL (N = 8) and 12.53 ± 6.20 μg/mL (N = 21), respectively, at Week 12; and 3.62 ± 1.43 μg/mL (N = 7) and 13.45 ± 5.84 μg/mL (N = 19), respectively, at Week 24. The trough serum secukinumab concentrations in foreign subjects were 3.01 ± 1.65 μg/mL (N = 32) and 14.41 ± 7.26 μg/mL (N = 148), respectively, at Week 12; and 3.35 ± 1.77 μg/mL (N = 26) and 14.85 ± 7.54 μg/mL (N = 130), respectively, at Week 24.

After study treatment, anti-secukinumab antibodies were detected in 3.1% of the subjects (8 of 262 subjects) and 6 of them tested positive for neutralizing antibodies.

4.(ii).A.(2).4) Foreign single and multiple intravenous dose study (5.3.5.1-3, Study A2212 [December 2008 to September 2010])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients with psoriasis (N = 100) and the pharmacokinetics of secukinumab was evaluated. Secukinumab was intravenously administratered as a single dose of 3 mg/kg or 10 mg/kg, or as multiple doses (3 × 10 mg/kg) every 2 weeks.

The serum secukinumab concentrations in the 3 mg/kg, 10 mg/kg, and 3 × 10 mg/kg groups were 14.9 ± 2.0 μg/mL (N = 30), 64.6 ± 40.2 μg/mL (N = 25), and 130.2 ± 31.0 μg/mL (N = 30), respectively, at Week 4; 6.9 ± 2.4 μg/mL (N = 30), 23.7 ± 5.8 μg/mL (N = 25), and 116.1 ± 30.3 μg/mL (N = 30), respectively, at Week 8; and 3.0 ± 1.7 μg/mL (N = 30), 12.7 ± 3.6 μg/mL (N = 25), and 58.3 ± 20.3 μg/mL (N = 30), respectively, at Week 12.

After treatment with secukinumab, reductions of mRNA levels of IL-17A and IFN-γ, decreases in IL-17A and IL-17A-positive neutrophil counts in the epidermis, and reductions in epidermal thickness, parakeratosis, CD3+ T cell counts, Munro's microabscesses, and MPO positive cell counts were observed in skin lesions.

None of the subjects tested positive for anti-secukinumab antibodies.

The applicant explained that the pharmacokinetic parameters of secukinumab derived from CHO cells following a single intravenous dose of 3 mg/kg in this study (C_{max}, 76.5 ± 16.7 μg/mL; AUC_{inf}, 1454 ± 396 μg·day/mL) were similar to the pharmacokinetic parameters of secukinumab derived from [redacted] cells following a single intravenous dose of 3 mg/kg in Study A2102 (C_{max}, 74.5 ± 13.1 μg/mL; AUC_{inf}, 1629 ± 361 μg·day/mL).

4.(ii).A.(2).5) Multiple subcutaneous dose study in Japanese and foreign patients with psoriasis (5.3.5.1-5, Study A2302 [June 2011 to March 2013])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in Japanese and foreign patients with psoriasis (including patients with psoriatic arthritis) (N = 737) and the pharmacokinetics of secukinumab was evaluated. Secukinumab 150 or 300 mg was subcutaneously administered weekly for the first 4 weeks and then every 4 weeks. In Japanese subjects, trough serum secukinumab concentrations in the secukinumab 150 mg and 300 mg groups were 16.7 ± 6.18 μg/mL (N = 26) and 30.9 ± 12.4 μg/mL (N = 28), respectively, at Week 24 and 17.3 ± 7.65 μg/mL (N = 24) and 31.9 ± 9.53 μg/mL (N = 27), respectively, at Week 52; and those in foreign subjects were 17.8 ± 9.81 μg/mL (N = 180) and 34.9 ± 17.1 μg/mL (N = 183), respectively, at Week 24 and 16.6 ± 8.29 μg/mL (N = 147) and 32.9 ± 15.1 μg/mL (N = 150), respectively, at Week 52.

Anti-secukinumab antibodies were detected in 0.3% of subjects in the secukinumab 150 mg group (2 of 738 subjects) and 0.01% of subjects in the placebo group (2 of 248 subjects) and of these subjects, 1 subject in the secukinumab 150 mg group tested positive for neutralizing antibodies.

4.(ii).A.(2).6) Multiple subcutaneous dose study in Japanese and foreign patients with psoriasis (5.3.5.2-1, Study A2304 [August 2011 to March 2013])

A randomized, double-blind, parallel-group study was conducted in Japanese and foreign patients with psoriasis (including patients with psoriatic arthritis) (N = 965) and the pharmacokinetics of secukinumab was evaluated. Secukinumab 150 or 300 mg was administered subcutaneously weekly for the first 4 weeks and then every 4 weeks. In Japanese subjects, trough serum secukinumab concentrations in the secukinumab 150

mg and 300 mg groups were 18.2 ± 5.37 μg/mL (N = 11) and 28.2 ± 11.5 μg/mL (N = 13), respectively, at Week 24 and 19.4 ± 5.45 μg/mL (N = 11) and 29.9 ± 13.7 μg/mL (N = 13), respectively, at Week 52, and those in foreign subjects were 18.9 ± 10.2 μg/mL (N = 172) and 37.0 ± 15.9 μg/mL (N = 181), respectively, at Week 24 and 16.7 ± 7.34 μg/mL (N = 157) and 34.8 ± 16.3 (N = 164), respectively, at Week 52.

Anti-secukinumab antibodies were detected in 0.5% of subjects (5 of 966 subjects). Of these, 2 subjects in the secukinumab 150 mg group tested positive for neutralizing antibodies.

4.(ii).A.(3) Population pharmacokinetic analysis (5.3.3.5-1)

Using the pooled serum secukinumab concentration data from clinical studies in Japanese and foreign patients with psoriasis (A2102, A2103, A2211, A2211E1, A2212, A2220, A2302) (10193 serum secukinumab concentrations from 1233 patients), a population pharmacokinetic analysis was performed using NONMEM (Version 7.2). In the clinical studies, secukinumab was administered at the doses of 3 to 10 mg/kg intravenously or 25 to 300 mg subcutaneously.

The pharmacokinetic analysis was based on a two-compartment model. The selected covariate[8] was body weight as a significant factor for clearance (CL), the central volume of distribution (V2), inter-compartmental clearance (Q), and the peripheral volume of distribution (V3). Body weight was included in the final model as a covariate. The population parameter estimates and inter-individual variability estimates (CV%) of the final model were 0.19 L/day and 32% for CL, 3.61 L and 30% for V2, 0.39 L/day and 0% for Q, and 2.87 L and 18% for V3 in a typical foreign psoriasis patient (male, weighing 90 kg, 45 years). Estimated population parameters of Japanese patients with psoriasis weighing 73.3 kg[9] were 0.18 L/day for CL, 3.25 L for V2, 0.33 L/day for Q, and 2.53 L for V3. Serum secukinumab concentrations following subcutaneous administration of 150 or 300 mg weekly for the first 4 weeks and then every 4 weeks were simulated. The trough serum secukinumab concentrations at Week 12 were estimated to be 22.1 μg/mL and 44.2 μg/mL, respectively.

4.(ii).A.(4) Population PK-PASI analysis (5.3.5.3-8)

Using the pooled Psoriasis Area and Severity Index (PASI)[10] data from clinical studies in Japanese and foreign patients with psoriasis (A2102, A2103, A2211, A2212, A2220, A2302) (26587 PASI measuring points with 1405 patients), a population pharmacokinetic (PK)-PASI analysis was performed (PASI: a common measure of the severity of skin symptoms). A previously built population pharmacokinetic model (5.3.3.5-1) was used to estimate PK, and a PK-PD indirect response model (Sharma A and Jusko WJ. *Br J Clin Pharmacol.* 1998;45:229-239) was used to estimate PASI scores. The PASI 75 response rate[11] over time was simulated for secukinumab 150 or 300 mg administered subcutaneously weekly for the first 4 weeks and then every 4 weeks. The 300 mg regimen was predicted to exhibit efficacy earlier than the 150 mg regimen. The PASI 75 response

[8] Suggested covariates included body weight, age, gender, race (Asian or non-Asian), and baseline PASI score.
[9] Body weight of Japanese patients with psoriasis included in the population pharmacokinetic analysis (mean).
[10] The body is divided into four parts for scoring: the head, trunk, upper limbs, and lower limbs. Each part is assessed separately for the severity of erythema, thickening (plaque elevation, induration), and scaling (desquamation), which are each rated on a 5-point scale (0 [none] to 4 [very severe]). For each body part, the percent of the area of affected skin is estimated to derive a part score. The sum of severity parameters for each body part is multiplied by the part score. Each body part score is then multiplied by the proportions to reflect its contribution to total body area (10% for head, 20% for upper limbs, 30% for trunk, 40% for lower limbs). The scores for all four body parts are added to yield the PASI score (a maximum of 72.0).
[11] Proportion of subjects achieving ≥75% reduction from baseline in PASI score.

rates at Week 12 and during the maintenance phase of treatment were estimated to be 83% and 72%, respectively, at 300 mg, and 68% and 62%, respectively, at 150 mg. The estimated final model-based EC_{50} value was 191.5 μg/mL.

4.(ii).A.(5) Pharmacodynamic studies

4.(ii).A.(5).1) Foreign single subcutaneous dose study (Reference data 5.3.3.2-2, Study A2225 [February 2012 to January 2013])

In an open-label study in healthy adult subjects and psoriatic patients (8 subjects each), a single dose of secukinumab was administered subcutaneously at a dose of 300 mg, and secukinumab, IL-17A, IL-17F, and human beta-defensin-2 (hBD-2) (an antimicrobial protein produced by keratinocytes, etc. stimulated with IL-17A) levels in serum and dermal interstitial fluid were assessed. In the percentages of the secukinumab concentrations in dermal interstitial fluid to serum secukinumab concentrations were 21.5% to 23.4% in healthy adult subjects and were 27.8% to 39.4% in patients with psoriasis. In patients with psoriasis, hBD-2 levels were higher in lesions than in non-lesion areas of the skin or than healthy subjects, and hBD-2 levels in lesions decreased after the administration of secukinumab. No changes were seen in IL-17F concentrations in patients with psoriasis after the treatment with secukinumab.

None of the subjects were positive for anti-secukinumab antibodies.

4.(ii).A.(5).2) Effects on the Th17/IL-23/IL-17A pathway-related molecules (Reference data 5.3.3.2-1, Study A2102 [February to November 2007])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in foreign patients with psoriasis (N = 36) and mRNA levels of the Th17/IL-23/IL-17A pathway-related molecules in skin lesions at Week 4 following a single intravenous dose of 3 mg/kg secukinumab were assessed. Reductions of mRNA levels of IL-12B, IL-17A, IL-17F, IL-21, and IL-22 (pro-inflammatory cytokines derived from Th17 cells), KRT16 and DEFB4 (the gene encoding h-BD2) (molecules derived from IL-17A responsive cells), CCL20 (molecules that facilitate Th17 cell generation and recruitment), and IFN-γ (molecules derived from Th1 cells) were observed in the secukinumab group as compared to the placebo group.

4.(ii).B Outline of the review

4.(ii).B.(1) Ethnic differences in the pharmacokinetics of secukinumab

The applicant explained the impact of ethnic factors upon the pharmacokinetics of secukinumab as follows:
Based on the data from phase I studies in healthy adult subjects (A1101, A2104, A2106), the pharmacokinetics of secukinumab following a single intravenous or subcutaneous administration were similar between Japanese and foreign subjects. Based on the data from phase II and III studies in Japanese and foreign patients with psoriasis (A2220, A2211, A2211E1, A2302, A2304), trough serum secukinumab concentrations following multiple subcutaneous administration of secukinumab were similar between Japanese and foreign patients with psoriasis. After adjusting for body weight, the CL values estimated from the population pharmacokinetic analysis (5.3.3.5-1) were compared between the different ethnic groups. The median CL in Japanese patients with psoriasis (0.21 L/day) was approximately 10% higher than the CL value (0.19 L/day) in a typical foreign

patient with psoriasis that was estimated from the population pharmacokinetic analysis. However, the distribution was similar to that in non-Asian patients (other than Japanese and Taiwanese patients) and no apparent ethnic differences were observed. The above findings indicate no substantial ethnic differences in the pharmacokinetics of secukinumab.

PMDA accepted the applicant's response and concluded that there were no apparent ethnic differences in the pharmacokinetics of secukinumab which may affect its efficacy and safety.

4.(ii).B.(2) Anti-secukinumab antibodies

The applicant explained the expression of anti-secukinumab antibodies and its relationship to the PK profile, efficacy, and safety of secukinumab, etc. as follows:

In phase I (A1101, A2103, A2225) and phase II (A2102, A2104, A2206, A2211, A2212, A2220) studies in healthy adult subjects and patients with psoriasis, immunogenicity was evaluated using surface plasmon resonance. No anti-secukinumab antibodies were detected in these studies.

In a phase I study in healthy adult subjects (A2106) and phase II (A2211E1, A2206E1) and phase III (A2302, A2303, A2304, A2307, A2308, A2309) studies in patients with psoriasis, immunogenicity was evaluated using the MSD assay that was more sensitive than the assay using surface plasmon resonance. In Study A2106 in healthy adult subjects, anti-secukinumab antibodies were detected in 1 subject in the secukinumab 300 mg group, but the safety and PK profiles of this subject did not tend to be different from those of anti-secukinumab antibody-negative subjects. In the clinical studies in patients with psoriasis, no anti-secukinumab antibodies were detected in Study A2206E1. In Study A2211E1, in which all subjects were treated with 150 mg of secukinumab, anti-secukinumab antibodies were detected in 3.1% of subjects (8 of 262 subjects) and 6 of them tested positive for neutralizing antibodies. As potentially immunogenicity-related adverse events, seasonal allergy and nausea (1 subject) and dermatitis (1 subject) were reported in anti-secukinumab antibody-positive subjects in Study A2211E1, which were all transient and mild in severity and were considered unrelated to the development of anti-secukinumab antibodies. Efficacy and PK profiles were similar between anti-secukinumab antibody-positive and -negative subjects. In the phase III studies (A2302, A2303, A2304, A2307, A2308, A2309), the immunogenicity of secukinumab was evaluated in 2842 subjects treated with secukinumab and the incidences of anti-secukinumab antibodies were 0.5% (7 of 1395 subjects) in the secukinumab 150 mg group and 0.2% (3 of 1410 subjects) in the secukinumab 300 mg group. Of these, 3 subjects in the secukinumab 150 mg group tested positive for neutralizing antibodies. Safety, efficacy, and PK profiles were similar between anti-secukinumab antibody-positive and -negative subjects.

Among Japanese patients with psoriasis enrolled into the phase III studies (A2302, A2304, A2307), 0.7% of subjects in the secukinumab 150 mg group (1 of 148 subjects) tested positive for both anti-secukinumab antibodies and neutralizing antibodies. Loss of efficacy or the impact of antibodies on PK profile was not evaluated for this subject. Safety profiles were similar between the subject and anti-secukinumab antibody-negative subjects.

PMDA considers as follows:

The analysis results indicate no clinically relevant problems associated with the development of anti-secukinumab antibodies at present. However, given that some of subjects who tested positive for anti-secukinumab antibodies also tested positive for neutralizing antibodies, it is necessary to continue to watch for the development of anti-secukinumab antibodies and neutralizing activity.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

As efficacy and safety evaluation data, the results from multinational phase II dose-ranging studies of subcutaneously administered secukinumab in patients with psoriasis (including Japan) (A2220 [5.3.5.1-4], A2211 [5.3.5.1-1]), multinational phase III studies to evaluate the efficacy and safety of secukinumab in patients with psoriasis (including Japan) (A2302 [5.3.5.1-5], A2302E1 [5.3.5.1-12], A2304 [5.3.5.2-1], A2304E1 [5.3.5.2-3], A2307 [5.3.5.2-2]), a foreign phase III study in patients with psoriasis (A2303 [5.3.5.1-6]), and a foreign phase III study in patients with psoriatic arthritis (F2306 [5.3.5.1-13]), etc. were submitted.

4.(iii).A.(1) Multinational phase II study (5.3.5.1-4, Study A2220 [March 2010 to February 2011])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients with moderate to severe plaque psoriasis[12] (target sample size of 120 [24 subjects per group]) in Japan, Estonia, Latvia, Iceland, Canada, and the US to evaluate the efficacy and safety of secukinumab.

A single subcutaneous dose of 25 mg secukinumab was to be administered or three subcutaneous doses of 25, 75, or 150 mg of secukinumab or placebo were to be administered every 4 weeks.

The randomization was stratified according to body weight (<90 kg or ≥90 kg). Subjects were randomized in a ratio of 1:1:1:1:1 to a single subcutaneous dose of 25 mg of secukinumab (secukinumab 1×25 mg group), multiple subcutaneous doses of 25, 75, or 150 mg of secukinumab (secukinumab 3×25 mg group, secukinumab 3×75 mg group, or secukinumab 3×150 mg group), or placebo. All of 125 randomized subjects (29 subjects in the secukinumab 1×25 mg group, 26 subjects in the secukinumab 3×25 mg group, 21 subjects in the secukinumab 3×75 mg group, 27 subjects in the secukinumab 3×150 mg group, and 22 subjects in the placebo group) were included in the Full-Analysis-Set (FAS) as well as in the Safety Analysis Set and the Efficacy Analysis Set. The discontinuation rates were 51.7% (15 of 29 subjects) in the secukinumab 1×25 mg group, 38.5% (10 of 26 subjects) in the secukinumab 3×25 mg group, 19.0% (4 of 21 subjects) in the secukinumab 3×75 mg group, 25.9% (7 of 27 subjects) in the secukinumab 3×150 mg group, and 50.0% (11 of 22 subjects) in the placebo group. The most common reasons for discontinuation included lack of efficacy (13.8% [4 of 29 subjects] in the secukinumab 1×25 mg group, 23.1% [6 of 26 subjects] in the secukinumab 3×25 mg group, 9.5% [2 of 21 subjects] in the secukinumab 3×75 mg group, 27.3% [6 of 22 subjects] in the placebo group).

[12] Patients with moderate to severe plaque psoriasis who met all of the following criteria: (a) PASI score of ≥12, (b) Investigator's global assessment (the overall severity of psoriasis is evaluated on a 6-point scale [from 0 (clear) to 5 (very severe)], "IGA") score of ≥3, (c) BSA (body surface area) affected by plaque psoriasis of ≥10%, and (d) At screening and randomization, plaque psoriasis considered inadequately controlled by topical treatment. In addition, patients may have failed to respond to phototherapy and/or previous systemic therapy.

The Japanese subgroup of the FAS consisted of 24 subjects (4 subjects in the secukinumab 1×25 mg group, 6 subjects in the secukinumab 3×25 mg group, 5 subjects in the secukinumab 3×75 mg group, 5 subjects in the secukinumab 3×150 mg group, 4 subjects in the placebo group). The discontinuation rates were 25.0% (1 of 4 subjects) in the secukinumab 1×25 mg group, 33.3% (2 of 6 subjects) in the secukinumab 3×25 mg group, 20.0% (1 of 5 subjects) in the secukinumab 3×75 mg group, and 25.0% (1 of 4 subjects) in the placebo group and the reason for discontinuation was lack of efficacy for all cases.

The primary efficacy endpoint of the Psoriasis Area and Severity Index (PASI)[10] 75 response rate[11] at 12 weeks after the start of treatment was as shown in Table 10 and pairwise comparisons showed no statistically significant differences between secukinumab 1×25 mg and placebo or between secukinumab 3×25 mg and placebo, whereas pairwise comparisons showed statistically significant differences between secukinumab 3×75 mg and placebo and between secukinumab 3×150 mg and placebo. The secondary endpoints of the PASI 50 response rate[13] and the PASI 90 response rate[14] were as shown in Table 10 and the results in the Japanese subgroup were as shown in Table 11.

Table 10. PASI 50, PASI 75 (primary endpoint), and PASI 90 response rates at Week 12 (FAS, LOCF [a])

	Secukinumab 1×25 mg	Secukinumab 3×25 mg	Secukinumab 3×75 mg	Secukinumab 3×150 mg	Placebo	Treatment difference [95% CI], *P*-value [b]			
						Secukinumab 1×25 mg	Secukinumab 3×25 mg	Secukinumab 3×75 mg	Secukinumab 3×150 mg
PASI 50 response rate	17.2 (5/29)	57.7 (15/26)	81.0 (17/21)	85.2 (23/27)	18.2 (4/22)	-0.9 [-28.3, 26.1]	39.5 [11.4, 63.0]	62.8 [34.2, 82.8]	67.0 [41.5, 84.5]
PASI 75 response rate	3.4 (1/29)	19.2 (5/26)	57.1 (12/21)	81.5 (22/27)	9.1 (2/22)	-5.6 [-32.6, 21.7] *P* = 0.308	10.1 [-18.2, 37.3] *P* = 0.362	48.1 [17.6, 70.8] *P* = 0.002	72.4 [48.4, 88.0] *P* < 0.001
PASI 90 response rate	0 (0/29)	7.7 (2/26)	19.0 (4/21)	51.9 (14/27)	4.5 (1/22)	-4.5 [-31.5, 22.8]	3.1 [-25.3, 31.1]	14.5 [-15.8, 41.9]	47.3 [20.1, 69.1]

% (n/N)
a) Last observation carried forward (missing data were imputed by carrying the last observation forward.)
b) Cochran-Mantel-Haenszel test stratified by geographical region and body weight stratum (<90 kg or ≥90 kg) (multiplicity was not taken into account.)

Table 11. PASI 50, PASI 75 (primary endpoint), and PASI 90 response rates at Week 12 (Japanese subgroup, LOCF)

	Secukinumab 1×25 mg	Secukinumab 3×25 mg	Secukinumab 3×75 mg	Secukinumab 3×150 mg	Placebo	Treatment difference [95% CI]			
						Secukinumab 1×25 mg	Secukinumab 3×25 mg	Secukinumab 3×75 mg	Secukinumab 3×150 mg
PASI 50 response rate	0 (0/4)	66.7 (4/6)	80.0 (4/5)	100 (5/5)	25.0 (1/4)	-25.0 [-83.0, 51.0]	41.7 [-26.6, 85.8]	55.0 [-18.0, 93.7]	75.0 [2.6, 99.4]
PASI 75 response rate	0 (0/4)	16.7 (1/6)	60.0 (3/5)	100 (5/5)	25.0 (1/4)	-25.0 [-83.0, 51.0]	-8.3 [-66.8, 54.5]	35.0 [-35.6, 84.4]	75.0 [2.6, 99.4]
PASI 90 response rate	0 (0/4)	0 (0/6)	20.0 (1/5)	40.0 (2/5)	0 (0/4)	—	—	20.0 [-41.8, 73.2]	40.0 [-26.2, 85.5]

% (n/N)

The incidences of adverse events were 75.9% (22 of 29 subjects) in the secukinumab 1×25 mg group, 73.1% (19 of 26 subjects) in the secukinumab 3×25 mg group, 76.2% (16 of 21 subjects) in the secukinumab 3×75 mg group, 88.9% (24 of 27 subjects) in the secukinumab 3×150 mg group, and 72.7% (16 of 22 subjects) in the placebo group. Major events were as shown in Table 12. A death was reported in the placebo group (myocardial infarction) and a causal relationship between the death and the study drug was ruled out. The

[13] Proportion of subjects achieving ≥50% reduction from baseline in PASI score.
[14] Proportion of subjects achieving ≥90% reduction from baseline in PASI score.

incidences of non-fatal serious adverse events were 7.7% in the secukinumab 3×25 mg group (2 of 26 subjects, psoriatic arthropathy; and atrial fibrillation, cardiomyopathy, gastroenteritis viral, and transient ischaemic attack, 1 subject each), 4.8% in the secukinumab 3×75 mg group (1 of 21 subjects, Wolff-Parkinson-White syndrome), and 4.5% in the placebo group (1 of 22 subjects, acute myocardial infarction), and a causal relationship to the study drug was ruled out for all events. The incidences of adverse events leading to discontinuation were 3.8% in the secukinumab 3×25 mg group (1 of 26 subjects, psoriatic arthropathy) and 3.7% in the secukinumab 3×150 mg group (1 of 27 subjects, alanine aminotransferase abnormal) and a causal relationship to the study drug was ruled out for both events.

The incidences of adverse events for which a causal relationship to the study drug could not be ruled out (adverse drug reactions) were 6.9% (2 of 29 subjects) in the secukinumab 1×25 mg group, 7.7% (2 of 26 subjects) in the secukinumab 3×25 mg group, 9.5% (2 of 21 subjects) in the secukinumab 3×75 mg group, 22.2% (6 of 27 subjects) in the secukinumab 3×150 mg group, and 22.7% (5 of 22 subjects) in the placebo group.

Table 12. Adverse events reported by ≥2 subjects in any group (through Week 12, Safety Set)

Event term	Secukinumab 1×25 mg (N = 29)	Secukinumab 3×25 mg (N = 26)	Secukinumab 3×75 mg (N = 21)	Secukinumab 3×150 mg (N = 27)	Placebo (N = 22)
Psoriasis	8 (27.6)	4 (15.4)	4 (19.0)	3 (11.1)	2 (9.1)
Upper respiratory tract infection	3 (10.3)	2 (7.7)	1 (4.8)	2 (7.4)	0
Myalgia	2 (6.9)	0	0	0	1 (4.5)
Nasopharyngitis	1 (3.4)	4 (15.4)	4 (19.0)	4 (14.8)	2 (9.1)
Respiratory tract infection viral	1 (3.4)	1 (3.8)	1 (4.8)	0	2 (9.1)
Headache	1 (3.4)	2 (7.7)	1 (4.8)	1 (3.7)	0
Hypertension	1 (3.4)	1 (3.8)	0	2 (7.4)	0
Muscle strain	1 (3.4)	0	0	2 (7.4)	0
Pruritus	1 (3.4)	0	0	1 (3.7)	3 (13.6)
Back pain	0	1 (3.8)	2 (9.5)	1 (3.7)	0
Pharyngitis	0	1 (3.8)	0	2 (7.4)	0
Fatigue	0	0	0	3 (11.1)	1 (4.5)
Oedema peripheral	0	0	0	2 (7.4)	1 (4.5)

n (%)

In the Japanese subgroup, the incidences of adverse events were 50.0% (2 of 4 subjects) in the secukinumab 1×25 mg group, 83.3% (5 of 6 subjects) in the secukinumab 3×25 mg group, 80.0% (4 of 5 subjects) in the secukinumab 3×75 mg group, 100% (5 of 5 subjects) in the secukinumab 3×150 mg group, and 75.0% (3 of 4 subjects) in the placebo group. Adverse events reported by ≥2 subjects in any group were nasopharyngitis (33.3% [2 of 6 subjects] in the secukinumab 3×25 mg group, 40.0% [2 of 5 subjects] in the secukinumab 3×75 mg group, 20.0% [1 of 5 subjects] in the secukinumab 3×150 mg group, 25.0% [1 of 4 subjects] in the placebo group) and pharyngitis (40.0% [2 of 5 subjects] in the secukinumab 3×150 mg group). There were no deaths. A serious adverse event occurred in 4.5% of subjects in the placebo group (1 of 22 subjects, acute myocardial infarction) and its causal relationship to the study drug was ruled out. No adverse events leading to discontinuation were reported.

The incidences of adverse drug reactions were 16.7% (1 of 6 subjects) in the secukinumab 3×25 mg group, 20.0% (1 of 5 subjects) in the secukinumab 3×75 mg group, 20.0% (1 of 5 subjects) in the secukinumab 3×150 mg group, and 50.0% (2 of 4 subjects) in the placebo group.

The applicant explained as follows:
In this study, the secukinumab 3×150 mg dosing regimen was superior to placebo in achieving PASI 90 response and PASI 75 response. Other than the 3×150 mg dosing regimen, only the secukinumab 3×75 mg dosing regimen was superior to placebo in the PASI 75 response rate. Therefore, it was considered that doses ≤75 mg do not produce sufficient efficacy.

4.(iii).A.(2) Multinational phase II study (5.3.5.1-1, Study A2211 [July 2009 to December 2010])
A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients with moderate to severe plaque psoriasis[15] (target sample size of 396 [66 subjects in the Single arm (a single injection), 132 subjects in the Monthly arm (monthly injections), 132 subjects in the Early arm (early loading injections), 66 subjects in the Placebo arm]) in Japan, France, Germany, Iceland, Israel, Norway, and the US to evaluate the efficacy and safety of secukinumab.

The treatment phase of the study consisted of 2 periods (through Week 12, the induction period; from Week 12 to Week 32, the maintenance period). Secukinumab 150 mg or placebo was to be administered subcutaneously according to Figure 3.

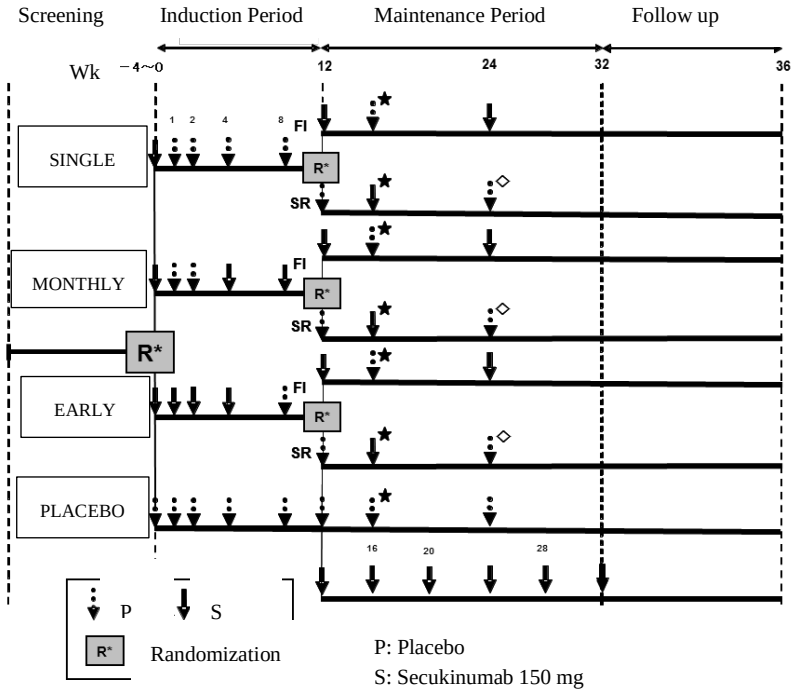


Figure 3. Study design and dosing schedule for Study A2211
★ If a relapse (a loss of ≥1/3 of the maximum PASI gain achieved during the study compared to baseline) was observed, blinded secukinumab or placebo was administered.

[15] Patients with moderate to severe plaque psoriasis who met all of the following criteria: (a) PASI score of ≥12, (b) IGA score of ≥3, (c) BSA affected by plaque psoriasis of ≥10%, and (d) At screening and randomization, plaque psoriasis considered inadequately controlled by topical treatment. In addition, patients may have failed to respond to phototherapy/photochemotherapy and/or previous systemic therapy.

◇ If no relapse was observed, placebo was administered. If a relapse was observed, secukinumab was administered.
At Week 12, PASI 75 responders (subjects achieving ≥75% reduction from baseline in PASI score) on secukinumab regimen during the induction period were re-randomized in a ratio of 1:1 to Fixed Interval regimen (FI) or treatment at Start of Relapse regimen (SR).
Subjects on secukinumab or placebo regimen during the maintenance period who experienced relapses (PASI partial responders[16] and PASI 50 non-responders[17]) received open-label secukinumab.

The randomization was stratified according to body weight (<90 kg or ≥90 kg). Subjects were randomized in a ratio of 1:2:2:1 to the Single, Monthly, Early, and Placebo arms. All of 404 randomized subjects (66 subjects in the Single arm, 138 subjects in the Monthly arm, 133 subjects in the Early arm, 67 subjects in the Placebo arm) were included in the FAS as well as in the Safety Analysis Set and the Efficacy Analysis set. The discontinuation rates during the induction period were 7.6% (5 of 66 subjects) in the Single arm, 2.9% (4 of 138 subjects) in the Monthly arm, 4.5% (6 of 133 subjects) in the Early arm, and 13.4% (9 of 67 subjects) in the Placebo arm. The most common reasons for discontinuation were lack of efficacy (3.0% [2 of 66 subjects] in the Single arm, 0.7% [1 of 138 subjects] in the Monthly arm, 7.5% [5 of 67 subjects] in the Placebo arm), etc. The discontinuation rates during the maintenance period were 13.8% (9 of 65 subjects) in the Fixed Interval Treatment arm, 9.0% (6 of 67 subjects) in the Start of Relapse arm, and 17.4% (43 of 247 subjects) in the Open-Label arm. The most common reasons for discontinuation were consent withdrawal (9.2% [6 of 65 subjects] in the Fixed Interval Treatment arm, 3.0% [2 of 67 subjects] in the Start of Relapse arm, 5.3% [13 of 247 subjects] in the Open-Label arm), etc. Of 380 subjects who completed the induction period (61 subjects in the Single arm, 134 subjects in the Monthly arm, 127 subjects[18] in the Early arm, 58 subjects in the Placebo arm), 11.5% of subjects in the Single arm (7 of 61 subjects), 41.8% of subjects in the Monthly arm (56 of 134 subjects), and 54.8% of subjects in the Early arm (69 of 126 subjects) were PASI 75 responders, and 132 subjects (65 subjects in the Fixed Interval Treatment arm, 67 subjects in the Start of Relapse arm) were re-randomized into the maintenance period, and 247 subjects entered the Open-Label arm.

The Japanese subgroup of the FAS consisted of 43 subjects (7 subjects in the Single arm, 15 subjects in the Monthly arm, 14 subjects in the Early arm, 7 subjects in the Placebo arm). The discontinuation rates during the induction period were 14.3% (1 of 7 subjects) in the Single arm, 14.3% (2 of 14 subjects) in the Early arm, and 14.3% (1 of 7 subjects) in the Placebo arm. The most common reasons for discontinuation were adverse event (14.3% [2 of 14 subjects] in the Early arm), etc. The discontinuation rates during the maintenance period were 5.3% in the Start of Relapse arm (1 of 19 subjects, consent withdrawal) and 5.0% in the Open-Label arm (1 of 20 subjects, adverse event). Of 40 subjects who completed the induction period (6 subjects in the Single arm, 15 subjects in the Monthly arm, 12 subjects[19] in the Early arm, 7 subjects in the Placebo arm), 33.3% of subjects in the Single arm (2 of 6 subjects), 66.7% of subjects in the Monthly arm (10 of 15 subjects), and 66.7% of subjects in the Early arm (8 of 12 subjects) were PASI 75 responders and 10 subjects each were re-randomized to the Fixed Interval Treatment and Start of Relapse arms in the maintenance period, and 20 subjects entered the Open-Label arm.

The primary efficacy endpoint of the PASI 75 response rate at Week 12 was as shown in Table 13. A pairwise

[16] Subjects achieving ≥50%, but not ≥75% reduction from baseline in PASI score.
[17] Subjects achieving <50% reduction from baseline in PASI score.
[18] One subject discontinued immediately after completing the induction period.
[19] One subject discontinued immediately after completing the induction period.

comparison showed no statistically significant differences between the Single and Placebo arms while pairwise comparisons showed statistically significant differences between the Monthly and Placebo arms and between the Early and Placebo arms. The secondary endpoints of the PASI 50 and PASI 90 response rates at Week 12 were as shown in Table 13, and the results in the Japanese subgroup were as shown in Table 14. The time-course of the PASI 75 response rate during the maintenance period was as shown in Table 15.

Table 13. PASI 50, PASI 75 (primary endpoint), and PASI 90 response rates at Week 12 (FAS, LOCF[a])

	Single	Monthly	Early	Placebo	Treatment difference [95% CI], *P*-value[b]		
					Single	Monthly	Early
PASI 50 response rate	27.3 (18/66)	60.1 (83/138)	76.5 (101/132)	10.6 (7/66)	16.7 [-1.1, 33.7]	49.5 [35.8, 61.9]	65.9 [53.0, 76.8]
PASI 75 response rate	10.6 (7/66)	42.0 (58/138)	54.5 (72/132)	1.5 (1/66)	9.1 [-8.7, 26.5] *P* = 0.225	40.5 [26.3, 53.6] *P* < 0.001	53.0 [39.1, 65.4] *P* < 0.001
PASI 90 response rate	3.0 (2/66)	17.4 (24/138)	31.8 (42/132)	1.5 (1/66)	1.5 [-16.2, 19.1]	15.9 [1.2, 30.2]	30.3 [15.4, 44.3]

% (n/N)
a) Last observation carried forward (Missing data were imputed by carrying the last observation forward.)
b) Adjusted for multiplicity using a stepwise Dunnett's procedure.

Table 14. PASI 50, PASI 75 (primary endpoint), and PASI 90 response rates at Week 12 (Japanese subgroup, LOCF)

	Single	Monthly	Early	Placebo	Treatment difference [95% CI]		
					Single	Monthly	Early
PASI 50 response rate	57.1 (4/7)	73.3 (11/15)	92.9 (13/14)	14.3 (1/7)	42.9 [-16.2, 83.2]	59.0 [13.1, 90.1]	78.6 [33.9, 97.0]
PASI 75 response rate	28.6 (2/7)	66.7 (10/15)	71.4 (10/14)	0 (0/7)	28.6 [-29.7, 74.5]	66.7 [25.0, 91.6]	71.4 [25.2, 96.3]
PASI 90 response rate	0 (0/7)	40.0 (6/15)	64.3 (9/14)	0 (0/7)	—	40.0 [-3.2, 74.9]	64.3 [17.0, 91.4]

% (n/N)

Table 15. PASI 75 response rate during the maintenance period (FAS, LOCF)

	Fixed Interval	Start of Relapse	Open-Label
Week 12 (at start of maintenance period)	100 (65/65)	100 (67/67)	0 (0/247)
Week 16	95.4 (62/65)	77.6 (52/67)	17.4 (43/247)
Week 20	83.1 (54/65)	62.7 (42/67)	30.0 (74/247)
Week 24	70.8 (46/65)	38.8 (26/67)	38.1 (94/247)
Week 28	70.8 (46/65)	35.8 (24/67)	40.1 (99/247)

% (n/N)

The incidences of adverse events during the induction period (through Week 12) were 62.1% (41 of 66 subjects) in the Single arm, 65.9% (91 of 138 subjects) in the Monthly arm, 66.9% (89 of 133 subjects) in the Early arm, and 70.1% (47 of 67 subjects) in the Placebo arm. Major events were as shown in Table 16. There were no deaths. The incidences of serious adverse events were 4.5% in the Single arm (3 of 66 subjects, hypertensive crisis; acute tonsillitis; and colon adenoma, 1 subject each), 2.2% in the Monthly arm (3 of 138 subjects, psoriasis; abdominal pain; and road traffic accident, 1 subject each), 4.5% in the Early arm (6 of 133 subjects, pneumonia bacterial; injury; erythrodermic psoriasis; angina pectoris; acute respiratory failure; and coronary artery disease, 1 subject each), and 1.5% in the Placebo arm (1 of 67 subjects, psoriasis) and a causal relationship to study drug could not be ruled out for the event reported by 1 subject in the Early arm (pneumonia

bacterial). The incidences of adverse events leading to discontinuation were 1.5% in the Single arm (1 of 66 subjects, psoriasis), 2.3% in the Early arm (3 of 133 subjects, erythrodermic psoriasis [2 subjects], pneumonia bacterial [1 subject]), and 1.5% in the Placebo arm (1 of 67 subjects, pharyngitis) and a causal relationship to the study drug could not be ruled out for those reported by 1 subject in the Early arm (pneumonia bacterial) and 1 subject in the placebo group. The incidences of adverse drug reactions were 15.2% (10 of 66 subjects) in the Single arm, 15.2% (21 of 138 subjects) in the Monthly arm, 16.5% (22 of 133 subjects) in the Early arm, and 16.4% (11 of 67 subjects) in the Placebo arm.

Table 16. Adverse events reported by ≥2% of subjects in any group (through Week 12, Safety Analysis Set)

Event term	Single (N = 66)	Monthly (N = 138)	Early (N = 133)	Placebo (N = 67)
Nasopharyngitis	8 (12.1)	31 (22.5)	30 (22.6)	12 (17.9)
Headache	6 (9.1)	8 (5.8)	11 (8.3)	3 (4.5)
Psoriasis	6 (9.1)	8 (5.8)	4 (3.0)	7 (10.4)
Upper respiratory tract infection	3 (4.5)	6 (4.3)	2 (1.5)	6 (9.0)
Vomiting	3 (4.5)	3 (2.2)	3 (2.3)	1 (1.5)
Abdominal pain upper	0	3 (2.2)	2 (1.5)	1 (1.5)
Diarrhoea	2 (3.0)	3 (2.2)	0	1 (1.5)
Hypertension	3 (4.5)	1 (0.7)	2 (1.5)	1 (1.5)
Arthralgia	2 (3.0)	8 (5.8)	0	0
Pruritus	2 (3.0)	3 (2.2)	1 (0.8)	1 (1.5)
Oropharyngeal pain	2 (3.0)	2 (1.4)	2 (1.5)	1 (1.5)
Contusion	2 (3.0)	2 (1.4)	2 (1.5)	0
Hypercholesterolaemia	2 (3.0)	1 (0.7)	0	1 (1.5)
Fatigue	2 (3.0)	0	2 (1.5)	2 (3.0)
Dermatitis contact	2 (3.0)	0	1 (0.8)	0
Sinusitis	1 (1.5)	5 (3.6)	0	0
Pruritus generalised	1 (1.5)	4 (2.9)	1 (0.8)	2 (3.0)
Nausea	1 (1.5)	4 (2.9)	0	1 (1.5)
Oedema peripheral	1 (1.5)	3 (2.2)	2 (1.5)	0
Cough	1 (1.5)	2 (1.4)	4 (3.0)	4 (6.0)
Bronchitis	0	3 (2.2)	0	0
Oral herpes	0	3 (2.2)	0	0
Toothache	0	2 (1.4)	5 (3.8)	2 (3.0)
Urinary tract infection	0	1 (0.7)	3 (2.3)	0
Folliculitis	0	1 (0.7)	2 (1.5)	2 (3.0)
Nasal congestion	0	1 (0.7)	3 (2.3)	0
Dizziness	0	1 (0.7)	1 (0.8)	2 (3.0)
Insomnia	0	1 (0.7)	1 (0.8)	2 (3.0)
Coronary artery disease	0	0	3 (2.3)	0
Lacrimation increased	0	0	0	2 (3.0)

n (%)

The incidences of adverse events during the maintenance period (from Week 12 to 32) were 66.2% (43 of 65 subjects) in the Fixed Interval Treatment arm, 64.2% (43 of 67 subjects) in the Start of Relapse arm, and 67.6% (167 of 247 subjects) in the Open-Label arm. Common events were nasopharyngitis (9.2% [6 of 65 subjects] in the Fixed Interval Treatment arm, 7.5% [5 of 67 subjects] in the Start of Relapse arm, 14.2% [35 of 247 subjects] in the Open-Label arm), psoriasis (6.2% [4 of 65 subjects] in the Fixed Interval Treatment arm, 9.0% [6 of 67 subjects] in the Start of Relapse arm, 6.9% [17 of 247 subjects] in the Open-Label arm), and upper respiratory tract infection (3.1% [2 of 65 subjects] in the Fixed Interval Treatment arm, 6.9% [17 of 247 subjects] in the Open-Label arm), etc. There were no deaths. The incidences of serious adverse events were 6.2% in the Fixed Interval Treatment arm (4 of 65 subjects, hepatic cirrhosis; upper limb fracture; anal abscess; and back pain and intervertebral disc disorder, 1 subject each), 3.0% in the Start of Relapse arm (2 of 67 subjects, enterocolitis infectious; and lower gastrointestinal haemorrhage, 1 subject each), and 4.9% in the

Open-Label arm (12 of 247 subjects, nephrolithiasis; appendicitis; muscle injury; bladder cancer; arrhythmia; colon cancer and colon stenosis; erythrodermic psoriasis; psoriasis; rhabdomyolysis; cataract; staphylococcal infection; and testis cancer, 1 subject each) and a causal relationship to the study drug could not be ruled out for the events reported by 1 subject in the Start of Relapse arm (enterocolitis infectious) and 3 subjects in the Open-Label arm (rhabdomyolysis; staphylococcal infection; and testis cancer, 1 subject each). The incidences of adverse events leading to discontinuation were 3.0% in the Start of Relapse arm (2 of 67 subjects, prurigo; and lower gastrointestinal haemorrhage, 1 subject each) and 3.2% in the Open-Label arm (8 of 247 subjects, ear infection; diarrhoea; appendicitis; colon cancer; erythrodermic psoriasis; psoriasis; rhabdomyolysis; and testis cancer, 1 subject each) and a causal relationship to the study drug could not be ruled out for those reported by 2 subjects in the Open-Label arm (rhabdomyolysis; and testis cancer, 1 subject each). The incidences of adverse drug reactions were 21.5% (14 of 65 subjects) in the Fixed Interval Treatment arm, 10.4% (7 of 67 subjects) in the Start of Relapse arm, and 15.0% (37 of 247 subjects) in the Open-Label arm.

In the Japanese subgroup, the incidences of adverse events during the induction period (through Week 12) were 85.7% (6 of 7 subjects) in the Single arm, 46.7% (7 of 15 subjects) in the Monthly arm, 57.1% (8 of 14 subjects) in the Early arm, and 42.9% (3 of 7 subjects) in the Placebo arm. Those reported by ≥2 subjects in any group were psoriasis (42.9% [3 of 7 subjects] in the Single arm, 6.7% [1 of 15 subjects] in the Monthly arm, 14.3% [1 of 7 subjects] in the Placebo arm), nasopharyngitis (20.0% [3 of 15 subjects] in the Monthly arm, 21.4% [3 of 14 subjects] in the Early arm), pruritus generalised (13.3% [2 of 15 subjects] in the Monthly arm), and erythrodermic psoriasis (14.3% [2 of 14 subjects] in the Early arm). There were no deaths. The incidences of serious adverse events were 14.3% in the Single arm (1 of 7 subjects, colon adenoma) and 7.1% in the Early arm (1 of 14 subjects, erythrodermic psoriasis), and a causal relationship to the study drug was ruled out for both events. Adverse events leading to discontinuation occurred in 14.3% of subjects in the Early arm (2 of 14 subjects, erythrodermic psoriasis [2 subjects]) and a causal relationship to the study drug was ruled out for both cases. The incidences of adverse drug reactions were 28.6% (2 of 7 subjects) in the Single arm, 6.7% (1 of 15 subjects) in the Monthly arm, and 28.6% (4 of 14 subjects) in the Early arm.

In the Japanese subgroup, the incidences of adverse events during the maintenance period (from Week 12 to 32) were 50.0% (5 of 10 subjects) in the Fixed Interval Treatment arm, 40.0% (4 of 10 subjects) in the Start of Relapse arm, and 70.0% (14 of 20 subjects) in the Open-Label arm. Those reported by ≥2 subjects in any group were nasopharyngitis (20.0% [2 of 10 subjects] in the Start of Relapse arm, 5.0% [1 of 20 subjects] in the Open-Label arm). There were no deaths. The incidences of serious adverse events were 10.0% in the Fixed Interval Treatment arm (1 of 10 subjects, back pain and intervertebral disc disorder), 10.0% in the Start of Relapse arm (1 of 10 subjects, enterocolitis infectious), and 10.0% in the Open-Label arm (2 of 20 subjects, rhabdomyolysis; and cataract, 1 subject each), and a causal relationship to the study drug could not be ruled out for those reported by 1 subject in the Start of Relapse arm (enterocolitis infectious) and 1 subject in the Open-Label arm (rhabdomyolysis). An adverse event leading to discontinuation occurred in 1 subject in the Open-Label arm (rhabdomyolysis) and its causal relationship to the study drug could not be ruled out. The incidences of adverse drug reactions were 30.0% (3 of 10 subjects) in the Fixed Interval Treatment arm, 20.0%

(2 of 10 subjects) in the Start of Relapse arm, and 15.0% (3 of 20 subjects) in the Open-Label arm.

Based on the results from a foreign phase II study (A2212)[20] and a multinational phase II study (A2211), the applicant explained the rationale for the dosing regimen of secukinumab selected for phase III studies as follows:

As the Early arm showed the highest PASI 75/90 response rates in Study A2211, an early loading regimen was considered beneficial. However, the PASI 75 response rate at Week 12 in the Early arm in Study A2211 was 54.5%, which was lower than 82.8% in the intravenous secukinumab 3×10 mg/kg group in Study A2212. This was considered attributable to low secukinumab exposure during the initial phase of the induction period since the trough serum secukinumab concentrations in the Early arm in Study A2211 were lower than those in the intravenous secukinumab 3×10 mg/kg group in Study A2212 [see "4.(ii) Summary of clinical pharmacology studies"]. Therefore, it was decided to further increase dosing frequency to once weekly (i.e., subcutaneously administered, initially at Weeks 0, 1, 2, 3, and 4) for phase III studies.

Maintenance treatment should be given every 4 weeks rather than every 12 weeks because the PASI 75 response rate decreased over time in the Fixed Interval Treatment arm (dosing every 12 weeks) but increased over time in the Open-Label arm (dosing every 4 weeks) during the maintenance period of Study A2211 (Table 15).

Overall, the PASI 75 response rates were low in Study A2211. Thus, the efficacy and safety of secukinumab should be evaluated in phase III studies not only at the dose of 150 mg but also at 300 mg.

Based on the above considerations, and taking account of serum secukinumab concentrations and PASI 75 response rates predicted by population pharmacokinetic modeling and population PK-PASI modeling of the data from Studies A2102, A2211, A2212, and A2220 [see "4.(ii) Summary of clinical pharmacology studies"], the dosing regimen selected for phase III studies was subcutaneous administration of secukinumab at a dose of 150 mg or 300 mg at Weeks 0, 1, 2, 3, and 4 followed by the same dose once every 4 weeks.

4.(iii).A.(3) Multinational phase III study (5.3.5.1-5, Study A2302 [June 2011 to March 2013])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients with moderate to severe plaque psoriasis[21] (including patients with psoriatic arthritis) (target sample size of 720 [240 subjects per group]) in Japan, Argentina, Canada, Colombia, Estonia, Iceland, Israel, Latvia, Lithuania, Mexico, Taiwan, and the US to evaluate the efficacy and safety of secukinumab.

The treatment phase of the study consisted of 2 periods (through Week 12, the induction period; from Week 12 to Week 52, the maintenance period). Secukinumab 150 or 300 mg or placebo was to be administered subcutaneously according to Figure 4.

[20] A placebo-controlled, randomized, double-blind, parallel-group study in which patients with moderate to severe plaque psoriasis (Target sample size of 100 [30 subjects each in the active treatment groups, 10 subjects in the placebo group]) received a single intravenous dose of 3 or 10 mg/kg of secukinumab or three intravenous doses of secukinumab 10 mg/kg or placebo administered every 2 weeks (5.3.5.1-3).

[21] Patients with moderate to severe plaque psoriasis who met all of the following criteria: (a) PASI score of ≥12, (b) IGA score of ≥3, (c) BSA affected by plaque psoriasis of ≥10%, and (d) plaque psoriasis considered inadequately controlled by topical treatment, phototherapy/photochemotherapy, and/or systemic therapy.

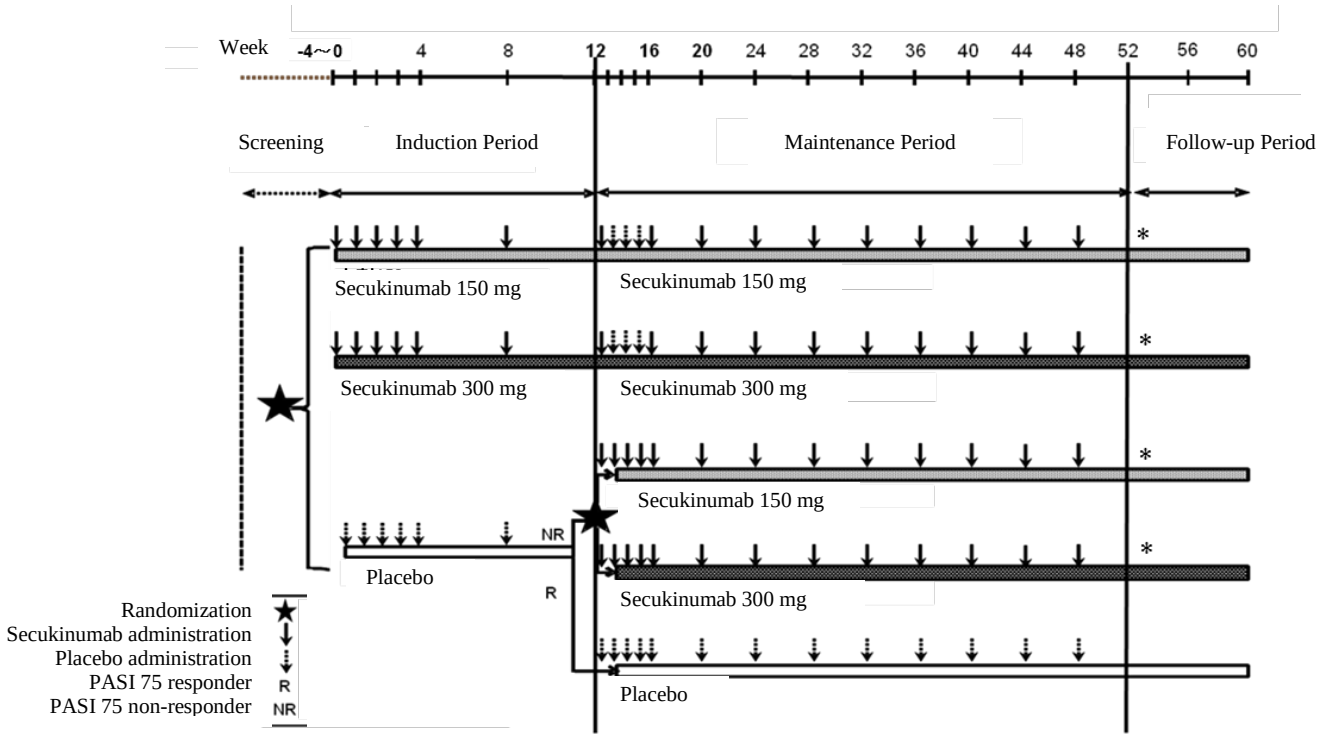


Figure 4. Study design and dosing schedule for Study A2302

At Week 12, PASI 75 responders in the placebo group continued on placebo (placebo→placebo group) and PASI 75 non-responders on placebo were re-randomized in a ratio of 1:1 to the secukinumab 150 or 300 mg group (placebo→secukinumab 150 mg group or placebo→secukinumab 300 mg group) for the maintenance period. This re-randomization was stratified by geographical region and by body weight (<90 kg or ≥90 kg).

The randomization was stratified by geographical region and by body weight (<90 kg or ≥90 kg). Subjects were randomized in a ratio of 1:1:1 to the secukinumab 150 or 300 mg or placebo group. Of 738 randomized subjects, 737 subjects excluding 1 subject in the placebo group[22] (245 subjects in the secukinumab 150 mg group, 245 subjects in the secukinumab 300 mg group, 247 subjects in the placebo group) were included in the FAS and in the Safety Set, which was used for efficacy analyses. The discontinuation rates during the induction period were 6.1% (15 of 245 subjects) in the secukinumab 150 mg group, 2.9% (7 of 245 subjects) in the secukinumab 300 mg group, and 6.5% (16 of 248 subjects) in the placebo group. The most common reasons for discontinuation were consent withdrawal (3.7% [9 of 245 subjects] in the secukinumab 150 mg group, 0.4% [1 of 245 subjects] in the secukinumab 300 mg group, 3.2% [8 of 248 subjects] in the placebo group), etc. Of 232 subjects in the placebo group who completed the induction period, 7.8% (18 of 232 subjects) continued on placebo in the maintenance period, 47.0% (109 of 232 subjects) were re-randomized to the placebo→secukinumab 150 mg group and 45.3% (105 of 232 subjects) were re-randomized to the placebo→secukinumab 300 mg group for the maintenance period.

The Japanese subgroup of the FAS consisted of 87 subjects (29 subjects each in the secukinumab 150 mg, secukinumab 300 mg, and placebo groups). The discontinuation percentages during the induction period were 10.3% (3 of 29 subjects) in the secukinumab 150 mg group, 3.4% (1 of 29 subjects) in the secukinumab 300 mg group, and 6.9% (2 of 29 subjects) in the placebo group. The most common reasons for discontinuation were adverse event (6.9% [2 of 29 subjects] in the secukinumab 150 mg group, 3.4% [1 of 29 subjects] in the placebo group), etc. Of 27 subjects in the placebo group who completed the induction period, 7.4% (2 of 27

[22] Consent was not obtained before the start of the study.

subjects) continued on placebo in the maintenance period, 51.9% (14 of 27 subjects) were re-randomized to the placebo→secukinumab 150 mg group and 40.7% (11 of 27 subjects) were re-randomized to the placebo→secukinumab 300 mg group for the maintenance period.

The co-primary efficacy endpoints were the PASI 75 response rate at Week 12 and the response rate to the Investigator's global assessment (IGA)[23] 0 or 1 at Week 12. The PASI 75 response rate at Week 12 was as shown in Table 17 and the IGA 0/1 response rate was as shown in Table 19. Pairwise comparisons showed statistically significant differences between secukinumab 150 mg and placebo and between secukinumab 300 mg and placebo, confirming the superiority of both secukinumab 150 mg and 300 mg over placebo. The secondary endpoints of the PASI 50 and 90 response rates were as shown in Table 17 and the results in the Japanese subgroup were as shown in Table 18.

Table 17. PASI 50, 75 (co-primary endpoint), and 90 response rates at Week 12 (FAS, NRI[a)])

	Secukinumab 150 mg	Secukinumab 300 mg	Placebo	Treatment difference [95% CI], *P*-value [b) c)]	
				Secukinumab 150 mg	Secukinumab 300 mg
PASI 50 response rate	83.5 (203/243)	90.6 (222/245)	8.9 (22/246)	74.6 [68.1, 80.1]	81.7 [75.9, 86.4]
PASI 75 response rate	71.6 (174/243)	81.6 (200/245)	4.5 (11/246)	67.1 [60.1, 73.3] *P* < 0.0001	77.2 [70.9, 82.4] *P* < 0.0001
PASI 90 response rate	39.1 (95/243)	59.2 (145/245)	1.2 (3/246)	37.9 [29.4, 46.0] *P* < 0.0001	58.0 [50.3, 64.7] *P* < 0.0001

% (n/N)

a) Non responder imputation (Missing data were imputed with non-responses.)

b) Cochran-Mantel-Haenszel test stratified by geographical region and body weight stratum (<90 kg or ≥90 kg).

c) The level of significance for each of pairwise comparisons between placebo and secukinumab 150 mg and between placebo and secukinumab 300 mg was set at α/2. If both null hypotheses for the co-primary endpoints were rejected and the subsequent null hypotheses for the key secondary endpoints (PASI 90 response rate at Week 12, changes from baseline in pain, itching, and scaling scores on the Psoriasis Symptom Diary at Week 12) were all rejected within a set referring to a secukinumab dose regimen, the corresponding α/2 could be passed onto the other group of null hypotheses (Bretz F, et al. *Stat Med*. 2009;28:586-604).

Table 18. PASI 50, PASI 75 (co-primary endpoint), and PASI 90 response rates at Week 12 (Japanese subgroup, NRI)

	Secukinumab 150 mg	Secukinumab 300 mg	Placebo	Treatment difference [95% CI]	
				Secukinumab 150 mg	Secukinumab 300 mg
PASI 50 response rate	93.1 (27/29)	86.2 (25/29)	10.3 (3/29)	82.8 [62.0, 94.3]	75.9 [53.4, 90.0]
PASI 75 response rate	86.2 (25/29)	82.8 (24/29)	6.9 (2/29)	79.3 [57.7, 92.2]	75.9 [53.4, 90.0]
PASI 90 response rate	55.2 (16/29)	62.1 (18/29)	0 (0/29)	55.2 [29.5, 75.0]	62.1 [37.2, 80.3]

% (n/N)

Table 19. IGA 0/1 response rates (co-primary endpoint) (FAS and Japanese subgroup, NRI)

	Secukinumab 150 mg	Secukinumab 300 mg	Placebo	Treatment difference [95% CI], *P*-value [a) b)]	
				Secukinumab 150 mg	Secukinumab 300 mg
FAS	51.2 (125/244)	65.3 (160/245)	2.4 (6/246)	48.8 [40.8, 56.2] *P* < 0.0001	62.9 [55.5, 69.2] *P* < 0.0001
Japanese subgroup	55.2 (16/29)	55.2 (16/29)	3.4 (1/29)	51.7 [25.7, 72.3]	51.7 [25.7, 72.3]

% (n/N)

a) Cochran-Mantel-Haenszel test stratified by geographical region and body weight stratum (<90 kg or ≥90 kg).

b) See Table 17.

The incidences of adverse events during the induction period (through Week 12) were 60.4% (148 of 245 subjects) in the secukinumab 150 mg group, 55.1% (135 of 245 subjects) in the secukinumab 300 mg group, and 47.0% (116 of 247 subjects) in the placebo group. Major events were as shown in Table 20. There were no deaths. The incidences of serious adverse events were 1.6% in the secukinumab 150 mg group (4 of 245 subjects, pulmonary oedema and cardiac failure; type 2 diabetes mellitus; basal cell carcinoma; and bladder cancer, 1 subject each), 2.4% in the secukinumab 300 mg group (6 of 245 subjects, laryngeal injury; uterine leiomyoma; bursitis; colitis ulcerative; cholelithiasis; and acute kidney injury, 1 subject each), and 1.6% in the

[23] The overall severity of psoriasis was assessed on a 5-point scale from 0 (clear) to 4 (severe).

placebo group (4 of 247 subjects, non-cardiac chest pain; alcohol withdrawal syndrome and panic attack; cellulitis; and psoriasis, 1 subject each). A causal relationship to the study drug could not be ruled out for those reported by 2 subjects in the secukinumab 150 mg group (bladder cancer; and pulmonary oedema and cardiac failure, 1 subject each), 1 subject in the secukinumab 300 mg group (bursitis), and 1 subject in the placebo group (psoriasis). The incidences of adverse events leading to discontinuation were 2.0% in the secukinumab 150 mg group (5 of 245 subjects, erythrodermic psoriasis; alopecia; thrombocytopenia; bladder cancer; and psoriatic arthropathy, 1 subject each), 1.2% in the secukinumab 300 mg group (3 of 245 subjects, eczema; bursitis; and colitis ulcerative, 1 subject each), and 1.6% in the placebo group (4 of 247 subjects, psoriasis [2 subjects]; cellulitis; and herpes virus infection, 1 subject each). A causal relationship to the study drug could not be ruled out for all those events reported in the secukinumab 150 mg group, those reported by 2 subjects in the secukinumab 300 mg group (eczema; and bursitis) and 3 subjects in the placebo group (psoriasis [2 subjects], herpes virus infection [1 subject]). The incidences of adverse drug reactions were 20.0% (49 of 245 subjects) in the secukinumab 150 mg group, 16.7% (41 of 245 subjects) in the secukinumab 300 mg group, and 11.3% (28 of 247 subjects) in the placebo group.

Table 20. Adverse events reported by ≥2% of subjects in any group (through Week 12, Safety Analysis Set)

Event term	Secukinumab 150 mg (N = 245)	Secukinumab 300 mg (N = 245)	Placebo (N = 247)
Nasopharyngitis	23 (9.4)	22 (9.0)	19 (7.7)
Headache	13 (5.3)	12 (4.9)	7 (2.8)
Upper respiratory tract infection	10 (4.1)	9 (3.7)	0
Oropharyngeal pain	10 (4.1)	4 (1.6)	3 (1.2)
Hypertension	9 (3.7)	0	3 (1.2)
Pruritus	8 (3.3)	9 (3.7)	5 (2.0)
Fatigue	8 (3.3)	2 (0.8)	2 (0.8)
Arthralgia	6 (2.4)	2 (0.8)	7 (2.8)
Nausea	6 (2.4)	1 (0.4)	6 (2.4)
Psoriasis	5 (2.0)	3 (1.2)	9 (3.6)
Diarrhoea	4 (1.6)	5 (2.0)	3 (1.2)
Influenza like illness	3 (1.2)	5 (2.0)	3 (1.2)
Vomiting	2 (0.8)	5 (2.0)	2 (0.8)
Contusion	2 (0.8)	5 (2.0)	1 (0.4)

n (%)

The incidences of adverse events over the entire treatment period (the induction and maintenance periods) were 81.3% (287 of 353 subjects) in the secukinumab 150 mg group[24], 81.9% (286 of 349 subjects) in the secukinumab 300 mg group[25], and 50.2% (124 of 247 subjects) in the placebo group[26], and major events were as shown in Table 21. There were no deaths. The incidences of serious adverse events were 5.4% (19 of 353 subjects) in the secukinumab 150 mg group, 5.4% (19 of 349 subjects) in the secukinumab 300 mg group, and 2.0% (5 of 247 subjects) in the placebo group. Adverse events reported by ≥2 subjects in any group were thyroid cancer (0.6% [2 of 353 subjects] in the secukinumab 150 mg group) and pneumonia (0.6% [2 of 349

[24] Defined as subjects treated with secukinumab 150 mg by Week 52 (including subjects on secukinumab 150 mg during the induction period who continued to receive secukinumab 150 mg and subjects in the placebo→secukinumab 150 mg group).
[25] Defined as subjects treated with secukinumab 300 mg by Week 52 (including subjects on secukinumab 300 mg during the induction period who continued to receive secukinumab 300 mg and subjects in the placebo→secukinumab 300 mg group).
[26] Defined as subjects treated with placebo by Week 52 (placebo→placebo group, placebo→secukinumab 150 mg group, and placebo→secukinumab 300 mg group. The data obtained after crossover to secukinumab are not included for subjects in the placebo→secukinumab 150 mg group and subjects in the placebo→secukinumab 300 mg group).

subjects] in the secukinumab 300 mg group). The incidences of adverse events leading to discontinuation were 5.1% (18 of 353 subjects) in the secukinumab 150 mg group, 3.4% (12 of 349 subjects) in the secukinumab 300 mg group, and 2.0% (5 of 247 subjects) in the placebo group. The incidences of adverse drug reactions were 30.0% (106 of 353 subjects) in the secukinumab 150 mg group, 25.2% (88 of 349 subjects) in the secukinumab 300 mg group, and 13.0% (32 of 247 subjects) in the placebo group.

Table 21. Adverse events reported by ≥2% of subjects in any group (through Week 52, Safety Analysis Set)

Preferred term	Secukinumab 150 mg (N = 353)	Secukinumab 300 mg (N = 349)	Placebo (N = 247)
Nasopharyngitis	69 (19.5)	57 (16.3)	20 (8.1)
Upper respiratory tract infection	36 (10.2)	32 (9.2)	2 (0.8)
Headache	24 (6.8)	31 (8.9)	10(4.0)
Hypertension	21 (5.9)	16 (4.6)	3 (1.2)
Influenza like illness	17 (4.8)	14 (4.0)	3 (1.2)
Pruritus	14 (4.0)	15 (4.3)	5 (2.0)
Arthralgia	13 (3.7)	14 (4.0)	8 (3.2)
Hyperlipidaemia	13 (3.7)	9 (2.6)	2 (0.8)
Oropharyngeal pain	12 (3.4)	12 (3.4)	3 (1.2)
Folliculitis	12 (3.4)	9 (2.6)	2 (0.8)
Eczema	11 (3.1)	9 (2.6)	0
Diarrhoea	10 (2.8)	16 (4.6)	4 (1.6)
Fatigue	10 (2.8)	3 (0.9)	2 (0.8)
Insomnia	10 (2.8)	2 (0.6)	0
Psoriasis	9 (2.5)	8 (2.3)	10 (4.0)
Back pain	9 (2.5)	9 (2.6)	4 (1.6)
Pharyngitis	9 (2.5)	9 (2.6)	0
Urticaria	9 (2.5)	9 (2.6)	0
Bronchitis	8 (2.3)	17 (4.9)	2 (0.8)
Influenza	8 (2.3)	10 (2.9)	3 (1.2)
Tinea pedis	8 (2.3)	10 (2.9)	0
Pain in extremity	8 (2.3)	8 (2.3)	3 (1.2)
Gastroenteritis	8 (2.3)	7 (2.0)	1 (0.4)
Muscle strain	8 (2.3)	7 (2.0)	1 (0.4)
Toothache	8 (2.3)	5 (1.4)	2 (0.8)
Nausea	8 (2.3)	3 (0.9)	8 (3.2)
Depression	8 (2.3)	2 (0.6)	1 (0.4)
Viral upper respiratory tract infection	7 (2.0)	11 (3.2)	2 (0.8)
Lymphadenopathy	7 (2.0)	3 (0.9)	0
Oral herpes	6 (1.7)	8 (2.3)	2 (0.8)
Cough	5 (1.4)	16 (4.6)	3 (1.2)
Contusion	5 (1.4)	9 (2.6)	1 (0.4)
Myalgia	5 (1.4)	5 (1.4)	4 (1.6)
Vomiting	4 (1.1)	7 (2.0)	4 (1.6)
Rhinitis	4 (1.1)	7 (2.0)	1 (0.4)
Ligament sprain	3 (0.8)	8 (2.3)	1 (0.4)
Periodontitis	3 (0.8)	7 (2.0)	1 (0.4)
Excoriation	3 (0.8)	7 (2.0)	0
Dermatitis contact	1 (0.3)	11 (3.2)	1 (0.4)

n (%)

In the Japanese subgroup, the incidences of adverse events during the induction period (through Week 12) were 55.2% (16 of 29 subjects) in the secukinumab 150 mg group, 48.3% (14 of 29 subjects) in the secukinumab 300 mg group, and 41.4% (12 of 29 subjects) in the placebo group. Those reported by ≥2 subjects in any group were nasopharyngitis (13.8% [4 of 29 subjects] in the secukinumab 150 mg group, 17.2% [5 of 29 subjects] in the secukinumab 300 mg group, 17.2% [5 of 29 subjects] in the placebo group), insomnia (6.9%

[2 of 29 subjects] in the secukinumab 150 mg group), oropharyngeal pain (6.9% [2 of 29 subjects] in the secukinumab 150 mg group), psoriasis (6.9% [2 of 29 subjects] in the secukinumab 150 mg group), furuncle (3.4% [1 of 29 subjects] in the secukinumab 150 mg group, 6.9% [2 of 29 subjects] in the secukinumab 300 mg group), pruritus (3.4% [1 of 29 subjects] in the secukinumab 150 mg group, 3.4% [1 of 29 subjects] in the secukinumab 300 mg group, 6.9% [2 of 29 subjects] in the placebo group), and oedema peripheral (3.4% [1 of 29 subjects] in the secukinumab 300 mg group, 6.9% [2 of 29 subjects] in the placebo group). There were no deaths. Serious adverse events occurred in 6.9% of subjects in the secukinumab 150 mg group (2 of 29 subjects, pulmonary oedema and cardiac failure; and type 2 diabetes mellitus, 1 subject each). A causal relationship to the study drug could not be ruled out for those reported by 1 subject (pulmonary oedema and cardiac failure). The incidences of adverse events leading to discontinuation were 6.9% in the secukinumab 150 mg group (2 of 29 subjects, erythrodermic psoriasis; and alopecia, 1 subject each) and 3.4% in the placebo group (1 of 29 subjects, herpes virus infection). A causal relationship to the study drug could not be ruled out for all events. The incidences of adverse drug reactions were 6.9% (2 of 29 subjects) in the secukinumab 150 mg group, 13.8% (4 of 29 subjects) in the secukinumab 300 mg group, and 6.9% (2 of 29 subjects) in the placebo group.

In the Japanese subgroup, the incidences of adverse events over the entire treatment period were 86.0% (37 of 43 subjects) in the secukinumab 150 mg group, 77.5% (31 of 40 subjects) in the secukinumab 300 mg group, and 44.8% (13 of 29 subjects) in the placebo group. Major events were as shown in Table 22. There were no deaths. The incidences of serious adverse events were 7.0% in the secukinumab 150 mg group (3 of 43 subjects, pulmonary oedema and cardiac failure; type 2 diabetes mellitus; and aortic aneurysm and aortic thrombosis, 1 subject each) and 2.5% in the secukinumab 300 mg group (1 of 40 subjects, pneumonia). The incidences of adverse events leading to discontinuation were 9.3% in the secukinumab 150 mg group (4 of 43 subjects, otitis external bacterial; erythrodermic psoriasis; alopecia; and aortic thrombosis and aortic aneurysm, 1 subject each) and 3.4% in the placebo group (1 of 29 subjects, herpes virus infection). The incidences of adverse drug reactions were 25.6% (11 of 43 subjects) in the secukinumab 150 mg group, 27.5% (11 of 40 subjects) in the secukinumab 300 mg group, and 10.3% (3 of 29 subjects) in the placebo group.

Table 22. Adverse events reported by ≥2 subjects in any group (through Week 52, Japanese subgroup)

Event term	Secukinumab 150 mg (N = 43)	Secukinumab 300 mg (N = 40)	Placebo (N = 29)
Nasopharyngitis	20 (46.5)	8(20.0)	5 (17.2)
Eczema	4 (9.3)	3 (7.5)	0
Pharyngitis	4 (9.3)	0	0
Urticaria	3 (7.0)	2 (5.0)	0
Oropharyngeal pain	3 (7.0)	0	0
Furuncle	2 (4.7)	2 (5.0)	0
Tinea pedis	2 (4.7)	2 (5.0)	0
Back pain	2 (4.7)	1 (2.5)	0
Psoriasis	2 (4.7)	0	0
Paronychia	2 (4.7)	0	0
Folliculitis	2 (4.7)	0	0
Alopecia	2 (4.7)	0	0
Insomnia	2 (4.7)	0	0
Pruritus	1 (2.3)	1 (2.5)	2 (6.9)
Herpes zoster	0	2 (5.0)	0
Dermatitis contact	0	2 (5.0)	0
Hyperlipidaemia	0	2 (5.0)	0
Arthralgia	0	2 (5.0)	0
Oedema peripheral	0	1 (2.5)	2 (6.9)

n (%)

4.(iii).A.(4) Multinational phase III study (5.3.5.2-1, Study A2304 [August 2011 to March 2013])

A randomized, double-blind, parallel-group study was conducted in patients with moderate to severe plaque psoriasis[21] (including patients with psoriatic arthritis) (target sample size of 918 [459 subjects per group]) in Japan, Austria, Canada, France, and the US, etc. to evaluate the efficacy and safety of secukinumab administered at the start of relapse (SoR) vs. the fixed interval (FI) regimen of secukinumab.

The treatment phase of the study consisted of 2 periods (through Week 12, the induction period; from Week 12 to Week 52, the maintenance period) and secukinumab 150 or 300 mg was to be administered subcutaneously according to Figure 5.

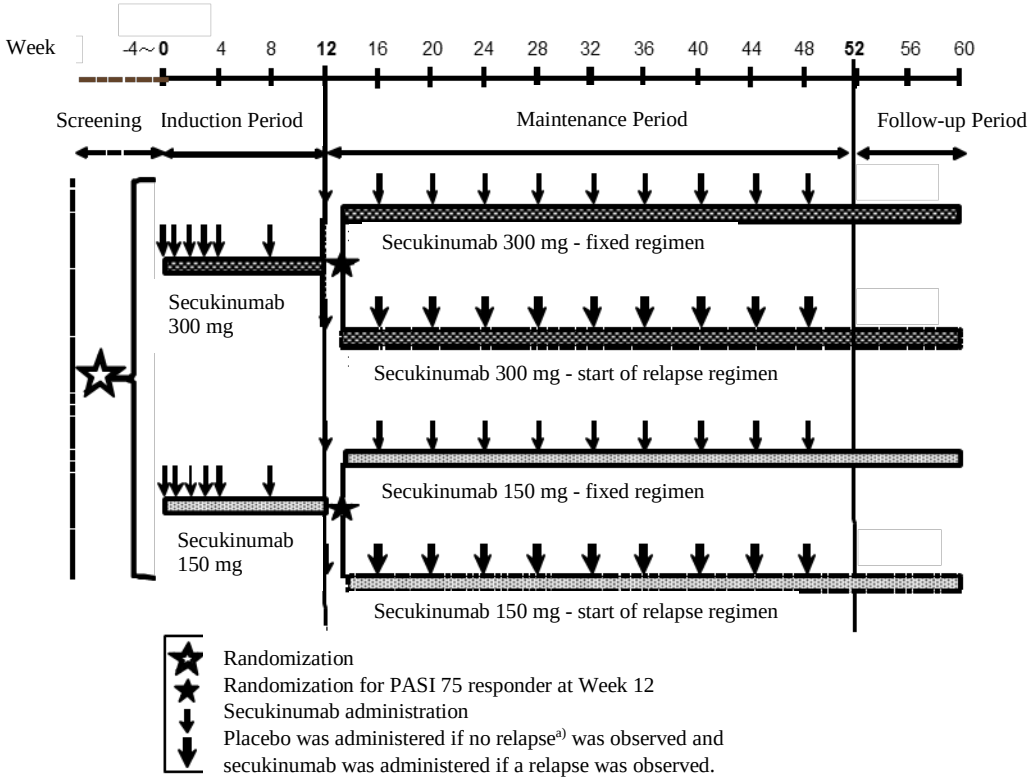


Figure 5. Study design and dosing schedule for Study A2304

a) Defined as a loss of ≥20% of the maximum PASI gain achieved during the study as compared to baseline, and a loss of PASI 75 response.
In the maintenance period, patients who had PASI 75 response at Week 12 were re-randomized into either the Fixed Interval regimen or the Retreatment at Start of Relapse regimen in a ratio of 1:1 by dose level in the induction period and stratified by geographical region and body weight (<90 kg or ≥90 kg).
At Week 12, PASI 50 non-responders did not continue treatment and PASI partial responders were given the option to enter Study A2307.

The randomization was stratified by geographical region and body weight (<90 kg or ≥90 kg), and the randomization for subjects in Japan was stratified by body weight and by history of psoriatic arthritis. Of 966 subjects randomized in a 1:1 ratio to either secukinumab 150 or 300 mg, 965 subjects excluding 1 subject in the secukinumab 300 mg group[27] (482 subjects in the secukinumab 150 mg group, 483 subjects in the secukinumab 300 mg group) were included in the FAS and in the Safety Analysis Set, which was used for efficacy analyses. The discontinuation rates during the induction period were 3.7% (18 of 482 subjects) in the secukinumab 150 mg group and 4.1% (20 of 484 subjects) in the secukinumab 300 mg group. The most common reasons for discontinuation were adverse event (1.7% [8 of 482 subjects] in the secukinumab 150 mg group, 1.9% [9 of 484 subjects] in the secukinumab 300 mg group), etc. The discontinuation rates during the maintenance period were 8.4% (17 of 203 subjects) in the secukinumab 150 mg FI group, 12.1% (25 of 206 subjects) in the secukinumab 150 mg SoR group, 8.3% (18 of 217 subjects) in the secukinumab 300 mg FI group, and 7.4% (16 of 217 subjects) in the secukinumab 300 mg SoR group. The most common reasons for discontinuation were consent withdrawal (5.4% [11 of 203 subjects] in the secukinumab 150 mg FI group, 4.9% [10 of 206 subjects] in the secukinumab 150 mg SoR group, 3.2% [7 of 217 subjects] in the secukinumab 300 mg FI group, and 3.2% [7 of 217 subjects] in the secukinumab 300 mg SoR group), etc. Of 928 subjects who completed the induction period, 843 subjects were PASI 75 responders and 203 subjects were re-

[27] The subject was excluded from the FAS because the date of a laboratory test performed (for one parameter) at screening was mistakenly recorded as being before the date of consent obtained.

randomized to the secukinumab 150 mg FI group, 206 subjects to the secukinumab 150 mg SoR group, 217 subjects to the secukinumab 300 mg FI group, and 217 subjects to the secukinumab 300 mg SoR group for the maintenance period.

The Japanese subgroup of the FAS consisted of 61 subjects (31 subjects in the secukinumab 150 mg group, 30 subjects in the secukinumab 300 mg group). The discontinuation rates during the induction period were 6.5% (2 of 31 subjects) in the secukinumab 150 mg group and 3.2% (1 of 31 subjects) in the secukinumab 300 mg group. The most common reasons for discontinuation were adverse event (3.2% [1 of 31 subjects] in the secukinumab 150 mg group, 3.2% [1 of 31 subjects] in the secukinumab 300 mg group), etc. The discontinuation rates during the maintenance period were 8.3% in the secukinumab 150 mg SoR group (1 of 12 subjects, consent withdrawal) and 6.7% in the secukinumab 300 mg SoR group (1 of 15 subjects, adverse event). Of 59 subjects who completed the induction period, 52 subjects were PASI 75 responders and 11 subjects were re-randomized to the secukinumab 150 mg FI group, 12 subjects to the secukinumab 150 mg SoR group, 14 subjects to the secukinumab 300 mg FI group, and 15 subjects to the secukinumab 300 mg SoR group for the maintenance period.

The primary efficacy endpoint of the sustained PASI 75 response rate from Week 12 to Week 40 or 52[28] was as shown in Table 23. The lower limit of the 98.75% confidence interval for the between-group difference was smaller than the prespecified non-inferiority margin (-15%). Thus, the non-inferiority of the SoR regimen to the FI regimen was not achieved at either dose level. The results in the Japanese subgroup were as shown in Table 24.

Table 23. Proportion of subjects who had sustained PASI 75 response (FAS, NRI)

	Secukinumab 150 mg SoR	Secukinumab 150 mg FI	Secukinumab 300 mg SoR	Secukinumab 300 mg FI	Between-group difference [98.75% CI] a)	
					Secukinumab 150 mg	Secukinumab 300 mg
Maintenance of PASI 75 response	52.4 (108/206)	62.1 (126/203)	67.7 (147/217)	78.2 (169/216)	-9.61 [-20.10, 0.88]	-10.34 [-19.37, -1.30]

% (n/N)

a) In order to adjust for multiplicity, the level of significance for the pairwise comparison for each of the two doses was set at α/2 and if the null hypothesis for one group comparison was rejected, the corresponding α/2 could be passed onto the null hypothesis for the other group comparison (Bretz F, et al. *Stat Med.* 2009;28: 586-604).

Table 24. Proportion of subjects who had sustained PASI 75 response (Japanese subgroup, NRI)

	Secukinumab 150 mg SoR	Secukinumab 150 mg FI	Secukinumab 300 mg SoR	Secukinumab 300 mg FI	Between-group difference [95% CI]	
					Secukinumab 150 mg	Secukinumab 300 mg
Maintenance of PASI 75 response	58.3 (7/12)	63.6 (7/11)	73.3 (11/15)	84.6 (11/13)	-5.3 [-46.0, 35.4]	-11.3 [-45.6, 25.9]

% (n/N)

The incidences of adverse events during the induction period (through Week 12) were 51.5% (248 of 482 subjects) in the secukinumab 150 mg group and 51.3% (248 of 483 subjects) in the secukinumab 300 mg group and major events were as shown in Table 25. There were no deaths. The incidences of serious adverse events were 1.7% in the secukinumab 150 mg group (8 of 482 subjects; abdominal pain lower and urine analysis

[28] Defined as PASI 75 response at Week 52 for subjects in the FI groups and PASI 75 response at Week 52 for subjects on secukinumab at Week 40 in the SoR groups and PASI 75 response at Week 40 for subjects on placebo at Week 40 in the SoR groups.

abnormal; angina pectoris; hepatic cirrhosis; generalised oedema and pleural effusion; femoral artery occlusion; palpitations, depression, and panic attack; peripheral artery stenosis; and appendicitis, 1 subject each) and 1.9% in the secukinumab 300 mg group (9 of 483 subjects, syncope; pemphigus; atrial fibrillation and acute myocardial infarction; concussion and hand fracture; gastrooesophageal reflux disease; nephrolithiasis; basal cell carcinoma; benign breast neoplasm; and liver injury, pancreatic injury, femur fracture, and tendon rupture, 1 subject each) and a causal relationship to the study drug could not be ruled out for those reported by 3 subjects in the secukinumab 150 mg group (palpitations; generalised oedema and pleural effusion; and femoral artery occlusion, 1 subject each) and 2 subjects in the secukinumab 300 mg group (gastrooesophageal reflux disease; and pemphigus, 1 subject each). The incidences of adverse events leading to discontinuation were 2.1% in the secukinumab 150 mg group (10 of 482 subjects, hypertension; gamma-glutamyltransferase increased; angina pectoris; hepatic cirrhosis; thrombocytopenia; generalised oedema; femoral artery occlusion; aspartate aminotransferase increased, alanine aminotransferase increased, and gamma-glutamyltransferase increased; neutropenia and leukopenia; and psoriatic arthropathy, 1 subject each) and 1.9% in the secukinumab 300 mg group (9 of 483 subjects, musculoskeletal stiffness; lymphadenitis; dermatitis atopic; pemphigus; hepatic enzyme increased; hepatomegaly; pustular psoriasis; atrial fibrillation; and dermatitis, 1 subject each). A causal relationship to the study drug could not be ruled out for those reported by 4 subjects in the secukinumab 150 mg group (neutropenia; femoral artery occlusion; generalised oedema; and gamma-glutamyltransferase increased, 1 subject each) and 5 subjects in the secukinumab 300 mg group (dermatitis; pustular psoriasis; pemphigus; dermatitis atopic; and musculoskeletal stiffness, 1 subject each). The incidences of adverse drug reactions were 16.0% (77 of 482 subjects) in the secukinumab 150 mg group and 13.0% (63 of 483 subjects) in the secukinumab 300 mg group.

Table 25. Adverse events reported by ≥2% of subjects in either group (through Week 12, Safety Analysis Set)

Event term	Secukinumab 150 mg (N = 482)	Secukinumab 300 mg (N = 483)
Nasopharyngitis	48 (10.0)	45 (9.3)
Headache	22 (4.6)	17 (3.5)
Pruritus	19 (3.9)	11 (2.3)
Upper respiratory tract infection	17 (3.5)	18 (3.7)
Hypertension	11 (2.3)	11 (2.3)
Cough	10 (2.1)	10 (2.1)
Nausea	10 (2.1)	4 (0.8)
Back pain	10 (2.1)	4 (0.8)

n (%)

The incidences of adverse events over the entire treatment period (the induction and maintenance periods) were 77.8% (158 of 203 subjects) in the secukinumab 150 mg FI group, 78.7% (170 of 216 subjects) in the secukinumab 300 mg FI group, 75.1% (154 of 205 subjects) in the secukinumab 150 mg SoR group, and 73.3% (159 of 217 subjects) in the secukinumab 300 mg SoR group. Major events were as shown in Table 26. A death was reported in the secukinumab 150 mg SoR group (cerebral haemorrhage). The incidences of non-fatal serious adverse events were 5.9% (12 of 203 subjects) in the secukinumab 150 mg FI group, 8.3% (18 of 216 subjects) in the secukinumab 300 mg FI group, 6.3% (13 of 205 subjects) in the secukinumab 150 mg SoR group, and 6.5% (14 of 217 subjects) in the secukinumab 300 mg SoR group. Adverse events reported by ≥2 subjects in any group were basal cell carcinoma (0.9% [2 of 216 subjects] in the secukinumab 300 mg FI group), osteoarthritis (1.0% [2 of 205 subjects] in the secukinumab 150 mg SoR group, 0.5% [1 of 217

subjects] in the secukinumab 300 mg SoR group), vomiting (1.0% [2 of 205 subjects] in the secukinumab 150 mg SoR group), and tendon rupture (0.9% [2 of 217 subjects] in the secukinumab 300 mg SoR group). The incidences of adverse events leading to discontinuation were 1.5% (3 of 203 subjects) in the secukinumab 150 mg FI group, 3.7% (8 of 216 subjects) in the secukinumab 300 mg FI group, 2.0% (4 of 205 subjects) in the secukinumab 150 mg SoR group, and 0.9% (2 of 217 subjects) in the secukinumab 300 mg SoR group.

The incidences of adverse drug reactions were 23.6% (48 of 203 subjects) in the secukinumab 150 mg FI group, 27.8% (60 of 216 subjects) in the secukinumab 300 mg FI group, 23.9% (49 of 205 subjects) in the secukinumab 150 mg SoR group, and 24.4% (53 of 217 subjects) in the secukinumab 300 mg SoR group.

Table 26. Adverse events reported by ≥2% of subjects in any group (through Week 52, Safety Analysis Set)

Event term	Secukinumab 150 mg FI (N = 203)	Secukinumab 300 mg FI (N = 216)	Secukinumab 150 mg SoR (N = 205)	Secukinumab 300 mg SoR (N = 217)
Nasopharyngitis	37 (18.2)	35 (16.2)	32 (15.6)	42 (19.4)
Upper respiratory tract infection	16 (7.9)	16 (7.4)	11 (5.4)	15 (6.9)
Headache	14 (6.9)	10 (4.6)	14 (6.8)	11 (5.1)
Cough	13 (6.4)	11 (5.1)	8 (3.9)	8 (3.7)
Pruritus	12 (5.9)	11 (5.1)	16 (7.8)	6 (2.8)
Back pain	12 (5.9)	10 (4.6)	9 (4.4)	7 (3.2)
Bronchitis	11 (5.4)	7 (3.2)	1 (0.5)	6 (2.8)
Influenza	10 (4.9)	6 (2.8)	5 (2.4)	8 (3.7)
Hypertension	9 (4.4)	16 (7.4)	10 (4.9)	12 (5.5)
Arthralgia	8 (3.9)	12 (5.6)	12 (5.9)	13 (6.0)
Pharyngitis	8 (3.9)	12 (5.6)	2 (1.0)	7 (3.2)
Gastroenteritis	7 (3.4)	5 (2.3)	4 (2.0)	5 (2.3)
Diarrhoea	6 (3.0)	7 (3.2)	8 (3.9)	10 (4.6)
Urticaria	6 (3.0)	2 (0.9)	1 (0.5)	4 (1.8)
Insomnia	6 (3.0)	1 (0.5)	3 (1.5)	1 (0.5)
Seborrhoeic dermatitis	5 (2.5)	6 (2.8)	3 (1.5)	1 (0.5)
Gastrooesophageal reflux disease	5 (2.5)	5 (2.3)	0	2 (0.9)
Nausea	5 (2.5)	3 (1.4)	6 (2.9)	1 (0.5)
Psoriatic arthropathy	5 (2.5)	2 (0.9)	6 (2.9)	2 (0.9)
Sinus congestion	5 (2.5)	1 (0.5)	0	3 (1.4)
Rhinitis	4 (2.0)	6 (2.8)	3 (1.5)	4 (1.8)
Hypercholesterolaemia	4 (2.0)	5 (2.3)	3 (1.5)	2 (0.9)
Pain in extremity	4 (2.0)	4 (1.9)	6 (2.9)	2 (0.9)
ALT increased	4 (2.0)	3 (1.4)	4 (2.0)	4 (1.8)
Oedema peripheral	4 (2.0)	3 (1.4)	2 (1.0)	3 (1.4)
Acne	4 (2.0)	2 (0.9)	2 (1.0)	0
γ-GTP increased	4 (2.0)	1 (0.5)	5 (2.4)	3 (1.4)
Toothache	4 (2.0)	1 (0.5)	4 (2.0)	2 (0.9)
Hypoaesthesia	4 (2.0)	1 (0.5)	1 (0.5)	1 (0.5)
Oropharyngeal pain	3 (1.5)	10 (4.6)	3 (1.5)	5 (2.3)
Sinusitis	3 (1.5)	6 (2.8)	7 (3.4)	4 (1.8)
Folliculitis	2 (1.0)	6 (2.8)	3 (1.5)	6 (2.8)
Dermatitis contact	3 (1.5)	5 (2.3)	5 (2.4)	3 (1.4)
Pyrexia	3 (1.5)	5 (2.3)	4 (2.0)	2 (0.9)
Conjunctivitis	3 (1.5)	5(2.3)	3(1.5)	2(0.9)
Viral upper respiratory tract infection	3 (1.5)	4 (1.9)	0	5 (2.3)
Diabetes mellitus	3 (1.5)	2 (0.9)	4 (2.0)	0
Hyperlipidaemia	2 (1.0)	6 (2.8)	2 (1.0)	1 (0.5)
Vomiting	2 (1.0)	5 (2.3)	2 (1.0)	1 (0.5)
Pruritus generalised	2 (1.0)	2 (0.9)	4 (2.0)	4 (1.8)
Oral herpes	2 (1.0)	2 (0.9)	4 (2.0)	2 (0.9)
Dyslipidaemia	2 (1.0)	1 (0.5)	6 (2.9)	1 (0.5)
Dyspepsia	2 (1.0)	1 (0.5)	4 (2.0)	1 (0.5)
Fatigue	1 (0.5)	4 (1.9)	4 (2.0)	4 (1.8)
Tinea pedis	1 (0.5)	2 (0.9)	4 (2.0)	1 (0.5)
Eczema	0	8 (3.7)	1 (0.5)	7 (3.2)
Dermatitis	0	5 (2.3)	5 (2.4)	1 (0.5)
Psoriasis	0	5 (2.3)	2 (1.0)	6 (2.8)
Injection site pain	0	4 (1.9)	3 (1.5)	5 (2.3)
Hyperuricaemia	0	1 (0.5)	4 (2.0)	2 (0.9)
Pharyngitis bacterial	0	0	0	5 (2.3)

n (%)

In the Japanese subgroup, the incidences of adverse events during the induction period (through Week 12) were 61.3% (19 of 31 subjects) in the secukinumab 150 mg group and 66.7% (20 of 30 subjects) in the secukinumab 300 mg group. Adverse events reported by ≥2 subjects in either group were nasopharyngitis (16.1% [5 of 31 subjects] in the secukinumab 150 mg group, 23.3% [7 of 30 subjects] in the secukinumab 300 mg group), pruritus (6.5% [2 of 31 subjects] in the secukinumab 150 mg group, 10.0% [3 of 30 subjects] in the secukinumab 300 mg group), eczema (3.2% [1 of 31 subjects] in the secukinumab 150 mg group, 10.0% [3 of 30 subjects] in the secukinumab 300 mg group), and folliculitis (6.7% [2 of 30 subjects] in the

secukinumab 300 mg group). There were no deaths. The incidences of serious adverse events were 3.2% in the secukinumab 150 mg group (1 of 31 subjects, generalised oedema and pleural effusion) and 6.7% in the secukinumab 300 mg group (2 of 30 subjects, pemphigus; and liver injury, pancreatic injury, femur fracture, and tendon rupture, 1 subject each). A causal relationship to the study drug could not be ruled out for those reported by 1 subject in the secukinumab 150 mg group and 1 subject in the secukinumab 300 mg group (pemphigus). The incidences of adverse events leading to discontinuation were 3.2% in the secukinumab 150 mg group (1 of 31 subjects, generalised oedema) and 3.3% in the secukinumab 300 mg group (1 of 30 subjects, pemphigus). A causal relationship to the study drug could not be ruled out for both events. The incidences of adverse drug reactions were 12.9% (4 of 31 subjects) in the secukinumab 150 mg group and 13.3% (4 of 30 subjects) in the secukinumab 300 mg group.

In the Japanese subgroup, the incidences of adverse events over the entire treatment period (the induction and maintenance periods) were 90.9% (10 of 11 subjects) in the secukinumab 150 mg FI group, 84.6% (11 of 13 subjects) in the secukinumab 300 mg FI group, 91.7% (11 of 12 subjects) in the secukinumab 150 mg SoR group, and 93.3% (14 of 15 subjects) in the secukinumab 300 mg SoR group. Major events were as shown in Table 27. There were no deaths. Serious adverse events occurred in 13.3% of subjects in the secukinumab 300 mg SoR group (2 of 15 subjects, liver injury, pancreatic injury, femur fracture, and tendon rupture; and tonsillitis bacterial, 1 subject each). An adverse event leading to discontinuation occurred in 6.7% of subjects in the secukinumab 300 mg SoR group (1 of 15 subjects, interstitial lung disease). The incidences of adverse drug reactions were 27.3% (3 of 11 subjects) in the secukinumab 150 mg FI group, 46.2% (6 of 13 subjects) in the secukinumab 300 mg FI group, 16.7% (2 of 12 subjects) in the secukinumab 150 mg SoR group, and 46.7% (7 of 15 subjects) in the secukinumab 300 mg SoR group.

Table 27. Adverse events reported by ≥2 subjects in any group (through Week 52, Japanese subgroup)

Event term	Secukinumab 150 mg FI (N = 11)	Secukinumab 300 mg FI (N = 13)	Secukinumab 150 mg SoR (N = 12)	Secukinumab 300 mg SoR (N = 15)
Nasopharyngitis	3 (27.3)	3 (23.1)	3 (25.0)	6 (40.0)
Headache	2 (18.2)	0	0	0
Pruritus	1 (9.1)	2 (15.4)	0	1 (6.7)
Urticaria	1 (9.1)	0	0	2 (13.3)
Eczema	0	2 (15.4)	0	1 (6.7)
Eosinophilia	0	2 (15.4)	0	0
Dermatitis	0	2 (15.4)	0	0
Dermatitis contact	0	0	2 (16.7)	0
Arthralgia	0	0	0	2 (13.3)

n (%)

The applicant explained as follows:

The non-inferiority of the SoR regimen to the FI regimen was not achieved for the sustained PASI 75 response rate in the study and the efficacy with the FI regimen was higher than that with the SoR regimen at both dose levels. Thus, patients treated with the SoR regimen do not achieve adequate maintenance of response, and secukinumab should be administered every 4 weeks continuously.

4.(iii).A.(5) Multinational phase III study (5.3.5.2-2, Study A2307 [December 2011 to February 2013])

A randomized, double-blind, parallel-group study was conducted in PASI partial responders in Study A2304 (target sample size of 140) to evaluate the efficacy and safety of secukinumab.

The treatment phase of the study consisted of 2 periods (through Week 8, the loading period; from Week 8 to Week 36, the maintenance period). During the loading period, secukinumab 300 mg was to be administered subcutaneously at Day 1 and at Week 4 (the secukinumab 300 mg s.c. group) or secukinumab 10 mg/kg was to be administered intravenously at Day 1 and at Weeks 2 and 4 (the secukinumab 10 mg/kg i.v. group) in a double-blind manner. During the maintenance period, all subjects were to receive open-label secukinumab 300 mg subcutaneously every 4 weeks until Week 36.

The randomization was stratified by the previous treatment group in Study A2304 (secukinumab 150 mg or 300 mg s.c.). All of 43 subjects[29] randomized in a 1:1 ratio to the secukinumab 300 mg s.c. or 10 mg/kg i.v. group (21 subjects in the secukinumab 300 mg s.c. group, 22 subjects in the secukinumab 10 mg/kg i.v. group) were included in the FAS, in the Safety Analysis Set, and the Efficacy Analysis Set. The discontinuation rates during the loading period were 4.8% in the secukinumab 300 mg s.c. group (1 of 21 subjects, consent withdrawal) and 9.1% in the secukinumab 10 mg/kg i.v. group (2 of 22 subjects, lost to follow-up; and a protocol deviation, 1 subject each).

The Japanese subgroup of the FAS consisted of 5 subjects (3 subjects in the secukinumab 300 mg s.c. group, 2 subjects in the secukinumab 10 mg/kg i.v. group). There were no subjects discontinued treatment.

The co-primary efficacy endpoints were the PASI 75 response rate at Week 8 and the IGA 0/1 response rate at Week 8. The PASI 75 response rates at Week 8 was as shown in Table 28, and the IGA 0/1 response rates at Week 8 were as shown in Table 29. A pairwise comparison showed no statistically significant differences in the PASI 75 response rate between the secukinumab 300 mg s.c. and 10 mg/kg i.v. groups while a statistically significant difference was observed for the IGA 0/1 response rate. The results in the Japanese subgroup were as shown in Table 28 and Table 29.

Table 28. PASI 50, 75 (co-primary endpoint), and 90 response rates at Week 8 (NRI)

	FAS			Japanese subgroup		
	Secukinumab 300 mg s.c.	Secukinumab 10 mg/kg i.v.	Between-group difference [95% CI], *P*-value [a)]	Secukinumab 300 mg s.c.	Secukinumab 10 mg/kg i.v.	Between-group difference [95% CI]
PASI 50 response rate	90.5 (19/21)	95.2 (20/21)	-4.8 [-36.0, 27.2]	100 (3/3)	100 (2/2)	―
PASI 75 response rate	66.7 (14/21)	90.5 (19/21)	23.8 [-8.7, 52.9] *P* = 0.0649	33.3 (1/3)	100 (2/2)	66.7 [-36.0, 99.2]
PASI 90 response rate	9.5 (2/21)	61.9 (13/21)	52.4 [21.1, 75.9]	33.3 (1/3)	100 (2/2)	66.7 [-36.0, 99.2]

% (n/N)

a) Cochran-Mantel-Haenszel test stratified by the previous treatment group in Study A2304 (secukinumab 150 mg or 300 mg s.c.)

[29] Although the number of PASI partial responders in Study A2304 was predicted to be 140, due to a higher than anticipated PASI 75 response rate in Study A2304, fewer patients were enrolled into the study.

Table 29. IGA 0/1 response rate at Week 8 (co-primary endpoint) (NRI)

FAS			Japanese subgroup		
Secukinumab 300 mg s.c.	Secukinumab 10 mg/kg i.v.	Between-group difference [95% CI], *P*-value [a)]	Secukinumab 300 mg s.c.	Secukinumab 10 mg/kg i.v.	Between-group difference [95% CI]
33.3 (7/21)	66.7 (14/21)	33.3 [0.9, 60.9] *P* = 0.0332	33.3 (1/3)	100 (2/2)	66.7 [-36.0, 99.2]

% (n/N)
a) Cochran-Mantel-Haenszel test stratified by the previous treatment group in Study A2304 (secukinumab 150 mg or 300 mg s.c.)

The incidences of adverse events during the loading period (through Week 8) were 52.4% (11 of 21 subjects) in the secukinumab 300 mg s.c. group and 45.5% (10 of 22 subjects) in the secukinumab 10 mg/kg i.v. group. Adverse events reported by ≥2 subjects in either group were nasopharyngitis (14.3% [3 of 21 subjects] in the secukinumab 300 mg s.c. group, 9.1% [2 of 22 subjects] in the secukinumab 10 mg/kg i.v. group), upper respiratory tract infection (9.1% [2 of 22 subjects] in the secukinumab 10 mg/kg i.v. group), and intertrigo (9.1% [2 of 22 subjects] in the secukinumab 10 mg/kg i.v. group). There were no deaths, serious adverse events, or adverse events leading to discontinuation. The incidences of adverse drug reactions were 14.3% (3 of 21 subjects) in the secukinumab 300 mg s.c. group and 18.2% (4 of 22 subjects) in the secukinumab 10 mg/kg i.v. group.

The incidences of adverse events over the entire treatment period were 71.4% (15 of 21 subjects) in the secukinumab 300 mg s.c. group and 81.8% (18 of 22 subjects) in the secukinumab 10 mg/kg i.v. group. Major events were as shown in Table 30. There were no deaths. A serious adverse event occurred in 4.5% of subjects in the secukinumab 10 mg/kg i.v. group (1 of 22 subjects, dermatitis allergic). An adverse event leading to discontinuation occurred in 4.5% of subjects in the secukinumab 10 mg/kg i.v. group (1 of 22 subjects, dermatitis allergic). The incidences of adverse drug reactions were 33.3% (7 of 21 subjects) in the secukinumab 300 mg s.c. group and 36.4% (8 of 22 subjects) in the secukinumab 10 mg/kg i.v. group.

Table 30. Adverse events reported by ≥2 subjects in either group (through Week 40, Safety Set)

Event term	Secukinumab 300 mg s.c. (N = 21)	Secukinumab 10 mg/kg i.v. (N = 22)
Nasopharyngitis	4 (19.0)	5 (22.7)
Pharyngitis	2 (9.5)	1 (4.5)
Upper respiratory tract infection	1 (4.8)	2 (9.1)
Folliculitis	0	3(13.6)
Headache	0	2 (9.1)
Intertrigo	0	2 (9.1)

n (%)

In the Japanese subgroup, the incidences of adverse events during the loading period (through Week 8) were 66.7% in the secukinumab 300 mg s.c. group (2 of 3 subjects, seasonal allergy and hypertension; and gingivitis ulcerative, diarrhoea, and pharyngitis, 1 subject each). There were no deaths, serious adverse events, and adverse events leading to discontinuation, or adverse drug reactions.

In the Japanese subgroup, the incidences of adverse events over the entire treatment period were 100% (3 of 3 subjects) in the secukinumab 300 mg s.c. group and 50% (1 of 2 subjects) in the secukinumab 10 mg/kg i.v.

group and those reported by ≥2 subjects in either group were pharyngitis (66.7% [2 of 3 subjects] in the secukinumab 300 mg s.c. group). There were no deaths, serious adverse events, or adverse events leading to discontinuation. The incidences of adverse drug reactions were 33.3% in the secukinumab 300 mg s.c. group (1 of 3 subjects, upper respiratory tract infection) and 50% in the secukinumab 10 mg/kg i.v. group (1 of 2 subjects, folliculitis).

4.(iii).A.(6) Multinational phase III study (5.3.5.1-12, Study A2302E1 [June 2012 to ongoing (data cutoff date of August 16, 2013; Week 68 data)])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in psoriatic patients (including patients with psoriatic arthritis) on secukinumab who achieved at least a PASI 50 response at Week 52 of Study A2302 or A2303 (the core studies) (target sample size of 1220) to evaluate the efficacy and safety of secukinumab.

The treatment phase of the study consisted of 2 periods (until the first relapse, the randomized withdrawal period; after the first relapse, the treatment period). Secukinumab 150 or 300 mg or placebo was to be administered subcutaneously according to Figure 6. Subjects were allowed to self-administer study drug.

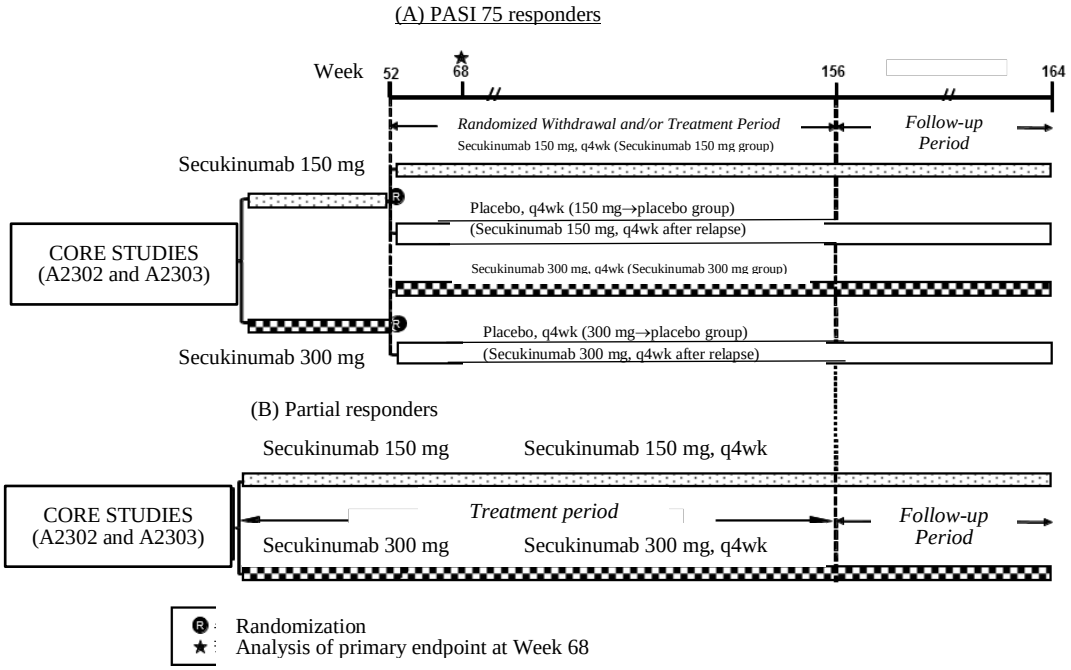


Figure 6. Study design and dosing schedule for Study A2302E1

During the randomized withdrawal period, PASI 75 responders at Week 52 of the core studies were to enter the treatment period when the first relapse (a >50% reduction of the maximal PASI improvement compared to baseline of Study A2302 or A2303) was observed. During the treatment period, PASI 75 responders in the secukinumab 150 mg and 300 mg groups were to receive placebo s.c. at study visit at which relapse was diagnosed and once weekly for 3 weeks and then the same s.c. dose of secukinumab as in the core studies every 4 weeks. PASI 75 responders in the 150 mg→placebo and 300 mg→placebo groups were to receive the same s.c. dose of secukinumab as in the core studies at study visit at which relapse was diagnosed and once weekly for 3 weeks followed by dosing every 4 weeks.

PASI partial responders at Week 52 of the core studies were not to participate in the randomized withdrawal period and were to participate in the treatment period only. The number of weeks was counted from the start of treatment n the core studies.

PASI 75 responders at Week 52 of the core studies were randomized in a ratio of 2:2:1:1 to the secukinumab 150 mg, secukinumab 300 mg, 150 mg→placebo, or 300 mg→placebo group and stratified by geographical

region and body weight at Week 52 of the core studies (<90 kg or ≥90 kg). All of 1146 PASI 75 responders and partial responders at Week 52 of the core studies (459 subjects in the secukinumab 150 mg group[30], 462 subjects in the secukinumab 300 mg group[31], 150 subjects in the 150 mg→placebo group, 181 subjects in the 300 mg→placebo group) were included in the Safety Analysis Set for the entire treatment period (the randomized withdrawal and treatment periods). Of these, 990 subjects who were PASI 75 responders at Week 52 and had at least one efficacy assessment (297 subjects in the secukinumab 150 mg group, 363 subjects in the secukinumab 300 mg group, 150 subjects in the 150 mg→placebo group, 180 subjects in the 300 mg→placebo group) were included in the FAS for the randomized withdrawal period, which was used for efficacy analyses. The discontinuation rates during the randomized withdrawal period were 3.0% (9 of 301 subjects) in the secukinumab 150 mg group, 1.1% (4 of 363 subjects) in the secukinumab 300 mg group, 2.0% (3 of 150 subjects) in the 150 mg→placebo group, and 2.8% (5 of 181 subjects) in the 300 mg→placebo group. The most common reasons for discontinuation were adverse event (1.0% [3 of 301 subjects] in the secukinumab 150 mg group, 0.6% [2 of 363 subjects] in the secukinumab 300 mg group, 0.7% [1 of 150 subjects] in the 150 mg→placebo group), etc.

The Japanese subgroup of the FAS (PASI 75 responders and partial responders at Week 52) consisted of 67 subjects (24 subjects in the secukinumab 150 mg group, 23 subjects in the secukinumab 300 mg group, 11 subjects in the 150 mg→placebo group, 9 subjects in the 300 mg→placebo group). Treatment was discontinued in 1 subject in the secukinumab 300 mg group (adverse event).

The primary efficacy endpoint of the cumulative rates of subjects with loss of PASI 75 response up to Week 68 were as shown in Table 31. Pairwise comparisons showed statistically significant differences between the secukinumab 150 mg and 150 mg→placebo groups and between the secukinumab 300 mg and 300 mg→placebo groups. The cumulative rates of subjects with loss of PASI 75 response up to Week 68 in the Japanese subgroup were as shown in Table 32.

Table 31. Cumulative rates of subjects with loss of PASI 75 response up to Week 68 (FAS)

	Secukinumab 150 mg	Secukinumab 300 mg	150 mg－Placebo	300 mg－Placebo
No. of events (N)	80 (297)	44 (363)	87 (150)	77 (180)
Cumulative rate [95% CI] [a)]	49.8 [25.8, 79.7]	25.4 [9.8, 56.5]	74.3 [56.9, 88.8]	64.7 [52.0, 77.2]
Hazard ratio [95% CI] [b)]	0.30 [0.22, 0.42]	0.20 [0.14, 0.29]		
P-value [c), d)]	$P < 0.0001$	$P < 0.0001$		

a) Kaplan-Meier method
b) Cox proportional hazards model stratified by geographical region and body weight at Week 52 (<90 kg or ≥90 kg) with treatment, core study, baseline PASI score in the core study, and baseline PASI score in the extension study as explanatory variables
c) Log-rank test stratified by geographical region and body weight at Week 52 (<90 kg or ≥90 kg)
d) In order to adjust for multiplicity, the level of significance for the pairwise comparison for each of the two doses was set at α/2 and if the null hypothesis for one group comparison was rejected, the corresponding α/2 could be passed onto the null hypothesis for the other group comparison (Bretz F, et al. *Stat Med*. 2009;28:586-604).

Table 32. Cumulative rates of subjects with loss of PASI 75 response up to Week 68 (Japanese subgroup, PASI 75 responders at Week 52)

	Secukinumab 150 mg	Secukinumab 300 mg	150 mg－Placebo	300 mg－Placebo
No. of events (N)	8 (24)	1 (23)	8 (11)	4 (9)
Cumulative rate [95% CI] [a)]	100.0 [100.0, 100.0]	4.3 [0.6, 27.1]	77.3 [48.9, 96.2]	48.1 [21.2, 83.6]

a) Kaplan-Meier method

[30] Including 59 subjects who entered the treatment period to receive secukinumab 150 mg among 150 subjects in the 150 mg→placebo group.
[31] Including 46 subjects who entered the treatment period to receive secukinumab 300 mg among 181 subjects in the 300 mg→placebo group.

The incidences of adverse events over the entire treatment period (the randomized withdrawal and treatment periods) were 44.0% (202 of 459 subjects) in the secukinumab 150 mg group, 51.1% (236 of 462 subjects) in the secukinumab 300 mg group, 46.0% (69 of 150 subjects) in the 150 mg→placebo group, and 48.1% (87 of 181 subjects) in the 300 mg→placebo group. Major events were as shown in Table 33. There were no deaths. The incidences of serious adverse events were 1.5% (7 of 459 subjects) in the secukinumab 150 mg group, 1.9% (9 of 462 subjects) in the secukinumab 300 mg group, 1.3% (2 of 150 subjects) in the 150 mg→placebo group, and 3.3% (6 of 181 subjects) in the 300 mg→placebo group. A causal relationship to the study drug could not be ruled out for those reported by 1 subject in the secukinumab 150 mg group (pericarditis), 1 subject in the secukinumab 300 mg group (gallbladder cancer, hepatic cancer metastatic, and hepatitis toxic), and 1 subject in the 150 mg→placebo group (appendicitis perforated). The incidences of adverse events leading to discontinuation were 1.5% (7 of 459 subjects) in the secukinumab 150 mg group, 0.6% (3 of 462 subjects) in the secukinumab 300 mg group, and 0.7% (1 of 150 subjects) in the 150 mg→placebo group. A causal relationship to the study drug could not be ruled out for those reported by 2 subjects in the secukinumab 150 mg group (dyshidrotic eczema; and liver function test abnormal, 1 subject each) and 2 subjects in the secukinumab 300 mg group (upper respiratory tract infection; and gallbladder cancer, 1 subject each). The incidences of adverse drug reactions were 10.9% (50 of 459 subjects) in the secukinumab 150 mg group, 11.3% (52 of 462 subjects) in the secukinumab 300 mg group, 9.3% (14 of 150 subjects) in the 150 mg→placebo group, and 11.6% (21 of 181 subjects) in the 300 mg→placebo group.

Table 33. Adverse events reported by ≥2% of subjects in any group (Entire treatment period, Safety Set)

Event term	Secukinumab 150 mg (N = 459)	Secukinumab 300 mg (N = 462)	150 mg－Placebo (N = 150)	300 mg－Placebo (N = 181)
Nasopharyngitis	41 (8.9)	49 (10.6)	13 (8.7)	10 (5.5)
Arthralgia	14 (3.1)	9 (1.9)	4 (2.7)	8 (4.4)
Headache	9 (2.0)	12 (2.6)	1 (0.7)	2 (1.1)
Upper respiratory tract infection	5 (1.1)	10 (2.2)	5 (3.3)	7 (3.9)

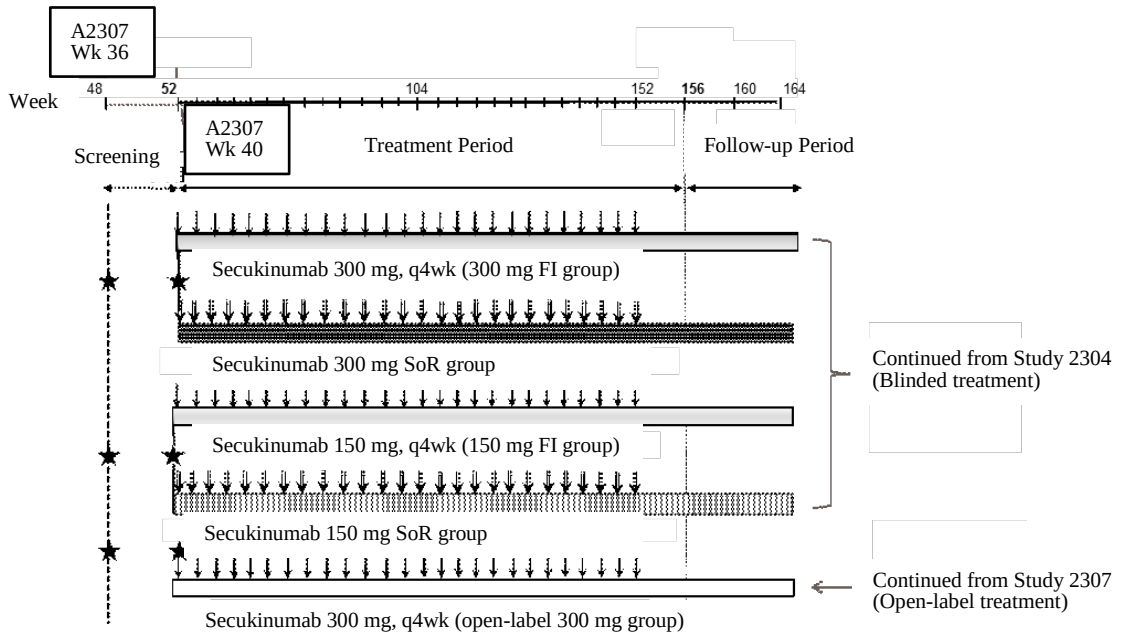
n (%)

In the Japanese subgroup, the incidences of adverse events over the entire treatment period (the randomized withdrawal and treatment periods) were 51.7% (15 of 29 subjects) in the secukinumab 150 mg group, 42.9% (12 of 28 subjects) in the secukinumab 300 mg group, 45.5% (5 of 11 subjects) in the 150 mg→placebo group, and 33.3% (3 of 9 subjects) in the 300 mg→placebo group. Adverse events reported by ≥2 subjects in any group were nasopharyngitis (24.1% [7 of 29 subjects] in the secukinumab 150 mg group, 14.3% [4 of 28 subjects] in the secukinumab 300 mg group, 27.3% [3 of 11 subjects] in the 150 mg→placebo group), gastrooesophageal reflux disease (7.1% [2 of 28 subjects] in the secukinumab 300 mg group), and gastroenteritis (6.9% [2 of 29 subjects] in the secukinumab 150 mg group). There were no deaths. Serious adverse events occurred in 1 subject in the secukinumab 150 mg group (cataract) and 2 subjects in the secukinumab 300 mg group (post procedural infection, gallbladder cancer, and hepatic cancer metastatic; and large intestine polyp, 1 subject each). An adverse event leading to discontinuation occurred in 1 subject in the secukinumab 300 mg group (gallbladder cancer). The incidences of adverse drug reactions were 3.4% (1 of 29 subjects) in the secukinumab 150 mg group, 14.3% (4 of 28 subjects) in the secukinumab 300 mg group, 18.2% (2 of 11 subjects) in the 150 mg→placebo group, and 11.1% (1 of 9 subjects) in the 300 mg→placebo group.

4.(iii).A.(7) Multinational phase III study (5.3.5.2-3, Study A2304E1 [September 2012 to ongoing (data cutoff date of August 9, 2013)])

A long-term extension study was conducted in patients with psoriasis (including patients with psoriatic arthritis) who completed Study A2304 or A2307 (Target sample size of 740) to evaluate the long-term safety and tolerability, etc. of secukinumab.

Secukinumab 150 or 300 mg or placebo was to be administered subcutaneously according to Figure 7. Subjects were allowed to self-administer study drug.



- Secukinumab 300 mg SoR group: Secukinumab 300 mg was administered if start of relapse was observed and placebo was administered if no start of relapse was observed or PASI 75 response was regained.
- Secukinumab 150 mg SoR group: Secukinumab 150 mg was administered if start of relapse was observed and placebo was administered if no start of relapse was observed or PASI 75 response was regained.

Figure 7. Study design and dosing schedule for Study A2304E1
The number of weeks was counted from treatment initiation in the core studies.

All of 675 subjects enrolled in the study were included in the FAS, which was used for efficacy analyses, and included in the Safety Set. The discontinuation rates were 2.6% (4 of 152 subjects) in the 150 mg FI group, 3.6% (6 of 168 subjects) in the 300 mg FI group, 9.3% (14 of 150 subjects) in the 150 mg SoR group, 9.3% (16 of 172 subjects) in the 300 mg SoR group, and 3.0% (1 of 33 subjects) in the open-label 300 mg group. The most common reasons for discontinuation included adverse event (2.4% [4 of 168 subjects] in the 300 mg FI group, 1.3% [2 of 150 subjects] in the 150 mg SoR group, 3.5% [6 of 172 subjects] in the 300 mg SoR group, 3.0% [1 of 33 subjects]) in the open-label 300 mg group), etc.

The Japanese subgroup of the FAS consisted of 51 subjects (10 subjects in the 150 mg FI group, 13 subjects in the 300 mg FI group, 10 subjects in the 150 mg SoR group, 14 subjects in the 300 mg SoR group, 4 subjects in the open-label 300 mg group). Two subjects in the 300 mg SoR group discontinued (adverse event; and the investigator's decision, 1 subject each).

The incidences of adverse events were 59.2% (90 of 152 subjects) in the 150 mg FI group, 58.9% (99 of 168 subjects) in the 300 mg FI group, 56.0% (84 of 150 subjects) in the 150 mg SoR group, 58.7% (101 of 172 subjects) in the 300 mg SoR group, and 69.7% (23 of 33 subjects) in the open-label 300 mg group. Major events were as shown in Table 34. There were no deaths. The incidences of serious adverse events were 5.3% (8 of 152 subjects) in the 150 mg FI group, 4.2% (7 of 168 subjects) in the 300 mg FI group, 2.7% (4 of 150 subjects) in the 150 mg SoR group, 2.9% (5 of 172 subjects) in the 300 mg SoR group, and 3.0% (1 of 33 subjects) in the open-label 300 mg group. A causal relationship to the study drug could not be ruled out for those reported by 1 subject in the 150 mg SoR group (anal abscess), 1 subject in the 300 mg SoR group (altered state of consciousness), and 2 subjects in the open-label 300 mg group (bursitis infective staphylococcal; and urinary tract infection, 1 subject each). The incidences of adverse events leading to discontinuation were 0.7% in the 150 mg FI group (1 of 152 subjects, abortion induced), 1.8% in the 300 mg FI group (3 of 168 subjects, clostridium difficile colitis; eczema; and cholangiocarcinoma, 1 subject each), 1.3% in the 150 mg SoR group (2 of 150 subjects, eczema impetiginous; and bronchitis, 1 subject each), 3.5% in the 300 mg SoR group (6 of 172 subjects, psoriasis; dermatitis; arthralgia; limb crushing injury; dyspnoea; and psoriatic arthropathy, 1 subject each), and 3.0% in the open-label 300 mg group (1 of 33 subjects, bursitis infective staphylococcal). A causal relationship to the study drug could not be ruled out for those reported by 1 subject in the 300 mg FI group (clostridium difficile colitis), 1 subject in the 150 mg SoR group (eczema impetiginous), 3 subjects in the 300 mg SoR group (psoriasis; dermatitis; and arthralgia, 1 subject each), and 1 subject in the open-label 300 mg group (bursitis infective staphylococcal).

The incidences of adverse drug reactions were 15.8% (24 of 152 subjects) in the 150 mg FI group, 14.9% (25 of 168 subjects) in the 300 mg FI group, 14.7% (22 of 150 subjects) in the 150 mg SoR group, 17.4% (30 of 172 subjects) in the 300 mg SoR group, and 33.3% (11 of 33 subjects) in the open-label 300 mg group.

Table 34. Adverse events reported by ≥2% of subjects in any group (≥2 subjects for the open-label 300 mg group) (Safety Analysis Set)

Event term	150 mg FI (N = 152)	300 mg FI (N = 168)	150 mg SoR (N = 150)	300 mg SoR (N = 172)	Open-label 300 mg (N = 33)
Nasopharyngitis	19 (12.5)	15 (8.9)	19 (12.7)	22 (12.8)	8 (24.2)
Upper respiratory tract infection	6 (3.9)	9 (5.4)	4 (2.7)	5 (2.9)	0
Headache	6 (3.9)	6 (3.6)	4 (2.7)	4 (2.3)	1 (3.0)
Arthralgia	6 (3.9)	5 (3.0)	5 (3.3)	5 (2.9)	2 (6.1)
Diarrhoea	5 (3.3)	2 (1.2)	3 (2.0)	3 (1.7)	1 (3.0)
Back pain	4 (2.6)	6 (3.6)	6 (4.0)	6 (3.5)	2 (6.1)
Influenza	4 (2.6)	3 (1.8)	3 (2.0)	6 (3.5)	0
Folliculitis	3 (2.0)	4 (2.4)	0	5 (2.9)	1 (3.0)
Sinusitis	3 (2.0)	1 (0.6)	1 (0.7)	5 (2.9)	1 (3.0)
Oropharyngeal pain	3 (2.0)	1 (0.6)	1 (0.7)	4 (2.3)	0
Gamma-glutamyltransferase increased	3 (2.0)	1 (0.6)	1 (0.7)	2 (1.2)	0
Toothache	3 (2.0)	1 (0.6)	1 (0.7)	1 (0.6)	0
Hypertension	2 (1.3)	7 (4.2)	1 (0.7)	6 (3.5)	1 (3.0)
Cough	2 (1.3)	6 (3.6)	2 (1.3)	5 (2.9)	0
Muscle strain	2 (1.3)	4 (2.4)	1 (0.7)	1 (0.6)	0
Abdominal pain	2 (1.3)	2 (1.2)	2 (1.3)	2 (1.2)	1 (3.0)
Nausea	2 (1.3)	1 (0.6)	3 (2.0)	1 (0.6)	1 (3.0)
Eczema	1 (0.7)	3 (1.8)	3 (2.0)	1 (0.6)	0
Psoriasis	0	2 (1.2)	4 (2.7)	2 (1.2)	0
Psoriatic arthritis	0	0	3 (2.0)	1 (0.6)	0
Spinal osteoarthritis	0	0	1 (0.7)	0	2 (6.1)

n (%)

In the Japanese subgroup, the incidences of adverse events were 50.0% (5 of 10 subjects) in the 150 mg FI group, 69.2% (9 of 13 subjects) in the 300 mg FI group, 70.0% (7 of 10 subjects) in the 150 mg SoR group, 78.6% (11 of 14 subjects) in the 300 mg SoR group, and 50.0% (2 of 4 subjects) in the open-label 300 mg group. Adverse events reported by ≥2 subjects in any group were nasopharyngitis (10.0% [1 of 10 subjects] in the 150 mg FI group, 30.8% [4 of 13 subjects] in the 300 mg FI group, 20.0% [2 of 10 subjects] in the 150 mg SoR group, 14.3% [2 of 14 subjects] in the 300 mg SoR group), folliculitis (15.4% [2 of 13 subjects] in the 300 mg FI group), seasonal allergy (14.3% [2 of 14 subjects] in the 300 mg SoR group), headache (20.0% [2 of 10 subjects] in the 150 mg FI group, 10.0% [1 of 10 subjects] in the 150 mg SoR group, 7.1% [1 of 14 subjects] in the 300 mg SoR group), and hypertension (15.4% [2 of 13 subjects] in the 300 mg FI group, 10.0% [1 of 10 subjects] in the 150 mg SoR group, 7.1% [1 of 14 subjects] in the 300 mg SoR group). There were no deaths. Serious adverse events occurred in 1 subject in the 150 mg SoR group (ligament injury and meniscus injury) and 1 subject in the 300 mg SoR group (altered state of consciousness). A causal relationship to the study drug could not be ruled out for the event reported by 1 subject in the 300 mg SoR group (altered state of consciousness). An adverse event leading to discontinuation occurred in 1 subject in the 300 mg SoR group (dermatitis) and its causal relationship to study drug could not be ruled out. The incidences of adverse drug reactions were 20.0% (2 of 10 subjects) in the 150 mg FI group, 30.8% (4 of 13 subjects) in the 300 mg FI group, and 21.4% (3 of 14 subjects) in the 300 mg SoR group.

The results of the efficacy endpoint of the PASI response rate at Week 76 in the FAS and in the Japanese subgroup were as shown in Table 35.

Table 35. PASI 50/75/90 response rate at Week 76 (OC)

	FAS				Japanese subgroup			
	150 mg FI	300 mg FI	150 mg SoR	300 mg SoR	150 mg FI	300 mg FI	150 mg SoR	300 mg SoR
PASI 50 response rate	90.8 (128/141)	97.3 (142/146)	89.9 (116/129)	93.3 (140/150)	90.0 (9/10)	100.0 (13/13)	80.0 (8/10)	92.9 (13/14)
PASI 75 response rate	66.0 (93/141)	83.6 (122/146)	47.3 (61/129)	45.3 (68/150)	80.0 (8/10)	100.0 (13/13)	50.0 (5/10)	57.1 (8/14)
PASI 90 response rate	40.4 (57/141)	67.8 (99/146)	12.4 (16/129)	17.3 (26/150)	40.0 (4/10)	76.9 (10/13)	0	7.1 (1/14)

% (n/N)

4.(iii).A.(8) Foreign phase III study (5.3.5.1-6, Study A2303 [June 2011 to April 2013])

A placebo- and etanercept (Genetical Recombination) (hereinafter referred to as etanercept)-controlled, randomized, double-blind, parallel-group study was conducted in patients with moderate to severe plaque psoriasis[21] (including patients with psoriatic arthritis) (target sample size of 1264 [316 subjects per group]) to evaluate the efficacy and safety of secukinumab. Among the approved biological products for psoriasis, etanercept is regarded as a standard biological therapy in the major countries especially in Europe. Therefore etanercept (unapproved for the indication of psoriasis in Japan) was chosen as the active control.

The treatment phase of the study consisted of 2 periods (through Week 12, the induction period; from Week 12 to Week 52, the maintenance period) and secukinumab 150 or 300 mg, etanercept 50 mg, or placebo was to be administered subcutaneously according to Figure 8.

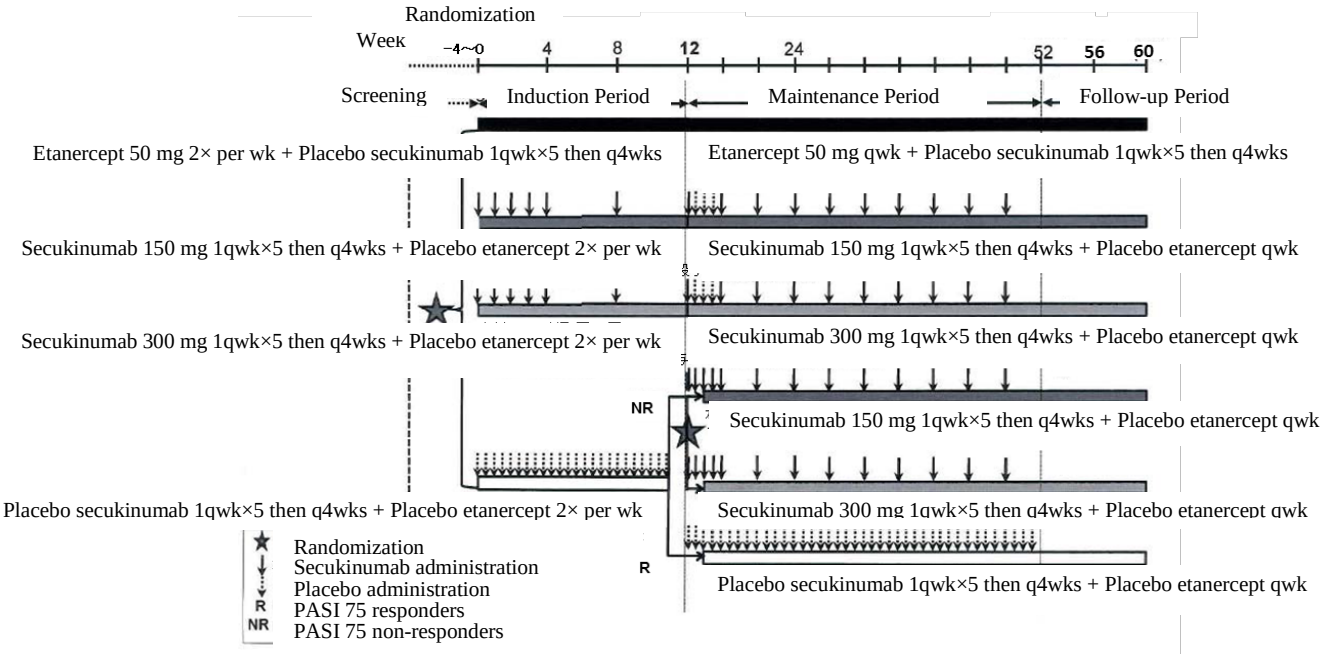


Figure 8. Study design and dosing schedule for Study A2303

At Week 12, PASI 75 responders in the placebo group were to continue to receive placebo (placebo→placebo group) in the maintenance period and PASI 75 non-responders in the placebo group were to be re-randomized in a 1:1 ratio to secukinumab 150 or 300 mg and receive their treatment weekly for 4 weeks and then every 4 weeks until Week 52 (placebo→secukinumab 150 mg group or placebo→secukinumab 300 mg group) for the maintenance period. The re-randomization was stratified by geographical region and body weight (<90 kg or ≥90 kg).

Of 1306 subjects randomized in a ratio of 1:1:1:1 to the secukinumab 150 mg, secukinumab 300 mg, etanercept, or placebo group and stratified by geographical region and body weight (<90 kg or ≥90 kg), 1305 subjects excluding 1 subject in the placebo group[32] (327 subjects in the secukinumab 150 mg group, 327 subjects in the secukinumab 300 mg group, 326 subjects in the etanercept group, 325 subjects in the placebo group) were included in the FAS, which was also used for efficacy analyses, and 1303 subjects excluding 2 subjects who did not receive study drug (327 subjects in the secukinumab 150 mg group, 326 subjects in the secukinumab 300 mg group, 323 subjects in the etanercept group, 327 subjects in the placebo group) were included in the Safety Set. The discontinuation rates during the induction period were 3.7% (12 of 327 subjects) in the secukinumab 150 mg group, 4.6% (15 of 327 subjects) in the secukinumab 300 mg group, 6.4% (21 of 326 subjects) in the etanercept group, and 7.7% (25 of 326 subjects) in the placebo group. The most common reasons for discontinuation were consent withdrawal (1.5% [5 of 327 subjects] in the secukinumab 150 mg group, 1.5% [5 of 327 subjects] in the secukinumab 300 mg group, 1.5% [5 of 326 subjects] in the etanercept group, 3.1% [10 of 326 subjects] in the placebo group), etc. Of 301 subjects in the placebo group who completed the induction period, 5.6% (17 of 301 subjects) received placebo in the maintenance period and 47.2% (142 of 301 subjects) were re-randomized to the placebo→secukinumab 150 mg group, and 47.2% (142 of 301 subjects) were re-randomized to the placebo→secukinumab 300 mg group for the maintenance period.

The co-primary efficacy endpoints were the PASI 75 response rate at Week 12 and the IGA 0/1 response rate at Week 12. PASI 75 response rates at Week 12 were as shown in Table 36, and IGA 0/1 response rates at Week

[32] The subject was excluded from the FAS and Safety Set because laboratory tests were performed before obtaining consent.

12 were as shown in Table 37. Pairwise comparisons showed statistically significant differences between secukinumab 150 mg and placebo and between secukinumab 300 mg and placebo, confirming the superiority of secukinumab 150 mg and 300 mg over placebo. The secondary endpoints of the PASI 50 and 90 response rates were as shown in Table 36.

Table 36. PASI 50, 75 (co-primary endpoint), and 90 response rates at Week 12 (FAS, NRI)

	Secukinumab 150 mg	Secukinumab 300 mg	Etanercept	Placebo	Difference from placebo [95% CI], *P*-value [a) b)]		Difference from etanercept [95% CI]	
					Secukinumab 150 mg	Secukinumab 300 mg	Secukinumab 150 mg	Secukinumab 300 mg
PASI 50 response rate	81.3 (266/327)	91.6 (296/323)	70.0 (226/323)	15.1 (49/324)	66.2 [60.1, 71.8]	76.5 [71.2, 81.3]	11.4 [3.6, 19.0]	21.7 [13.9, 29.2]
PASI 75 response rate	67.0 (219/327)	77.1 (249/323)	44.0 (142/323)	4.9 (16/324)	62.0 [55.8, 67.8] *P* < 0.0001	72.2 [66.4, 77.1] *P* < 0.0001	23.0 [15.3, 30.4]	33.1 [25.6, 40.4]
PASI 90 response rate	41.9 (137/327)	54.2 (175/323)	20.7 (67/323)	1.5 (5/324)	40.4 [33.0, 47.2] *P* < 0.0001	52.6 [45.8, 58.9] *P* < 0.0001	21.2 [13.5, 28.5]	33.4 [25.9, 40.7]

% (n/N)

a) Cochran-Mantel-Haenszel test stratified by geographical region and body weight stratum (<90 kg or ≥90 kg).

b) In order to adjust for multiplicity, the level of significance for each of pairwise comparisons between placebo and secukinumab 150 mg and between placebo and secukinumab 300 mg was set at α/2, and if both null hypotheses for the co-primary endpoints were rejected and the subsequent null hypotheses for the key secondary endpoints (PASI 90 response rate at Week 12, non-inferiority and superiority of secukinumab to etanercept with respect to PASI 75 response rate and IGA 0/1 response rate at Week 12, non-inferiority and superiority of secukinumab to etanercept in maintaining PASI75 response and IGA 0/1 response from Week 12 to Week 52, changes from baseline in pain, itching, and scaling scores on the Psoriasis Symptom Diary at Week 12) were all rejected within a set referring to a secukinumab dose regimen, the corresponding α/2 could be passed onto the other group of null hypotheses (Bretz F et al, *Stat Med*, 28: 586-604, 2009).

Table 37. IGA 0/1 response rates at Week 12 (co-primary endpoint) (FAS, NRI)

Secukinumab 150 mg	Secukinumab 300 mg	Etanercept	Placebo	Difference from placebo [95% CI], *P*-value [a) b)]		Difference from etanercept [95% CI]	
				Secukinumab 150 mg	Secukinumab 300 mg	Secukinumab 150 mg	Secukinumab 300 mg
51.1 (167/327)	62.5 (202/323)	27.2 (88/323)	2.8 (9/324)	48.3 [41.3, 54.7] *P* < 0.0001	59.8 [53.2, 65.6] *P* < 0.0001	23.8 [16.3, 31.2]	35.3 [27.8, 42.5]

% (n/N)

a) Cochran-Mantel-Haenszel test stratified by geographical region and body weight (<90 kg or ≥90 kg).

b) See Table 36.

The incidences of adverse events during the induction period (through Week 12) were 58.4% (191 of 327 subjects) in the secukinumab 150 mg group, 55.5% (181 of 326 subjects) in the secukinumab 300 mg group, 57.6% (186 of 323 subjects) in the etanercept group, and 49.8% (163 of 327 subjects) in the placebo group. Major events were as shown in Table 38. There were no deaths. The incidences of serious adverse events were 2.1% in the secukinumab 150 mg group (7 of 327 subjects, VIth nerve paralysis; oropharyngeal pain and dysphagia; Crohn's disease; pain of skin, insomnia, and non-cardiac chest pain; head injury; overdose; and laceration, 1 subject each), 1.2% in the secukinumab 300 mg group (4 of 326 subjects, prostatomegaly; anal abscess; rib fracture; and overdose, 1 subject each), 0.9% in the etanercept group (3 of 323 subjects, cholecystitis acute; transient ischaemic attack; and calculus urethral, 1 subject each), and 1.8% in the placebo group (6 of 327 subjects; psoriasis [2 subjects]; overdose; tendon injury; alcohol poisoning and abstains from alcohol; and cellulitis, 1 subject each). A causal relationship to the study drug could not be ruled out for those reported by 2 subjects in the secukinumab 150 mg group (VIth nerve paralysis; and Crohn's disease, 1 subject each), 1 subject in the secukinumab 300 mg group (overdose), 1 subject in the etanercept group (transient ischaemic attack), and 1 subject in the placebo group (cellulitis). The incidences of adverse events leading to discontinuation were 0.9% in the secukinumab 150 mg group (3 of 327 subjects, pharyngitis bacterial;

erythrodermic psoriasis; and Crohn's disease, 1 subject each), 1.5% in the secukinumab 300 mg group (5 of 326 subjects; drug eruption; fall; eczema nummular; transaminases increased; and urticaria, 1 subject each), 1.9% in the etanercept group (6 of 323 subjects, transient ischaemic attack; injection site oedema; colitis ulcerative; neutropenia; injection site rash; and hepatic enzyme increased, 1 subject each), and 0.9% in the placebo group (3 of 327 subjects, psoriasis [3 subjects]). A causal relationship to the study drug could not be ruled out for those reported by 1 subject in the secukinumab 150 mg group (Crohn's disease), 2 subjects in the secukinumab 300 mg group (eczema nummular; and urticaria, 1 subject each), 4 subjects in the etanercept group (transient ischaemic attack; injection site oedema; colitis ulcerative; and injection site rash, 1 subject each), and 1 subject in the placebo group (psoriasis). The incidences of adverse drug reactions were 21.4% (70 of 327 subjects) in the secukinumab 150 mg group, 18.7% (61 of 326 subjects) in the secukinumab 300 mg group, 22.9% (74 of 323 subjects) in the etanercept group, and 14.7% (48 of 327 subjects) in the placebo group.

Table 38. Adverse events reported by ≥2% of subjects in any group (through Week 12, Safety Analysis Set)

Event term	Secukinumab 150 mg (N = 327)	Secukinumab 300 mg (N = 326)	Etanercept (N = 323)	Placebo (N = 327)
Nasopharyngitis	45 (13.8)	35 (10.7)	36 (11.1)	26 (8.0)
Headache	16 (4.9)	30 (9.2)	23 (7.1)	23 (7.0)
Arthralgia	14 (4.3)	5 (1.5)	12 (3.7)	10 (3.1)
Diarrhoea	12 (3.7)	17 (5.2)	11 (3.4)	6 (1.8)
Pruritus	12 (3.7)	8 (2.5)	8 (2.5)	11 (3.4)
Upper respiratory tract infection	10 (3.1)	7 (2.1)	7 (2.2)	3 (0.9)
Hypertension	10 (3.1)	5 (1.5)	5 (1.5)	4 (1.2)
Back pain	8 (2.4)	8 (2.5)	9 (2.8)	6 (1.8)
Nausea	6 (1.8)	8 (2.5)	4 (1.2)	7 (2.1)
Cough	5 (1.5)	11 (3.4)	4 (1.2)	4 (1.2)
Oropharyngeal pain	5 (1.5)	9 (2.8)	4 (1.2)	7 (2.1)
Fatigue	5 (1.5)	7 (2.1)	5 (1.5)	3 (0.9)
Psoriasis	5 (1.5)	1 (0.3)	2 (0.6)	8 (2.4)
Rhinitis	4 (1.2)	7 (2.1)	3 (0.9)	4 (1.2)
Pyrexia	2 (0.6)	5 (1.5)	7 (2.2)	3 (0.9)
Rhinorrhoea	1 (0.3)	7 (2.1)	2 (0.6)	1 (0.3)
Injection site erythema	0	0	16 (5.0)	0

n (%)

The incidences of adverse events over the entire treatment period were 77.6% (364 of 469 subjects) in the secukinumab 150 mg group[33], 80.5% (376 of 467 subjects) in the secukinumab 300 mg group[34], 78.3% (253 of 323 subjects) in the etanercept group, and 51.4% (168 of 327 subjects) in the placebo group[35]. Major events were as shown in Table 39. There were no deaths. The incidences of serious adverse events were 5.1% (24 of 469 subjects) in the secukinumab 150 mg group, 5.8% (27 of 467 subjects) in the secukinumab 300 mg group, 6.2% (20 of 323 subjects) in the etanercept group, and 2.1% (7 of 327 subjects) in the placebo group. Adverse events reported by ≥2 subjects in any group were transient ischaemic attack (0.6% [2 of 323 subjects] in the etanercept group, 0.3% [1 of 327 subjects] in the placebo group). The incidences of adverse events leading to discontinuation were 2.1% (10 of 469 subjects) in the secukinumab 150 mg group, 3.0% (14 of 467 subjects) in the secukinumab 300 mg group, 3.7% (12 of 323 subjects) in the etanercept group, and 0.9% (3 of 327

[33] Defined as subjects treated with secukinumab 150 mg by Week 52 (including subjects on secukinumab 150 mg during the induction period who continued to receive secukinumab 150 mg and subjects in the placebo→secukinumab 150 mg group).

[34] Defined as subjects treated with secukinumab 300 mg by Week 52 (including subjects on secukinumab 300 mg during the induction period who continued to receive secukinumab 300 mg and subjects in the placebo→secukinumab 300 mg group).

[35] Defined as subjects treated with placebo by Week 52 (placebo→placebo group, placebo→secukinumab 150 mg group, and placebo→secukinumab 300 mg group. The data obtained after crossover to secukinumab are not included for subjects in the placebo→secukinumab 150 mg group and subjects in the placebo→secukinumab 300 mg group).

subjects) in the placebo group. The incidences of adverse drug reactions were 28.8% (135 of 469 subjects) in the secukinumab 150 mg group, 30.8% (144 of 467 subjects) in the secukinumab 300 mg group, 33.1% (107 of 467 subjects) in the etanercept group, and 14.7% (48 of 327 subjects) in the placebo group.

Table 39. Adverse events reported by ≥2% of subjects in any group (through Week 52, Safety Analysis Set)

Event term	Secukinumab 150 mg (N = 469)	Secukinumab 300 mg (N = 467)	Etanercept (N = 323)	Placebo (N = 327)
Nasopharyngitis	108 (23.0)	122 (26.1)	86 (26.6)	26 (8.0)
Headache	47 (10.0)	58 (12.4)	40 (12.4)	24 (7.3)
Diarrhoea	36 (7.7)	38 (8.1)	22(6.8)	7 (2.1)
Arthralgia	33 (7.0)	24 (5.1)	23 (7.1)	10 (3.1)
Upper respiratory tract infection	26 (5.5)	26 (5.6)	18 (5.6)	3 (0.9)
Hypertension	22 (4.7)	20 (4.3)	14 (4.3)	4 (1.2)
Pruritus	21 (4.5)	16 (3.4)	16 (5.0)	11 (3.4)
Back pain	20 (4.3)	31 (6.6)	26 (8.0)	6 (1.8)
Oropharyngeal pain	20 (4.3)	25 (5.4)	10 (3.1)	7 (2.1)
Cough	15 (3.2)	30 (6.4)	12 (3.7)	4 (1.2)
Pyrexia	14 (3.0)	18 (3.9)	15 (4.6)	3 (0.9)
Bronchitis	14 (3.0)	17 (3.6)	9 (2.8)	2 (0.6)
Folliculitis	14 (3.0)	13 (2.8)	8 (2.5)	1 (0.3)
Influenza	12 (2.6)	22 (4.7)	11 (3.4)	3 (0.9)
Gastroenteritis	12 (2.6)	18 (3.9)	8 (2.5)	3 (0.9)
Fatigue	12 (2.6)	16 (3.4)	6 (1.9)	3 (0.9)
Abdominal pain upper	12 (2.6)	14 (3.0)	3 (0.9)	4 (1.2)
Toothache	12 (2.6)	13(2.8)	7 (2.2)	6 (1.8)
Sinusitis	11 (2.3)	9 (1.9)	5 (1.5)	1 (0.3)
Psoriasis	11 (2.3)	8 (1.7)	7 (2.2)	8 (2.4)
Abdominal pain	11 (2.3)	6 (1.3)	8(2.5)	4 (1.2)
Pharyngitis	10 (2.1)	13 (2.8)	6 (1.9)	0
Tonsillitis	10 (2.1)	12 (2.6)	3 (0.9)	2 (0.6)
Nausea	10 (2.1)	11 (2.4)	7 (2.2)	7 (2.1)
Eczema	10 (2.1)	11 (2.4)	2 (0.6)	0
Hypercholesterolaemia	10 (2.1)	6 (1.3)	7 (2.2)	5 (1.5)
Oedema peripheral	10 (2.1)	3 (0.6)	6 (1.9)	4 (1.2)
Myalgia	9 (1.9)	10 (2.1)	9 (2.8)	4 (1.2)
Rhinitis	8 (1.7)	14 (3.0)	6 (1.9)	4 (1.2)
Urinary tract infection	8 (1.7)	13 (2.8)	10 (3.1)	3 (0.9)
Pain in extremity	8 (1.7)	13 (2.8)	4 (1.2)	4 (1.2)
Influenza like illness	8 (1.7)	8 (1.7)	9 (2.8)	1 (0.3)
Tinea pedis	7 (1.5)	10 (2.1)	4 (1.2)	0
Oral candidiasis	6 (1.3)	12 (2.6)	0	0
Viral upper respiratory tract infection	6 (1.3)	11 (2.4)	1 (0.3)	1 (0.3)
Vomiting	4 (0.9)	10 (2.1)	9 (2.8)	1 (0.3)
Oral herpes	4 (0.9)	10 (2.1)	9 (2.8)	0
Conjunctivitis	3 (0.6)	10 (2.1)	3 (0.9)	1 (0.3)
Rhinorrhoea	3 (0.6)	10 (2.1)	2 (0.6)	1 (0.3)
Injection site erythema	0	0	17 (5.3)	0

n (%)

4.(iii).A.(9) Foreign phase III study (5.3.5.1-13, Study F2306 [September 2011 to ongoing (data cutoff date of October 9, 2013; Week 52 data])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients with psoriatic arthritis[36] (target sample size of 600 [200 subjects per group]) to evaluate the efficacy and safety of secukinumab.

Secukinumab or placebo was to be administered according to Figure 9.

[36] Patients who had a diagnosis of psoriatic arthritis according to the Classification Criteria for Psoriatic Arthritis (CASPAR) and met the following criteria: (a) ≥3 swollen joints and ≥3 tender joints and (b) inadequate response to NSAIDs, DMARD, or anti-TNFα therapy.

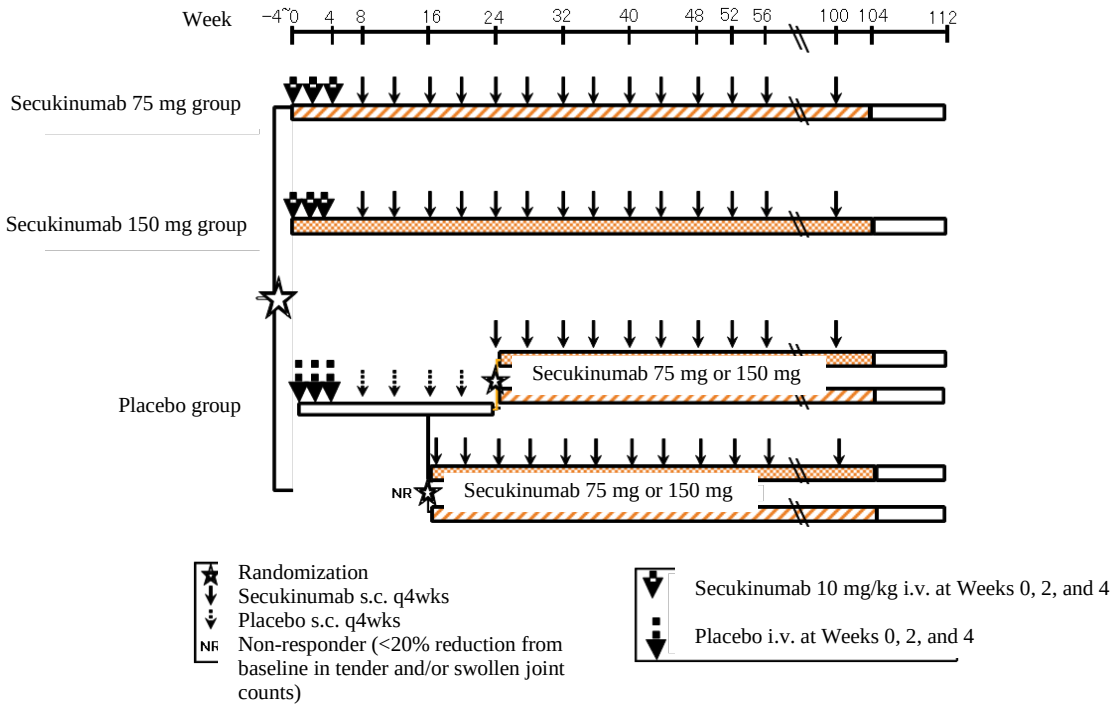


Figure 9. Study design and dosing schedule for Study F2306

Subjects were randomized in a ratio of 1:1:1 to the secukinumab 75 or 150 mg or placebo group and stratified by prior anti-TNFα therapy status (inadequate response/anti-TNFα-experienced or anti-TNFα-naïve) and 606 randomized subjects (202 subjects in the secukinumab 75 mg group, 202 subjects in the secukinumab 150 mg group, 202 subjects in the placebo group) were included in the FAS, the Safety Analysis Set, and the Efficacy Analysis Set. The discontinuation rates were 13.9% (28 of 202 subjects) in the secukinumab 75 mg group, 10.9% (22 of 202 subjects) in the secukinumab 150 mg group, and 20.3% (41 of 202 subjects) in the placebo group. The most common reasons for discontinuation included lack of efficacy (3.0% [6 of 202 subjects] in the secukinumab 75 mg group, 3.5% [7 of 202 subjects] in the secukinumab 150 mg group, 6.4% [13 of 202 subjects] in the placebo group), etc.

The primary efficacy endpoint of the ACR20 response rates at Week 24 were as shown in Table 40. Pairwise comparisons showed statistically significant differences between secukinumab 75 mg and placebo and between secukinumab 150 mg and placebo, confirming the superiority of secukinumab 75 mg and 150 mg over placebo. The secondary endpoint of the ACR50 response rates and the exploratory endpoint of the ACR70 response rates were as shown in Table 40.

Table 40. ACR20 (primary endpoint), ACR50, and ACR70 response rates at Week 24 (FAS, NRI)

	Secukinumab 75 mg	Secukinumab 150 mg	Placebo	Treatment difference [95% CI], *P*-value [a) b)]	
				Secukinumab 75 mg	Secukinumab 150 mg
ACR20 response rate	50.5 (102/202)	50.0 (101/202)	17.3 (35/202)	33.2 [24.5, 41.8] *P* < 0.0001	32.7 [24.0, 41.3] *P* < 0.0001
ACR50 response rate	30.7 (62/202)	34.7 (70/202)	7.4 (15/202)	23.3 [16.0, 30.6] *P* < 0.0001	27.2 [19.7, 34.7] *P* < 0.0001
ACR70 response rate	16.8 (34/202)	18.8 (38/202)	2.0 (4/202)	14.9 [9.4, 20.4]	16.8 [11.1, 22.6]

% (n/N)

a) Logistic regression model with treatment, prior anti-TNFα therapy status, and body weight as explanatory variables.

b) In order to adjust for multiplicity, the level of significance for each of pairwise comparisons between placebo and secukinumab 75 mg and between placebo and secukinumab 150 mg was set at α/2, and if the null hypothesis for the primary endpoint was rejected and the subsequent null hypotheses for the secondary endpoints (PASI 75 and 90 response rates at Week 24 for patients who had ≥3% skin involvement with psoriasis, changes from baseline in DAS28-CRP score, SF-36 physical component summary score, and HAQ-DI at Week 24, ACR50 response rate at Week 24) were all rejected within a set referring to a secukinumab dose regimen, the corresponding α/2 could be passed onto the other group of null hypotheses (Bretz F, et al. *Stat Med.* 2009;28:586-604).

The secondary efficacy endpoint of the change from baseline to Week 24 in van der Heijde modified total Sharp score (mTSS) was as shown in Table 41.

Table 41. Change from baseline to Week 24 in mTSS (FAS, Linear Extrapolation [a)])

	Secukinumab 75 mg	Secukinumab 150 mg	Placebo
Baseline	20.4 ± 39.4 (181)	22.3 ± 48.0 (185)	28.5 ± 63.5 (179)
Week 24	20.42 ± 39.63 (181)	22.40 ± 48.01 (185)	29.03 ± 63.90 (179)
Change	0.02 ± 1.60 (181)	0.13 ± 1.18 (185)	0.57 ± 2.48 (179)
Difference from placebo [95% CI], *P*-value [b) c)]	-0.54 [-0.96, -0.11] *P* = 0.0132	-0.47 [-0.87, -0.07] *P* = 0.0212	
Difference between pooled secukinumab and placebo [95% CI], *P*-value [b) c)]	-0.50 [-0.89, -0.11] *P* = 0.0113		

Mean ± SD (N)

a) Missing values were imputed using a linear extrapolation method.

b) Nonparametric analysis of covariance model with treatment, prior anti-TNFα therapy status, body weight, and baseline value as explanatory variables.

c) In order to adjust for multiplicity, if all of the null hypotheses pertaining to Table 40 Note b) in the first family were rejected, the null hypotheses in the second family could be tested as follows: If the null hypotheses for pooled secukinumab vs. placebo comparison for changes from baseline to Week 24 in mTSS, the proportion of subjects with dactylitis, and the proportion of subjects with enthesitis were rejected sequentially, each dose of secukinumab was compared to placebo in a pairwise fashion for the change from baseline to Week 24 in mTSS, and if the null hypothesis for one group comparison was rejected at a α/2 significance level, the corresponding α/2 could be passed onto the null hypothesis for the other group comparison (Bretz F, et al. *Stat Med.* 2009;28:586-604).

The incidences of adverse events through Week 16 were 60.4% (122 of 202 subjects) in the secukinumab 75 mg group, 64.9% (131 of 202 subjects) in the secukinumab 150 mg group, and 58.4% (118 of 202 subjects) in the placebo group. Major events were as shown in Table 42. There were no deaths. The incidences of serious adverse events were 2.5% (5 of 202 subjects) in the secukinumab 75 mg group, 4.5% (9 of 202 subjects) in the secukinumab 150 mg group, and 5.0% (10 of 202 subjects) in the placebo group. A causal relationship to the study drug could not be ruled out for those reported by 1 subject in the secukinumab 75 mg group (pneumonia and cardiac failure) and 4 subjects in the secukinumab 150 mg group (non-cardiac chest pain and abdominal pain; lobar pneumonia and lung abscess; viral infection; and cellulitis, 1 subject each). The incidences of adverse events leading to discontinuation were 2.0% (4 of 202 subjects) in the secukinumab 75 mg group, 1.5% (3 of 202 subjects) in the secukinumab 150 mg group, and 2.5% (5 of 202 subjects) in the placebo group. A causal relationship to the study drug could not be ruled out for those reported by 3 subjects in the secukinumab 75 mg group (cholelithiasis; angioedema; and musculoskeletal chest pain, 1 subject each), 3 subjects in the secukinumab 150 mg group (hypersensitivity; non-cardiac chest pain and abdominal pain; and viral infection, 1 subject each), and 3 subjects in the placebo group (rash; hypersensitivity; and depression, 1 subject each). The incidences of adverse drug reactions were 22.3% (45 of 202 subjects) in the secukinumab

75 mg group, 26.7% (54 of 202 subjects) in the secukinumab 150 mg group, and 19.8% (40 of 202 subjects) in the placebo group.

Table 42. Adverse events reported by ≥2% of subjects in any group (through Week 16, Safety Analysis Set)

Event term	Secukinumab 75 mg (N = 202)	Secukinumab 150 mg (N = 202)	Placebo (N = 202)
Nasopharyngitis	14 (6.9)	19 (9.4)	9 (4.5)
Headache	11 (5.4)	11 (5.4)	6 (3.0)
Upper respiratory tract infection	9 (4.5)	13 (6.4)	10 (5.0)
Hypercholesterolaemia	8 (4.0)	6 (3.0)	5 (2.5)
Hypertension	7 (3.5)	3 (1.5)	5 (2.5)
Nausea	5 (2.5)	4 (2.0)	2 (1.0)
Back pain	5 (2.5)	3 (1.5)	2 (1.0)
Fatigue	5 (2.5)	1 (0.5)	5 (2.5)
Gastrooesophageal reflux disease	5 (2.5)	1 (0.5)	2 (1.0)
Diarrhoea	4 (2.0)	6 (3.0)	6 (3.0)
Oropharyngeal pain	4 (2.0)	3 (1.5)	3 (1.5)
Depression	4 (2.0)	2 (1.0)	6 (3.0)
Dyslipidaemia	3 (1.5)	4 (2.0)	7 (3.5)
Bronchitis	3 (1.5)	3 (1.5)	6 (3.0)
Urinary tract infection	2 (1.0)	4 (2.0)	2 (1.0)
Dizziness	2 (1.0)	4 (2.0)	1 (0.5)
Pharyngitis	2 (1.0)	4 (2.0)	0
Rash	2 (1.0)	3 (1.5)	8 (4.0)
Anaemia	1 (0.5)	0	6 (3.0)
Excoriation	1 (0.5)	5 (2.5)	1 (0.5)
Pyrexia	1 (0.5)	4 (2.0)	1 (0.5)
Ear infection	1 (0.5)	4 (2.0)	1 (0.5)
Cough	1 (0.5)	4 (2.0)	6 (3.0)
Hyperlipidaemia	1 (0.5)	0	4 (2.0)
Pruritus	0	6 (3.0)	3 (1.5)
Oral herpes	0	5 (2.5)	1 (0.5)

n (%)

4.(iii).B Outline of the review

4.(iii).B.(1) Efficacy

4.(iii).B.(1).1) Efficacy in the treatment of psoriasis vulgaris and plaque psoriasis with psoriatic arthritis

The applicant explained as follows:

There seem no major ethnic differences in the pathology and symptoms, etc. of psoriasis. There are no important differences between Japan and overseas also for extrinsic ethnic factors, e.g. the diagnosis, treatment goals, and treatment system of psoriasis. No ethnic differences were observed in the pharmacokinetics of secukinumab [see "4.(ii).B.(1) Ethnic differences in the pharmacokinetics of secukinumab"]. Efficacy and safety results from a multinational phase II study were also similar between the overall population and Japanese subgroup. Thus, it is considered that Japan can participate in a multinational phase III study to evaluate the efficacy of secukinumab in patients with plaque psoriasis (A2302). Each multinational study had a certain number of Japanese patients and yielded similar results between the overall population and the Japanese subgroup as described in the "Summary of the submitted data" section. Therefore, the efficacy of secukinumab in Japanese patients can be assessed based on the results from these studies.

PMDA concluded as follows:

Study A2302 is a pivotal multinational phase III study in patients with plaque psoriasis that demonstrated the superiority of secukinumab over placebo based on the PASI 75 response rate (assessment of the severity of skin symptoms). Similarly, a foreign phase III study (A2303) demonstrated the superiority of secukinumab over placebo based on the PASI 75 response rate. The results with secukinumab were not substantially different

from those with etanercept, a standard treatment for psoriasis overseas. Thus, the efficacy of secukinumab in the treatment of psoriasis vulgaris has been demonstrated. Plaque psoriasis is a skin symptom seen in both psoriasis vulgaris and psoriatic arthritis. Therefore, secukinumab is expected to be effective for the treatment of plaque psoriasis with psoriatic arthritis based on the results of the multinational phase III study (A2302), etc.

Furthermore, Study A2302 confirmed consistency between the overall population and Japanese subgroup in the study results. Therefore, secukinumab is also expected to be effective for the treatment of plaque psoriasis experienced by Japanese patients with psoriasis vulgaris or psoriatic arthritis.

4.(iii).B.(1).2) Efficacy of secukinumab in reducing joint symptoms of psoriatic arthritis

The applicant explained the efficacy of secukinumab in reducing the joint symptoms of psoriatic arthritis as follows:

The number of patients with psoriasis in Japan is reported to be approximately 100,000, and 3.6% of these patients have psoriatic arthritis (Ozawa A. *Jpn J Dermatol.* 2006;116:143-63). That is to say, the estimated number of patients with psoriatic arthritis in Japan is approximately 3600, and the conduct of a confirmatory study enrolling patients with psoriatic arthritis in Japan alone seemed not feasible. Even if Japan participated in a multinational confirmatory study in patients with psoriatic arthritis, it would be difficult to enroll a sufficient number of Japanese patients to assess the consistency in the results between the overall population and the Japanese subgroup. Therefore, the applicant decided to include Japanese patients with psoriatic arthritis in multinational phase III studies that were designed to evaluate the efficacy of secukinumab in patients with plaque psoriasis (A2302, A2304). The enrolled Japanese subjects who met the specific criteria at baseline[37] were subject to the assessment of not only skin symptoms but also joint symptoms on the basis of the ACR core set. The ACR core set variables were assessed in 14 of 30 Japanese patients with psoriatic arthritis enrolled in these studies. The ACR20 response rates at Week 12 were 71.4% (5 of 7 subjects) in the secukinumab 150 mg group, 60.0% (3 of 5 subjects) in the secukinumab 300 mg group, and 0% (0 of 2 subjects) in the placebo group, suggesting that secukinumab improves joint symptoms.

A foreign phase III study in patients with psoriatic arthritis (F2306) evaluated the efficacy of secukinumab at 10 mg/kg administered intravenously at Day 1, Week 2, and Week 4, followed by subcutaneous injections of 75 or 150 mg of secukinumab. The primary endpoint of the ACR20 response rates at Week 24 were 50.5% (102 of 202 subjects) in the secukinumab 75 mg group, 50.0% (101 of 202 subjects) in the secukinumab 150 mg group, and 17.3% (35 of 202 subjects) in the placebo group. Pairwise comparisons showed statistically significant differences between secukinumab 75 mg and placebo and between secukinumab 150 mg and placebo [see “4.(iii).A.(9) Foreign phase III study”]. Furthermore, a foreign phase III study to evaluate the efficacy and safety of 75, 150, and 300 mg of subcutaneous secukinumab in patients with psoriatic arthritis (F2312) is ongoing. According to preliminary figures, the primary endpoint of the ACR20 response rates at Week 24 were 29.3% (29 of 99 subjects) in the secukinumab 75 mg group, 51.0% (51 of 100 subjects) in the secukinumab 150 mg group, 54.0% (54 of 100 subjects) in the secukinumab 300 mg group, and 15.3% (15 of

[37] Patients who had a diagnosis of psoriatic arthritis according to the CASPAR criteria, with ≥3 tender joints and ≥3 swollen joints.

98 subjects) in the placebo group. Pairwise comparisons showed statistically significant differences between secukinumab 75 mg and placebo, between secukinumab 150 mg and placebo, and between secukinumab 300 mg and placebo ($P = 0.02$, $P < 0.0001$, and $P < 0.001$, respectively. Logistic regression model).

Based on the above results and taking account of foreign clinical data, the efficacy of secukinumab in reducing joint symptoms in Japanese patients with psoriatic arthritis is expected.

PMDA considers as follows:
Given the limited number of patients with psoriatic arthritis in Japan, it is understandable that the efficacy of secukinumab in reducing joint symptoms could not be confirmed in a clinical study including Japanese patients with psoriatic arthritis. Meanwhile, secukinumab tended to improve joint symptoms in Japanese patients with psoriatic arthritis treated with 150 or 300 mg of secukinumab in multinational phase III studies (A2302, A2304), though limited in number, and foreign phase III studies (F2306 and F2312) demonstrated the efficacy of 150 or 300 mg secukinumab in reducing joint symptoms of patients with psoriatic arthritis. Taking account of these findings, the efficacy of secukinumab 150 or 300 mg in reducing joint symptoms in Japanese patients with psoriatic arthritis is expected. However, data from Japanese patients with psoriatic arthritis are very limited. The efficacy of secukinumab in reducing joint symptoms needs to be further investigated via post-marketing surveillance, etc.

4.(iii).B.(2) Safety
The applicant explained the safety of secukinumab based on the pooled data from the induction period (through Week 12) of 4 phase III placebo-controlled studies (A2302, A2303, A2308, A2309) (hereinafter referred to as “Pool A”) and the pooled data from the entire treatment period (the induction and maintenance periods) of 10 clinical studies on psoriasis (A2211, A2211E1 [data cutoff date of January 21, 2013], A2212, A2220, A2302, A2303, A2304, A2307, A2308 [data cutoff date of January 15, 2013], A2309 [data cutoff date of April 10, 2013]) (hereinafter referred to as “Pool B”) as follows:
Comparisons of adverse events between secukinumab and placebo and between the two dose levels of secukinumab (150 mg, 300 mg) were assessed, using primarily Pool A and Pool B including psoriasis patients as reference. Deaths and less common events such as serious adverse events were assessed, primarily using Pool B.

A summary of adverse events in Pool A and Pool B was as shown in Table 43.

Table 43. Summary of adverse events in psoriasis clinical studies (Pool A and Pool B)

	Pool A (Induction period)				Pool B (Entire treatment period)				
	Secukinumab 150 mg (N = 692)	Secukinumab 300 mg (N = 690)	Placebo (N = 694)	Etanercept (N = 323)	Secukinumab 150 mg[a)] (N = 1395)	Secukinumab 300 mg[b)] (N = 1410)	Any secukinumab dose[c)] (N = 3430)	Placebo[d)] (N = 793)	Etanercept (N = 323)
Death	0	0	0	0	1	0	1	0	0
Adverse event	412 (59.5)	388 (56.2)	340 (49.0)	186 (57.6)	1066 (76.4)	1091 (77.4)	2637 (76.9)	413(52.1)	253 (78.3)
Serious adverse event	14 (2.0)	14 (2.0)	12 (1.7)	3 (0.9)	76 (5.5)	85 (6.0)	207 (6.0)	15(1.9)	20 (6.2)
Adverse event leading to discontinuation	8 (1.2)	9 (1.3)	9 (1.3)	6 (1.9)	43 (3.1)	46 (3.3)	118 (3.4)	11(1.4)	12 (3.7)
Adverse event for which a causal relationship to study drug could not be ruled out (adverse drug reaction)	140 (20.2)	120 (17.4)	90 (13.0)	74 (22.9)	373 (26.7)	377 (26.7)	892 (26.0)	107 (13.5)	107 (33.1)
Total exposure (Patient-years)	157.2	157.5	155.4	73.0	1142.0	1177.5	2724.6	201.3	293.5

n (%)

a) Defined as subjects treated with secukinumab 150 mg by Week 52 (including subjects on secukinumab 150 mg during the induction period who continued to receive secukinumab 150 mg, subjects on secukinumab 150 mg during the induction period who were retreated at start of relapse in the maintenance period, and subjects in the placebo→secukinumab 150 mg group).

b) Defined as subjects treated with secukinumab 300 mg by Week 52 (including subjects on secukinumab 300 mg during the induction period who continued to receive secukinumab 300 mg, subjects on secukinumab 300 mg during the induction period who were retreated at start of relapse in the maintenance period, and subjects in the placebo→secukinumab 300 mg group).

c) Defined as subjects treated with secukinumab in phase III and II studies including various doses and dosing regimens and durations of treatment.

d) Defined as subjects treated with placebo by Week 52 (placebo→secukinumab 150 mg group and placebo→secukinumab 300 mg group. The data obtained after crossover to secukinumab are not included for subjects in the placebo→secukinumab 150 mg group and subjects in the placebo→secukinumab 300 mg group. The placebo groups of phase II studies are included).

In Pool A, adverse events reported by ≥3% of subjects in either the secukinumab 150 mg or 300 mg group were as shown in Table 44. There were no deaths. A summary of serious adverse events was as shown in Table 43. Adverse events reported by ≥2 subjects treated with secukinumab were overdose (1 subject in the secukinumab 150 mg group, 1 subject the secukinumab 300 mg group) and pulmonary oedema (2 subjects in the secukinumab 150 mg group).

Table 44. Adverse events reported by ≥3% of subjects in either secukinumab group (Pool A)

Event term	Secukinumab 150 mg (N = 692)	Secukinumab 300 mg (N = 690)	Placebo (N = 694)	Etanercept (N = 323)
Nasopharyngitis	85 (12.3)	79 (11.4)	60 (8.6)	36 (11.1)
Headache	38 (5.5)	45 (6.5)	36 (5.2)	23 (7.1)
Upper respiratory tract infection	22 (3.2)	17 (2.5)	5 (0.7)	7 (2.2)
Hypertension	22 (3.2)	7 (1.0)	12 (1.7)	5 (1.5)
Pruritus	21 (3.0)	23 (3.3)	18 (2.6)	8 (2.5)
Diarrhoea	18 (2.6)	28 (4.1)	10 (1.4)	11 (3.4)

n (%)

In Pool B, frequent adverse events (≥5%) in the secukinumab 150 mg or 300 mg group were nasopharyngitis (19.1% [267 of 1395 subjects] in the secukinumab 150 mg group, 19.9% [281 of 1410 subjects] in the secukinumab 300 mg group, 20.0% [687 of 3430 subjects] in the any secukinumab dose group, 9.2% [73 of 793 subjects] in the placebo group, 26.6% [86 of 323 subjects] in the etanercept group), headache (8.0% [111 of 1395 subjects] in the secukinumab 150 mg group, 8.2% [115 of 1410 subjects] in the secukinumab 300 mg group, 8.2% [280 of 3430 subjects] in the any secukinumab dose group, 5.4% [43 of 793 subjects] in the placebo group, 12.4% [40 of 323 subjects] in the etanercept group), upper respiratory tract infection (6.6% [92

of 1395 subjects] in the secukinumab 150 mg group, 6.5% [91 of 1410 subjects] in the secukinumab 300 mg group, 6.7% [228 of 3430 subjects] in the any secukinumab dose group, 1.6% [13 of 793 subjects] in the placebo group, 5.6% [18 of 323 subjects] in the etanercept group), arthralgia (5.0% [69 of 1395 subjects] in the secukinumab 150 mg group, 4.8% [68 of 1410 subjects] in the secukinumab 300 mg group, 5.1% [174 of 3430 subjects] in the any secukinumab dose group, 2.3% [18 of 793 subjects] in the placebo group, 7.1% [23 of 323 subjects] in the etanercept group), and diarrhoea (4.5% [63 of 1395 subjects] in the secukinumab 150 mg group, 5.6% [79 of 1410 subjects] in the secukinumab 300 mg group, 4.8% [163 of 3430 subjects] in the any secukinumab dose group, 1.6% [13 of 793 subjects] in the placebo group, 6.8% [22 of 323 subjects] in the etanercept group).

A total of 6 deaths including 1 during the study treatment period (cerebral haemorrhage in the secukinumab 150 mg group) were reported by July 31, 2013. The causes of the other 5 deaths were intestinal ischaemia, hyperkalaemia, and renal failure (extension[38], phase II secukinumab group), aspergillosis (after study discontinuation, phase II secukinumab group), unknown (post-study, secukinumab 300 mg group), myocardial infarction (follow-up, placebo group), and completed suicide (before study drug randomization). A causal relationship to study drug was ruled out for all deaths. A summary of serious adverse events was as shown in Table 43. Major events were pneumonia (0.2% [3 of 1395 subjects] in the secukinumab 150 mg group, 0.2% [3 of 1410 subjects] in the secukinumab 300 mg group, 0.2% [6 of 3430 subjects] in the any secukinumab dose group) and cellulitis (0.1% [2 of 1395 subjects] in the secukinumab 150 mg group, 0.1% [1 of 1410 subjects] in the secukinumab 300 mg group, 0.2% [5 of 3430 subjects] in the any secukinumab dose group, 0.3% [2 of 793 subjects] in the placebo group, 0.3% [1 of 323 subjects] in the etanercept group), etc.

The safety analysis in the Japanese subgroup revealed that Pool A provides safety data from only 87 Japanese subjects in Study A2302 [see 4.(iii).A.(3) Multinational phase III study (5.3.5.1-5, Study A2302) for safety in the Japanese subgroup in Study A2302].

In Japanese subjects, the incidences of adverse events for Pool B were 87.1% (61 of 70 subjects) in the secukinumab 150 mg group, 82.9% (58 of 70 subjects) in the secukinumab 300 mg group, 82.6% (171 of 207 subjects) in the any secukinumab dose group, and 42.5% (17 of 40 subjects) in the placebo group. Major events were nasopharyngitis (38.6% [27 of 70 subjects] in the secukinumab 150 mg group, 24.3% [17 of 70 subjects] in the secukinumab 300 mg group, 28.5% (59 of 207 subjects) in the any secukinumab dose group, 12.5% [5 of 40 subjects] in the placebo group) and eczema (7.1% [5 of 70 subjects] in the secukinumab 150 mg group, 10.0% [7 of 70 subjects] in the secukinumab 300 mg group, 6.8% [14 of 207 subjects] in the any secukinumab dose group). There were no deaths. The incidences of serious adverse events were 5.7% in the secukinumab 150 mg group (4 of 70 subjects, pulmonary oedema and cardiac failure; type 2 diabetes mellitus; aortic thrombosis, aortic aneurysm, and non-cardiac chest pain; and generalised oedema and pleural effusion, 1 subject each), 5.7% in the secukinumab 300 mg group (4 of 70 subjects, pneumonia; pemphigus; liver injury, pancreatic injury, femur fracture, and tendon rupture; and tonsillitis bacterial, 1 subject each), and 6.8% in the any secukinumab dose group (14 of 207 subjects, back pain and intervertebral disc disorder; colon adenoma;

[38] The death was reported after database lock and was not included in the clinical study report.

enterocolitis infectious; erythrodermic psoriasis; rhabdomyolysis, ventricular fibrillation, and septic shock; and cataract, 1 subject each, in the phase II secukinumab group, in addition to those reported in the secukinumab 150 mg and 300 mg groups).

Based on the above, the incidence of adverse events tended to be slightly higher in the Japanese subgroup as compared to the overall population, which was considered attributable to higher incidences of nasopharyngitis, etc. Meanwhile, the nature of the reported events was similar between the Japanese subgroup and the overall population. Most of the adverse events were mild or moderate in severity. Thus, there should be no particular safety concerns for Japanese patients with psoriasis.

Considering adverse events observed in clinical studies and the pharmacological effects of secukinumab, etc., PMDA's review focused on the following specific events.

4.(iii).B.(2).1) Serious infections

The applicant explained the occurrence of serious infections in patients treated with secukinumab as follows: IL-17 is thought to be involved in the immune response to only a limited extent as compared to pro-inflammatory cytokines targeted by approved biological products (TNFα, IL-12/23, IL-6, etc.). Even so, the Th17/IL-17A pathway plays an important role in the immune surveillance of mucocutaneous barrier tissues (gastrointestinal and respiratory tracts, and skin). IL-17 helps protect against infections by inducing neutrophil activation and migration, etc. and is involved in host defense against mucocutaneous infections with *Candida albicans* and with *Staphylococcus aureus* [see "3.(iii).B. *Outline of the review*"].

The incidences of serious infections (serious adverse events classified as "infections and infestations" [SOC]) in clinical studies were 0.1% (1 of 692 subjects) in the secukinumab 150 mg group, 0.1% (1 of 690 subjects) in the secukinumab 300 mg group, 0.3% (2 of 694 subjects) in the placebo group, and 0% in the etanercept group in Pool A. In Pool B, the incidences of serious infections were 0.9% (12 of 1395 subjects) in the secukinumab 150 mg group, 1.1% (16 of 1410 subjects) in the secukinumab 300 mg group, 1.2% (4 of 323 subjects) in the etanercept group, and 0.3% (2 of 793 subjects) in the placebo group.

In Pool B, serious infections reported by ≥2 subjects in the any secukinumab dose group were pneumonia (6 subjects: 3 subjects in the secukinumab 150 mg group and 3 subjects in the secukinumab 300 mg group), cellulitis (5 subjects: 2 subjects in the secukinumab 150 mg group, 1 subject in the secukinumab 300 mg group, and 2 subjects in the phase II secukinumab group), abscess bacterial (4 subjects: 3 subjects in the secukinumab 150 mg group and 1 subject in the phase II secukinumab group), appendicitis (4 subjects: 1 subject in the secukinumab 150 mg group, 2 subjects in the secukinumab 300 mg group, and 1 subject in the phase II secukinumab group), anal abscess (2 subjects: 1 subject in the secukinumab 300 mg group and 1 subject in the phase II secukinumab group), and urosepsis (2 subjects: 1 subject in the secukinumab 150 mg group and 1 subject in the secukinumab 300 mg group).

No new tuberculosis infection or reactivation of latent tuberculosis was observed during the study treatment

period in any treatment group of Pool A or B.

There were 2 cases of hepatitis B in the secukinumab 150 mg group of Pool B, which were both reported as serious. However, the both subjects tested negative for viral hepatitis at baseline. One of them had liver function test abnormal, for which a relationship to the study drug could not be ruled out. The event was improved by medication therapy. The other subject was not noted with worsening of liver function tests.

In Pool B, the incidences of opportunistic infections were 0.1% in the secukinumab 150 mg group (1 of 1395 subjects, oesophageal candidiasis), 0.2% in the secukinumab 300 mg group (3 of 1410 subjects, oesophageal candidiasis), 0.1% in the placebo group (1 of 793 subjects, cytomegalovirus gastroenteritis), and 0.3% in the etanercept group (1 of 323 subjects, gastrointestinal candidiasis). No serious events were reported.

In Pool B, staphylococcal infection-related adverse events occurred in 0.2% of subjects in the secukinumab 150 mg group (3 of 1395 subjects, staphylococcal infection; staphylococcal skin infection; and eye infection staphylococcal) and 0.1% of subjects in the secukinumab 300 mg group (1 of 1410 subjects, staphylococcal infection) and did not occur in the placebo group or the etanercept group. A serious event occurred in 1 subject in the phase II secukinumab group (staphylococcal infection) and its relationship to the study drug could not be ruled out, but the event did not lead to treatment discontinuation and resolved with medication therapy.

Given the facts including the high incidence of infections with secukinumab as compared to placebo in clinical studies, patients with infection or suspected infection will be listed in the “Careful Administration” section of the package insert, and a precautionary statement about infections will be included in the sections of “Important Precautions” and “Clinically Significant Adverse Reactions”.

PMDA asked the applicant to discuss risks of tuberculosis associated with secukinumab, making use of published literature, etc., as appropriate.

The applicant explained as follows:
According to a report, IL-17A is not associated with infection by Mycobacterium tuberculosis or other pathogens (Notarangelo LD, et al. *J Allergy Clin Immunol.* 2009;124:1161-1178, Maródi L and Casanova JL. *J Allergy Clin Immunol.* 2010;126:910-917, Puel A, et al. *Curr Opin Allergy Clin Immunol.* 2012;12:616-622, Bousfiha AA, et al. *J Clin Immunol.* 2013;33:1-7). In mouse models of infection, IL-17 was found to be involved in the prevention of infection with extracellular bacterial and fungal pathogens. However, a role of IL-17 in the defense mechanism against infection with intracellular bacterial pathogens such as Mycobacterium tuberculosis, parasitic, and viral pathogens is unclear (Okamoto Yoshida Y, et al. *J Immunol.* 2010;184:4414-4422, Freches D, et al. *Immunol.* 2013;140:220-231, O’Garra A, et al. *Immunol.* 2013;31:475-527).

Also in clinical studies of secukinumab, no initial tuberculosis infection or reactivation of latent tuberculosis was observed. Thus, there has so far been no signal indicating that administration of secukinumab induces an

increased susceptibility to tuberculosis infection. However, as patients with active tuberculosis were excluded from clinical studies of secukinumab and there is no clinical experience with secukinumab in such patients, patients with active tuberculosis will be listed in the “Careful Administration” section of the package insert.

Furthermore, decreases in neutrophil counts were observed also in non-clinical studies of secukinumab [see “3.(iii).A.(2).4) Six-month intravenous injection toxicity study in monkeys (4.2.3.2-4)”]. PMDA asked the applicant to explain the occurrence of neutrophil count decreased in clinical studies and its relationship to infections.

The applicant explained as follows:
In Pool A and Pool B, the incidence of neutrophil count decreased was comparable for the secukinumab 150 mg, secukinumab 300 mg, and etanercept groups and neutrophil count decreased was not noted in the placebo group (Pool A: 0.3% [2 of 692 subjects] in the secukinumab 150 mg group, 0.6% [4 of 690 subjects] in the secukinumab 300 mg group, 0.6% [2 of 323 subjects] in the etanercept group; Pool B: 1.1% [15 of 1395 subjects] in the secukinumab 150 mg group, 1.1% [16 of 1410 subjects] in the secukinumab 300 mg group, 1.5% [5 of 323 subjects] in the etanercept group). In Pool B, major events were leukopenia (0.6% [8 of 1395 subjects] in the secukinumab 150 mg group, 0.6% [8 of 1410 subjects] in the secukinumab 300 mg group, 0.9% [3 of 323 subjects] in the etanercept group) and neutropenia (0.7% [9 of 1395 subjects] in the secukinumab 150 mg group, 0.5% [7 of 1410 subjects] in the secukinumab 300 mg group, 1.2% [4 of 323 subjects] in the etanercept group), etc. No serious adverse events were reported.

In Pool B, Grade 3 neutropenia was noted on laboratory analysis in 0.6% (8 of 1395) of subjects in the secukinumab 150 mg group, 0.7% (10 of 1410) of subjects in the secukinumab 300 mg group, and 0.1% (1 of 793) of subjects in the placebo group, but not in the etanercept group. Grade 4 neutropenia was observed in 0.3% (1 of 323) of subjects in the etanercept group. Of 18 subjects with Grade 3 neutropenia in the secukinumab groups, 2 subjects had an infection (cystitis; and viral upper respiratory tract infection, 1 subject each) within 1 week before or after neutropenia was found and the remaining 16 subjects did not have an infection within 2 weeks before or after neutropenia was found. The applicant considers the result suggested no relationship between neutropenia and infections.

PMDA considers as follows:
In light of the pharmacological effects of secukinumab, serious infection is of greatest concern with secukinumab as is the case with other approved biological products. Serious infections associated with secukinumab have been reported in clinical studies on psoriasis. Thus, relevant precautionary statements should be included in the package insert as in the case of other approved biological products for the treatment of psoriasis. In addition to safety measures proposed by the applicant, inclusion of precautionary statements about serious infections in the “Warnings” section of the package insert and a contraindication of secukinumab in patients with a serious infection, etc. are required. Investigation on the onset of serious infections in patients treated with secukinumab should be continued via post-marketing surveillance, etc. Measures for prevention of and early detection of serious infections should be thoroughly taken with cooperation between

dermatologists, who play the main role in treating psoriasis, and specialists who are capable of detecting and treating serious infections [see "4.(iii).B.(7) Post-marketing safety measures"].

Although no initial tuberculosis infection or reactivation of latent tuberculosis was noted in clinical studies of secukinumab, the number of subjects assessed in clinical studies was not sufficient to evaluate the risk of tuberculosis. According to a report, γδ T cell-derived IL-17 is essential for the formation of mature granulomas that play a role in the prevention of Mycobacterium tuberculosis infection (Okamoto Yoshida Y, et al. *J Immunol.* 2010;184:4414-4422). Based on these findings, etc., the relationship between secukinumab and tuberculosis cannot be ruled out, and precautionary statements about the development of tuberculosis should also be included in the package insert, as in the case of approved biological products for the treatment of psoriasis. Therefore, in addition to safety measures proposed by the applicant, the following actions should be taken: secukinumab will be contraindicated in patients with active tuberculosis; patients with a history of tuberculosis will be listed in the "Careful Administration" section; and the "Important Precautions" section will advise that patients should be tested for tuberculosis infection prior to the use of secukinumab and be treated with anti-tuberculous drugs if tested positive.

Although the currently available data show no clear relationship between decreased neutrophil count and infections, decreased neutrophil count is considered due to the pharmacological effects of secukinumab, the incidence of decreased neutrophil count tended to be higher with secukinumab as compared to placebo in clinical studies. The incidence of severe decrease in neutrophil count noted on laboratory analysis tended to be higher with secukinumab as compared to placebo. Taking account of these findings, the possibility cannot be ruled out that decreased neutrophil count associated with secukinumab can trigger infections. Precautionary statements about decreased neutrophil count associated with secukinumab should be included in the package insert, and investigation should be further continued via post-marketing surveillance, etc. on the occurrence of decreased neutrophil count and its relationship to infections.

4.(iii).B.(2).2) Fungal infections, candidiasis

The applicant explained the occurrence of fungal infections including candidiasis as follows:
It is known that genetic defects in IL-17 signaling are likely to increase susceptibility to candidiasis (Gaffen SL, et al. *Immunol Res*. 2011;50:181-187), and it is suggested that IL-17 plays a central role in the mucosal defense to *Candida albicans* (Cypowyj S, et al. *Eur J Immunol*. 2012;42:2246-2254).

In Pool A, the incidences of fungal infections were as shown in Table 45. In Pool B, the incidences of fungal infections were 5.0% (69 of 1395 subjects) in the secukinumab 150 mg group, 6.3% (89 of 1410 subjects) in the secukinumab 300 mg group, 1.0% (8 of 793 subjects) in the placebo group, and 3.7% (12 of 323 subjects) in the etanercept group. Exposure-adjusted incidence rates for the secukinumab 150 mg, 300 mg, placebo, and etanercept groups were 6.2, 7.9, 4.0, and 4.2 per 100 patient-years, respectively. The incidence rates tended to be higher in the secukinumab groups as compared with the placebo group or the etanercept group.

In order to call attention to fungal infections, candidiasis and tinea pedis will be listed in the "Other Adverse

Reactions" section of the package insert.

Table 45. Incidences of fungal infections (Pool A)

Event term	Secukinumab 150 mg (N = 692)	Secukinumab 300 mg (N = 690)	Placebo (N = 694)	Etanercept (N = 323)
Fungal infections	12 (1.7)	15 (2.2)	6 (0.9)	3 (0.9)
Candida infections	3 (0.4)	8 (1.2)	2 (0.3)	1 (0.3)
Vulvovaginal candidiasis	2 (0.3)	1 (0.1)	1 (0.1)	0
Oral candidiasis	1 (0.1)	4 (0.6)	1 (0.1)	0
Candidiasis	0	1 (0.1)	0	0
Balanitis candida	0	1 (0.1)	0	0
Oesophageal candidiasis	0	1 (0.1)	0	0
Gastrointestinal candidiasis	0	0	0	1 (0.3)
Tinea infections	8 (1.2)	5 (0.7)	1 (0.1)	1 (0.3)
Tinea pedis	5 (0.7)	5 (0.7)	0	0
Body tinea	1 (0.1)	1 (0.1)	0	0
Tinea versicolour	1 (0.1)	0	1 (0.1)	0
Tinea cruris	1 (0.1)	0	0	0
Trichophytosis	0	0	0	1 (0.3)

n (%)

Taking account of high incidences of fungal infections with secukinumab, PMDA asked the applicant to explain the possibility that secukinumab increases the risk of deep fungal infections as well as superficial fungal infections such as candidasis and tinea.

The applicant explained as follows:

Although the incidences of fungal infections tended to be higher with secukinumab, all cases of fungal infections were non-serious and responsive to standard drug therapy and did not require the interruption or discontinuation of secukinumab. A type of deep fungal infection, disseminated aspergillosis infection occurred in 1 subject. Since this subject had discontinued secukinumab ≥1 year prior to the diagnosis of aspergillosis, the event may have been related to immunosuppression after two liver transplantation rather than to treatment with secukinumab. The result is not suggestive of a risk of deep fungal infections associated with secukinumab.

PMDA considers as follows:

It is suggested that IL-17 plays a central role in the mucosal defense to *Candida albicans* (Cypowyj S, et al. *Eur J Immunol*. 2012;42:2246-2254). The incidences of superficial fungal infections, i.e. candidiasis and tinea infections, tended to be higher in the secukinumab groups than in the placebo group or the etanercept group also in the clinical studies of secukinumab, adequate caution should be exercised against the possible development of superficial fungal infections including candidiasis during treatment with secukinumab. Although the data from the clinical studies showed no trend towards increased risk of deep fungal infections in patients treated with secukinumab, the possibility cannot be ruled out that this risk is increased in immunocompromised patients by prior or concomitant immunosuppressive therapy, etc. The occurrence of fungal infections including deep fungal infections in patients treated with secukinumab should be investigated via post-marketing surveillance, etc.

4.(iii).B.(2).3) Malignancy

The applicant explained the occurrence of malignancies as follows:

According to a report, patients with psoriasis have increased risks of cancers of the liver, esophagus, oral cavity,

and pharynx, etc (Boffetta P, et al. *J Invest Dermatol*. 2001;117:1531-1537). In monkey repeat-dose toxicity studies, secukinumab did not induce proliferative changes or atypia suggestive of carcinogenicity at doses of up to 150 mg/kg. However, the studies suggested both anti-tumor and pro-tumor activities of Th17 cells and Th17-related cytokines [see "3.(iii).B.(2) Carcinogenicity"].

In the clinical studies, the incidences of malignancies were <0.5% in all treatment groups of Pool A and no dose-dependent increase was seen.

In Pool B, the incidences of malignancies were as shown in Table 46. Many of the noted malignancies were skin cancers (mostly non-melanoma skin cancers) and there were no reports of lymphoma. The exposure-adjusted incidence rates were comparable across the treatment groups (1.0, 0.8, 1.5, and 0.7 per 100 patient-years for secukinumab 150 mg, secukinumab 300 mg, placebo, and etanercept, respectively).

Table 46. Incidences of malignancies (Pool B)

Event term	Secukinumab 150 mg (N = 1395)	Secukinumab 300 mg (N = 1410)	Placebo (N = 793)	Etanercept (N = 323)
Malignant or unspecified tumors	11 (0.8)	9 (0.6)	3 (0.4)	2 (0.6)
Basal cell carcinoma	5 (0.4)	4 (0.3)	1 (0.1)	0
Thyroid cancer	2 (0.1)	0	0	0
Squamous cell carcinoma	1 (0.1)	1 (0.1)	2 (0.3)	0
Malignant melanoma in situ	1 (0.1)	1 (0.1)	0	0
Follicular thyroid cancer	1 (0.1)	0	0	0
Bladder cancer	1 (0.1)	0	0	0
Neoplasm malignant	1 (0.1)	0	0	0
Squamous cell carcinoma of skin	1 (0.1)	0	0	0
Neoplasm	0	1 (0.1)	0	1 (0.3)
Malignant melanoma	0	1 (0.1)	0	0
Renal cancer	0	1 (0.1)	0	0
Bowen's disease	0	0	0	1 (0.3)

n (%)

The standardized incidence rates (SIRs) of malignancies excluding non-melanoma skin cancer in Pool B and its 95% confidence interval were calculated from the US National Cancer Institute Surveillance Epidemiology and End Results (SEER) database. The SIRs [95% CI] were 0.67 [0.18, 1.72] in the secukinumab 150 mg group and 0.64 [0.17, 1.63] in the secukinumab 300 mg group, and the incidence rates of malignancies in patients treated with secukinumab were similar to those expected in the general US population.

Furthermore, the exposure-adjusted incidence rates of non-melanoma skin cancer in Pool B were compared to those in the clinical studies of approved biological products. Since the comparisons were made among different studies, the results must be interpreted carefully. The incidence rates of non-melanoma skin cancer were 0.6 per 100 patient-years in the secukinumab 150 mg group, 0.4 per 100 patient-years in the secukinumab 300 mg group, 0.4 per 100 patient-years with infliximab,[39] 0.7 per 100 patient-years with adalimumab,[40] and 0.5 per 100 patient-years with ustekinumab.[41] There was no trend towards a higher risk of non-melanoma skin cancer with secukinumab as compared to the approved biological products.

[39] All clinical studies with infliximab. See the package insert, Clinical Studies 7. Incidence rate of malignancies after foreign clinical studies.
[40] Clinical studies in patients with psoriasis vulgaris, psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis, or Crohn's disease. See the package insert, Clinical Studies 8. Incidence rate of malignancies (foreign clinical studies).
[41] Clinical studies in patients with psoriasis. See the package insert, Clinical studies 2. Incidence rate of malignancies (foreign clinical studies).

Since secukinumab did not tend to increase the risk of malignancy in the clinical studies, no special precautions in the package insert, etc. are necessary. As secukinumab is an immunomodulator, patients treated with secukinumab are to be closely watched for the occurrence of malignancy also after the market launch.

PMDA considers as follows:
Although the causal relationship between secukinumab and the development of malignancy is unclear at present, the number of subjects investigated in the clinical studies was not sufficient to evaluate the risk of malignancy. The possibility that secukinumab, as with the approved biological products, affects the anti-tumor immune defense mechanisms cannot be ruled out. Thus, a warning about malignancy should also be included in the package insert, etc., as with the case of the approved biological products for the treatment of psoriasis. Generally, many patients with psoriasis have experienced phototherapy or immunosuppressants and are particularly at risk of developing skin cancer. Therefore, the occurrence of malignancies including skin cancer in patients with psoriasis who are treated with secukinumab should be further investigated via post-marketing surveillance, etc.

4.(iii).B.(2).4) Administration site reactions or immune reactions
The applicant explained the occurrence of administration site reactions or immune reactions as follows:
In Pool A and Pool B, the incidence of hypersensitivity was comparable among the secukinumab 150 mg, secukinumab 300 mg, and etanercept groups and was higher than that in the placebo group (Pool A: 4.5% [31 of 692 subjects] in the secukinumab 150 mg group, 4.5% [31 of 690 subjects] in the secukinumab 300 mg group, 1.3% [9 of 694 subjects] in the placebo group, 4.6% [15 of 323 subjects] in the etanercept group; Pool B: 8.2% [115 of 1395 subjects] in the secukinumab 150 mg group, 9.4% [132 of 1410 subjects] in the secukinumab 300 mg group, 1.1% [9 of 793 subjects] in the placebo group, 8.4% [27 of 323 subjects] in the etanercept group).

In Pool B, major events were eczema (1.7% [23 of 1395 subjects] in the secukinumab 150 mg group, 2.6% [37 of 1410 subjects] in the secukinumab 300 mg group, 0.1% [1 of 793 subjects] in the placebo group, 0.6% [2 of 323 subjects] in the etanercept group) and urticaria (1.8% [25 of 1395 subjects] in the secukinumab 150 mg group, 1.4% [20 of 1410 subjects] in the secukinumab 300 mg group, 0.1% [1 of 793 subjects] in the placebo group, 0.9% [3 of 323 subjects] in the etanercept group), etc. Serious adverse events occurred in 1 subject in the secukinumab 150 mg group (contact dermatitis), 1 subject in the secukinumab 300 mg group (dermatitis), 1 subject in the phase II secukinumab group (allergic dermatitis), and 1 subject in the placebo group (exfoliative dermatitis).

The incidences of administration site reactions or immune reactions were comparable among the secukinumab 150 mg, secukinumab 300 mg, and placebo groups in Pool A. The incidences were lower with secukinumab as compared to etanercept in both Pool A and Pool B (Pool A: 12.3% [85 of 692 subjects] in the secukinumab 150 mg group, 14.2% [98 of 690 subjects] in the secukinumab 300 mg group, 11.8% [82 of 694 subjects] in the placebo group, 18.3% [59 of 323 subjects] in the etanercept group; Pool B: 21.0% [292 of 1395 subjects] in the secukinumab 150 mg group, 22.6% [318 of 1410 subjects] in the secukinumab 300 mg group, 13.2%

[105 of 793 subjects] in the placebo group, 29.4% [95 of 323 subjects] in the etanercept group).

In Pool B, major events were pruritus (4.7% [66 of 1395 subjects] in the secukinumab 150 mg group, 3.8% [54 of 1410 subjects] in the secukinumab 300 mg group, 2.6% [21 of 793 subjects] in the placebo group, 5.0% [16 of 323 subjects] in the etanercept group) and cough (3.2% [44 of 1395 subjects] in the secukinumab 150 mg group, 5.0% [70 of 1410 subjects] in the secukinumab 300 mg group, 1.6% [13 of 793 subjects] in the placebo group, 3.7% [12 of 323 subjects] in the etanercept group), etc. The incidences of serious adverse events were 0.5% (7 of 1395 subjects) in the secukinumab 150 mg group, 0.4% (5 of 1410 subjects) in the secukinumab 300 mg group, 0.5% (17 of 3430 subjects) in the any secukinumab dose group, 0.6% (5 of 793 subjects) in the placebo group, and 0.6% (2 of 323 subjects) in the etanercept group and those reported by ≥2 subjects treated with secukinumab were ulcerative colitis (1 subject in the secukinumab 150 mg group, 2 subjects in the secukinumab 300 mg group), psoriasis (1 subject in the secukinumab 150 mg group, 1 subject in the secukinumab 300 mg group), and Crohn's disease (2 subjects in the secukinumab 150 mg group).

An event reported as an anaphylactic reaction occurred in 1 subject in the secukinumab 150 mg group of Study A2303. The event was non-serious. The subject had a history of nut allergy. A moderate anaphylactic reaction developed 12 days after the start of treatment (2 days after the latest dose of study drug), and its relationship to the study drug was ruled out. One serious anaphylactic reaction was reported in the secukinumab i.v. 2×10 mg/kg group in a clinical study in patients with ankylosing spondylitis. The subject had anaphylactic symptoms (generalized hives, lip oedema, shortness of breath) on the day of the first dose and recovered from the event with drug therapy, though its relationship to the study drug could not be ruled out.

The package insert will call attention to administration site reactions or immune reactions by contraindicating secukinumab for patients with a history of serious hypersensitivity to any of the components of secukinumab and by adding "hypersensitivity reactions" in the "Clinically Significant Adverse Reactions" section and "urticaria" in the "Other Adverse Reactions" section.

PMDA considers as follows:
Taking into account the fact that serious anaphylaxis was reported in a clinical study of secukinumab, the occurrence of hypersensitivity including anaphylaxis should be further investigated via post-marketing surveillance, etc.

4.(iii).B.(2).5) Inflammatory bowel diseases including exacerbation or new onset of Crohn's disease
The applicant explained the relationship between treatment with secukinumab and the exacerbation or new onset of Crohn's disease as follows:
According to a report, the pathogenesis of Crohn's disease and psoriasis is believed to be associated with IL-17 and IL-17-producing T cells (Skroza N, et al. *Biomed Res Int.* 2013;2013:983902). There is also a report that concurrent Crohn's disease is common in patients with psoriasis and that the incidence of concurrent Crohn's disease among patients with psoriasis is about 4 times that in other patients (Lee FI, et al. *Am J Gastroenterol.* 1990;85:962-963, Li WQ, et al. *Ann Rheum Dis.* 2013;72:1200-1205). Both psoriasis and

Crohn's disease are responsive to anti-TNFα therapy, which indicates a possible common pathogenesis of both diseases. On the other hand, a clinical study failed to show the efficacy of secukinumab in patients with Crohn's disease and the symptoms of active Crohn's disease tended to worsen in the secukinumab group as compared to the placebo group (Hueber W, et al. *Gut.* 2012;61:1693-1700).

In Pool A, the incidences of inflammatory bowel diseases including Crohn's disease were 0.1% [1 of 692 subjects] in the secukinumab 150 mg group, 0.1% [1 of 690 subjects] in the secukinumab 300 mg group, and 0.3% [1 of 323 subjects] in the etanercept group. No inflammatory bowel disease was observed in the placebo group.

In Pool B, the incidences of inflammatory bowel diseases were 0.3% in the secukinumab 150 mg group (4 of 1395 subjects, ulcerative colitis; and Crohn's disease, 2 subjects each), 0.2% in the secukinumab 300 mg group (3 of 1410 subjects, ulcerative colitis [2 subjects], anal fistula [1 subject]), 0.3% in the any secukinumab dose group (9 of 3430 subjects, Crohn's disease; and cholangitis sclerosing, 1 subject each, in the phase II secukinumab group, in addition to those reported in the secukinumab 150 mg and 300 mg groups), and 0.3% in the etanercept group (1 of 323 subjects, ulcerative colitis). No inflammatory bowel disease was observed in the placebo group. Serious adverse events occurred in 3 subjects in the secukinumab 150 mg group (ulcerative colitis [1 subject], Crohn's disease [2 subjects]), 3 subjects in the secukinumab 300 mg group (ulcerative colitis [2 subjects], anal fistula [1 subject]), and 7 subjects in the any secukinumab dose group (Crohn's disease [1 subject] in the phase II secukinumab group, in addition to those reported in the secukinumab 150 mg and 300 mg groups). A total of 3 cases of Crohn's disease were reported in the secukinumab group of Pool B, 1 of which was a new case and other two were considered the exacerbation of the existing disease. A causal relationship to the study drug could not be ruled out for the two cases with flare.

There are no consistent reports concerning the pathophysiological role of IL-17 in Crohn's disease (Fuss IJ. *Mucosal Immunology.* 2011;4:366-367, Monteleone I, et al. *Current Molecular Medicine.* 2012;12: 592-597). Taking also into account the fact that the incidence of Crohn's disease among patients with psoriasis is about 4 times that in other patients (Li WQ, et al. *Ann Rheum Dis*. 2013;72:1200-1205), secukinumab is unlikely to cause the exacerbation or new onset of Crohn's disease. However, a clinical study for Crohn's disease revealed that the symptoms of active Crohn's disease tended to worsen in the secukinumab group as compared to the placebo group. Clinical studies in patients with psoriasis also showed exacerbated or new onset of Crohn's disease in subjects treated with secukinumab. Crohn's disease is thought to involve an abnormal immune response. IL-17 may play a key role to protect the intestinal mucosa for anti-bacterial immunity in the gastrointestinal tract. Taking account of these findings, patients with active Crohn's disease will be listed in the "Careful Administration" section of the package insert, and it will be advised that said patients should be monitored closely during treatment with secukinumab.

PMDA considers as follows:
Although the relationship between treatment with secukinumab and the exacerbation or new onset of Crohn's disease is unclear at present, the symptoms of active Crohn's disease tended to worsen in the secukinumab

group as compared to the placebo group in a Crohn's disease clinical study. Given this finding, etc., the precautionary information on the use of secukinumab in patients with active Crohn's disease should be included in the package insert as per the applicant's explanation. As an adverse event of ulcerative colitis was also reported sporadically in clinical studies in patients with psoriasis, the relationship between treatment with secukinumab and the exacerbation or new onset of inflammatory bowel diseases including ulcerative colitis and Crohn's disease should be further investigated via post-marketing surveillance, etc.

4.(iii).B.(2).6) Exacerbation or new onset of psoriasis

The applicant explained the exacerbation or new onset of psoriatic symptoms as follows:

In the context of the possible association of treatment with anti-TNFα agents with exacerbated and newly diagnosed psoriasis, the effect of secukinumab on the exacerbation and new onset of psoriasis was evaluated. Adverse events related to the exacerbation or new onset of psoriatic symptoms were defined as erythrodermic psoriasis, guttate psoriasis, nail psoriasis, parapsoriasis, psoriasis, psoriatic arthritis, pustular psoriasis, psoriatic dermatitis, and rebound psoriasis.

In Pool B, the most frequent psoriatic symptom-related adverse event was psoriasis (1.6% [22 of 1395 subjects] in the secukinumab 150 mg group, 2.2% [31 of 1410 subjects] in the secukinumab 300 mg group, 3.5% [28 of 793 subjects] in the placebo group, 2.2% [7 of 323 subjects] in the etanercept group) followed by psoriatic arthropathy (1.3% [18 of 1395 subjects] in the secukinumab 150 mg group, 1.0% [14 of 1410 subjects] in the secukinumab 300 mg group, 0.6% [5 of 793 subjects] in the placebo group, 0.3% [1 of 323 subjects] in the etanercept group). Although there were no significant differences in the incidence of psoriasis among the treatment groups, the incidence of psoriatic arthropathy tended to be higher in the secukinumab group as compared to the placebo group or the etanercept group.

The exposure-adjusted incidences of psoriatic symptom-related adverse events in Pool B were as shown in Table 47 and there were no significant differences among the treatment groups.

Table 47. Exposure-adjusted incidence rates of psoriatic symptom-related adverse events (Pool B)

Event term	Secukinumab 150 mg (N = 1395)	Secukinumab 300 mg (N = 1410)	Placebo (N = 793)	Etanercept (N = 323)
Psoriasis	22 (1.9)	31 (2.7)	28 (14.2)	7 (2.4)
Psoriatic arthropathy	18 (1.6)	14 (1.2)	5 (2.5)	1 (0.3)
Erythrodermic psoriasis	5 (0.4)	1 (0.1)	1 (0.5)	1 (0.3)
Pustular psoriasis	2 (0.2)	4 (0.3)	1 (0.5)	0
Psoriatic dermatitis	1 (0.1)	1 (0.1)	0	0
Guttate psoriasis	0	1 (0.1)	1 (0.5)	1 (0.3)
Nail psoriasis	0	1 (0.1)	0	0

n (Exposure-adjusted incidence rate per patient-year)

Of subjects who had psoriatic symptom-related adverse events in the secukinumab 150 or 300 mg group, only 11 subjects in the secukinumab 150 mg group and 2 subjects in the secukinumab 300 mg group[42] were considered having the exacerbated primary disease (psoriasis) (if the PASI score increased from baseline at the time of or near the time of onset of the adverse event).

[42] Of these subjects, 4 subjects in the secukinumab 150 mg group and 2 subjects in the secukinumab 300 mg group developed a psoriatic symptom-related adverse event while on placebo treatment.

Based on the above, secukinumab is unlikely to exacerbate psoriatic symptoms.

In clinical studies in patients with other than psoriasis (1068 subjects in the secukinumab group, 367 subjects in the placebo group), psoriatic symptom-related adverse events occurred in 2 subjects in the secukinumab group in a study involving patients with rheumatoid arthritis and 1 subject in a study involving patients with noninfective uveitis. The events were all mild to moderate in severity and study drug was continued. Taking also account of the prevalence of psoriasis of 2% to 3%, secukinumab is unlikely to cause new onset of psoriasis.

PMDA considers as follows:
Although the currently available data show no clear relationship between treatment with secukinumab and the exacerbation of psoriasis, the possible association of anti-TNFα agents with exacerbation and new onset of psoriasis is suggested. The possibility that secukinumab has a similar effect cannot be ruled out due to its effect on the immune system. Appropriate evaluation of the exacerbation and new onset of psoriasis is difficult in clinical studies of secukinumab in patients with psoriasis. Therefore, information on the effects of secukinumab in patients with diseases other than psoriasis should be further collected so that the evaluation of the secukinumab-associated risks is continued.

4.(iii).B.(2).7) Cardiovascular/cerebrovascular events
The applicant explained the occurrence of cardiovascular/cerebrovascular events as follows:
According to a report, hypertension, diabetes mellitus, obesity, dyslipidaemia, or metabolic syndrome is common in patients with psoriasis (Neimann AL, et al. *J Am Acad Dermatol*. 2006;55:829-835, Langan SM, et al. *J Invest Dermatol*. 2012;132:556-562). Patients with psoriasis are known to be at high risk of cardiovascular adverse events, and it is suggested that cardiovascular event risks increase with the severity of psoriasis (Armstrong AW, et al. *Dermatology.* 2012;225:121-126, Golden JB, et al. *Cytokine.* 2013;62:195-201). There is also a report suggesting an increased risk of cardiovascular adverse events in patients with myocardial infarction with low blood IL-17A levels (Simon T, et al. *Eur Heart J*. 2013;34:570-577). On the other hand, another report reveals high blood IL-17A levels in patients with cardiac failure (Todd J, et al. *Cytokine.* 2013;64:660-665).

A summary of cardiovascular/cerebrovascular events in Pool A and Pool B was as shown in Table 48. In Pool B, the total exposure-adjusted incidence rates of cardiovascular/cerebrovascular events were 2.7 per patient-year in the secukinumab 150 mg group, 3.3 per patient-year in the secukinumab 300 mg group, 6.5 per patient-year in the placebo group, and 4.9 per patient-year in the etanercept group. There was no trend towards higher incidence rates in the secukinumab group as compared to the placebo or etanercept group. There were no clinically important differences in the incidences of major adverse cardiovascular events (MACE)[43] between the secukinumab and placebo or etanercept groups and between the secukinumab 150 mg and 300 mg groups. Most of the subjects with MACE had its risk factors, e.g. a prior or concomitant cardiovascular/cerebrovascular

[43] Defined as myocardial infarction, stroke, and cardiovascular death.

disease and the smoking habit.

Although secukinumab did not tend to increase the incidence of cardiovascular adverse events, the possible association between psoriasis and cardiovascular events has been suggested. Patients treated with secukinumab will be closely watched for the onset of cardiovascular/cerebrovascular adverse events also via post-marketing surveillance, etc.

Table 48. Incidences of cardiovascular/cerebrovascular events and MACE (Pool A and Pool B)

Pool A	Secukinumab 150 mg (N = 692)	Secukinumab 300 mg (N = 690)	Placebo (N = 694)	Etanercept (N = 323)
Cardiovascular/cerebrovascular events	7 (1.0)	3 (0.4)	11 (1.6)	6 (1.9)
MACE	0	2 (0.3)	0	0
Pool B	Secukinumab 150 mg (N = 1395)	Secukinumab 300 mg (N = 1410)	Placebo (N = 793)	Etanercept (N = 323)
Cardiovascular/cerebrovascular events	30 (2.2)	38 (2.7)	13 (1.6)	14 (4.3)
MACE	5 (0.4)	6 (0.4)	1 (0.1)	1 (0.3)

n (%)

PMDA considers as follows:

The relationship between treatment with secukinumab and cardiovascular/cerebrovascular adverse events is unclear at present. The number of subjects enrolled in clinical studies was not large enough to evaluate the risk of cardiovascular/cerebrovascular adverse events. The effects of secukinumab on the cardiovascular/cerebrovascular system should be further investigated via post-marketing surveillance, etc.

As discussed above, adequate caution should be exercised against the possible onset of adverse events related to the immunosuppressive effect of secukinumab, especially serious infections, etc. However, as the clinical studies indicated no trend towards higher risks with secukinumab as compared to the comparator etanercept, these adverse events can be managed with safety measures similar to those for the approved biological products. Safety data from the Japanese subgroup also indicated no noteworthy events in Japanese patients with psoriasis. However, clinical experiences with secukinumab have been limited so far. Thus, sufficient information should be collected via post-marketing surveillance, etc. to further clarify the safety profile of secukinumab.

4.(iii).B.(3) Dosage and administration

4.(iii).B.(3).1) Usual dose (300 mg) and a dose of 150 mg

Based on the results of placebo-controlled phase III studies assessing the efficacy of 150 mg and 300 mg of secukinumab (A2302, A2303, A2308,[44] A2309[45]), the applicant explained the rationale for the proposed dosage and administration ("the usual adult dosage is 300 mg of Secukinumab [Genetical Recombination] by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3, followed by dosing every 4 weeks, starting at Week 4. A dose of 150 mg may be acceptable for some patients, depending on their symptoms.") as follows:

The results of the efficacy endpoints for a multinational phase III study (A2302) were as shown in Table 49. Secukinumab 300 mg demonstrated greater improvement as compared with 150 mg across all endpoints (PASI

[44] A placebo-controlled, randomized, double-blind, parallel-group study (5.3.5.1-7) in patients with moderate to severe plaque psoriasis (target sample size of 171 [57 subjects/group]) in which secukinumab (PFS formulation) 150 mg or 300 mg was administered subcutaneously using the same dosing schedule as in a multinational phase III study (A2302). The study drug was to be self-administered.

[45] A placebo-controlled, randomized, double-blind, parallel-group study (5.3.5.1-8) in patients with moderate to severe plaque psoriasis (target sample size of 171 [57 subjects/group]) in which secukinumab (auto-injector formulation) 150 mg or 300 mg was administered subcutaneously using the same dosing schedule as in a multinational phase III study (A2302). The study drug was to be self-administered.

75 response rate representing clinically significant improvement, PASI 90 response rate and IGA 0/1 response rate representing clear or almost clear skin, PASI 100 response rate and IGA 0 response rate representing completely clear skin [complete remission]), and similar results were obtained in the Japanese subgroup. Similarly, secukinumab 300 mg was superior in improvement in skin symptoms to secukinumab 150 mg also in the other foreign phase III studies (A2303, A2308, A2309).

Generally, time to PASI 50 response is considered as time to response to treatment. Response to treatment with the study drug was defined as 50% reduction in the mean PASI score from baseline. In Studies A2302 and A2303, time to response to treatment was 3 weeks with secukinumab 300 mg and 4 weeks with secukinumab 150 mg, showing faster response with secukinumab 300 mg. Considering that there were no significant differences in the safety profile between secukinumab 300 mg and 150 mg [see "4.(iii).B.(2) Safety"], 300 mg was considered the usual dose of secukinumab.

Table 49. PASI 50/75/90/100 response rates and IGA 0/1 response rates at Week 12 or 52 (Study A2302)

	Time point	Overall population			Japanese subgroup		
		Secukinumab 150 mg	Secukinumab 300 mg	Placebo	Secukinumab 150 mg	Secukinumab 300 mg	Placebo
PASI 50 response rate	Week 12	83.5 (203/243)	90.6 (222/245)	8.9 (22/246)	93.1 (27/29)	86.2 (25/29)	10.3 (3/29)
	Week 52	77.0 (187/243)	84.5 (207/245)		79.3 (23/29)	93.1 (27/29)	
PASI 75 response rate	Week 12	71.6 (174/243)	81.6 (200/245)	4.5 (11/246)	86.2 (25/29)	82.8 (24/29)	6.9 (2/29)
	Week 52	60.1 (146/243)	74.3 (182/245)		75.9 (22/29)	86.2 (25/29)	
PASI 90 response rate	Week 12	39.1 (95/243)	59.2 (145/245)	1.2 (3/246)	55.2 (16/29)	62.1 (18/29)	0 (0/29)
	Week 52	36.2 (88/243)	60.0 (147/245)		41.4 (12/29)	69.0 (20/29)	
PASI 100 response rate	Week 12	12.8 (31/243)	28.6 (70/245)	0.8 (2/246)	10.3 (3/29)	27.6 (8/29)	0 (0/29)
	Week 52	20.2 (49/243)	39.2 (96/245)		10.3 (3/29)	41.4 (12/29)	
IGA 0/1 response rate	Week 12	51.2 (125/244)	65.3 (160/245)	2.4 (6/246)	55.2 (16/29)	55.2 (16/29)	3.4 (1/29)
	Week 52	41.4 (101/244)	60.4 (148/245)		34.5 (10/29)	62.1 (18/29)	
IGA 0 response rate	Week 12	16.4 (40/244)	32.2 (79/245)	0.8 (2/246)	10.3 (3/29)	24.1 (7/29)	0 (0/29)
	Week 52	25.8 (63/244)	43.3 (106/245)		10.3 (3/29)	41.4 (12/29)	

% (n/N)

On the other hand, almost clear or clear skin (as evidenced by PASI 90/100 response and IGA 0/1 response) was achieved and was maintained until Week 52 in a certain number of patients in the secukinumab 150 mg group (Table 49). The PASI 75 response rate at Week 12 (71.6%) with secukinumab 150 mg in the multinational phase III study (A2302) was similar to those with the approved biological products [see "4.(iii).B.(5) Clinical positioning"]. Therefore, the dose of 150 mg should also be recommended.

As discussed above, 300 mg was selected as the usual dose and the dose of 150 mg may be acceptable for some patients, depending on their symptoms, as presented in the proposed dosage and administration statement.

In the multinational phase III study (A2302), the efficacy of secukinumab 300 mg tended to be greater than that of secukinumab 150 mg in the overall population while there were no significant differences in efficacy between secukinumab 150 mg and 300 mg in the Japanese subgroup. PMDA asked the applicant to discuss its causes and to provide a justification for the proposed usual dose of 300 mg in Japan.

The applicant explained as follows:
Because of a trend towards different body weight between the overall population and Japanese subgroup in Study A2302 (88.55 kg in the overall population, 74.4 kg in the Japanese subgroup), the effect of body weight on serum secukinumab concentrations and on the efficacy of secukinumab was evaluated.

As shown in Figure 10, trough serum secukinumab concentrations tended to be higher in patients with lower body weight than in patients with higher body weight in Study A2302.

Further, in Study A2302, trough serum secukinumab concentrations were classified into low level (≤22.5 μg/mL), intermediate level (>22.5 μg/mL and ≤38.0 μg/mL), and high level (>38.0 μg/mL) to analyze exposure-response for efficacy (PASI score). The percent changes from baseline in PASI score (mean ± SD) for low, intermediate, and high trough concentrations were −77.60 ± 21.47 (N = 119), −83.26 ± 19.79 (N = 81), and −92.87 ± 8.20 (N = 16), respectively, in the secukinumab 150 mg group and −77.34 ± 25.67 (N = 26), −89.00 ± 12.055 (N = 64), and −92.10 ± 13.36 (N = 129), respectively, in the secukinumab 300 mg group. The percent change from baseline in PASI score tended to increase with increasing trough concentration.

Furthermore, the effect of body weight on efficacy was analyzed using the pooled 12-week data from 4 placebo-controlled phase III studies. The relationship between body weight in 10 kg increments and the PASI 75/90/100 response rate was evaluated. As shown in Figure 11, there was a negative correlation between body weight and efficacy, and the efficacy of secukinumab 300 mg was greater than that of secukinumab 150 mg except for the body weight stratum of ≤60 kg.

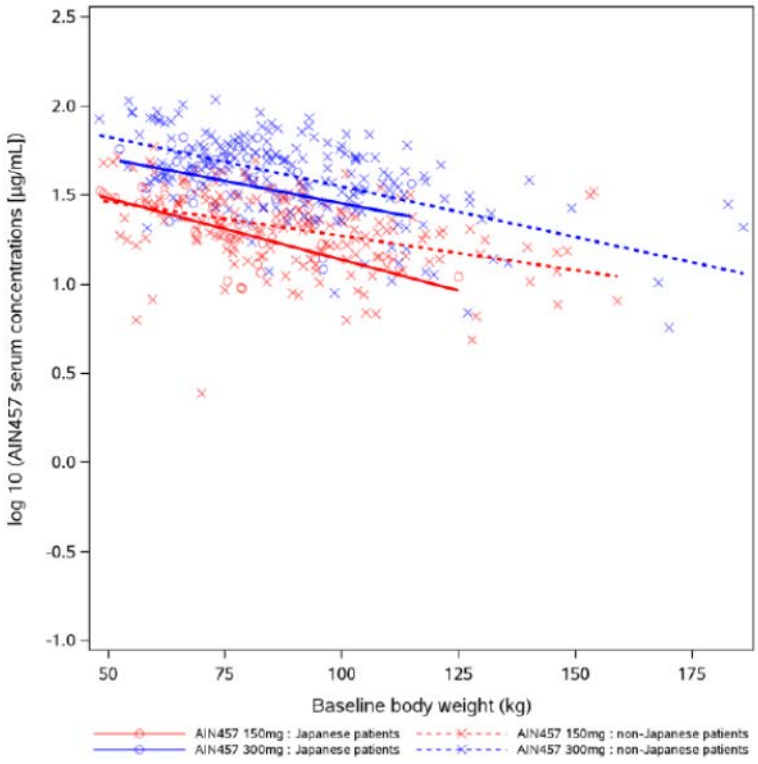


Figure 10. Serum secukinumab concentration at Week 12 by body weight (Study A2302)
Red, secukinumab 150 mg group; Blue, secukinumab 300 mg group; × and dotted line, non-Japanese patients; ○ and solid line, Japanese patients

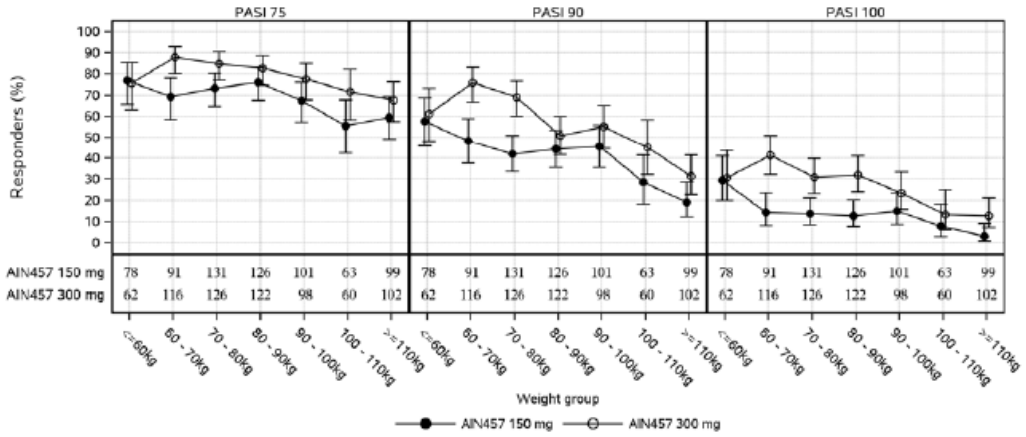


Figure 11. Body weight and PASI 75/90/100 response rate at Week 12 (Pooled data from Studies A2302, A2303, A2308, and A2309)

For the secukinumab 150 mg and 300 mg groups in the Japanese subgroup of Study A2302, the distribution of body weight was analyzed. The number of patients weighing ≤60 kg tended to be smaller in the secukinumab 300 mg group (2 of 29 subjects) than in the secukinumab 150 mg group (5 of 29 subjects). Because of the negative correlation seen between body weight and efficacy as mentioned earlier, patients with low body weight are expected to show high response rates. The relatively smaller number of patients in the secukinumab 300 mg group possibly contributed to insignificant differences in efficacy between secukinumab 150 mg and 300 mg in the Japanese subgroup. Moreover, efficacy at Week 12 was evaluated using a logistic regression model based on the pooled data from 4 placebo-controlled phase III studies and Study A2304 (a multinational study including Japanese patients). As a result, the odds ratio (150 mg/300 mg) adjusted for body weight was <1, showing greater efficacy with secukinumab 300 mg than with secukinumab 150 mg. The result also supported the efficacy of the 300 mg dose; secukinumab 300 mg would have been more effective than secukinumab 150 mg also in the Japanese subgroup as in the overall population in Study A2302, if there had been no imbalance in distribution of body weight between the secukinumab dose groups in the Japanese subgroup.

In addition, in the Japanese subgroup of Study A2302, the PASI 90 or 100 response rate representing clear or almost clear skin tended to be higher in the secukinumab 300 mg group than in the secukinumab 150 mg group. In view of the introduction of biological products, etc., the goal of the treatment for psoriasis is shifting from the achievement of PASI 75 response to the achievement of PASI 90 response both in and outside Japan (Torii H and Nakagawa H. *Jpn J Dermatol.* 2013;123:1935-1944, Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis, CHMP/EWP/2454/02, 2004). Taking account of these facts, the usual dose for Japanese patients with psoriasis should also be determined as 300 mg.

PMDA accepted the applicant's explanation and concluded that the proposed usual dose of 300 mg for Japanese patients with psoriasis is justified.

Given that multiple placebo-controlled phase III studies confirmed the superiority of secukinumab 150 mg over placebo and that a certain number of subjects achieved PASI 90 or 100 response with secukinumab 150 mg, the dose of 150 mg of secukinumab is also considered clinically significant and can be recommended.

However, the superiority of 300 mg to 150 mg in terms of efficacy was consistent in all subgroups of baseline characteristics of symptoms (severity of psoriasis, baseline PASI score, baseline IGA score) (Table 50). While the proposed package insert states that "a dose of 150 mg may be acceptable for some patients, depending on their symptoms," there seems to be little need of dose adjustment according to symptoms. On the other hand, the serum secukinumab concentrations and the efficacy of secukinumab tended to be higher in patients with lower body weight as compared to patients with higher body weight. PMDA asked the applicant to examine whether the 150 mg dose of secukinumab can be recommended, depending on body weight.

Table 50. PASI 75/90 response rates and IGA 0/1 response rates at Week 12 in subgroups
(Pooled data from Studies A2302, A2303, A2308, and A2309, Non-responder imputation)

			Secukinumab 150 mg (N = 692)	Secukinumab 300 mg (N = 691)	Placebo (N = 692)	Etanercept (N = 326)
Severity	Moderate	PASI 75 response rate	69.5 (139/200)	78.1 (157/201)	1.6 (3/193)	34.4 (31/90)
		PASI 90 response rate	30.5 (61/200)	53.7 (108/201)	0 (0/193)	8.9 (8/90)
		IGA 0/1 response rate	50.0 (100/200)	68.7 (138/201)	1.0 (2/193)	18.9 (17/90)
	Severe	PASI 75 response rate	69.1 (338/489)	80.0 (388/485)	5.2 (26/496)	47.6 (111/233)
		PASI 90 response rate	45.4 (222/489)	57.7 (280/485)	1.6 (8/496)	25.3 (59/233)
		IGA 0/1 response rate	52.0 (255/490)	63.5 (308/485)	2.6 (13/496)	30.5 (71/233)
Baseline PASI score	≤20	PASI 75 response rate	69.5 (255/367)	77.8 (274/352)	4.1 (15/364)	39.8 (64/161)
		PASI 90 response rate	37.1 (136/367)	56.0 (197/352)	0.8 (3/364)	14.9 (24/161)
		IGA 0/1 response rate	52.9 (194/367)	67.6 (238/352)	2.2 (8/364)	26.7 (43/161)
	>20	PASI 75 response rate	68.9 (222/322)	81.1 (271/334)	4.3 (14/325)	48.1 (78/162)
		PASI 90 response rate	45.7 (147/322)	57.2 (191/334)	1.5 (5/325)	26.5 (43/162)
		IGA 0/1 response rate	49.8 (161/323)	62.3 (208/334)	2.2 (7/325)	27.8 (45/162)
Baseline IGA score	3	PASI 75 response rate	71.2 (311/437)	81.3 (353/434)	4.5 (19/423)	40.7 (79/194)
		PASI 90 response rate	42.3 (185/437)	59.2 (257/434)	0.5 (2/423)	19.1 (37/194)
		IGA 0/1 response rate	55.3 (242/438)	69.6 (302/434)	2.4 (10/423)	27.8 (54/194)
	4	PASI 75 response rate	65.9 (166/252)	76.2 (192/252)	3.7 (10/267)	48.8 (63/129)
		PASI 90 response rate	38.9 (98/252)	52.0 (131/252)	2.2 (6/267)	23.3 (30/129)
		IGA 0/1 response rate	44.8 (113/252)	57.1 (144/252)	1.9 (5/267)	26.4 (34/129)

% (n/N)

The applicant explained as follows:

Based on the pooled data from 4 placebo-controlled phase III studies, the between-group differences for the PASI 75/90 response rates and IGA 0/1 response rates at Week 12 by body weight (in 10 kg increments) and their 95% confidence intervals were as shown in Figure 12. While the efficacy of secukinumab 300 mg tended to be greater than that of secukinumab 150 mg across all body weight subgroups of >60 kg, little between-group difference was observed in the subgroup of ≤60 kg and the benefits of secukinumab 300 mg were considered limited in patients with body weight ≤60 kg as compared to patients with body weight >60 kg.

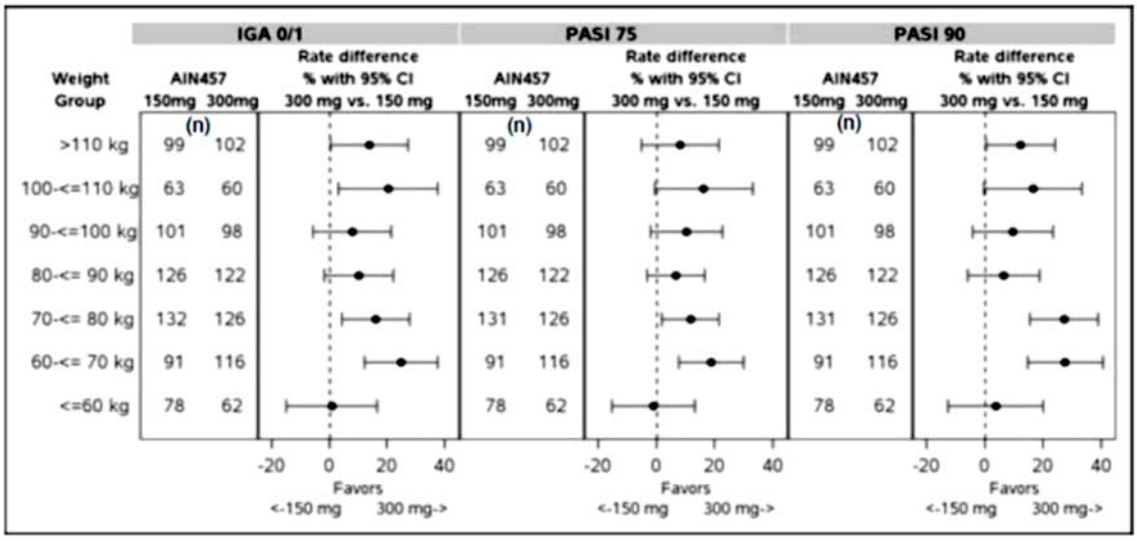


Figure 12. Differences between doses for IGA 0/1 response rate and PASI 75/90 response rate at Week 12 by body weight and their 95% confidence intervals
(Pooled data from Studies A2302, A2303, A2308, and A2309, Non-responder imputation)

Based on the pooled data from Studies A2302 and A2303, time to 75% decrease from baseline in the mean PASI score in the subgroup of >60 kg was 9.5 weeks with secukinumab 150 mg and was 6.7 weeks with secukinumab 300 mg, showing a decrease approximately 3 weeks earlier in the secukinumab 300 mg group. In the subgroup of ≤60 kg, time to 75% decrease from baseline in the mean PASI score was 6.2 weeks with secukinumab 150 mg and was 5.0 weeks with secukinumab 300 mg, showing no significant differences between the dose groups. These data support the possibility of the use of secukinumab 150 mg in patients weighing ≤60 kg. In the body weight distribution data in Japanese patients with psoriasis, patients weighing ≤60 kg were estimated to account for 16% to 27% of the overall population of Japanese patients with psoriasis based on the results of Studies A2302 and A2304 and a post-marketing surveillance study covering all adalimumab-treated patients[46],

As a conclusion, the usual dose of secukinumab should be 300 mg, and a dose of 150 mg may be acceptable for patients with low body weight, roughly ≤60 kg.

PMDA considers as follows:
Secukinumab achieved clinically significant responses at the dose of 150 mg as well. The relationship between body weight and serum secukinumab concentration/efficacy was suggested, though in the post-hoc analysis. No significant differences were suggested in efficacy between secukinumab 150 mg and secukinumab 300 mg in patients weighing ≤60 kg. Taking account of these findings, selecting 300 mg as the usual dose of secukinumab and allowing the use of 150 mg in patients with low body weight are reasonable.

Accordingly, the proposed dosage and administration statement should be modified as shown below. The "Precautions for Dosage and Administration" section should note that the use of the dose of 150 mg should be

[46] Eisai Co., Ltd. (2012) Proper use information Vol. 3 (psoriasis vulgaris and psoriatic arthritis) Humira Pre-filled Syringe 40 mg/0.8 mL for subcutaneous injection.

considered for patients with low body weight, ≤60 kg. The above conclusions by PMDA will be discussed at the Expert Discussion.

[Dosage and administration]
The usual adult dosage is 300 mg of Secukinumab (Genetical Recombination) by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. A dose of 150 mg may be acceptable for some patients, depending on their body weight.

(The underlined parts are the changes.)

4.(iii).B.(4) Indications

PMDA concluded as follows:

Approved biological products for the treatment of psoriasis have the potential risk of serious infections, etc. which may be fatal, and this holds true for secukinumab. The long-term safety of secukinumab including the risk of malignancy has not fully been elucidated. Taking account of these facts, secukinumab should be indicated for patients who have had an inadequate response or intolerance to standard therapies for psoriasis, i.e., phototherapy or systemic therapy (e.g., with cyclosporine or etretinate). The proposed indication (Treatment of the following diseases in patients who have had an inadequate response to conventional therapy: Psoriasis vulgaris and psoriatic arthritis) is the same as that for the approved biological products and is acceptable.

4.(iii).B.(5) Clinical positioning

4.(iii).B.(5).1) Positioning of secukinumab relative to the approved biological products

The applicant explained the positioning of secukinumab relative to the approved biological products in the treatment of psoriasis as follows:

The efficacy results from the pivotal clinical studies of secukinumab and the approved biological products (adalimumab, infliximab, and ustekinumab) were as shown in Table 51. Since comparisons were made among different studies, the results of the comparisons should be interpreted carefully. For the primary efficacy endpoint, secukinumab 150 mg was considered comparable or slightly superior to the approved biologics, and secukinumab 300 mg was considered superior to the approved biological products. Similarly, the efficacy of secukinumab in reducing joint symptoms was compared with that of the approved biological products based on the data from foreign clinical studies. The ACR20 response rates at the time of primary endpoint assessment were 51.5% with secukinumab 75 mg and 55.9% with secukinumab 150 mg (Study F2306, at Week 12), 58.0% with infliximab (at Week 14), 58% with adalimumab (at Week 12), and 42.1% with ustekinumab (at Week 12).[47] The results indicated that the efficacy of secukinumab in reducing joint symptoms is almost comparable to that of other biological products. The safety analysis revealed that the incidences of serious infections and infestations, MACE, cardiovascular/cerebrovascular events, malignancies, hypersensitivity, immune or administration site reactions, autoimmune disease, inflammatory bowel disease, and neutropenia were similar between secukinumab and an active control, etanercept. There was no increase in the risk of any specific

[47] Patients with psoriatic arthritis were enrolled into clinical studies of secukinumab or ustekinumab, regardless of previous anti-TNFα therapy status, while patients not previously exposed to anti-TNFα therapy were enrolled into clinical studies of infliximab or adalimumab.

adverse event [see “4.(iii).B.(2) Safety”]. The incidences of major adverse events in clinical studies with secukinumab were compared with those with the approved biological products (Table 52), which also raised no safety concerns that are characteristic of secukinumab.

Taking account of the above-mentioned efficacy, safety, and convenience for users (e.g. route of administration, dosing intervals), secukinumab can become a first-line biological product for the treatment of psoriasis.

According to the pooled 12-week data from placebo-controlled phase III studies, the PASI 75 response rates in the subgroup of patients previously exposed to biological therapy (patients who had responded to or who had failed to respond to previous biological therapy) were as shown in Table 53. The data suggested that secukinumab is expected to be effective also in those who have failed previous biological therapy. In the safety analysis for secukinumab used in patients in whom the use of approved biological products were difficult for safety reasons, the incidences of adverse events were 50% (9 of 18 subjects) in the secukinumab 150 mg group, 52.6% (10 of 19 subjects) in the secukinumab 300 mg group, 77.8% (7 of 9 subjects) in the placebo group, and 0% (0 of 1 subject) in the etanercept group. Although a limited number of subjects were assessed, there were no significant differences in the incidence or nature of events between the secukinumab and placebo groups. Thus, secukinumab can also be an option for patients with an inadequate response to or intolerance to the approved biological products, etc. However, as there are no sufficient data from patients who are replacing a conventional biological product with secukinumab, information on the safety and efficacy of secukinumab in these patients will be collected via post-marketing surveillance, etc.

Table 51. Comparison of the efficacy of secukinumab vs. other biological products in patients with psoriasis

	Secukinumab	Adalimumab	Infliximab	Ustekinumab
Study ID	Multinational study (A2302)	Japanese clinical study (M04-688)	Japanese clinical study (TA-650-15)	Japanese clinical study
Dosing regimen	150 or 300 mg administered subcutaneously at Weeks 0, 1, 2, 3, 4, and 8	80 mg administered subcutaneously at Week 0 followed by 40 mg at Weeks 2, 4, and 6	5 mg/kg administered intravenously at Weeks 0, 2, and 6	45 mg administered subcutaneously at Weeks 0 and 4
Primary endpoint	PASI 75 response rate at Week 12	PASI 75 response rate at Week 16	PASI 75 response rate at Week 10	PASI 75 response rate at Week 12
PASI 75 response rate with the proposed or approved dosing regimen	150 mg group: 71.6% (174/243) 300 mg group: 81.6% (200/245) Placebo group: 4.5% (11/246)	62.8% (27/43) Placebo group: 4.3% (2/46)	68.6% (24/35) Placebo group: 0% (0/19)	59.4% (38/64) Placebo group: 6.5% (2/31)

Table 52. Comparison of the safety of secukinumab vs. other biological products in patients with psoriasis (multinational and foreign clinical studies)

	Secukinumab 150 mg (N = 1395)	Secukinumab 300 mg (N = 1410)	Adalimumab (N = 1696)	Infliximab (N = 1564)	Ustekinumab (N = 2266)
Any adverse event	1066 (76.4)	1091 (77.4)	1300 (76.7)	1371 (87.7)	1676 (74.0)
Serious infections and infestations	12 (0.9)	16 (1.1)	21 (1.2)	26 (1.7)	15 (0.7)
Candida infection	21 (1.5)	41 (2.9)	—	—	—
Tuberculosis	1 (<0.1)	0	3 (0.2)	2 (0.1)	0
Cardiac disorders	46 (3.3)	46 (3.3)	—	54 (3.5)	35 (1.5)
Vascular disorders	91 (6.5)	88 (6.2)	—	189 (12.1)	89 (3.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	47 (3.4)	42 (3.0)	22 (1.3)	46 (2.9)	45 (2.0)
General disorders and administration site conditions	158 (11.3)	164 (11.6)	—	465 (29.7)	268 (11.8)
Immune system disorders	18 (1.3)	16 (1.1)	—	60 (3.8)	24 (1.1)
Hypersensitivity	115 (8.2)	132 (9.4)	—	48 (3.1)	5 (0.2)
Colitis ulcerative	2 (0.1)	2 (0.1)	—	0	1 (<0.1)
Crohn's disease	2 (0.1)	0	—	0	0
Neutropenia	15 (1.1)	16 (1.1)	—	16 (1.0)	0

n (%), — unknown/unavailable

Table 53. PASI 75 response rate at Week 12 in patients who were previously exposed to and failed to respond to biological therapy and those who were previously exposed to and not failed to respond to biological therapy
(Pooled data from Studies A2302, A2303, A2308, and A2309, Non-responder imputation)

	Secukinumab 150 mg	Secukinumab 300 mg	Placebo	Etanercept
Previously exposed to biological therapy	60.0 (96/160)	74.0 (108/146)	2.7 (4/147)	53.3 (24/45)
Previously exposed to and failed to respond to biological therapy	47.8 (33/69)	66.0 (33/50)	7.1 (4/56)	37.5 (6/16)
Previously exposed to and not failed to respond to biological therapy	69.2 (63/91)	78.1 (75/96)	0 (0/91)	62.1 (18/29)

% (n/N)

PMDA considers as follows:

No clinical studies have been conducted in Japan to directly compare the efficacy of secukinumab with that of other biological products indicated for the treatment of psoriasis. Limited clinical experience with secukinumab precludes exact comparisons of safety profiles between secukinumab and approved biological products at present, and thus secukinumab should be considered as one of biological products for the treatment of psoriasis for now. In future, the clinical positioning of secukinumab will be discussed at relevant academic societies, etc., based on the available clinical study data as well as the results of a post-marketing surveillance study and reports from studies conducted properly in and outside Japan. Secukinumab has a different mechanism of action from that of the approved biological products. Although available clinical study data indicate the potential usefulness of secukinumab also in patients who have an inadequate response to or intolerance to the approved biological products, such data are limited. Therefore, information on patients who are replacing a conventional biological product with secukinumab should be gathered via post-marketing surveillance, etc., and obtained information should be offered to healthcare professionals in clinical practice appropriately.

4.(iii).B.(5).2) Concomitant use with existing therapy

PMDA considers as follows:

Although it is envisaged that secukinumab may be used in combination with systemic therapy with drugs such as cyclosporine and etretinate, phototherapy, or topical treatments for refractory psoriatic skin lesions, etc., no

sufficient data on these combinations have been obtained from clinical studies of secukinumab. Especially, when secukinumab is used in combination with immunosuppressive systemic therapy, the possibility of developing infections or malignancy due to enhanced immunosuppression cannot be ruled out. When secukinumab is concomitantly used with phototherapy, the possibility of an increased risk of skin cancer cannot be excluded either. Thus, the package insert, etc. should highlight that the safety of secukinumab in combination with immunosuppressants or phototherapy has not been established, so that the risks and benefits of such combination therapy will be determined after consideration of the safety of each therapy.

The combination use of different biological products is reported to increase the incidence of serious infections in patients with rheumatoid arthritis. Despite no specific evidence, the use of secukinumab in combination with other biological products should be avoided. Likewise, adequate caution should be exercised against the possible serious infections, etc. when a conventional biological product is replaced with secukinumab, and precautionary statements about such combination use should also be included in the package insert, etc. Furthermore, the actual use of secukinumab in combination with systemic therapy, phototherapy, or topical therapy (proportions, patient characteristics, durations of concomitant use, etc.), the safety and efficacy of the concomitant use, the replacement of conventional biological products with secukinumab (proportions, patient characteristics, washout periods, etc.), and the safety and efficacy of secukinumab replacing conventional biological products, etc., should also be investigated carefully in the postmarketing surveillance, etc., and obtained information should be offered to healthcare professionals in clinical practice appropriately.

4.(iii).B.(6) Self-administration

The applicant explained the efficacy and safety of self-administered secukinumab based on the data from the Japanese subgroups of multinational phase III extension studies (A2302E1, A2304E1) as follows:

Of 1146 subjects who entered the extension study (A2302E1), 70 subjects were Japanese. Of the Japanese subjects, 16 self-injected the study drug. Of 675 subjects who entered the other extension study (A2304E1), 51 subjects were Japanese. Of the Japanese subjects, 10 self-injected the study drug.

The PASI 75/90/100 response rates in the secukinumab 150 mg and 300 mg groups after the start of self-administration in the Japanese subgroups of Studies A2302E1 and A2304E1 were as shown in Table 54. The results indicate that the efficacy of secukinumab was maintained even after the start of self-administration.

Table 54. PASI 75/90/100 response rates up to 16 weeks after the start of self-administration[a)] in Japanese subgroups (A2302E1, A2304E1)

		Study A2302E1		Study A2304E1	
		Secukinumab 150 mg	Secukinumab 300 mg	Secukinumab 150 mg	Secukinumab 300 mg
Week 52 (before the start of self-administration)	PASI 75	100 (8/8)	100 (4/4)	66.7 (2/3)	100 (2/2)
	PASI 90	50.0 (4/8)	100 (4/4)	33.3 (1/3)	100 (2/2)
	PASI 100	0	75.0 (3/4)	0	50.0 (1/2)
Week 56	PASI 75	87.5 (7/8)	100 (4/4)	66.7 (2/3)	100 (2/2)
	PASI 90	37.5 (3/8)	100 (4/4)	33.3 (1/3)	100 (2/2)
	PASI 100	0	50.0 (2/4)	0	0
Week 60	PASI 75	87.5 (7/8)	100 (4/4)	66.7 (2/3)	100 (2/2)
	PASI 90	50.0 (4/8)	100 (4/4)	33.3 (1/3)	100 (2/2)
	PASI 100	0	50.0 (2/4)	0	100 (2/2)
Week 64	PASI 75	87.5 (7/8)	100 (4/4)	66.7 (2/3)	100 (2/2)
	PASI 90	50.0 (4/8)	50.0 (2/4)	33.3 (1/3)	100 (2/2)
	PASI 100	12.5 (1/8)	50.0 (2/4)	0	50.0 (1/2)
Week 68	PASI 75	87.5 (7/8)	100 (4/4)	66.7 (2/3)	100 (2/2)
	PASI 90	50.0 (4/8)	100 (4/4)	33.3 (1/3)	100 (2/2)
	PASI 100	12.5 (1/8)	50.0 (2/4)	0	50.0 (1/2)

% (No. of responders/No. of subjects assessed at each time point)
a) Subjects who performed at least one self-injection.

The incidences of overall adverse events, immune or administration site reactions, and hypersensitivity by mode of administration (self-injection or injection performed by healthcare providers) in the Japanese subgroups of Studies A2302E1 and A2304E1 were as shown in Table 55 and Table 56, respectively.

Although the incidence of overall adverse events tended to be higher in patients who performed self-injection as compared to patients who received injections by healthcare providers, the adverse events noted in subjects with self-injection were all mild to moderate in severity. There was no trend towards higher incidences of immune or administration site reactions and hypersensitivity in patients who performed self-injection as compared to patients who received injections by healthcare providers. Thus, there were no safety concerns associated with self-injection.

Table 55. Incidences of adverse events by mode of administration in a Japanese subgroup (Study A2302E1)

	Self-injection (N = 16)			Injection by healthcare providers (N = 54)		
	Secukinumab 150 mg (N = 9)	Secukinumab 300 mg (N = 4)	Placebo (N = 4)	Secukinumab 150 mg (N = 20)	Secukinumab 300 mg (N = 24)	Placebo (N = 16)
All adverse events	6 (66.7)	2 (50.0)	2 (50.0)	9 (45.0)	10 (41.7)	6 (37.5)
Immune or administration site reactions	1 (11.1)	0	0	0	2 (8.3)	1 (6.3)
Hypersensitivity	1 (11.1)	0	0	0	1 (4.2)	0

n (%)

Table 56. Incidences of adverse events by mode of administration in Japanese subgroup (Study A2304E1)

	Self-injection (N = 10)		Injection by healthcare providers (N = 41)	
	Secukinumab 150 mg (N = 5)	Secukinumab 300 mg (N = 5)	Secukinumab 150 mg (N = 15)	Secukinumab 300 mg (N = 26)
All adverse events	2 (40.0)	4 (80.0)	10 (66.7)	18 (69.2)
Immune or administration site reactions	0	1 (20.0)	1 (6.7)	4 (15.4)
Hypersensitivity	0	1 (20.0)	0	5 (19.2)

n (%)

As shown in the above, the safety and efficacy results of self-administration in the Japanese subgroups of Studies A2302E1 and A2304E1 were consistent with those from foreign phase III studies in which all doses of the study drug were self-administered during both the induction and maintenance periods (Studies A2308,

A2309). Thus, there should be no particular problems with the efficacy and safety of self-administered secukinumab in Japanese patients with psoriasis.

PMDA asked the applicant to explain how the self-administration of secukinumab would be explained to healthcare providers and what training would be provided to patients after the market launch of secukinumab.

The applicant explained as follows:
The self-injection of secukinumab may be started only with patients who have been informed of the risks of self-injection and secukinumab itself and have learned the method of self-injection. The eligible patients must understand the risks and need to be capable of taking all steps to administer secukinumab without problems. Self-administration should be suspended if the patient fails to perform self-injection properly or is not confident in performing self-injection. The patient needs to be retrained for self-injection, or subsequent injections should be continued by healthcare providers.

The applicant plans to develop explanatory materials including a guidance booklet for healthcare providers on how to give instructions on self-injection to patients, and another booklet on self-injection for patients, etc. Information pertaining to self-injection of secukinumab will be posted on the website.

PMDA considers as follows:
No particular problems with the safety and efficacy of self-injected secukinumab have been suggested up to now. However, information on the safety and efficacy of self-injected secukinumab in Japanese patients with psoriasis is limited, therefore investigation must be continued via postmarketing surveillance, etc. A management scheme must be established for patients starting self-injection by using examples from the experiences with similar drugs in Japan.

4.(iii).B.(7) Post-marketing safety measures
PMDA considers as follows:
The safety profile of secukinumab is not substantially different from those of the approved biological products, and secukinumab has so far posed no safety concerns that are more significant than those of the approved biological products. However, there is limited clinical experience with secukinumab in long-term use. As with the approved biological products, further information should be collected on serious infections, malignancy, etc. which are common risks to immunosuppressive drugs. A long-term post-marketing surveillance study, etc. should be conducted to collect relevant information on such risks.

It is important that secukinumab is used under the supervision of a physician with adequate knowledge and experience in the treatment of psoriasis and that adverse drug reactions such as serious infections are managed in cooperation with other departments/medical institutions. It must be ensured via post-marketing surveillance, etc. that secukinumab is used in cooperation with other departments/medical institutions also in routine clinical practice.

In order to promote the proper use of secukinumab, relevant information should be provided to healthcare providers and patients in an appropriate and timely manner. The applicant should develop informative materials for healthcare providers including physicians and a guidance booklet for patients, etc. that explain the safety of secukinumab in a proper and comprehensive manner. Updated post-marketing safety information should be made available on the applicant's website, etc.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

A GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1-4, 5.3.5.1-5, 5.3.5.2-1). PMDA concluded that since the clinical studies as a whole were conducted in compliance with GCP, there should be no problem with proceeding to a regulatory review based on the submitted application documents. The following issues were identified at some study sites and the heads of the relevant medical institutions were notified of these issues as findings requiring improvement. However, the issues did not affect the outcome of the overall assessment of the studies significantly

[Findings requiring improvement]

Study sites

- The head of a medical institution failed to seek the opinions of the institutional review board at least once a year, concerning the appropriateness of continuing the clinical study at the site.
- Flaws in a contract for outsourcing a part of study-related activities.

IV. Overall Evaluation

Based on the submitted data, the efficacy of secukinumab (Cosentyx) in the treatment of psoriasis vulgaris and psoriatic arthritis in patients who have had an inadequate response to conventional therapy has been demonstrated, and its safety is acceptable in view of its observed benefits. Cosentyx is a biological product with a novel mechanism of action and thus provides a new therapeutic option, which is of clinical significance. The description of the proposed dosage and administration needs to be further discussed. From a safety view point, the occurrence of adverse events, e.g., serious infections, during short-term and long-term treatment should be investigated via post-marketing surveillance, etc.

The application for Cosentyx may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

November 14, 2014

I. Product Submitted for Registration

[Brand name]	(a) Cosentyx for Subcutaneous Injection 150 mg Syringe
	(b) Cosentyx for Subcutaneous Injection 150 mg
[Non-proprietary name]	Secukinumab (Genetical Recombination)
[Name of applicant]	Novartis Pharma K.K.
[Date of application]	December 26, 2013

II. Content of the Review

The outlines of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are given in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

PMDA's conclusions described in the Review Report (1) were supported at the Expert Discussion. PMDA conducted an additional review of the following two points and took necessary actions.

(1) Dosage and administration

PMDA's conclusions on the dosage and administration for secukinumab as described in the Review Report (1) were supported at the Expert Discussion. The expert advisors commented that 300 mg is appropriate as usual dose of secukinumab, and that the use of 150 mg of secukinumab should be allowed in patients with low body weight, roughly ≤60 kg, and that it is important that the package insert specifies the body weight cut-off point.

In response to the comments from the Expert Discussion, PMDA instructed the applicant to modify the description of dosage and administration as shown below and include a precautionary statement in the "Precautions for Dosage and Administration" section of the package insert as written below. The applicant responded appropriately.

[Dosage and administration]
The usual adult dosage is 300 mg of Secukinumab (Genetical Recombination) by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. A dose of 150 mg may be acceptable for some patients, depending on their body weight.

[Precautions for dosage and administration]
A dose of 150 mg should be considered for patients with body weight ≤60 kg.

(2) Draft risk management plan

PMDA's conclusions on post-marketing safety measures described in the Review Report (1) were supported at the Expert Discussion. The expert advisors pointed out that adequate safety measures should be taken against serious infections including tuberculosis associated with the use of secukinumab as with the approved immunosuppressive biological products, and that the occurrence of adverse events including serious infections and malignancy during long-term treatment with secukinumab should be further investigated.

Based on the Review Report (1) "4.(iii).B.(7) Post-marketing safety measures" and the comments raised in the Expert Discussion, PMDA concluded that the safety and efficacy specification listed in Table 57 should be included in the current draft risk management plan, and that additional pharmacovigilance activities and risk minimization activities listed in Table 58 should be carried out.

Table 57. Safety and efficacy specification of the draft risk management plan

Safety specification		
Important identified risks	Important potential risks	Important missing information
・Serious infections ・Neutropenia ・Hypersensitivity reactions	・Malignancy ・Cardiovascular/cerebrovascular events ・Tuberculosis ・Immunogenicity ・Inflammatory bowel disease	・None
Efficacy specification		
・Confirm efficacy in routine clinical settings.		

Table 58. Summary of additional pharmacovigilance activities and risk minimization activities in the draft risk management plan

Additional pharmacovigilance activities	Additional risk minimization activities
・Early Post-marketing Phase Vigilance (EPPV) ・Specified drug use-results survey ・Post-marketing clinical studies[a)]	・Develop a proper-use guidebook to be distributed to healthcare providers. ・Develop informative materials for self-injection to be distributed to healthcare providers and patients ・Ensure that information on the proper use is provided before the delivery of the product. ・EPPV

a) After secukinumab is approved, Studies A2302E1 and A2304E1 (ongoing) will be reclassified as post-marketing clinical studies and the long-term safety of secukinumab up to 4 years will be assessed.

Accordingly, PMDA instructed the applicant to conduct a post-marketing surveillance study to investigate the above issues.

The applicant explained as follows:

As shown in Table 59, a specified drug use-results survey involving patients with psoriasis vulgaris or psoriatic arthritis who have had an inadequate response to conventional therapy (a total of 900 patients for the safety analysis population, an observation period of 52 weeks) is to be conducted to evaluate the safety and efficacy of secukinumab in routine clinical settings. The identified priority items were serious infections, tuberculosis, neutropenia, fungal infection, hypersensitivity reactions, inflammatory bowel disease, malignancy, and cardiovascular/cerebrovascular adverse events. After the completion of the observation period, patients will

be followed for the incidence of serious infections and malignancy until 3 years after the start of treatment so that the long-term safety of secukinumab is further investigated.

Table 59. Outline of the draft specified drug use-results survey plan

Objective	To confirm the long-term safety and efficacy of secukinumab in routine clinical settings.
Survey method	Central registry system
Patients to be surveyed	Patients with psoriasis vulgaris or psoriatic arthritis who have had an inadequate response to conventional therapy
Observation period	52 weeks (after the completion of the observation period, patients will be followed until 3 years after the start of treatment, regardless of whether they continue or discontinue treatment.)
Planned sample size	900
Priority items	・Serious infections ・Tuberculosis ・Neutropenia ・Fungal infection ・Hypersensitivity reactions ・Inflammatory bowel disease ・Malignancy ・Cardiovascular/cerebrovascular events
Main information to be collected	・Patient characteristics ・Medical history ・Use of secukinumab ・Use of concomitant medications/therapies ・Clinical laboratory tests ・Efficacy assessment ・Adverse events

PMDA considers that the survey results should be provided appropriately to healthcare professionals in clinical practice.

III. Overall Evaluation

As a result of the above review, PMDA has concluded that Cosentyx (secukinumab) may be approved after modifying “Indications” and “Dosage and Administration” as shown below, with the following conditions. As secukinumab is a drug with a new active ingredient, the re-examination period is 8 years, and the drug substance and the drug product are both classified as powerful drugs and the product is classified as a biological product.

[Indications] Treatment of the following diseases in patients who have had an inadequate response to conventional therapy:
Psoriasis vulgaris and psoriatic arthritis

[Dosage and administration] The usual adult dosage is 300 mg of Secukinumab (Genetical Recombination) by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. A dose of 150 mg may be acceptable for some patients, depending on their body weight.

[Conditions for approval] The applicant is required to:

1. Develop a risk management plan for the product and implement it appropriately.
2. Conduct an appropriate post-marketing surveillance study to fully evaluate the long-term safety and efficacy of the product, including the occurrence of infections, etc.