Report on the Deliberation Results

June 1, 2016

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

Brand Name	Taltz 80 mg Syringe for SC Injection
	Taltz 80 mg Auto-Injector for SC Injection
Non-proprietary Name	Ixekizumab (Genetical Recombination) (JAN*)
Applicant	Eli Lilly Japan K.K.
Date of Application	July 28, 2015

Results of Deliberation
In its meeting held on May 30, 2016, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented 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. The product is classified as a biological product.

Condition of Approval
The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

May 17, 2016
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency.

Brand Name	Taltz 80 mg Syringe for SC Injection Taltz 80 mg Auto-Injector for SC Injection
Non-proprietary Name	Ixekizumab (Genetical Recombination)
Applicant	Eli Lilly Japan K.K.
Date of Application	July 28, 2015
Dosage Form/Strength	Solution for injection in a syringe: Each syringe contains 80 mg of Ixekizumab (Genetical Recombination).
Application Classification	Prescription drug (1) Drug with a new active ingredient
Definition	Ixekizumab is a recombinant humanized monoclonal antibody composed of complementarity-determining regions derived from mouse anti-human interleukin-17 monoclonal antibody and framework regions and constant regions derived from human IgG4, and Ser residue at position 227 is substituted by Pro residue and C-terminus Lys residue is deleted in the H -chains. Ixekizumab is produced in Chinese hamster ovary cells. Ixekizumab is a glycoprotein (molecular weight: ca.149,000) composed of 2 H-chains (γ4-chains) consisting of 445 amino acid residues each and 2 L-chains (κ-chains) consisting of 219 amino acid residues each.

Structure
Amino acid sequence:

L chain

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DIVMTQTPLS LSVTPGQPAS ISCRSSRSLV HSRGNTYLHW YLQKPGQSPQ
LLIYKVSNRF IGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCSQSTHLP
FTFGQGTKLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE
VTHQGLSSPV TKSFNRGEC
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H chain

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QVQLVQSGAE VKKPGSSVKV SCKASGYSFT DYHIHWVRQA PGQGLEWMGV
INPMYGTTDY NQRFKGRVTI TADESTSTAY MELSSLRSED TAVYYCARYD
YFTGTGVYWG QGTLVTVSSA STKGPSVFPL APCSRSTSES TAALGCLVKD
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTKTY
TCNVDHKPSN TKVDKRVESK YGPPCPPCPA PEFLGGPSVF LFPPKPKDTL
MISRTPEVTC VVVDVSQEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTYR
VVSVLTVLHQ DWLNGKEYKC KVSNKGLPSS IEKTISKAKG QPREPQVYTL
PPSQEEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD
GSFFLYSRLT VDKSRWQEGN VFSCSVMHEA LHNHYTQKSL SLSLG
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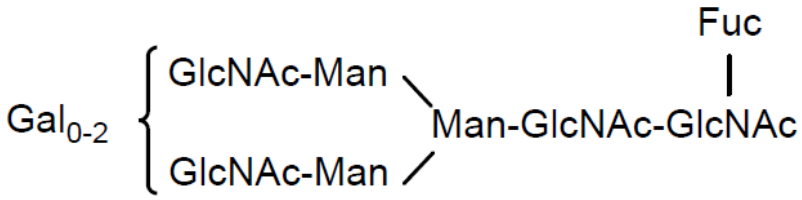
Pyroglutamic acid (partial): Q1 in H chain
Glycosylation site: N296 in H chain
Partial processing: G445 in H chain
Interchain disulfide bonds: C219 in L chain - C133 in H chain, C225 in H chain - C225 in H chain, C228 in H chain - C228 in H chain
Intrachain disulfide bonds: Shown in solid line

Proposed structure of main glycan



Molecular formula: (L chain) $C_{1064}H_{1661}N_{291}O_{336}S_6$
(H chain) $C_{2182}H_{3349}N_{573}O_{678}S_{17}$
Molecular weight: 146,190.31 (4-stranded DNA structure)

Items Warranting Special Mention None
Reviewing Office Office of New Drug IV

Results of Review
On the basis of the data submitted, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the product has efficacy in the treatment of patients with psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis who have had an inadequate response to conventional therapies, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following conditions. Because the product potentially causes serious events such as infections, patients should be carefully monitored before use of the product to assess its risk-benefit balance. In addition, the applicant should conduct a post-marketing surveillance study that allows monitoring of serious infections, malignant tumors, etc., and should provide information to healthcare professionals and patients whenever such information becomes available.

Indication
Treatment of the following diseases in patients who have had an inadequate response to conventional therapies:
Psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis

Dosage and Administration
The usual adult dosage is 160 mg of Ixekizumab (Genetical Recombination) administered by subcutaneous injection at Week 0, followed by 80 mg once every 2 weeks from Week 2 to Week 12, and then 80 mg once every 4 weeks.

Condition for Approval
The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

April 6, 2016

The following is an outline of the data submitted by the applicant and the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Taltz 80 mg Syringe for SC Injection Taltz 80 mg Auto-Injector for SC Injection
Non-proprietary Name	Ixekizumab (Genetical Recombination)
Applicant	Eli Lilly Japan K.K.
Date of application	July 28, 2015
Dosage Form/Strength	Solution for injection in a syringe: Each syringe contains 80 mg of Ixekizumab (Genetical Recombination).
Proposed Indication	Moderate to severe psoriasis vulgaris, pustular psoriasis, erythrodermic psoriasis, and psoriatic arthritis
Proposed Dosage and Administration	The usual adult dosage is 160 mg of Ixekizumab (Genetical Recombination) administered by subcutaneous injection at Week 0, followed by 80 mg every 2 weeks from Week 2 to Week 12, and then 80 mg every 4 weeks.

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List of Abbreviations

ACR20 response rate, ACR50 response rate, ACR70 response rate	American College of Rheumatology 20, 50, 70 responder index
ADA	Anti-drug antibody
Adalimumab	Adalimumab (Genetical Recombination) (brand name: Humira 20 mg for S.C. Injection Syringe 0.4 mL, Humira 40 mg for S.C. Injection Syringe 0.8 mL)
ALT	Alanine aminotransferase
APS	All psoriasis Ixekizumab exposures integrated analysis set
AST	Aspartate transaminase
AUC	Area under plasma or serum concentration-time curve
bDMARDs	Biologic DMARDs
CASPAR	Classification criteria for psoriatic arthritis
CE-SDS	Capillary electrophoresis sodium dodecyl sulfate
CHO cells	Chinese hamster ovary cells
CI	Confidence interval
CL	Total body clearance
C_{max}	Maximum concentration of drug in serum
DMARDs	Disease-modifying antirheumatic drugs
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
Etanercept	Etanercept (Genetical Recombination) (brand name: Enbrel 10 mg for S.C. Injection, Enbrel 25 mg for S.C. Injection, Enbrel 25 mg Syringe 0.5 mL for S.C. Injection, Enbrel 50 mg Syringe 1.0 mL for S.C. Injection, Enbrel 50 mg Pen 1.0 mL for S.C. Injection)
Fab	Fragment, antigen binding
FAS	Full analysis set
Fc	Fragment, crystallizable
Glu-C	Endoproteinase Glu-C
IC_{50}	50% inhibitory concentration
IgG	Immunoglobulin G
IL	Interleukin
IL-17A/F	Heterodimer of IL-17A and IL-17F
Infliximab	Infliximab (Genetical Recombination) (brand name: Remicade for I.V. Infusion 100)
Ixekizumab	Ixekizumab (Genetical Recombination)
J-APS	All Japanese psoriasis Ixekizumab exposures integrated analysis set
K_D	Dissociation constant
KLH	Keyhole limpet hemocyanin
LC-MS	Liquid chromatography-mass spectrometry
LC-MS/MS	Liquid chromatography tandem-mass spectrometry
LOCF	Last observation carried forward
Lys-C	Endoproteinase Lys-C
MACE	Major adverse cardiovascular events
MCB	Master cell bank
MPP	Psoriasis Maintenance Integrated Analysis Set
mITT	Modified intent-to-treat
mTSS	van der Heijde modified Total Sharp Score
NK cells	Natural killer cells
NMSC	Non-melanoma skin cancers
NRI	Non-responder imputation
NSAIDs	Non-steroidal anti-inflammatory drugs

PAC	Psoriasis placebo- and active-controlled integrated analysis set
PASI	Psoriasis area and severity index
PASI 75 response rate, PASI 90 response rate, PASI 100 response rate	Percentage of patients who achieved ≥75%, ≥90%, or 100% improvement in the PASI score from baseline
PNGase F	Peptide-N-glycosidase F
PPC	Primary psoriasis placebo-controlled integrated analysis set
Q12W	Every 12 weeks
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QbD	Quality by design
QIDS-SR16	Quick inventory of depressive symptomatology 16 items self-report
RH	Relative humidity
Secukinumab	Secukinumab (Genetical Recombination) (brand name: Cosentyx for Subcutaneous Injection 150 mg, Cosentyx for Subcutaneous Injection 150 mg Syringe)
Study RHAL	Study I1F-JE-RHAL
Study RHAM	Study I1F-JE-RHAM
Study RHAT	Study I1F-JE-RHAT
Study RHAG	Study I1F-MC-RHAG
Study RHAK	Study I1F-MC-RHAK
Study RHAJ	Study I1F-MC-RHAJ
Study RHAP	Study I1F-MC-RHAP
Study RHAZ	Study I1F-MC-RHAZ
Study RHBA	Study I1F-MC-RHBA
Study RHBC	Study I1F-MC-RHBC
Study RHBL	Study I1F-MC-RHBL
sPGA	Static physician global assessment
sPGA (0 or 1) response rate	Percentage of patients who achieved an sPGA score of 0 or 1 and who achieved at least 2-point improvement in the sPGA score from baseline
Taltz	Taltz 80 mg Syringe for SC Injection, Taltz 80 mg Auto-Injector for SC Injection
T_{max}	Time to reach maximum plasma or serum concentration
$t_{1/2}$	Elimination half-life
TNFα	Tumor necrosis factor α
Ustekinumab	Ustekinumab (Genetical Recombination) (brand name: Stelara Subcutaneous Injection 45 mg Syringe)
UV spectrophotometry	Ultraviolet-visible spectrophotometry
VAS	Visual analog scale
V_{ss}	Volume of distribution at steady state
WCB	Working cell bank
γ-GTP	γ-glutamyl transpeptidase

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

The active ingredient of Taltz 80 mg Syringe for SC Injection and Taltz 80 mg Auto-Injector for SC Injection (hereinafter collectively referred to as Taltz) is Ixekizumab (Genetical Recombination) (hereinafter referred to as ixekizumab). Ixekizumab is a humanized immunoglobulin G subclass-4 (IgG4) anti-human interleukin (IL)-17A monoclonal antibody developed by Eli Lilly and Company (US).

Psoriasis is a chronic, relapsing and remitting inflammatory skin disease characterized by erythema and scale. Psoriasis can be classified into 5 types according to its clinical manifestations: psoriasis vulgaris (the most common type of psoriasis which appears as skin plaque), psoriatic arthritis (psoriasis accompanied by generalized inflammatory arthritis), erythrodermic psoriasis (characterized by marked systemic inflammation, such as pyrexia, and the presentation of red, scaly patches of skin), pustular psoriasis (characterized by generalized sterile pustule and systemic symptoms such as pyrexia), and guttate psoriasis (characterized by the transient onset of multiple small erythematous scaly papules). Treatment options for psoriasis include topical therapy with agents such as corticosteroids and vitamin D3 derivatives, phototherapy, and systemic therapy with agents such as cyclosporine and etretinate, and an appropriate therapy is determined based on the location and severity of psoriatic skin lesion. Approved agents available for patients who have had an inadequate response to these therapies include secukinumab (anti-IL-17 antibody), infliximab and adalimumab (anti-tumor necrosis factor α [TNFα] antibody), and ustekinumab (anti-IL-12/IL-23 antibody).

IL-17A is a pro-inflammatory cytokine produced mainly by Th17 cells and is considered to play a role in the pathogenesis of psoriasis and the induction of chronic inflammatory reaction in the skin (*N Engl J Med.* 2009;361:888-98). Ixekizumab binds to human IL-17A, a member of the IL-17 family, with high affinity and thereby inhibits IL-17A from binding to the IL-17 receptor, consequently neutralizing the biological activity of IL-17A. Ixekizumab was therefore developed as a therapeutic agent for psoriasis.

Outside Japan, the clinical development of ixekizumab for the treatment of psoriasis was initiated in April 2010. Ixekizumab was approved in March 2016 in the US and is under review in Europe as of March 2016.

In Japan, the clinical development of ixekizumab for psoriasis was initiated in December 2011. On the basis of results from global clinical studies including Japan, the applicant has filed the marketing application for ixekizumab.

The initially proposed Japanese brand name of ixekizumab was changed (without changes to the English brand name) to prevent medication errors.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrates

[redacted] library was generated from [redacted] cells of [redacted] immunized with human IL-17A. Clones were selected from the library based on [redacted], [redacted], and [redacted]. [redacted] antibodies comprising the fragment antigen-binding (Fab) linked to human IgG4 fragment crystallizable (Fc) were generated to select antibody clones based on [redacted], [redacted], and [redacted]. The selected antibody clones were humanized and the humanized anti-IL-17A antibodies were screened based on [redacted], [redacted], etc. Nucleotide sequences coding the heavy chain and light chain of the Fab fragments as well as leader sequence were introduced into an expression vector to prepare the expression construct of ixekizumab. The expression construct was transfected into Chinese hamster ovary (CHO) cells to generate CHO cell clones expressing the gene, from which the primary cell bank was prepared. Subsequently, to reduce [redacted], a new expression construct was created after [redacted] by [redacted] mRNA encoding causative [redacted]. The new expression construct was transfected into CHO cells to generate CHO cell clones expressing the target gene. The selected CHO cell clone was used to establish the master cell bank (MCB) and working cell bank (WCB).

The MCB, WCB, and cells at the limit of *in vitro* cell age were characterized by isozyme analysis, copy number measurement, nucleotide sequencing, or Southern blot analysis, and consequently their genetic stability throughout the manufacturing period was confirmed.

In addition, the MCB, WCB, and cells at the limit of *in vitro* cell age were subjected to the following purity tests: sterility testing, mycoplasma testing, *in vitro* virus testing, *in vivo* virus testing, bacteriostasis/fungistasis test, mycoplasma stasis test, electron microscopy, focus induction test, hamster antibody production test, mouse antibody production test, reverse transcriptase activity assay, bovine polyomavirus testing, *in vitro* bovine virus testing, minute virus of mice testing, *Mus dunni* cell test, S^+L^- focus assay, testing for bovine viral contaminants, and testing for porcine viral contaminants. None of these tests showed any evidence of viral or non-viral adventitious agents.

The MCB and WCB are stored in the vapor phase of liquid nitrogen. Although no regeneration of the MCB is planned, additional WCBs are generated as needed.

2.1.2 Manufacturing process

The manufacturing process of the drug substance consists of flask culture expansion, seed culture, production culture, harvest, [redacted] as well as dispensing, freezing, and storage. The obtained drug substance is filled in high-density polyethylene containers with [redacted] screw caps and stored at ≤[redacted]°C, protected from light.

The manufacturing process was developed using the quality by design (QbD) approach. A quality control strategy was developed based on the following considerations:

- Identification of the following critical quality attributes of the drug substance and drug product: potency, aggregates, truncated forms, host cell deoxyribonucleic acid (DNA), host cell proteins, Protein A, [redacted] ([redacted]), [redacted], metal impurities, microbiological safety, viral safety, particulate matter, identification, description, protein content, pH, osmolality, and [redacted] ([redacted]).

- Identification of process steps that have an impact on critical quality attributes as well as critical process parameters and critical process controls for these steps.

- Development of the method of controlling critical quality attributes (release testing, stability studies or studies for process validation and comparability exercise in response to a change in the manufacturing process).

Identified critical steps are production culture, [redacted] and [redacted].

The commercial-scale manufacturing process for the drug substance has been validated.

2.1.3 Safety evaluation of adventitious agents

Except for the host CHO cell line, no raw materials of biological origin are used in the manufacturing process for the drug substance.

The MCB, WCB, and cells at the limit of *in vitro* cell age were subjected to purity tests [see Section "2.1.1 Generation and control of cell substrates"]. Pre-harvest unprocessed bulk at a commercial scale was subjected to a bioburden test, mycoplasma testing, *in vitro* virus testing, and minute virus of mice testing. None of these tests showed any evidence of viral or non-viral adventitious agents. These tests have been included in the in-process controls for unprocessed bulk.

Viral clearance studies for the purification process were conducted with model viruses. The studies has demonstrated that the purification step has certain virus clearance capacity (Table 1).

Table 1. Viral clearance studies

Manufacturing process	Virus reduction factor (log_{10})			
	Xenotropic murine leukemia virus	Porcine parvovirus	Pseudorabies virus	Reovirus type 3
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minimum overall virus reduction factor	>16.80	7.66	>11.29	>8.77

2.1.4 Manufacturing process development (comparability)

Major changes made to the drug substance manufacturing process during development are shown below (manufacturing processes are referred to as Process 1, Process 2, Process 3, and Process 4 [which is the proposed manufacturing process]):

- Process 1 → Process 2: Changes in [redacted], [redacted], manufacturing scale, chromatography used in the purification process, [redacted], drug substance concentration, materials of the drug substance storage container, etc.

- Process 2 → Process 3: Changes in manufacturing scale, chromatography used in the purification process, [redacted], drug substance concentration, materials of the drug substance storage container, etc.

- Process 3 → Process 4 (the proposed manufacturing process): Changes in drug substance concentration, etc.

Foreign phase [redacted] studies used the formulation containing the drug substance manufactured by Process [redacted], Japanese phase [redacted] and [redacted] studies used the formulation containing the drug substance manufactured by Process [redacted], and phase [redacted] studies used the formulation containing the drug substance manufactured by Process [redacted] and [redacted]. When any of these process changes was made, comparability exercise for the quality attributes was implemented to confirm the comparability of the drug substance between before and after the change.

2.1.5 Characterization

2.1.5.1 Structure

- The primary structure was analyzed by amino acid composition analysis, Edman sequencing, reduced and alkylated endoproteinase Lys-C (Lys-C) and tryptic digestion peptide mapping liquid chromatography tandem-mass spectrometry (LC-MS/MS), and reduced and alkylated endoproteinase Glu-C (Glu-C) digestion peptide mapping LC-MS/MS.

- The higher-order structure was determined by non-reduced and reduced, alkylated trypsin and Lys-C digestion peptide mapping LC-MS/MS, free sulfhydryl group analysis, far-ultraviolet circular dichroism spectroscopy, Fourier transform infrared spectroscopy, near-ultraviolet circular dichroism spectroscopy, endogenous tryptophan fluorescence spectroscopy, sedimentation velocity analytical ultracentrifuge, static light scattering, and differential scanning calorimetry.

- The glycosylation sites and glycan structure were determined by high-pH anion-exchange chromatography, reduced capillary electrophoresis sodium dodecyl sulfate (CE-SDS), peptide-N-glycosidase F (PNGase F) treatment, capillary electrophoresis, hydrophilic interaction chromatography-mass spectrometry after PNGaseF treatment, reverse-phased LC-MS/MS analysis, and mass spectrometry after exoglycosidase treatment.

2.1.5.2 Physicochemical properties

- The molecular weight was determined by liquid chromatography-mass spectrometry (LC-MS) (non-reduced, non-reduced deglycosylated, and reduced deglycosylated), sedimentation velocity analytical ultracentrifuge, and static light scattering.

- Charge variants were identified by capillary isoelectric focusing and cation exchange chromatography.

- Size variants were identified by CE-SDS ([redacted] and [redacted]) and size exclusion chromatography.

- The IgG subclass was identified by human IgG subclass enzyme-linked immunosorbent assay (ELISA) and based on the result of the above primary structure analysis.

- The extinction coefficient was determined by quantitative amino acid composition analysis.

2.1.5.3 Biological properties

- The binding specificity of ixekizumab to IL-17A among IL-17 family members was confirmed by ELISA [see Section "3.1.1.1 Binding specificity to human IL-17A and other cytokines"].

- The binding of ixekizumab to human and cynomolgus monkey IL-17A was shown by surface plasmon resonance assay. The binding affinity of ixekizumab to rabbit IL-17A was found to be low, and ixekizumab did not bind to mouse or rat IL-17A [see Section "3.1.1.2 Binding affinity of ixekizumab to human molecules" and Section "3.1.1.3 Binding affinity of ixekizumab to IL-17A of various animal origins].

- Surface plasmon resonance assay confirmed that ixekizumab blocks the binding of human IL-17A to human IL-17A receptor [see Section "3.1.1.4 Ability to block binding of human IL-17A to human IL-17A receptor"].

- In human colorectal adenocarcinoma cell line (HT-29), ixekizumab inhibited human IL-17A-induced production of growth-related oncogene α [see Section "3.1.2 Effect on human IL-17A-induced secretion of chemokine in HT-29 cells"]. In mice, ixekizumab inhibited human IL-17A-induced production of keratinocyte chemoattractant [see Section "3.1.3 Effect on human IL-17A-induced secretion of chemokine in the mouse"].

- The binding affinity of ixekizumab, classified as IgG4, to human FcγR I, FcγR IIa, FcγR IIIa and complement was found to be low [see Section "3.1.4 Binding to human Fcγ receptor and complement"].

2.1.5.4 Product-related substances and product-related impurities

On the basis of the analysis results shown in Sections 2.1.5.1 to 2.1.5.3, the oxidized form, deamidated form, amino acid isomer, [redacted]/[redacted] form, pyroglutamic acid form, glycated form, and free sulfhydryl form of ixekizumab were identified as the product-related substances. In addition, aggregates and truncated forms were identified as the product-related impurities, which are controlled by the specifications (size exclusion chromatography) for the drug substance and drug product.

2.1.5.5 Process-related impurities

Host cell DNA, host cell protein, Protein A, [redacted] ([redacted]), [redacted], metals, [redacted], and [redacted] were identified as the process-related impurities. All of the process-related impurities have been confirmed to be adequately removed during the manufacturing process.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include strength, description (appearance), identification (cation exchange chromatography, neutralizing activity, and peptide mapping), pH, purity (size exclusion chromatography and CE-SDS [[redacted] and [redacted]]), [redacted] (cation exchange

chromatography), bacterial endotoxins, microbial limit, potency ([redacted]) and assay (ultraviolet-visible spectrophotometry [UV spectrophotometry]).

2.1.7 Stability of drug substance

Table 2 shows primary stability studies for the drug substance. Batches of the drug substance manufactured by the proposed manufacturing process were used.

Table 2. Overview of primary stability studies of the drug substance

	Number of batches	Storage conditions	Storage period	Storage package
Long-term testing	3 batches	≤ –65°C	36 months	High-density polyethylene container with [redacted] screw cap
Accelerated testing		5°C	6 months	
Stress testing	1 batch	40°C	4 weeks	Glass container (non-packaged or packaged in aluminum foil)
Photostability testing		20°C, an overall illumination of ≥1.2 million lx·h, an integrated near ultraviolet energy of ≥200 W·h/m^2		

The long-term stability testing showed no clear changes in quality attributes throughout the storage period.

In the accelerated testing and stress testing, increased aggregate formation was detected by size exclusion chromatography, a decreased intensity of the main band was identified by [redacted] ([redacted] and [redacted]), and changes in [redacted].

The photostability testing has shown that the drug substance is photolabile.

Based on the above, a shelf-life of 36 months has been proposed for the drug substance when stored in a high-density polyethylene container with [redacted] screw cap at ≤[redacted]°C, protected from light.

2.2 Drug product

2.2.1 Description and composition of the drug product, and formulation development

The drug product is supplied in a prefilled glass syringe with a fixed needle (the syringe is equipped with a plunger rod and other components) or in an auto-injector (containing the prefilled syringe). Both devices are prefilled with a drug solution containing 80 mg of ixekizumab per mL. The prefilled syringe and auto-injector drug products are classified as the combination product. Excipients contained in the drug product are sodium citrate, anhydrous citric acid, sodium chloride, polysorbate 80, and water for injection.

The primary container for the syringe drug product and auto-injector drug product is a glass syringe with a fixed needle. The syringe is sealed with a bromobutyl rubber gasket. Both drug products are packed in cartons.

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of preparation of excipient buffer solution, preparation of the drug solution, sterile filtration, filling and closure, assembly, storage, labeling and packaging, storage, and testing. Identified critical steps are sterile filtration, and filling and closure.

The commercial-scale manufacturing process for the drug product has been validated.

2.2.3 Manufacturing process development

During the development of the drug product, the dosage form was changed from lyophilized powder to solution (proposed formulation). The lyophilized powder formulation was used in phase [redacted] and phase [redacted] studies (except for [redacted] study), and the solution formulation was used in [redacted] phase [redacted], all the phase [redacted] studies, and [redacted].

2.2.4 Control of drug product

The proposed specifications for the drug product include strength, description (appearance), identification (cation exchange chromatography and neutralizing activity), pH, purity (size exclusion chromatography and CE-SDS [and]), (cation exchange chromatography), foreign insoluble matter, insoluble particulate matter, sterility, potency ( ), and assay (UVspectrophotometry).

2.2.5 Stability of drug product

Table 3 shows primary stability studies for the drug product. The stability studies used the solution drug product prepared from the drug substance manufactured through the proposed process (the drug product filled in a glass syringe sealed with a rubber plunger [the primary container], excluding syringe components such as a plunger rod).

Table 3. Overview of primary stability studies of the drug product

	Number of batches	Storage conditions	Storage period	Storage form
Long-term testing	3	5 ± 3°C	24 months	Glass syringe with a bromobutyl rubber plunger
Accelerated testing	3	25°C, 60%RH	6 months	
Stress testing	1	40°C	1 month	
Photostability testing	1	20°C, an overall illumination of ≥1.2 million lx·h, an integrated near ultraviolet energy of ≥200 W·h/m^2		Glass syringe with a bromobutyl rubber plunger (not packaged or packaged in aluminum foil)

The long-term testing and accelerated testing showed no clear changes in quality attributes throughout the storage period.

In stress testing, increased aggregate formulation was detected by size exclusion chromatography, a decreased intensity of the main band was identified by (and), and changes in .

Photostability testing has shown that the drug product is photolabile.

Based on the above stability data, a shelf-life of 24 months has been proposed for both syringe drug product and autoinjector drug product when stored at 2°C to 8°C (avoid freezing), protected from light.

2.3 Reference materials

The primary reference material and working reference material are prepared from the drug substance and stored at °C. The stability of the reference material during storage is confirmed at months, months, months, and months. The proposed specifications for the reference material are strength, description (appearance), identification (and), pH, purity (size exclusion chromatography and [and]), ( ), potency ( ), and assay (UV spectrophotometry).

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA has concluded that the quality of the drug substance, drug product, syringe, and autoinjector is adequately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The applicant submitted primary pharmacodynamics data, which included the results from *in vitro* studies on binding to IL-17A, inhibition of ligand binding to IL-17A receptor, inhibition of biological activity of IL-17A, and binding to human Fcγ receptor and complement. Safety pharmacology data included the results of 8-week and 39-week repeat-dose toxicity studies in cynomolgus monkeys which investigated effects on the central nervous system, cardiovascular system, and respiratory system. Neither secondary pharmacodynamic nor pharmacodynamic drug interaction studies were conducted to support the present application.

Unless otherwise specified, pharmacological parameter values are expressed as the mean.

3.1 Primary pharmacodynamics

3.1.1 Binding specificity and binding affinity

3.1.1.1 Binding specificity of ixekizumab to human IL-17A and other cytokines (CTD 4.2.1.1.1)

The binding specificity of ixekizumab to human IL-17 family members (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F) and human IL-22 was investigated by ELISA. Ixekizumab bound to human IL-17A in a concentration-dependent manner, but did not bind to other IL-17 family members or IL-22.

3.1.1.2 Binding affinity of ixekizumab to human molecules (CTD 4.2.1.1.3)

The binding affinity of ixekizumab to human IL-17A and human heterodimer of IL-17A and IL-17F (IL-17A/F) was investigated by surface plasmon resonance assay. Ixekizumab bound to human IL-17A and human IL-17A/F in a concentration-dependent manner, and dissociation constant (K_D) was calculated to be <3 pmol/L for both molecules.

3.1.1.3 Binding affinity of ixekizumab to IL-17A of various animal origins (CTD 4.2.1.1.2)

The binding affinity of ixekizumab to human, cynomolgus monkey, rabbit, mouse, and rat IL-17A was investigated by surface plasmon resonance assay. Ixekizumab bound to human and cynomolgus monkey IL-17A in a concentration-dependent manner, and K_D was calculated to be 1.8 pmol/L and 0.8 pmol/L, respectively. The binding of ixekizumab to rabbit IL-17A was found to be biphasic and K_D was calculated to be 1.3 and 14 nmol/L. Ixekizumab did not bind to mouse or rat IL-17A.

3.1.1.4 Ability to block binding of human IL-17A to human IL-17A receptor (CTD 4.2.1.1.6)

The ability of ixekizumab to block the binding of human IL-17A to human IL-17A receptor was investigated by surface plasmon resonance assay. Ixekizumab at 500 nmol/L blocked ligand binding to the receptor.

3.1.2 Effect on human IL-17A-induced secretion of chemokine in HT-29 cells (CTD 4.2.1.1.4 and 4.2.1.1.5)

The effect of ixekizumab on secretion of growth-related oncogene α induced by human and cynomolgus monkey IL-17A and human IL-17A/F was investigated using human colorectal adenocarcinoma cell line HT-29. Ixekizumab inhibited the secretion of growth-related oncogene α induced by human and cynomolgus monkey IL-17A and human IL-17A/F in a concentration-dependent manner with the 50% inhibitory concentration (IC_{50}) of 422.2, 699.5, and 261.3 pmol/L, respectively.

3.1.3 Effect on human IL-17A-induced secretion of chemokine in mice (CTD 4.2.1.1.9)

Because ixekizumab does not bind to mouse IL-17A, this study investigated the effect of ixekizumab on the secretion of keratinocyte chemoattractant as the mouse counterpart of human growth-related oncogene α. A single dose of 3 μg of human IL-17A was administered subcutaneously to mice to induce the secretion of keratinocyte chemoattractant. Ixekizumab (0.02 to 20 μg) was administered intravenously to the mice to evaluate the effect of ixekizumab on human IL-17A-induced secretion of keratinocyte chemoattractant. Compared with the IgG4 group (negative control), the plasma concentration of keratinocyte chemoattractant decreased in the ixekizumab 20 μg group, demonstrating that ixekizumab inhibits human IL-17A activity in the mouse.

3.1.4 Binding of ixekizumab to human Fcγ receptor and complement (CTD 4.2.1.1.8)

The binding of ixekizumab to human Fcγ receptor I, human Fcγ receptor IIa, human Fcγ receptor IIIa, and complement C1q was investigated to evaluate the antibody-dependent and complement-dependent cytotoxicity potential of ixekizumab. While IgG1, a positive control antibody, bound to any of these molecules in a concentration-dependent manner, the binding affinity of ixekizumab to them was found to be low and comparable to that of IgG4, a negative control antibody. On the basis of the above findings, the applicant claims that ixekizumab is unlikely to cause antibody-dependent and complement-dependent cytotoxicity.

3.2 Safety pharmacology (CTD 4.2.3.2.1 and 4.2.3.2.2)

The safety pharmacology core battery parameters were investigated in 8-week and 39-week repeat-dose toxicity studies in juvenile cynomolgus monkeys (aged 2-4 years). In these studies, ixekizumab (5, 15, or 50 mg/kg) was intravenously administered to juvenile cynomolgus monkeys once weekly for 8 weeks, or ixekizumab (0.5, 5, or 50 mg/kg) was subcutaneously administered to juvenile cynomolgus monkeys once weekly for 39 weeks. Ixekizumab did not affect central nervous system parameters (e.g., clinical signs, behavior), cardiovascular system parameters (e.g., electrocardiography telemetry, electrocardiography under ketamine anesthesia), or respiratory system parameters (e.g., respiratory rate, respiratory depth assessment).

3.R Outline of the review conducted by PMDA

The applicant's discussion about the roles of IL-17A in the pathogenesis of psoriasis and the mechanism of action of ixekizumab:

IL-17A, a IL-17 family member, is a homodimer or can exist as a biologically active heterodimer, IL-17A/IL-17F (*Nat Rev Immunol.* 2009;9:556-67). IL-17A produced mainly by Th17 cells is involved in host defense against extracellular bacterial and fungal infections and homeostasis of neutrophils (*Eur J Immunol.* 2012;42:2246-54, *Cell Host Microbe.* 2012;11:425-35). In the skin of patients with psoriasis, the synergistic effect of IL-17A and TNFα is thought to activate keratinocytes, thereby inducing production of antimicrobial peptides, such as β-defensin-2, and pro-inflammatory cytokines, which results in inflammation of the skin (*Annu Rev Immunol.* 2014;32:227-55). The published literature showed that the number of IL-17A producing cells in blood was increased in patients with psoriasis compared with healthy adults, and that increased Th17 cells in blood and increased IL-17A expression levels in the skin lesion and synovial fluid were found in patients with psoriatic arthritis (*Arthritis Rheum*. 2008;58:2307-17, *Autoimmun Rev.* 2014;13:496-502, and other reports). The above findings indicate that ixekizumab, anti-IL-17A antibody, neutralizes the biological activity of IL-17A, thereby exhibiting effects on psoriatic skin lesions and joint symptoms.

PMDA's conclusion:

The data submitted have demonstrated that ixekizumab inhibits the biological activity of IL-17A. Ixekizumab is thus expected to be effective against psoriasis because IL-17A is considered to be involved in the pathogenesis of the disease.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The applicant submitted data from the studies investigating the absorption, distribution, and excretion of ixekizumab, including results of subcutaneous and intravenous administration studies in cynomolgus monkeys. Ixekizumab concentrations in plasma, serum, milk, and amniotic fluid were determined by ELISA (lower limit of quantification (LLOQ); 0.4, 7.5, 0.5, and 7.5 ng/mL, respectively). Anti-drug antibody (ADA) was determined by ELISA (LLOQ, 0.678-0.7 μg/mL).

Unless otherwise specified, pharmacokinetic parameter values are expressed as the mean, or the mean ± standard deviation (SD).

4.1 Absorption

4.1.1 Single-dose study (CTD 4.2.2.2.1)

A single dose of ixekizumab (1 mg/kg) was subcutaneously or intravenously administered to male cynomolgus monkeys (n = 2/group). Table 4 shows the pharmacokinetic parameters.

Table 4. Pharmacokinetic parameters following single intravenous or subcutaneous administration of ixekizumab to cynomolgus monkeys

Dose (mg/kg)	Route of administration	C_{max} (μg/mL)	$AUC_{0\text{-}672h}$ (μg·h/mL)	T_{max} (h)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_{ss} (mL/kg)
1	Subcutaneous	11.1	3314	72	246	0.262	-
1	Intravenous	21.1	2253	-	156	0.448	87.0

Mean

4.1.2 Repeat-dose studies (toxicokinetics) (CTD 4.2.3.2.1, 4.2.3.2.2, and 4.2.3.5.1.1)

The toxicokinetics of ixekizumab was evaluated in 8-week repeated intravenous dose toxicity study (CTD 4.2.3.2.1), 39-week repeated subcutaneous dose toxicity study (CTD 4.2.3.2.2), and 13-week repeat-dose toxicity study for male and female reproductive capability (CTD 4.2.3.5.1.1). In these studies, ixekizumab was subcutaneously or intravenously administered once weekly to male and female cynomolgus monkeys (n = 3-6/sex/group). The pharmacokinetic parameters of ixekizumab are shown in Table 5. C_{max} and $AUC_{0\text{-}168h}$ after the first dose showed a nearly dose-proportional increase. In any study, C_{max} and $AUC_{0\text{-}168h}$ after repeated doses were higher than those after the first dose. There were no apparent gender-related differences.

In the 8-week and 39-week repeat-dose toxicity studies, immunogenicity was investigated in animals receiving ixekizumab 50 mg/kg. In many of the samples, serum ixekizumab concentrations exceeded the threshold at which detection of ADA would not be affected (10 and 100 µg/mL in 8-week and 39-week studies, respectively), but all the animals tested in the 8-week repeat-dose toxicity study were determined to be negative for ADA. No animals had decreased ixekizumab exposure suggestive of development of ADA. In the 39-week repeat-dose toxicity study, ADA was detected in 2 females. Exposure to ixekizumab decreased in 1 animal on Day 267 and in the other animal on Day 22 thereafter.

Table 5. Pharmacokinetic parameters following once-weekly, repeated doses of ixekizumab in cynomolgus monkeys

Treatment duration	Dose (mg/kg)	Route of administration	Time point	Male					Female				
				N	C_{max} (µg/mL)	$AUC_{0\text{-}168h}$ (µg·h/mL)	$t_{1/2}$ (h)	T_{max} (h)	N	C_{max} (µg/mL)	$AUC_{0\text{-}168h}$ (µg·h/mL)	$t_{1/2}$ (h)	T_{max} (h)
8 weeks	5	Intravenous	Day 1	3	104 ± 1.53	7160 ± 359	-	-	3	110 ± 14.6	8580 ± 995	-	-
	15		Day 1	3	463 ± 73.1	30,100 ± 5370	-	-	3	507 ± 87.5	35,100 ± 5610	-	-
	50		Day 1	6	1700 ± 262	104,000 ± 11,600	-	-	6	1670 ± 257	109,000 ± 16,700	-	-
			Day 57	3	2610 ± 81.4	241,000 ± 25,400	303 ± 71.6	-	3	1900 ± 356	180,000 ± 4000	276 ± 61.5	-
39 weeks	0.5	Subcutaneous	Day 1	4	5.11 ± 0.58	705 ± 89	-	96.0 ± 27.7	4	4.62 ± 0.34	615 ± 30	-	102 ± 53
	5		Day 1	4	43.9 ± 5.1	6043 ± 698	-	72.0 ± 0.0	4	45.8 ± 3.2	6166 ± 268	-	66.0 ± 12.0
	50		Day 1	6	423 ± 59	57,160 ± 7322	-	52.0 ± 9.8	6	450 ± 60	58,312 ± 4249	-	40.0 ± 12.4
			Day 267[a)]	2	1140, 1290	158,747, 178,443	329, 346	48.0, 48.0	2[b)]	1055, 655	144,261, 94,349	265, 111	48.0, 48.0
13 weeks	50	Subcutaneous	Day 1	6	426 ± 63.9	59,995 ± 10,771	-	60.0 ± 29.4	6	456 ± 60.6	63,398 ± 6686	-	48.0 ± 26.3
			Day 85	6	1238 ± 259	179,279 ± 40,962	-	40.0 ± 29.1	6	1073 ± 125	153,865 ± 18,128	-	36.0 ± 13.1

Mean ± SD

a) Pharmacokinetic parameters in each animal

b) One animal which tested positive for ADA showed decreased exposure on Day 267.

4.2 Distribution

4.2.1 Transfer to fetuses and placental transfer (CTD 4.2.3.5.2.1)

In a study for effects on embryo-fetal development in pregnant cynomolgus monkeys (n = 12/group), ixekizumab (5 or 50 mg/kg) was subcutaneously administered once weekly from Day 20 of gestation to Day 139 of gestation to investigate its toxicokinetics. Table 6 shows ixekizumab concentrations in maternal and fetal serum as well as amniotic fluid on the day of caesarean section (24-72 hours after the final dose [Day 140 of gestation to Day 142 of gestation]). Ixekizumab concentrations in maternal serum increased in an almost dose-proportional manner. Ixekizumab concentrations in fetal serum were approximately 22% of ixekizumab concentrations in maternal serum, indicating the transfer of ixekizumab across the placenta to the fetus. Ixekizumab concentrations in amniotic fluid were approximately 2% of ixekizumab concentrations in maternal serum.

ADA was detected in 4 of 12 dams at 5 mg/kg and 5 of 12 dams at 50 mg/kg, while it was detected in 3 of 10 fetuses at 5 mg/kg and 1 of 10 fetuses at 50 mg/kg.

Table 6. Ixekizumab concentrations in maternal and fetal serum as well as amniotic fluid in the study for effects on embryo-fetal development in cynomolgus monkeys

Dose (mg/kg)	Dam		Fetus		Amniotic fluid	
	N	Concentration (μg/mL)	N	Concentration (μg/mL)	N	Concentration (μg/mL)
5	11	78.7 ± 16.6	10	20.0 ± 6.7	10	2.1 ± 1.7
50	11	835.9 ± 202.0	10	153.7 ± 33.0	10	13.6 ± 12.1

Mean ± SD

4.3 Excretion

4.3.1 Excretion into milk (CTD 4.2.3.5.3.1)

In a study for effects on pre- and postnatal development in pregnant cynomolgus monkeys, ixekizumab (5 or 50 mg/kg) was subcutaneously administered once weekly from Day 20 of gestation to Day 22 of gestation to parturition to investigate the toxicokinetics. Table 7 shows ixekizumab concentrations in maternal and infant serum as well as milk. Ixekizumab concentrations in maternal serum on Day 20 of gestation to Day 22 of gestation, Day 70 of gestation, and Day 140 of gestation increased in an almost dose-proportional manner. Ixekizumab concentrations in milk ranged from 0.095% to 0.26% of the concentrations in maternal serum, indicating excretion of ixekizumab into milk. Serum ixekizumab concentrations in the F1 offspring in the 50 mg/kg group on post-natal day 7 were approximately 20-fold higher than those in the 5 mg/kg group, but did not exceed the range of ixekizumab concentrations in maternal serum.

Table 7. Ixekizumab concentrations in maternal and infant serum as well as milk in the study for effects on pre- and postnatal development in cynomolgus monkeys

	5 mg/kg				50 mg/kg			
	Ixekizumab concentrations in maternal serum (N = 10)	Serum ixekizumab concentrations in infants		Ixekizumab concentrations in milk (N = 9)	Ixekizumab concentrations in maternal serum (N = 9)	Serum ixekizumab concentration in infants		Ixekizumab concentrations in milk (N = 9)
		Male[a)] (N = 2)	Female (N = 8)			Male (N = 4)	Female (N = 5)	
7 days postpartum	44.2 ± 21.3	15.9, 14.4	11.7 ± 7.64	–	432 ± 231	337 ± 179	201 ± 89.6	–
14 days postpartum	22.8 ± 13.5	16.2, 9.34	9.14 ± 5.18	0.051 ± 0.028[b)]	281 ± 155	234 ± 127	146 ± 61.7	0.29 ± 0.19[c)]
28 days postpartum	10.2 ± 6.0	8.66, 4.30	4.22 ± 2.41	0.021 ± 0.013	104 ± 66.5	95.7 ± 68.7[e)]	65.7 ± 29.2	0.11 ± 0.07[b)]
42 days postpartum	3.22 ± 2.00	3.82, 1.88	1.70 ± 0.956	0.00639 ± 0.00595	49.1 ± 37.1	60.0 ± 35.5[e)]	30.2 ± 15.7	0.0432 ± 0.0371
56 days postpartum	1.32 ± 0.897	1.84, 1.06	0.805 ± 0.505	0.00130 ± 0.00179[d)]	20.3 ± 13.4	22.0 ± 14.5	11.9 ± 4.54	0.0284 ± 0.0430[b)]
84 days postpartum	0.288 ± 0.284	0.718, 0.280	0.196 ± 0.159	–	4.53 ± 4.96	6.50 ± 4.94	3.29 ± 1.53	–
205 days postpartum	0.00 ± 0.00	–	0.00 ± 0.00	–	0.0185 ± 0.0344	0.0176 ± 0.0352	0.00888 ± 0.00541	–

Mean ± SD

a) Pharmacokinetic parameters in individual animals, b) N = 8, c) N = 7, d) N = 5, e) N = 3

4.R Outline of the review conducted by PMDA

Based on the non-clinical pharmacokinetic data submitted, PMDA has concluded that prediction of the kinetics of ixekizumab is possible to a certain extent.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the toxicity data of ixekizumab which include results from repeat-dose toxicity studies, reproductive and developmental toxicity study, and other toxicity studies (studies for tissue cross-reactivity and for blood compatibility in human and cynomolgus monkeys). Because ixekizumab does not bind to rodent IL-17A but binds to cynomolgus monkey IL-17A with affinity comparable to that of human IL-17A [see Section "3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA"], toxicity studies of ixekizumab were conducted using cynomolgus monkeys. In addition, a solution of 10 mmol/L citric acid buffer, 150 mmol/L sodium chloride, and 0.02% polysorbate 80 prepared in water for injection was used as a vehicle control in *in vivo* studies and a blood compatibility study.

5.1 Single-dose toxicity

No single-dose toxicity studies were conducted. The toxicity of ixekizumab administered at ≤50 mg/kg subcutaneously or intravenously was evaluated based on the results obtained following the first dose in the 8-week and 39-week repeat-dose toxicity studies in cynomolgus monkeys (CTD 4.2.3.2.1 and 4.2.3.2.2). Ixekizumab showed a favorable tolerability profile, and no deaths occurred. Based on the above, the approximate lethal dose of ixekizumab was determined to be >50 mg/kg for both subcutaneous and intravenous administration.

5.2 Repeat-dose toxicity

An 8-week repeated intravenous dose toxicity study and a 39-week repeated subcutaneous dose toxicity study were conducted in cynomolgus monkeys. In the 39-week repeated subcutaneous dose toxicity study, the no observed adverse effect level (NOAEL) was determined to be 5 mg/kg. The estimated $AUC_{0\text{-}168h}$ at steady state (15.3 mg·h/mL) was 6.1-fold the estimated $AUC_{0\text{-}168h}$ (2.52 mg·h/mL) in Japanese patients with psoriasis receiving multiple subcutaneous doses of ixekizumab at the clinical dose.

5.2.1 Eight-week repeated intravenous dose study in cynomolgus monkeys (CTD 4.2.3.2.1)

Ixekizumab was intravenously administered at 0 (vehicle), 5, 15, or 50 mg/kg once weekly for 8 weeks (9 doses in total) to male and female cynomolgus monkeys, followed by a 6-week recovery period. No deaths occurred. Ixekizumab did not affect clinical signs, ophthalmologic findings, lymphocyte subset analysis, T-cell dependent antibody response to keyhole limpet hemocyanin, necropsy or histopathological findings [for ADA assay results, see Section "4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA"]. Based on the above, the NOAEL was determined to be 50 mg/kg.

5.2.2 Thirty-nine-week repeated subcutaneous dose study in cynomolgus monkeys (CTD 4.2.3.2.2)

Ixekizumab was subcutaneously administered at 0 (vehicle), 0.5, 5, or 50 mg/kg once weekly for 39 weeks (39 doses in total) to male and female cynomolgus monkeys, followed by a 16-week recovery period. No deaths associated with ixekizumab occurred. Injection site swelling was observed at ≥0.5 mg/kg, and injection site necrosis and other findings at ≥5 mg/kg. One animal[1)] in the 50 mg/kg group showed marked exacerbation of injection site reactions such as swelling, redness, and scab formation along with laboratory test values suggesting inflammation after 3 months of treatment, and thus treatment was discontinued. According to the applicant, decreased serum ixekizumab concentrations and high ADA levels in the animal suggested that the marked exacerbation of injection site reactions was attributable to immune reactions to ixekizumab. In the 0.5 and 5 mg/kg groups as well as the 50 mg/kg group excluding one animal in which treatment was discontinued, ixekizumab did not affect ophthalmologic findings, lymphocyte subset analysis, or T-cell dependent antibody response to keyhole limpet hemocyanin [for ADA assay results, see Section "4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA"]. In addition, findings at the injection site (swelling and necrosis) were reversible. Based on the above, the NOAEL was determined to be 5 mg/kg.

5.3 Genotoxicity

Ixekizumab is an antibody drug product that is unlikely to have a direct effect on DNA or other chromosomal components, and thus no genotoxicity studies were conducted.

5.4 Carcinogenicity

Ixekizumab is not pharmacologically active in rodent animals. Commercially available 2 rat anti-mouse IL-17A antibodies differ from ixekizumab in terms of binding affinity and epitope for IL-17A as well as IgG isotype. Thus, the applicant considered that the toxicity of ixekizumab should not be evaluated using these antibodies as the surrogates. No carcinogenicity studies were conducted in rodent animals. According to the applicant, the carcinogenic potential of ixekizumab that acts by neutralizing IL-17A is low, because (1) no preneoplastic lesions were observed in the 8-week or 39-week repeat-dose toxicity

1) In this animal, treatment was discontinued after 30 doses of ixekizumab. The injection site reactions resolved after a 9-week recovery period. Ixekizumab was re-administered 2 days before scheduled necropsy. The necropsy revealed injection site swelling, and the histopathological findings at the injection site were more serious than those in the other animals. Such findings included vasculitis.

study in cynomolgus monkeys; and (2) a report presented that *IL-17A*-gene deficiency-induced suppression of IL-17A activity resulted in inhibition of tumor growth (*J Immunol.* 2010;184:2281-8, *J Exp Med.* 2009;206:1457-64, and other reports).

5.5 Reproductive and developmental toxicity

Studies were conducted in cynomolgus monkeys to evaluate male and female reproductive toxicity, embryo-fetal developmental toxicity, and pre- and postnatal developmental toxicity. The NOAELs were determined to be all 50 mg/kg for male and female reproductive systems, dams, embryo-fetal development, and offspring. In the 39-week repeat-dose toxicity study in cynomolgus monkeys, $AUC_{0\text{-}168h}$ in animals at 50 mg/kg on Day 267 was 144 mg·h/mL, which was 57-fold the estimated $AUC_{0\text{-}168h}$ (2.52 mg·h/mL) in Japanese patients with psoriasis receiving multiple subcutaneous doses of ixekizumab at the clinical dose. According to the applicant, ixekizumab that acts by neutralizing IL-17A is unlikely to have reproductive and developmental toxicity, taking into account that (1) a report on *IL-17A*-deficient mice showed the normal development and intact reproductive capability (*Immunity*. 2002;17:375-87); and (2) data on the reproductive and developmental toxicity of secukinumab, an anti-IL-17A antibody, presented no findings suggesting effects on the embryo-fetal development or offspring.

5.5.1 Male and female reproductive toxicity study in cynomolgus monkeys (CTD 4.2.3.5.1.1)

Ixekizumab (0 [vehicle] or 50 mg/kg) was subcutaneously administered to sexually mature cynomolgus monkeys once weekly for 13 weeks (13 doses in total). No abnormalities were observed in clinical signs, reproductive function parameters (estrous cycle, sperm motility, sperm morphology, sperm concentration, and sperm count per ejaculation), male and female reproductive organ weight, or histopathological findings. Based on the above, the NOAEL for reproductive functions was determined to be 50 mg/kg.

5.5.2 Study for effects on embryo-fetal development in cynomolgus monkeys (CTD 4.2.3.5.2.1)

Ixekizumab (0 [vehicle], 5, or 50 mg/kg) was subcutaneously administered to pregnant cynomolgus monkeys once weekly from Day 20 of gestation to Day 139 of gestation for 18 weeks (18 doses in total).[2)] No abnormalities were observed in dams. In 3 of 11 fetuses in the 50 mg/kg group, the absolute number and relative ratio of natural killer cells (NK cells) in cord blood increased,[3)] but there were no changes in the other lymphocyte subset. NK cells did not increase in the remaining fetuses in the same group. The finding was therefore determined to be of no toxicological significance. Based on the above, the NOAELs for dams and embryo-fetal development were determined to be all 50 mg/kg.

5.5.3 Study for effects on enhanced pre- and postnatal development in cynomolgus monkeys (CTD 4.2.3.5.3.1)

Ixekizumab (0 [vehicle], 5, or 50 mg/kg) was subcutaneously administered to pregnant cynomolgus monkeys once weekly from Day 20 of gestation to Day 22 of gestation to parturition (18 to 22 doses in total).[4)] No abnormalities were observed in dams or embryos/fetuses. In the 5 mg/kg group, 2 of 12 infants died or were euthanized (neonatal death in 1 infants and congenital defect [imperforate anus] in 1 infant); and in the 50 mg/kg group, 5 of 14 infants died or were euthanized (neonatal death in 2 of 5 infants, maternal neglect in 3 of 5 infants [including neonatal death in 1 infant], and injury in 1 of 5 infants). In these infants, there were no findings suggesting association with ixekizumab, and thus findings in dead or euthanized infants were unlikely to be related to ixekizumab. No abnormalities were observed in surviving infants. Based on the above, the NOAEL for dams and infants was determined to be 50 mg/kg.

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2) Dams were subjected to lymphocyte subset analysis and ADA measurement, and fetuses were subjected to lymphocyte subset analysis, histopathological examination on fetal lymphoid organs, measurement of ixekizumab concentrations in fetal serum and amniotic fluid as well as ADA measurement.

3) The relative ratio of NK cells in these fetuses was 1.7- to 2.8-fold the maximum in the fetuses in the vehicle group, and the relative ratio (mean) of NK cells in fetuses in the 50 mg/kg group was approximately 2-fold that in the vehicle group.

4) Dams were subjected to lymphocyte subset analysis, and infants were subjected to lymphocyte subset analysis, T-cell dependent antibody response to keyhole limpet hemocyanin, NK cell activity measurement, neuroethological examination, neurological examination, necropsy, and histopathological examination.

5.6 Local tolerance

No local tolerance studies of ixekizumab were conducted. Local tolerance was evaluated in the 39-week repeated subcutaneous dose study in cynomolgus monkeys. Necrosis at the injection site was observed at ≥5 mg/kg, but the change tended to be reversible after the recovery period.

5.7 Other toxicity studies

5.7.1 Tissue cross-reactivity study using human and cynomolgus monkey tissues (CTD 4.2.3.7.7.1)

A study was conducted to evaluate the cross reactivity of ixekizumab in normal tissues from humans and cynomolgus monkeys. No cross-reactivity specific to ixekizumab was observed in any tissue.

5.7.2 Blood compatibility study (CTD 4.2.3.7.7.2)

In this study, ixekizumab (0 [vehicle], 5, or 25 mg/mL) was mixed with human or cynomolgus monkey whole blood at a ratio of 1:1, or with human or cynomolgus monkey serum at a ratio of 1:2 to 1:50 to evaluate the potential of ixekizumab to cause hemolysis and serum flocculation. Although serum flocculation did not occur, hemolysis occurred in both species tested (0.5%-0.6% in the 5 mg/mL group, 4%-7% in the 25 mg/mL group). The applicant considers that ixekizumab is unlikely to raise the concern of hemolysis in clinical use, because (1) hemolysis observed in this study was minor; and (2) the estimated C_{max} (21.5 μg/mL) in patients with psoriasis receiving multiple subcutaneous doses of ixekizumab at the clinical dose is approximately 1% of the ixekizumab concentration (final concentration of 2.5 mg/mL) at which 0.5% hemolysis was observed.

5.R Outline of the review conducted by PMDA

PMDA considers that the data submitted suggest no particular toxicological concerns about the clinical use of ixekizumab.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

The applicant submitted evaluation data which include results from global study (CTD 5.3.5.1.2, Study RHAZ) and foreign clinical study (CTD 5.3.5.1.1, Study RHAJ) in patients with plaque psoriasis vulgaris or psoriatic arthritis, global study in patients with psoriatic arthritis (CTD 5.3.5.1.5, Study RHAP), Japanese long-term treatment study in patients with psoriasis (CTD 5.3.5.2.1, Study RHAT), clinical studies in patients with rheumatoid arthritis (CTD 5.3.3.2.1, Study RHAL; CTD 5.3.5.4.2, Study RHAK), population pharmacokinetic analysis, and exposure-response analysis (CTD 5.3.3.5.2, CTD 5.3.3.5.3, CTD 5.3.3.5.4). The applicant submitted reference data which include results from foreign clinical pharmacology studies in patients with psoriasis (CTD 5.3.3.2.3, Study RHAG; CTD 5.3.3.4.1, Study RHBL).

Serum ixekizumab concentrations, ADA, and neutralizing antibodies were measured by ELISA (LLOQ of serum ixekizumab concentrations, 7.5 ng/mL).

Unless otherwise specified, the dose of Taltz indicates the dose of ixekizumab, and pharmacokinetic parameter values and measured values are expressed as the mean ± SD.

6.1 Studies in patients with psoriasis

6.1.1 Global study (CTD 5.3.5.1.2, Study RHAZ [ongoing since December 2011 (data cut-off on June 24, 2014; up to Week 60)])

A global study was conducted to investigate the pharmacokinetics of ixekizumab in patients with psoriasis vulgaris or psoriatic arthritis [see Section “7.2.1 Global phase III study”] who received a starting dose of 160 mg of ixekizumab subcutaneously, followed by 80 mg every 4 weeks (Q4W) or every 2 weeks (Q2W) through Week 12, and then 80 mg every 12 weeks (Q12W) or Q4W from Week 12 to Week 60. Table 8 shows trough serum ixekizumab concentrations at Weeks 8, 12, 24, 36, and 48.

During the induction dosing period, 99 of 1276 subjects (7.8%) tested positive for ADA, and 10 of 99 subjects (10.1%) were found to have neutralizing antibodies.

Table 8. Trough serum ixekizumab concentrations following multiple subcutaneous doses of ixekizumab in patients with psoriasis vulgaris or psoriatic arthritis (μg/mL)

	Japanese subgroup		Overall study population	
	Q4W	Q2W	Q4W	Q2W
Week 8	3.25 (−) [1]	6.83 (−) [1]	2.50 (97) [93]	6.56 (118) [67]
Week 12	3.46 (43.9) [6]	8.83 (44.4) [6]	2.94 (89) [215]	7.73 (79) [192]
	Q12W	Q4W	Q12W	Q4W
Week 24	−	2.43 (−) [2]	0.281 (175) [60]	2.36 (111) [223]
Week 36	0.211 (−) [2]	2.92 (39.0) [3]	0.195 (114) [55]	2.68 (114) [262]
Week 48	−	1.90 (195) [6]	0.259 (152) [38]	2.70 (123) [227]

Geometric mean (geometric coefficient of variation [CV]) [number of subjects]

6.1.2 Global study (CTD 5.3.5.1.5, Study RHAP [ongoing since January 2013 (data cut-off on September [redacted], 2015; up to Week 52)])

A global study was conducted to investigate the pharmacokinetics of ixekizumab in patients with psoriatic arthritis [see Section "7.2.5 Global phase III study"] who received a starting dose of 160 mg of ixekizumab subcutaneously, followed by 80 mg Q4W or Q2W. Table 9 shows trough serum ixekizumab concentrations.

Table 9. Trough serum ixekizumab concentrations following multiple subcutaneous doses of ixekizumab in patients with psoriatic arthritis (μg/mL)

	Japanese subgroup		Overall study population	
	Q4W	Q2W	Q4W	Q2W
Week 2	−	7.55 (−) [2]	9.19 (36.6) [28]	8.97 (35.0) [22]
Week 4	6.97 (−) [1]	−	4.92 (51.3) [26]	10.2 (56.5) [33]
Week 8	−	9.00 (−) [2]	4.20 (66.0) [19]	8.60 (55.8) [18]
Week 12	−	5.92 (59.1) [3]	4.05 (51.4) [44]	9.45 (50.9) [39]
Week 16	5.10 (−) [1]	−	3.83 (67.6) [22]	10.8 (55.5) [28]
Week 24	−	6.62 (−) [2]	3.17 (73.2) [29]	8.65 (62.7) [23]

Geometric mean (geometric CV) [number of subjects]

6.1.3 Long-term treatment study (CTD 5.3.5.2.1, Study RHAT [ongoing since July 2012 (data cut-off on [redacted], 2014; up to Week 52)])

A Japanese long-term treatment study was conducted to investigate the pharmacokinetics of ixekizumab in patients with psoriasis [see Section "7.2.4 Japanese long-term treatment study"] who received a starting dose of 160 mg of ixekizumab subcutaneously, followed by 80 mg Q2W from Week 2 to Week 12, and then 80 mg Q4W from Week 12 to Week 52. Table 10 shows trough serum ixekizumab concentrations. No differences were observed among disease types.

In addition, 10 of 91 subjects (11.0%) tested positive for ADA, and all of the 10 subjects were found to have plaque psoriasis. No neutralizing antibody was detected.

Table 10. Serum ixekizumab concentrations in following multiple subcutaneous doses of ixekizumab in Japanese patients with psoriasis (μg/mL)

	Overall	Psoriasis vulgaris	Psoriatic arthritis	Pustular psoriasis	Erythrodermic psoriasis
Week 2	8.69 (46.7) [24]	8.18 (47.7) [19]	4.94 (41.0) [5]	13.3 (−) [2]	9.67 (32.7) [3]
Week 4	11.6 (40.2) [44]	11.9 (40.2) [39]	9.61 (36.6) [6]	11.5 (17.7) [3]	7.64 (−) [2]
Week 8	11.2 (41.8) [24]	11.5 (42.5) [22]	10.6 (–) [2]	−	8.27 (−) [2]
Week 12	9.35 (44.6) [26]	9.43 (41.0) [20]	8.04 (40.6) [6]	13.4 (−) [2]	7.49 (66.9) [4]
Week 16	6.31 (66.1) [26]	7.09 (50.5) [22]	4.37 (44.6) [4]	3.57 (−) [2]	3.06 (−) [2]
Week 24	3.15 (86.6) [34]	3.30 (92.3) [29]	1.28 (212) [4]	4.75 (−) [1]	2.05 (28.3) [4]
Week 36	3.19 (90.4) [11]	3.19 (90.4) [11]	1.60 (−) [1]	−	−
Week 52	2.57 (66.2) [12]	2.57 (70.2) [11]	2.23 (−) [2]	−	2.60 (−) [1]

Geometric mean (geometric CV) [number of subjects]

6.1.4 Clinical pharmacology study (CTD 5.3.3.2.3, Study RHAG [[redacted] 20[redacted] to [redacted] 20[redacted]])

A foreign clinical pharmacology study was conducted to investigate the pharmacokinetics of ixekizumab in patients with psoriasis vulgaris who received ixekizumab at 5, 15, 50, or 150 mg subcutaneously, or at 15 mg intravenously. Table 11 shows pharmacokinetic parameters. C_{max} and AUC increased in a dose-proportional manner.

Of 37 subjects in the ixekizumab group, 21 subjects (57%) were ADA positive.

Table 11. Pharmacokinetic parameters following single dose of ixekizumab in patients with psoriasis vulgaris

Dose (mg)	Route of administration	N	C_{max} (ng/mL)	T_{max}[a] (day)	$AUC_{0\text{-tlast}}$ (μg·day/mL)	$AUC_{0\text{-14days}}$ (μg·day/mL)
15	Intravenous	5	3640 (24)	0.13 (0.05-0.38)	21.2 (29)	21.4 (25)
5	Subcutaneous	8	336 (44)	7.06 (1.99-10.26)	3.72 (41)	3.66 (40)
15	Subcutaneous	8	612 (48)	5.65 (3.93-10.02)	7.01 (49)	6.75 (52)
50	Subcutaneous	8	3000 (67)	3.98 (1.93-9.99)	34.0 (70)	32.8 (70)
150	Subcutaneous	8	8190 (39)	4.01 (2.00-10.29)	101 (41)	95.1 (39)

Geometric mean (CV)
a) Median (range)

6.1.5 Phase II study (CTD 5.3.5.1.1, Study RHAJ [ongoing since April 2010 (data cut-off on ■■, 2011; up to Week 20)])

A foreign clinical study was conducted to investigate the pharmacokinetics of ixekizumab in patients with psoriasis vulgaris or psoriatic arthritis [see Section "7.1.1 Foreign phase II study"] who received ixekizumab (10, 25, 75, or 150 mg) subcutaneously at Weeks 0, 2, 4, 8, 12, and 16.

Population pharmacokinetic analysis was performed with serum ixekizumab concentration data (651 serum concentration samples from 115 subjects) by NONMEM version 7. A 2-compartment model with first-order absorption and linear elimination including body weight as a covariate on total body clearance (CL) was identified as the final model. Major population pharmacokinetic parameters [95% confidence interval (CI)] estimated from the final model were 0.0177 [0.0160, 0.0199] L/h for CL, 5.88 [5.12, 6.60] L for volume of distribution in the central compartment (V2), and 2.79 L for volume of distribution in the peripheral compartment (V3). Table 12 shows estimated pharmacokinetic parameter values in individual subjects.

Table 12. Estimated pharmacokinetic parameters following multiple subcutaneous doses of ixekizumab in patients with psoriasis vulgaris or psoriatic arthritis (Study RHAJ)

Dose	N	C_{max} (μg/mL)	T_{max} (day)[a]	C_{trough} (μg/mL)	$AUC_{0\text{-}\tau}$ (μg·day /mL)	CL (L/h)
10 mg	28	0.772 (59.0)	7.00 (6.50-8.00)	0.202 (158)	12.1 (84.4)	0.0225 (51.6)
25 mg	30	1.90 (37.8)	7.00 (7.00-8.00)	0.653 (58.3)	32.5 (45.2)	0.0191 (24.0)
75 mg	29	5.49 (42.3)	7.00 (7.00-8.00)	1.82 (89.4)	93.3 (57.3)	0.0190 (39.3)
150 mg	28	10.8 (45.1)	7.00 (7.00-8.00)	3.86 (65.8)	188 (52.9)	0.0184 (21.8)

Geometric mean (CV)
a) Median (range)

6.1.6 Clinical pharmacology study (CTD 5.3.3.4.1, Study RHBL [ongoing since March 2013 (data cut-off on May 8, 2014; up to Week 12)])

A foreign clinical pharmacology study was conducted to investigate impacts of injector type (prefilled syringe or autoinjector) and injection site (upper arm, thigh, or abdomen) on the pharmacokinetics of ixekizumab in patients with psoriasis. Table 13 shows the pharmacokinetic parameters following single subcutaneous administration of ixekizumab 160 mg using prefilled syringe and autoinjector.

Table 13. Pharmacokinetic parameters following a single subcutaneous dose of ixekizumab 160 mg in patients with psoriasis

Injector	N	C_{max} (μg/mL)	T_{max}[a] (day)	C_{last} (μg/mL)	$AUC_{0\text{-tlast}}$[b] (μg·day/mL)
Prefilled syringe	94	15.0 (45) [13.9, 16.1]	3.97 (1.88-13.96)	8.98 (40) [8.41, 9.59]	157 (41) [147, 168]
Auto-injector	98	14.8 (46) [13.8, 15.9]	4.00 (1.88-14.01)	9.22 (51) [8.52, 9.98]	154 (44) [144, 165]

Geometric mean (CV) [90% CI]
a) Median (range)
b) Last time point was within 24 hours before and after Day 14

Table 14 shows pharmacokinetic parameters by injection site following single subcutaneous administration of ixekizumab 160 mg using prefilled syringe and autoinjector. Serum ixekizumab

concentrations tended to be higher following injection on the thigh than those following injection on the upper arm or abdomen.

Table 14. Pharmacokinetic parameters following a single subcutaneous dose of ixekizumab 160 mg in patients with psoriasis

	Injection site	N	C_{max} (μg/mL)	T_{max}[a] (day)	C_{last} (μg/mL)	AUC $_{0\text{-}tlast}$[b] (μg·day/mL)
Prefilled syringe	Upper arm	30	14.4 (53) [12.4, 16.8]	3.97 (1.96-13.96)	8.88 (42) [7.87, 10.0]	151 (48) [131, 173]
	Abdomen	34	12.7 (42) [11.3, 14.2]	4.01 (1.88-9.93)	8.09 (40) [7.26, 9.02]	135 (38) [122, 150]
	Thigh	28	18.5 (27) [17.0, 20.1]	3.97 (2.02-7.04)	10.2 (36) [9.20, 11.4]	190 (26) [176, 206]
Autoinjector	Upper arm	29	11.5 (43) [10.1, 13.0]	4.02 (2.07-10.03)	7.91 (48) [6.89, 9.08]	124 (45) [109, 142]
	Abdomen	32	15.4 (47) [13.5, 17.5]	4.00 (1.88-14.01)	9.77 (45) [8.62, 11.1]	159 (46) [140, 180]
	Thigh	37	17.6 (36) [16.0, 19.4]	3.99 (1.94-13.99)	9.88 (56) [8.59, 11.4]	178 (33) [163, 194]

Geometric mean (CV) [90% CI]
a) Median (range)
b) Last time point was within 24 hours before and after Day 14

6.2 Studies in patients with rheumatoid arthritis

6.2.1 Japanese phase I study (CTD 5.3.3.2.1, Study RHAL [[redacted] 2010 to [redacted] 20[redacted]])

A Japanese clinical study was conducted to investigate the pharmacokinetics of ixekizumab in combination with methotrexate in patients with rheumatoid arthritis (N = 32). Patients received ixekizumab (30, 80, or 180 mg) subcutaneously at Weeks 0, 1, 2, 4, 6, 8, and 10, or a starting dose of 240 mg of ixekizumab subcutaneously at Week 0, followed by 120 mg once weekly. Table 15 shows the pharmacokinetic parameters.

Table 15. Pharmacokinetic parameters following multiple subcutaneous doses of ixekizumab in Japanese patients with rheumatoid arthritis

Regimen	Dose (mg)	N	C_{max} (μg/mL)	C_{min} (μg/mL)	T_{max}[a] (day)	AUC_{τ}[b] (μg·day/mL)	CL/F (L/h)	V/F (L)	$t_{1/2}$ (day)
Q2W	30	5	7.05 (26)	4.25 (33)	1.96 (1.91-7.00)	77.2 (26)	0.0162 (26)	8.54 (31)	13.9 (15)
	80	6	13.5 (43)	8.08 (50)	1.93 (1.89-3.97)	151 (44)	0.0220 (44)	10.3 (26)	12.9 (33)
	180	6	39.3 (42)	23.8 (46)	1.95 (1.88-2.02)	437 (42)	0.0171 (42)	9.53 (29)	16.5 (27)
Q1W	120	6	33.1 (56)	25.0 (37)	3.89 (1.93-3.99)	208 (48)	0.0240 (48)	13.0 (41)	15.2 (19)

Geometric mean (CV)
a) Median (range)
b) τ = 2 weeks or 1 week

6.2.2 Phase II study (CTD 5.3.5.4.2, Study RHAK [[redacted] 2009 to June 2012])

A foreign clinical study was conducted to investigate the pharmacokinetics of ixekizumab in combination with disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis (260 subjects naïve to any biological product, 188 subjects with inadequate response to TNFα antagonists).

This study consisted of 2 parts (Part A and Part B). In Part A, patients naïve to biological products received ixekizumab (3, 10, 30, 80, or 180 mg) subcutaneously, and patients with inadequate response to TNFα antagonists received ixekizumab (80 or 180 mg) subcutaneously at Weeks 0, 1, 2, 4, 6, 8, and 10. In Part B, all patients received ixekizumab 160 mg Q2W subcutaneously from Week 16 to Week 20, followed by Q4W dosing regimen through Week 60.

Population pharmacokinetic analysis was performed with serum ixekizumab concentration data (2753 serum concentration samples from 406 subjects) by NONMEM version 7. A 2-compartment model with first-order absorption and linear elimination including dose and BMI as covariates on CL and age as

covariate on volume of distribution in the central compartment (V2) was identified as the final model. Major population pharmacokinetic parameters [95% CI] estimated from the final model were 0.0142 [0.0133, 0.0151] L/h for CL, 4.25 [2.99, 5.26] L for V2, and 2.10 [1.51, 2.64] L for volume of distribution in the peripheral compartment (V3). Table 16 shows estimated pharmacokinetic parameters in subjects treated in the study.

Table 16. Estimated pharmacokinetic parameters following multiple subcutaneous doses of ixekizumab in patients with rheumatoid arthritis (Study RHAK)

Dose	N	C_{max} (μg/mL)	T_{max} (day)[a)]	C_{trough} (μg/mL)	$AUC_{0-\tau}$ (μg·day/mL)	CL (L/h)
10 mg	32	1.25 (63.6)	4.00 (1.50-8.00)	0.794 (67.4)	14.8 (60.8)	0.0150 (39.6)
30 mg	34	4.19 (47.6)	4.00 (3.00-5.00)	2.77 (44.3)	50.5 (44.8)	0.0135 (26.7)
80 mg	107	9.08 (52.5)	4.00 (1.00-6.00)	5.38 (57.5)	105 (50.3)	0.0170 (32.3)
180 mg	78	20.2 (47.5)	4.00 (3.00-5.50)	12.6 (52.1)	239 (47.7)	0.0168 (30.3)

Geometric mean (CV)
a) Median (range)

6.3 Population pharmacokinetic analysis (CTD 5.3.3.5.2)

Population pharmacokinetic analysis was performed with serum ixekizumab concentration data (6059 serum concentration samples from 1399 subjects) obtained from Japanese and foreign clinical studies in patients with psoriasis (Studies RHAG, RHAJ, and RHAZ) by NONMEM Version 7.3.0.

A 2-compartment model was identified as the basic model, and covariates selected were body weight, ADA titer, and neutralizing antibody as covariates on CL, body weight as one on volume of distribution in the central compartment (V2), body weight as one on peripheral compartment (V3), and study and injection site as ones on bioavailability. A 2-compartment model with first-order absorption and linear elimination including the selected covariates was identified as the final model. Major population pharmacokinetic parameters [95% CI] estimated from the final model were 0.0156 [0.0151, 0.0161] L/h for CL, 2.59 [1.83, 3.35] L for V2, and 4.32 [3.95, 4.69] L for V3.

The analysis with the covariates selected revealed that bioavailability was influenced by study. Bioavailability was estimated to be 81% in Study RHAZ and 60% in Studies RHAG and RHAJ. This result was considered partly attributable to a difference in dosage form, for the following reasons: Pharmacokinetic parameters following administration of ixekizumab 160 mg presented by non-compartment analysis (Studies RHAG and RHBL) were compared with those estimated from the population pharmacokinetic model at the ixekizumab dose of 160 mg (Studies RHAZ and RHAT), and AUC tended to be higher in studies using the solution formulation than in a study using the lyophilized formulation. The solution formulation was used in Study RHAZ ($AUC_{0\text{-}14\ days}$, 154 μg·day/mL), Study RHAT ($AUC_{0\text{-}14days}$, 174 μg·day/mL), and Study RHBL ($AUC_{0\text{-}14days}$, 157 μg·day/mL), and the lyophilized formulation was used in Study RHAG ($AUC_{0\text{-}14days}$, 72.0-117 μg·day/mL).

In addition, the injection site had an impact on bioavailability, which was estimated to be 11% to 25% higher following injection on the thigh than that following injection on the upper arm, abdomen, or hip.

Body weight had an impact on CL, V2, and V3. Trough serum ixekizumab concentrations tended to decrease with increasing body weight (Table 17).

Table 17. Relationship between body weight and estimated trough serum ixekizumab concentrations (μg/mL) based on population pharmacokinetic analysis (Study RHAZ)

Body weight	Q2W	Q4W
≥100 kg	7.13 (1.25, 14.4)	2.45 (0.00544, 5.89)
<100 kg	10.8 (0.0106, 21.1)	4.07 (0.00171, 8.60)

Median (first quartile point + interquartile range × 1.5, third quartile point + interquartile range × 1.5)

6.4 Exposure-response analysis (CTD 5.3.3.5.2 and CTD 5.3.3.5.3)

Exposure-response analysis was performed using psoriasis area and severity index (PASI) and static physician global assessment (sPGA) scores obtained from clinical studies in patients with psoriasis (Studies RHAJ and RHAZ) as well as trough serum ixekizumab concentrations at Week 12 in Studies RHAJ and RHAZ estimated from the population pharmacokinetic model.

An ordered categorical model best described the sPGA data, and a logistic regression model best described the PASI data.

Exposure-response models were developed to predict sPGA (0 or 1) response rate, sPGA (0) response rate, and the percentage of patients who achieved ≥75%, ≥90%, or 100% improvement in the PASI score from baseline (PASI 75, PASI 90, and PASI 100 response rates, respectively) based on exposure at Week 12. Table 18 shows the model-predicted estimates. The response rates were predicted to be higher with the ixekizumab 80 mg Q2W dosing regimen than with the 80 mg Q4W dosing regimen. Table 19 shows sPGA (0 or 1), sPGA (0), and PASI 75/90/100 response rates predicted by quartile of the simulated trough levels. The lowest quartile category showed a trend toward increasing differences in response rate between the Q2W and Q4W dosing regimens.

Table 18. sPGA and PASI response rates (Study RHAZ) predicted from exposure-response model (Studies RHAG, RHAJ, and RHAZ)

Treatment group	N	sPGA (0 or 1) response rate	sPGA (0) response rate	PASI 75 response rate	PASI 90 response rate	PASI 100 response rate
Q2W	406	87 (84)	41 (38)	94 (92)	77 (73)	39 (37)
Q4W	390	83 (80)	34 (36)	90 (87)	70 (67)	32 (35)
Difference in dosing frequency (%)		4 (4)	7 (2)	4 (5)	7 (6)	7 (2)

Predicted data (observed data): Estimates based on the median trough serum ixekizumab concentration (observed data from Study RHAZ)

Table 19. sPGA and PASI response rates by trough serum ixekizumab concentration quartile, predicted from exposure-response model (Studies RHAG, RHAJ, and RHAZ)

C_{trough} (µg/mL) Median (range)	Q2W				
	sPGA (0 or 1) response rate	sPGA (0) response rate	PASI 75 response rate	PASI 90 response rate	PASI 100 response rate
5.2 (0.0-6.7)	82	32	92	68	29
8.1 (6.7-9.2)	86	39	93	76	37
11 (9.2-12)	88	44	94	78	42
14 (12-27)	92	54	94	84	54
C_{trough} (µg/mL) Median (range)	Q4W				
	sPGA (0 or 1) response rate	sPGA (0) response rate	PASI 75 response rate	PASI 90 response rate	PASI 100 response rate
1.7 (0.0-2.3)	70	19	83	54	17
2.9 (2.4-3.4)	82	32	89	67	30
4.1 (3.4-4.7)	85	37	91	73	35
5.8 (4.8-16)	90	48	93	80	47

Predicted data: Estimates based on the median trough serum ixekizumab concentration.

Exposure-response analysis was performed using PASI score, sPGA, and trough serum ixekizumab concentrations (observed data) obtained from clinical studies in patients with psoriasis (Studies RHAZ, RHBA, and RHBC).

Table 20 shows exposure-response model-predicted sPGA (0 or 1), sPGA (0), and PASI 75/90/100 response rates based on the observed data of exposure at Week 12. Table 21 shows the model-predicted sPGA (0 or 1), sPGA (0), and PASI 75/90/100 response rates by quartile of the simulated trough levels.

Table 20. sPGA and PASI response rate predicted from exposure-response model (Studies RHAZ, RHBA, and RHBC)

Treatment group	N	sPGA (0 or 1) response rate	sPGA (0) response rate	PASI 75 response rate	PASI 90 response rate	PASI 100 response rate
Q2W	1062	86 (85)	42 (41)	93 (92)	74 (72)	39 (39)
Q4W	1035	84 (79)	37 (36)	90 (86)	68 (67)	34 (35)
Difference in dosing frequency (%)		2 (5)	5 (5)	3 (6)	6 (5)	5 (4)

Predicted data (observed data): Estimates based on the median trough serum ixekizumab concentration (observed data from the pooled analysis of Studies RHAZ, RHBA, and RHBC).

Table 21. sPGA and PASI response rates by trough serum ixekizumab concentration quartile, predicted from exposure-response model (Studies RHAZ, RHBA, and RHBC)

C_{trough} (μg/mL) Median (range)	Q2W				
	sPGA (0 or 1) response rate	sPGA (0) response rate	PASI 75 response rate	PASI 90 response rate	PASI 100 response rate
4.4 (0.0-6.2)	81	32	90	66	31
7.7 (6.3-9.1)	85	40	93	73	37
1.1 (9.1-12)	88	45	94	76	42
14 (12-37)	90	50	95	80	47
C_{trough} (μg/mL) Median (range)	Q4W				
	sPGA (0 or 1) response rate	sPGA (0) response rate	PASI 75 response rate	PASI 90 response rate	PASI 100 response rate
1.3 (0.0-1.9)	69	20	80	52	22
2.4 (1.9-3.0)	82	35	89	66	33
3.7 (3.0-4.5)	86	42	91	71	38
5.7 (4.5-13)	89	47	94	77	44

Predicted data: Estimates based on the median trough serum ixekizumab concentration.

The relationships of trough serum ixekizumab concentrations at Week 12 and Week 60 predicted from the population pharmacokinetic model with data from Studies RHAZ, RHBA, and RHBC with the incidences of infections (especially, Candida infection, Staphylococcal infection), neutrophil count decreased, injection site reaction, and hypersensitivity were investigated by dosing period, based on the exposure-response analysis (Studies RHAZ, RHBA, and RHBC). As shown in Table 22, there was a trend toward higher incidences of the injection site reaction at higher serum ixekizumab concentrations during both induction and maintenance dosing periods. In addition, only during the induction dosing period, the incidences of Candida infection and Grade 2 neutrophil count decreased were found to be related to serum ixekizumab concentrations.

Table 22. Incidences of adverse events by trough serum ixekizumab concentration quartile (predicted data), based on exposure-response analysis

C_{trough} (μg/mL) (N)	Induction dosing period					
	Infections	Candida infection	Staphylococcal infection	Grade 2 neutrophil count decreased	Injection site reaction	Hypersensitivity
<2.79 (N = 525)	141 (26.9)	4 (0.8)	2 (0.4)	7 (1.3)	59 (11.2)	21 (4.0)
≥2.79 and <5.25 (N = 524)	146 (27.9)	5 (1.0)	0	10 (1.9)	55 (10.5)	18 (3.4)
≥5.25 and <9.40 (N = 522)	142 (27.2)	4 (0.8)	0	10 (1.9)	89 (17.0)	20 (3.8)
≥9.40 (N = 528)	143 (27.1)	8 (1.5)	1 (0.2)	25 (4.7)	107 (20.3)	19 (3.6)
Placebo (N = 791)	181 (22.9)	4 (0.5)	2 (0.3)	7 (0.9)	26 (3.3)	15 (1.9)
C_{trough} (μg/mL) (N)	Maintenance dosing period					
	Infections	Candida infection	Staphylococcal infection	Grade 2 neutrophil count decreased	Injection site reaction	Hypersensitivity
<1.30 (N = 405)	218 (53.8)	10 (2.5)	0	11 (2.7)	26 (6.4)	28 (6.9)
≥1.30 and <2.48 (N = 410)	222 (54.1)	14 (3.4)	1 (0.2)	5 (1.2)	31 (7.6)	28 (6.8)
≥2.48 and <3.98 (N = 410)	211 (51.5)	20 (4.9)	1 (0.2)	11 (2.7)	30 (7.3)	30 (7.3)
≥3.98 (N = 403)	245 (60.8)	12 (3.0)	3 (0.7)	12 (3.0)	79 (19.6)	33 (8.2)

n (%)

6.R Outline of the review conducted by PMDA

6.R.1 Ethnic differences in pharmacokinetics of ixekizumab

The applicant's explanation about ethnic differences in the pharmacokinetics of ixekizumab:

Median trough serum ixekizumab concentrations in Japanese patients with rheumatoid arthritis receiving multiple subcutaneous doses of ixekizumab 80 mg (7.57-10.7 μg/mL) in Study RHAL were

higher than the trough concentrations in non-Japanese patients with rheumatoid arthritis predicted from the population pharmacokinetic model of Study RHAK (6.54-7.40 μg/mL). The population pharmacokinetic analysis revealed that body weight influenced the pharmacokinetics of ixekizumab, and that the exposure thus tended to decrease with increasing body weight. In light of this finding, the difference in the trough concentrations was partly attributable to lower body weight of Japanese patients with rheumatoid arthritis in Study RHAL (median [range], 51 kg [40-92 kg]) compared with that of non-Japanese patients with rheumatoid arthritis in Study RHAK (median [range] in Part A, 71 kg [39-163 kg]).

Trough serum ixekizumab concentrations (mean ± SD) at Week 12 after treatment with the 80 mg Q2W dosing regimen in non-Japanese patients with psoriasis in Study RHAZ, Japanese patients with psoriasis in Study RHAZ, and Japanese patients with psoriasis in Studies RHAZ and RHAT were 10.3 ± 5.33 μg/mL, 9.47 ± 3.58 μg/mL, and 10.1 ± 3.63 μg/mL, respectively, which were almost comparable. In the population pharmacokinetic analysis (CTD 5.3.3.5.2), race and ethnicity were not selected as covariates. In another population pharmacokinetic analysis[5)] (CTD 5.3.3.5.4) including Study RHAT, "Japanese" was included in the final model as a covariate on CL. As a result, the model-predicted CL [95% CI] and exposure were 13.9% [7.67, 21.5] higher and approximately 12% lower, respectively, in Japanese patients with psoriasis than in non-Japanese patients with psoriasis. Table 23 shows pharmacokinetic parameters in Japanese and non-Japanese patients predicted from the population pharmacokinetic model, indicating no large differences between the two subgroups.

Table 23. Pharmacokinetic parameters in Japanese and non-Japanese patients, predicted by population pharmacokinetic analysis including Study RHAT

Study	Dosing regimen		N	C_{max} (μg/mL)	AUC (μg·day/mL)	C_{trough} (μg/mL)	$t_{1/2}$ (days)
RHAZ	80 mg Q2W	Japanese	9	14.9 (25.4)	164 (27.7)	8.04 (34.8)	11.4 (6.40-13.4)
		Non-Japanese	424	14.4 (34.0)	164 (41.5)	8.49 (59.3)	13.2 (0.410-44.0)
	80 mg Q4W	Japanese	12	11.0 (15.7)	183 (23.1)	3.00 (41.9)	11.8 (7.83-18.9)
		Non-Japanese	420	9.94 (32.5)	175 (43.0)	3.05 (86.4)	13.5 (0.916-121)
RHAT	80 mg Q2W	Japanese	91	17.1 (27.8)	195 (31.5)	10.1 (39.1)	12.2 (5.58-28.5)

Geometric mean (CV)

Figure 1 shows exposure-response relationships for sPGA (0 or 1) response rate and PASI 75 response rate at Week 12 in Japanese and non-Japanese patients, indicating no marked differences between the two subgroups. The incidences of injection site reaction, Candida infection, and Grade 2 neutrophil count decreased, which were related to trough serum ixekizumab concentrations (predicted data), were 13.2% (16 of 121 subjects), 1.7% (2 of 121 subjects), and 5.0% (6 of 121 subjects), respectively, in the Japanese subgroup (all Japanese psoriasis Ixekizumab exposures integrated analysis set [J-APS]), and 15.2% (638 of 4204 subjects), 3.0% (128 of 4204 subjects), and 3.0% (124 of 4204 subjects), respectively, in the overall study population (all psoriasis Ixekizumab exposures integrated analysis set [APS]). There were no events that occurred with a markedly higher incidence in the Japanese subgroup than in the overall study population.

5) Population pharmacokinetic analysis (including 6476 serum concentration samples from 1490 subjects) was performed using the population pharmacokinetic analysis model and data as well as serum ixekizumab concentration data in Study RHAT.

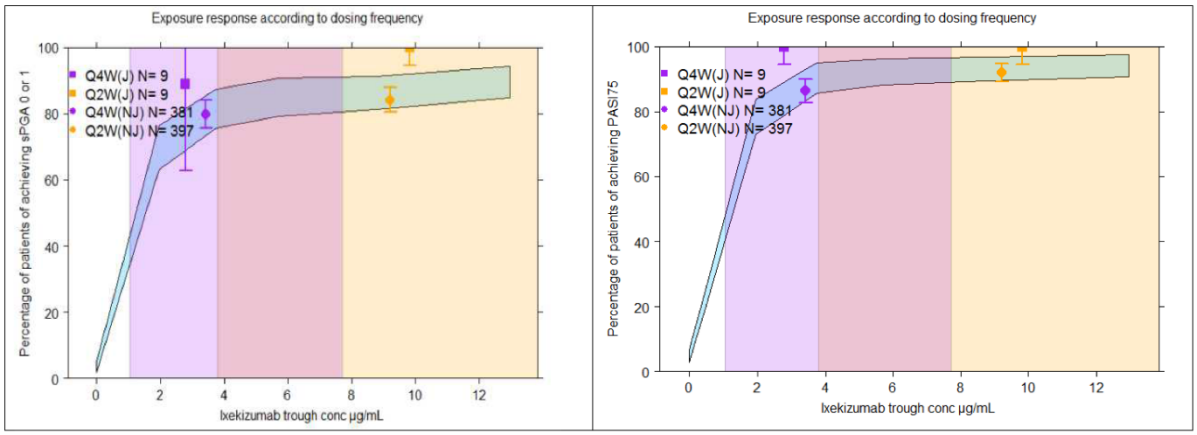

Figure 1. Exposure-response relationships for sPGA (0 or 1) response rate (left) and PASI 75 response rate (right) at Week 12 presented by population pharmacokinetic analysis and exposure-response analysis

Blue area, 95% CI of the response; purple area, 95% CI of the predicted serum ixekizumab concentration with Q4W dosing regimen; orange area, 95% CI of the predicted serum ixekizumab concentration with Q2W dosing regimen

●, Measured values in non-Japanese patients; ■, measured values in Japanese patients

The above data did not indicate any substantial ethnic differences in the pharmacokinetics of ixekizumab. The applicant considers that there are no differences in pharmacokinetics between Japanese and non-Japanese patients that potentially affect the efficacy or safety.

PMDA accepted the above explanation and has concluded that there are no clear ethnic differences in pharmacokinetics that potentially affect the efficacy or safety.

6.R.2 ADA

The applicant's explanation about ADA development as well as its effects on pharmacokinetics, efficacy, and safety:

Table 24 shows the development of ADA and neutralizing antibody in clinical studies in patients with psoriasis. In the APS, the number of neutralizing antibody positive subjects was smaller than that of subjects with undetermined neutralizing antibody status[6)] or neutralizing antibody negative subjects, giving a limitation to comparison between neutralizing antibody positive subjects and subjects with undetermined neutralizing antibody status or neutralizing antibody negative subjects. No clear differences, however, were found in demographic characteristics, baseline patient characteristics, or previous therapies for psoriasis between ADA negative subjects and ADA positive subjects or between ADA positive subjects and subjects with undetermined neutralizing antibody status[6)] or negative subjects. Patient characteristics that were common between ADA positive subjects and neutralizing antibody positive subjects were not identified clearly.

6) Subjects provided samples in which neutralizing antibody was not detected, but ixekizumab concentrations exceeded 622 ng/mL, resulting in a failure to determine neutralizing antibody negative status.

Table 24. Development of ADA and neutralizing antibody

Dosing period	Treatment group		N	ADA positive			
				Overall	Low ADA titer[b)]	Neutralizing antibody positive	Undetermined neutralizing antibody status
Induction dosing period (PPC)	Pooled ixekizumab	Overall	2293	256 (11.2)	157 (61.3)	24 (1.0)	213 (9.3)
	Q2W	Overall	1150	103 (9.0)	66 (64.1)	5 (0.4)	94 (8.2)
	Q4W	Overall	1143	153 (13.4)	91 (59.5)	19 (1.7)	119 (10.4)
	Placebo	Overall	781	4 (0.5)	3 (75.0)	1 (0.1)	1 (0.1)
Maintenance dosing period[a)] (MPP)	Ixekizumab/pooled ixekizumab	Overall	659	141 (21.4)	128 (90.8)	5 (0.8)	73 (11.1)
	Ixekizumab/Q4W	Overall	330	57 (17.3)	54 (94.7)	1 (0.3)	55 (16.7)
	Ixekizumab/Q12W	Overall	329	84 (25.5)	74 (88.1)	4 (1.2)	18 (5.5)
	Ixekizumab/placebo	Overall	330	80 (24.2)	68 (85.0)	4 (1.2)	8 (2.4)
Total dosing period (APS)	Ixekizumab (subjects who received at least 1 dose of ixekizumab)	Overall	4107	826 (20.1)		89 (2.2)	637 (15.5)
		Japanese	121	13 (10.7)		0	12 (9.9)

n (%)

a) Tabulation of data from subgroups of subjects who received ixekizumab during the induction dosing period and then achieved sPGA (0 or 1) in Studies RHAZ and RHBA.

b) Percentage of subjects with low ADA titer relative to overall ADA positive subjects

Table 25 shows relationships of trough serum ixekizumab concentrations (observed data) with ADA titer and neutralizing antibody status during the induction dosing period in Study RHAZ. Ixekizumab exposure in ADA positive subjects with a low titer (<1:160[7)]) was comparable to that in ADA negative subjects, but the exposure in ADA positive subjects with a moderate-to-high titer (≥1:160) tended to be lower than that in ADA negative subjects. A similar trend was observed in the Q4W dosing group during the maintenance period. In addition, trough serum ixekizumab concentrations in neutralizing antibody positive subjects were extremely low. On the other hand, the range of trough serum ixekizumab concentrations in subjects with undetermined neutralizing antibody status was similar to that in ADA negative subjects.

In the population pharmacokinetic analysis, ADA and neutralizing antibody were selected as covariates on CL, and both ADA titer and neutralizing antibody status were factors that affected the CL in the population pharmacokinetic model. The median CL in ADA positive subjects with a moderate-to-high titer predicted from the population pharmacokinetic model was 0.0325 L/h, which was approximately 2-fold that in ADA negative subjects (0.0158 L/h) or ADA positive subjects with a low titer (0.0179 L/h). The median CL in subjects who were positive for both ADA and neutralizing antibody was estimated to be 0.286 L/h, which was approximately 18-fold that in ADA negative subjects.

Table 25. Trough serum ixekizumab concentrations by antibody titer category or neutralizing antibody category (Study RHAZ)

	Trough serum ixekizumab concentration (μg/mL)			
Antibody titer category	Induction dosing period (12 weeks)		Maintenance dosing period	
	Q2W	Q4W	Q4W	Q12W
ADA negative	10.2 ± 4.83 (265)	4.36 ± 2.29 (259)	3.88 ± 2.45 (456)	0.565 ± 0.981 (73)
ADA positive (low titer)	6.35 ± 4.10 (54)	3.00 ± 2.15 (66)	2.95 ± 2.11 (198)	0.234 ± 0.231 (75)
ADA positive (high titer)	2.69 ± 3.14 (27)	0.71 ± 1.03 (36)	1.43 ± 1.71 (119)	0.337 ± 0.355 (18)
Neutralizing antibody status category	Induction dosing period (12 weeks)		Maintenance dosing period	
	Q2W	Q4W	Q4W	Q12W
ADA negative	10.2 ± 4.83 (265)	4.36 ± 2.29 (259)	3.88 ± 2.45 (456)	0.565 ± 0.981 (73)
ADA positive and neutralizing antibody negative	0.304 ± 0.198 (6)	0.158 ± 0.156 (18)	0.344 ± 0.206 (27)	0.192 ± 0.150 (84)
ADA positive and neutralizing antibody indefinitive	6.08 ± 3.88 (68)	2.86 ± 2.04 (71)	2.93 ± 2.00 (253)	0.926 ± 0.235 (8)
Both ADA and neutralizing antibody positive	0.00376 ± 0.0506 (7)	0.00375 ± 0 (9)	0.111 ± 0.403 (37)	0.00375 (1)

Mean ± SD (N)

7) Dilution factor. Equivalent to ADA concentration of approximately 147.2 ng/mL

Pooled analysis of the primary psoriasis placebo-controlled integrated analysis set (PPC) revealed that the sPGA (0 or 1) and PASI 75 response rate in ADA positive subjects with a low titer were 76.4% (120 of 157 subjects) and 84.7% (133 of 157 subjects), respectively, and these results were comparable to those in ADA negative subjects (81.1% [1652 of 2037 subjects] and 87.9% [1791 of 2037 subjects], respectively). Furthermore, sPGA (0 or 1) and PASI 75 response rates were 48.5% (48 of 99 subjects) and 53.5% (53 of 99 subjects), respectively, in ADA positive subjects with a moderate-to-high titer, and 4.2% (1 of 24 subjects) and 8.3% (2 of 24 subjects), respectively, in neutralizing antibody positive subjects. The results in both subgroups were lower than those in ADA negative subjects. Based on the above, decreased serum ixekizumab concentrations in neutralizing antibody positive subjects potentially result in lower responses.

In the APS, there was no clear relationship between ADA status and adverse events including allergic reaction, hypersensitivity, and injection site reaction. No findings related to hypersensitivity reaction were observed in ADA positive subjects with a high titer. Although the number of affected subjects was limited, serious non-anaphylactic symptoms occurred in ADA positive subjects.

PMDA has concluded that attention should be continuously paid to the development of ADA and neutralizing antibody in patients who have a markedly decreased response to the treatment and who has experienced hypersensitivity reaction, because (i) neutralizing antibody was detected in ADA positive subjects; (ii) decreased serum ixekizumab concentrations in subjects positive for neutralizing antibody tended to result in a decrease in the response to ixekizumab; and (iii) serious adverse events occurred in ADA positive subjects, although the number of affected subjects was limited.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, which included results from a foreign phase II study (Study RHAJ [CTD 5.3.5.1.1]), global phase III studies including Japan (Study RHAZ [CTD 5.3.5.1.2], Study RHAP [CTD 5.3.5.1.5]), foreign phase III studies (Study RHBA [CTD 5.3.5.1.3], Study RHBC [CTD 5.3.5.1.4]), and a Japanese long-term treatment study (Study RHAT [CTD 5.3.5.2.1]). All of these studies enrolled patients with psoriasis.

7.1 Phase II studies

7.1.1 Foreign phase II study (CTD 5.3.5.1.1, Study RHAJ [ongoing since April 2010 (data cut-off on June 24, 2011; up to Week 20)])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in the US and Denmark to investigate the efficacy and safety of ixekizumab in patients with moderate to severe plaque psoriasis vulgaris and patients with moderate to severe plaque psoriatic arthritis[8] (target sample size, 125 subjects [n = 25 per group]).

Ixekizumab 10, 25, 75, or 150 mg, or placebo was subcutaneously administered at Weeks 0, 2, 4, 8, 12, and 16.

All of the 142 randomized subjects (28 in the 10 mg group, 30 in the 25 mg group, 29 in the 75 mg group, 28 in the 150 mg group, 27 in the placebo group) were included in the safety analysis population. Of these, 141 subjects who received at least 1 dose of the study drug and who had at least 1 post-baseline assessment of PASI (28 in the 10 mg group, 30 in the 25 mg group, 29 in the 75 mg group, 28 in the 150 mg group, 26 in the placebo group) were included in the modified intent-to-treat (mITT) population. The mITT population was used for the efficacy analysis. Study treatment was discontinued in 25.0% (7 of 28) of subjects in the 10 mg group, 3.3% (1 of 30) of subjects in the 25 mg group, 10.3% (3 of 29) of subjects in the 75 mg group, 3.6% (1 of 28) of subjects in the 150 mg group, and 18.5% (5 of 27) of subjects in the placebo group. Main reasons for discontinuation were consent withdrawal (10.7% [3 of 28] of subjects in the 10 mg group, 10.3% [3 of 29] of subjects in the 75 mg group, 3.6% [1 of 28] of subjects in the 150 mg group, 11.1% [3 of 27] of subjects in the placebo group) and adverse events (7.1% [2 of 28] of subjects in the 10 mg group, 3.3% [1 of 30] of subjects in the 25 mg group, 3.7% [1 of 27] of subjects in the placebo group).

[8] Patients with (a) chronic plaque psoriasis persistent for ≥6 months; (b) PASI score ≥12; (c) sPGA score ≥3; (d) psoriasis lesions involving ≥10% body surface area; and (e) psoriasis except for pustular psoriasis, erythrodermic psoriasis, and guttate psoriasis.

Table 26 shows the PASI[9] 75 response rate and sPGA[10] (0 or 1) response rate at Week 12, which were the primary and secondary efficacy endpoints, respectively.

Table 26. PASI 75 response rate (primary endpoint) and sPGA (0 or 1) response rate at Week 12 (mITT population, LOCF)

	10 mg	25 mg	75 mg	150 mg	Placebo	Difference between groups [95% CI], *P* value[a]			
						10 mg	25 mg	75 mg	150 mg
PASI 75 response rate	28.6 (8/28)	76.7 (23/30)	82.8 (24/29)	82.1 (23/28)	7.7 (2/26)	20.9 [1.3, 40.5] *P* = 0.079	69.0 [50.7, 87.2] *P* < 0.001	75.1 [57.9, 92.2] *P* < 0.001	74.5 [57.0, 91.9] *P* < 0.001
sPGA (0 or 1) response rate	25.0 (7/28)	70.0 (21/30)	72.4 (21/29)	71.4 (20/28)	7.7 (2/26)	17.3 [-1.7, 36.3]	62.3 [43.0, 81.6]	64.7 [45.5, 83.9]	63.7 [44.1, 83.4]

% (n/N)
a) Fisher's exact test, multiplicity is not considered.

Adverse events (up to Week 20) occurred in 75.0% (21 of 28) of subjects in the 10 mg group, 70.0% (21 of 30) of subjects in the 25 mg group, 58.6% (17 of 29) of subjects in the 75 mg group, 46.4% (13 of 28) of subjects in the 150 mg group, and 63.0% (17 of 27) of subjects in the placebo group. Table 27 shows major events. Neither deaths nor serious adverse events were reported.

Adverse events leading to discontinuation occurred in 7.1% (2 of 28 subjects, hypersensitivity and oedema peripheral in 1 subject each) of subjects in the 10 mg group, 3.3% (1 of 30 subjects, urticaria) of subjects in the 25 mg group, and 3.7% (1 of 27 subjects, hypertriglyceridaemia) of subjects in the placebo group.

Adverse drug reactions occurred in 10.7% (3 of 28) of subjects in the 10 mg group, 6.7% (2 of 30) of subjects in the 25 mg group, 13.8% (4 of 29) of subjects in the 75 mg group, 3.6% (1 of 28) of subjects in the 150 mg group, and 3.7% (1 of 27) of subjects in the placebo group.

Table 27. Adverse events reported by ≥2 subjects in any group (up to Week 20, safety analysis set)

Event	10 mg (N = 28)	25 mg (N = 30)	75 mg (N = 29)	150 mg (N = 28)	Placebo (N = 27)
Headache	4 (14.3)	4 (13.3)	1 (3.4)	1 (3.6)	1 (3.7)
Nasopharyngitis	3 (10.7)	3 (10.0)	3 (10.3)	4 (14.3)	5 (18.5)
Dizziness	2 (7.1)	0	2 (6.9)	0	0
Ear infection	2 (7.1)	0	0	0	0
Upper respiratory tract infection	1 (3.6)	3 (10.0)	1 (3.4)	1 (3.6)	1 (3.7)
Nausea	1 (3.6)	0	2 (6.9)	0	1 (3.7)
Cough	1 (3.6)	0	2 (6.9)	0	0
Oedema peripheral	1 (3.6)	0	0	0	2 (7.4)
Injection site reaction	0	3 (10.0)	1 (3.4)	2 (7.1)	0
Dermatitis contact	0	1 (3.3)	0	2 (7.1)	0
Laceration	0	0	2 (6.9)	1 (3.6)	0
Dry skin	0	0	1 (3.4)	2 (7.1)	0
Hypertriglyceridaemia	0	0	0	0	2 (7.4)

n (%)

7.2 Phase III studies

7.2.1 Global phase III study (CTD 5.3.5.1.2, Study RHAZ [ongoing since December 2011 (data cut-off on June 24, 2014; up to Week 60)])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in 11 countries including Japan, the US, Germany, and Canada to investigate the efficacy and safety of ixekizumab in

9) For each of 4 regions of the body (head, arms, trunk, and legs), the percentage of area affected is determined by rating the severity of erythema, infiltration and acanthosis (raise and induration of plaques), and scaling (desquamation) on a 5-point scale of 0 (none) to 4 (very severe). The severity score (the sum of the above scores) is then multiplied by the percentage of area affected and the percentage of the body surface area for each body region (head, 10%; arms, 20%; trunk, 30%; legs, 40%) to give the PASI (max. 72.0).

10) The overall severity of psoriasis was assessed on a 6-point scale of 0 (clear) to 5 (severe).

patients with moderate to severe plaque psoriasis vulgaris and patients with moderate to severe plaque psoriatic arthritis[11] (target sample size, 1296 subjects [n = 432 per group]).

The study consisted of 3 periods, namely the induction dosing period up to Week 12, maintenance dosing period from Week 12 to Week 60, and extension period from Week 60 to Week 264 (Figure 2). In the induction dosing period, subjects received a starting dose of 160 mg of ixekizumab or placebo subcutaneously, followed by ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, or placebo subcutaneously. In the maintenance dosing period, subjects on ixekizumab during the induction dosing period who achieved sPGA (0 or 1) at Week 12 (responders) were re-randomized at a 1:1:1 ratio to 1 of 3 treatment groups (Q4W, Q12W, and placebo) to receive ixekizumab 80 mg Q4W, ixekizumab 80 mg Q12W, or placebo subcutaneously, while subjects on ixekizumab during the induction dosing period who failed to achieve sPGA (0 or 1) at Week 12 (non-responders) received ixekizumab 80 mg Q4W subcutaneously.

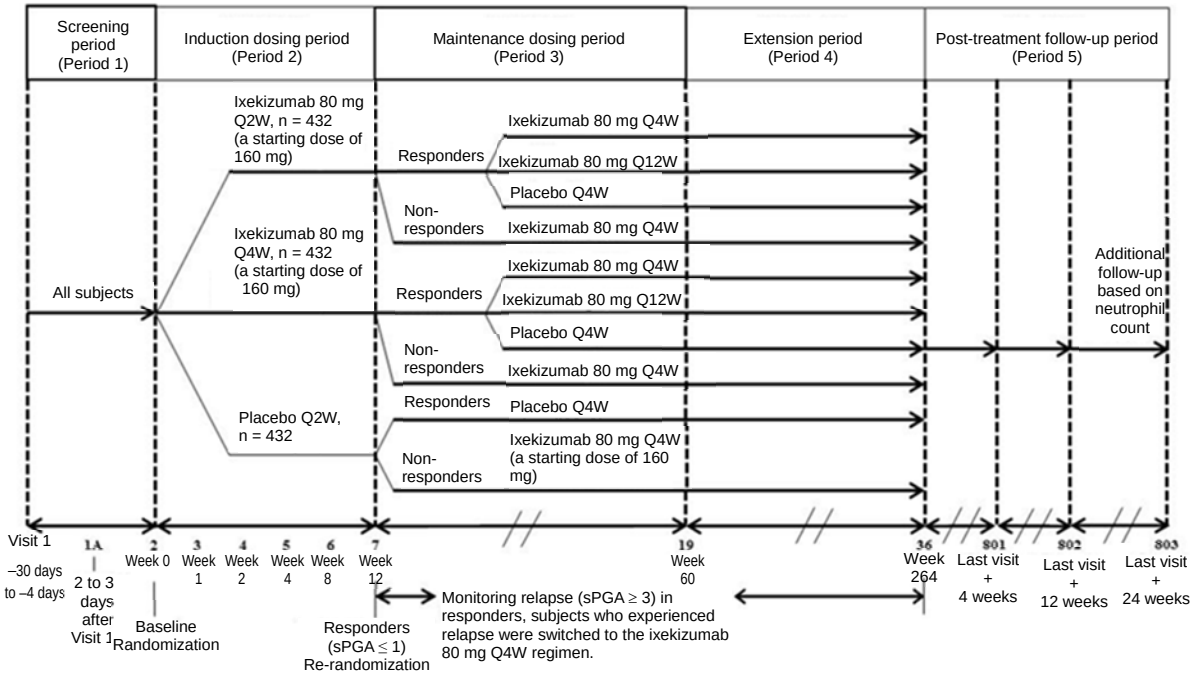

Figure 2. Randomization and dosing plan in Study RHAZ

Among subjects on placebo during the induction dosing period, those who achieved sPGA (0 or 1) at Week 12 (responders) were to receive placebo Q4W subcutaneously, and those who failed to achieve sPGA (0 or 1) at Week 12 (non-responders) were to receive ixekizumab160 mg at Week 12 subcutaneously followed by ixekizumab 80 mg Q4W subcutaneously.
Subjects on ixekizumab Q12W or placebo during the maintenance dosing period who had an sPGA score of ≥3 were to receive ixekizumab 80 mg Q4W subcutaneously.

All of the 1296 randomized subjects (432 in the Q4W group, 433 in the Q2W group, 431 in the placebo group [treatment groups in the induction dosing period]) were included in the safety analysis and ITT populations. The ITT population was used for the efficacy analysis in the induction dosing period. During the induction dosing period, study treatment was discontinued in 5.6% (24 of 432) of subjects in the Q4W group, 4.2% (18 of 433) of subjects in the Q2W group, and 5.6% (24 of 431) of subjects in the placebo group. Main reasons for discontinuation included adverse events (2.3% [10 of 432] of subjects in the Q4W group, 2.3% [10 of 433] of subjects in the Q2W group, 1.4% [6 of 431] of subjects in the placebo group).

The ITT population included 33 Japanese subjects (12 in the Q4W group, 8 in the Q2W group, 13 in the placebo group). During the induction dosing period, study treatment was discontinued in 25.0% (3 of 12) of subjects in the Q4W group and 23.1% (3 of 13) of subjects in the placebo group. Main reasons

[11] Patients with (a) chronic plaque psoriasis persistent for ≥6 months; (b) PASI score ≥12; (c) sPGA score ≥3; (d) psoriasis lesions involving ≥10% body surface area; and (e) psoriasis except for pustular psoriasis, erythrodermic psoriasis, and guttate psoriasis.

for discontinuation included adverse events (25.0% [3 of 12] of subjects in the Q4W group, 7.7% [1 of 13] of subjects in the placebo group).

Table 28 shows the sPGA (0 or 1) response rate and PASI 75 response rate at Week 12 (the primary efficacy endpoints). Pairwise comparisons showed statistically significant differences between the placebo group and the Q4W group or Q2W group, demonstrating the superiority of ixekizumab Q4W and ixekizumab Q2W to placebo. Table 29 shows data from the Japanese subgroup.

Table 28. sPGA (0 or 1) response rate and PASI 75 response rate at Week 12 (ITT population, NRI)

	Q4W	Q2W	Placebo	Difference from placebo [95% CI], *P* value[a) b)]	
				Q4W	Q2W
sPGA (0 or 1) response rate	76.4 (330/432)	81.8 (354/433)	3.2 (14/431)	73.1 [68.8, 77.5] *P* < 0.001	78.5 [74.5, 82.5] *P* < 0.001
PASI 75 response rate	82.6 (357/432)	89.1 (386/433)	3.9 (17/431)	78.7 [74.7, 82.7] *P* < 0.001	85.2 [81.7, 88.7] *P* < 0.001

% (n/N)

a) Logistic regression model using treatment, geographic region, previous non-biologic systemic therapy (inadequate response to, intolerance to, or contraindication to <3 or ≥3 conventional systemic therapies), and weight (<100 kg or ≥100 kg) as explanatory variables.

b) The primary and secondary endpoints were tested by pairwise comparisons of ixekizumab regimens and placebo in the following hierarchical order: the sPGA (0 or 1) response rate at Week 12 and PASI 75 response rate at Week 12 as the primary endpoints and sPGA (0) response rate at Week 12, PASI 90 response rate at Week 12, PASI 100 response rate at Week 12, and sPGA (0 or 1) response rate at Week 60 as the secondary endpoints. For multiple pairwise comparisons between each ixekizumab regimen and placebo for one endpoint, the *P* values were adjusted for multiplicity by a gatekeeping procedure based on the Bonferroni test at 2-sided significance level.

Table 29. sPGA (0 or 1) response rate and PASI 75 response rate at Week 12 (Japanese subgroup, NRI)

	Q4W	Q2W	Placebo	Difference from placebo [95% CI]	
				Q4W	Q2W
sPGA (0 or 1) response rate	66.7 (8/12)	100 (8/8)	0 (0/13)	66.7 [40.0, 93.3]	100 [100, 100]
PASI 75 response rate	75.0 (9/12)	100 (8/8)	0 (0/13)	75.0 [50.5, 99.5]	100 [100, 100]

% (n/N)

During the induction dosing period (up to Week 12), adverse events occurred in 61.1% (264 of 432) of subjects in the Q4W group, 59.4% (257 of 433) of subjects in the Q2W group, and 48.7% (210 of 431) of subjects in the placebo group. Major adverse events are shown in Table 30. No deaths were reported.

Serious adverse events occurred in 2.8% (12 of 432) of subjects in the Q4W group, 1.4% (6 of 433) of subjects in the Q2W group, and 1.2% (5 of 431) of subjects in the placebo group. A causal relationship to the study drug could not be ruled out for the events in 6 subjects in the Q4W group (cellulitis in 2 subjects; acute myocardial infarction, bronchopneumonia, colitis ischaemic, and Crohn's disease in 1 subject each) and 3 subjects in the Q2W group (cellulitis, drug hypersensitivity, and urticaria in 1 subject each).

Adverse events leading to discontinuation occurred in 2.3% (10 of 432) of subjects in the Q4W group, 2.3% (10 of 433) of subjects in the Q2W group, and 1.4% (6 of 431) of subjects in the placebo group.

Adverse drug reactions occurred in 25.7% (111 of 432) of subjects in the Q4W group, 29.3% (127 of 433) of subjects in the Q2W group, and 11.4% (49 of 431) of subjects in the placebo group.

Table 30. Adverse events reported by ≥2% of subjects in any group (safety analysis set in the induction dosing period)

Event	Q4W (N = 432)	Q2W (N = 433)	Placebo (N = 431)
Nasopharyngitis	46 (10.6)	50 (11.5)	41 (9.5)
Injection site reaction	26 (6.0)	42 (9.7)	5 (1.2)
Injection site erythema	18 (4.2)	27 (6.2)	0
Upper respiratory tract infection	21 (4.9)	24 (5.5)	16 (3.7)
Headache	16 (3.7)	18 (4.2)	15 (3.5)
Arthralgia	4 (0.9)	9 (2.1)	9 (2.1)
Diarrhoea	10 (2.3)	8 (1.8)	5 (1.2)
Injection site pain	7 (1.6)	7 (1.6)	9 (2.1)
Pruritus	10 (2.3)	6 (1.4)	13 (3.0)
Psoriasis	2 (0.5)	4 (0.9)	16 (3.7)

n (%)

Adverse events reported in the Japanese subgroup during the induction dosing period (up to Week 12) were summarized. Adverse events occurred in 75.0% (9 of 12) of subjects in the Q4W group, 87.5% (7 of 8) of subjects in the Q2W group, and 76.9% (10 of 13) of subjects in the placebo group. Major adverse events are shown in Table 31. No deaths were reported.

Serious adverse events occurred in 8.3% (1 of 12 subjects, bronchopneumonia) of subjects in the Q4W group and 7.7% (1 of 13 subjects, hypopharyngeal cancer) of subjects in the placebo group. A causal relationship to the study drug could not be ruled out for bronchopneumonia.

Adverse events leading to discontinuation occurred in 25.0% (3 of 12 subjects; allergic oedema, bronchopneumonia, and pruritus generalised in 1 subject each) of subjects in the Q4W group and 7.7% (1 of 13 subjects, hypopharyngeal cancer) of subjects in the placebo group.

Adverse drug reactions occurred in 50.0% (6 of 12) of subjects in the Q4W group, 37.5% (3 of 8) of subjects in the Q2W group, and 0% (0 of 13) of subjects in the placebo group.

Table 31. Adverse events reported by ≥2 subjects in any group (safety analysis set in the induction dosing period [Japanese subgroup])

Event	Q4W (N = 12)	Q2W (N = 8)	Placebo (N = 13)
Pruritus generalised	2 (16.7)	1 (12.5)	0
Tinea pedis	2 (16.7)	0	0
Laceration	2 (16.7)	0	0

n (%)

Of 865 subjects on ixekizumab during the induction dosing period, 682 subjects (227 in the Q12W group, 229 in the Q4W group, 226 in the placebo group) were re-randomized at Week 12 to receive at least 1 dose of the study drug during the maintenance dosing period. The re-randomized subjects were included in the efficacy and safety analyses in the maintenance dosing period. During the maintenance dosing period, study treatment was discontinued in 3.1% (7 of 227) of subjects in the Q12W group, 5.7% (13 of 229) of subjects in the Q4W group, and 7.1% (16 of 226) of subjects in the placebo group. Main reasons for discontinuation included adverse events (0.9% [2 of 227] of subjects in the Q12W group, 3.1% [7 of 229] of subjects in the Q4W group, 1.8% [4 of 226] of subjects in the placebo group) and consent withdrawal (0.9% [2 of 227] of subjects in the Q12W group, 1.3% [3 of 229] of subjects in the Q4W group, 2.7% [6 of 226] of subjects in the placebo group).

The safety analysis set in the maintenance dosing period included 16 Japanese subjects (5 in the Q12W group, 5 in the Q4W group, 6 in the placebo group). During the maintenance dosing period, study treatment was discontinued in 33.3% (2 of 6) of subjects in the placebo group due to adverse events or consent withdrawal.

During the maintenance dosing period (from Week 12 to Week 60), adverse events occurred in 74.0% (168 of 227) of subjects in the Q12W group, 79.5% (182 of 229) of subjects in the Q4W group, and 54.4% (123 of 226) of subjects in the placebo group. Major adverse events are shown in Table 32.

Deaths occurred in 2 subjects (myocardial infarction and death[12)] in 1 subject each) in the Q4W group. A causal relationship to the study drug could not be ruled out for either death.

Serious adverse events occurred in 4.0% (9 of 227) of subjects in the Q12W group, 6.6% (15 of 229) of subjects in the Q4W group, and 3.1% (7 of 226) of subjects in the placebo group. A causal relationship to the study drug could not be ruled out for the events in 1 subject in the Q12W group (encephalopathy), 4 subjects in the Q4W group (abscess/subcutaneous abscess, congenital ectopic pancreas, asthma, and myocardial infarction in 1 subject each).

Adverse events leading to discontinuation occurred in 0.9% (2 of 227) of subjects in the Q12W group, 3.9% (9 of 229) of subjects in the Q4W group, and 1.8% (4 of 226) of subjects in the placebo group.

Adverse drug reactions occurred in 18.5% (42 of 227) of subjects in the Q12W group, 31.0% (71 of 229) of subjects in the Q4W group, and 17.3% (39 of 226) of subjects in the placebo group.

Table 32. Adverse events reported by ≥2% of subjects in any group (safety analysis set in the maintenance dosing period)

Event	Q12W (N = 227)	Q4W (N = 229)	Placebo (N = 226)
Nasopharyngitis	41 (18.1)	50 (21.8)	26 (11.5)
Upper respiratory tract infection	20 (8.8)	17 (7.4)	17 (7.5)
Arthralgia	14 (6.2)	12 (5.2)	7 (3.1)
Injection site reaction	8 (3.5)	12 (5.2)	2 (0.9)
Urinary tract infection	2 (0.9)	10 (4.4)	4 (1.8)
Headache	17 (7.5)	9 (3.9)	5 (2.2)
Oropharyngeal pain	5 (2.2)	9 (3.9)	4 (1.8)
Sinusitis	11 (4.8)	8 (3.5)	7 (3.1)
Diarrhoea	4 (1.8)	8 (3.5)	8 (3.5)
Influenza	8 (3.5)	7 (3.1)	4 (1.8)
Blood creatine phosphokinase increased	4 (1.8)	7 (3.1)	2 (0.9)
Abdominal pain upper	1 (0.4)	7 (3.1)	2 (0.9)
Bronchitis	6 (2.6)	6 (2.6)	1 (0.4)
Gastroenteritis	5 (2.2)	6 (2.6)	2 (0.9)
Back pain	13 (5.7)	5 (2.2)	7 (3.1)
Hypertension	8 (3.5)	5 (2.2)	4 (1.8)
Pruritus	4 (1.8)	5 (2.2)	3 (1.3)
Seasonal allergy	2 (0.9)	5 (2.2)	1 (0.4)
Injection site erythema	2 (0.9)	5 (2.2)	0
Sinus congestion	1 (0.4)	5 (2.2)	2 (0.9)
Otitis externa	1 (0.4)	5 (2.2)	0
Toothache	6 (2.6)	3 (1.3)	2 (0.9)
Pain in extremity	6 (2.6)	3 (1.3)	1 (0.4)
Oral herpes	5 (2.2)	2 (0.9)	3 (1.3)
Skin papilloma	5 (2.2)	2 (0.9)	2 (0.9)
Pharyngitis	8 (3.5)	1 (0.4)	5 (2.2)
Psoriasis	6 (2.6)	1 (0.4)	5 (2.2)
Cystitis	5 (2.2)	1 (0.4)	1 (0.4)

n (%)

Adverse events reported in the Japanese subgroup during the maintenance dosing period (from Week 12 to Week 60) were summarized. Adverse events occurred in 100% (5 of 5) of subjects in the Q12W group, 100% (5 of 5) of subjects in the Q4W group, and 66.7% (4 of 6) of subjects in the placebo group. Major events are as shown in Table 33. Neither deaths nor serious adverse events were reported.

An adverse event leading to discontinuation occurred in 16.7% (1 of 6 subjects, hepatic function abnormal) of subjects in the placebo group.

[12)] The sponsor has not obtained information about history and cause of the death.

Adverse drug reactions occurred in 20.0% (1 of 5) of subjects in the Q12W group, 20.0% (1 of 5) of subjects in the Q4W group, and 16.7% (1 of 6) of subjects in the placebo group.

Table 33. Adverse events reported by ≥2 subjects in any group (safety analysis set in the maintenance dosing period [Japanese subgroup])

Event	Q12W (N = 5)	Q4W (N = 5)	Placebo (N = 6)
Nasopharyngitis	3 (60.0)	2 (40.0)	1 (16.7)
Diarrhoea	1 (20.0)	2 (40.0)	0
Hepatic enzyme increased	0	2 (40.0)	0
Arthralgia	0	2 (40.0)	0
Urticaria	0	2 (40.0)	0

n (%)

7.2.2 Foreign phase III study (CTD 5.3.5.1.3, Study RHBA [ongoing since May 2012 (data cut-off on [redacted], 20[redacted]; up to Week 60)])

A randomized, double-blind, placebo- and etanercept-controlled, parallel-group study was conducted in 12 countries including the US, Canada, and Germany to investigate the efficacy and safety of ixekizumab in patients with moderate to severe plaque psoriasis vulgaris and patients with moderate to severe plaque psoriatic arthritis[13] (target sample size, 1225 subjects [350 in the active drug group, 175 in the placebo group]). Etanercept (which has not been approved in Japan for the indication of psoriasis) has been approved for indications including psoriasis in major countries (mainly in Europe).

The study consisted of 3 periods, namely the induction dosing period up to Week 12, maintenance dosing period from Week 12 to Week 60, and extension period from Week 60 to Week 264 (Figure 3). In the induction dosing period, subjects received a starting dose of 160 mg of ixekizumab or placebo subcutaneously, followed by ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, or placebo subcutaneously, or etanercept 50 mg twice weekly subcutaneously. To ensure blindness for etanercept, placebo was administered twice weekly in the placebo group and ixekizumab group. In the maintenance dosing period, subjects on ixekizumab during the induction dosing period who achieved sPGA (0 or 1) at Week 12 (responders) were re-randomized at a 1:1:1 ratio to 1 of 3 treatment groups (Q4W, Q12W, and placebo) to receive ixekizumab 80 mg Q4W, ixekizumab 80 mg Q12W, or placebo subcutaneously, while subjects who had failed to achieve sPGA (0 or 1) at Week 12 (non-responders) received ixekizumab 80 mg Q4W subcutaneously.

[13] Patients with (a) chronic plaque psoriasis persistent for ≥6 months; (b) PASI score ≥12; (c) sPGA score ≥3; (d) psoriasis lesions involving ≥10% body surface area; and (e) psoriasis except for pustular psoriasis, erythrodermic psoriasis, and guttate psoriasis.

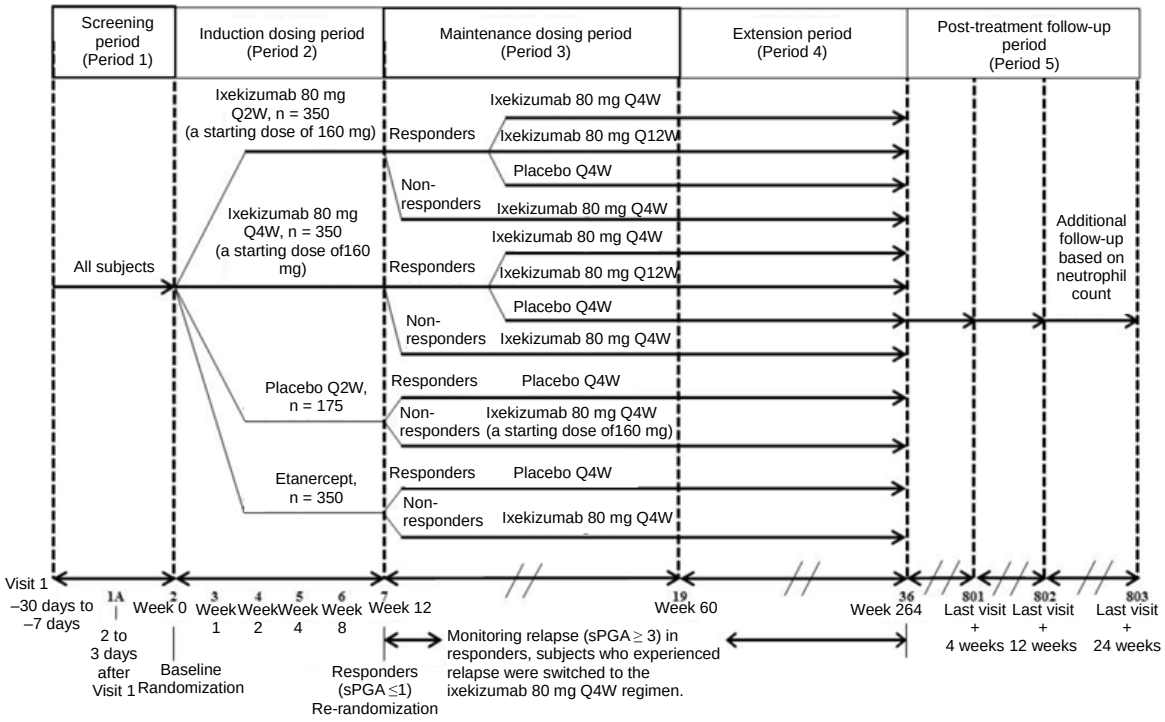

Figure 3. Randomization and dosing plan in Study RHBA

Among subjects on placebo or etanercept during the induction dosing period, those who achieved sPGA (0 or 1) at Week 12 (responders) were to receive placebo Q4W subcutaneously, while subjects on placebo who failed to achieve sPGA (0 or 1) at Week 12 (non-responders) were to receive ixekizumab 160 mg and non-responder on etanercept received placebo subcutaneously, followed by ixekizumab 80 mg Q4W subcutaneously. Subjects on ixekizumab Q12W or placebo during the maintenance dosing period who had an sPGA score of ≥3 were to receive ixekizumab 80 mg Q4W subcutaneously.

All of the 1224 randomized subjects (347 in the Q4W group, 351 in the Q2W group, 358 in the etanercept group, 168 in the placebo group) were included in the ITT population. The efficacy analysis for the induction dosing period was performed based on the ITT population. Of the randomized subjects, 1221 subjects (347 in the Q4W group, 350 in the Q2W group, 357 in the etanercept group, 167 in the placebo group) were included in the safety analysis for the induction dosing period, and the remaining 3 subjects were excluded from the analysis because they did not receive the study drug. During the induction dosing period, study treatment was discontinued in 5.5% (19 of 347) of subjects in the Q4W group, 2.6% (9 of 351) of subjects in the Q2W group, 7.0% (25 of 358) of subjects in the etanercept group, 6.0% (10 of 168) of subjects in the placebo group. Main reasons for discontinuation included consent withdrawal (1.7% [6 of 347] of subjects in the Q4W group, 0.6% [2 of 351] of subjects in the Q2W group, 2.2% [8 of 358] of subjects in the etanercept group, 1.2% [2 of 168] of subjects in the placebo group) and adverse events (1.4% [5 of 347] of subjects in the Q4W group, 1.1% [4 of 351] of subjects in the Q2W group, 1.4% [5 of 358] of subjects in the etanercept group, 0.6% [1 of 168] of subjects in the placebo group).

Table 34 shows the sPGA (0 or 1) response rate and PASI 75 response rate at Week 12 (the primary efficacy endpoints). Pairwise comparisons showed statistically significant differences between the placebo group and the Q4W group or Q2W group, demonstrating the superiority of ixekizumab Q4W and ixekizumab Q2W to placebo.

Table 34. sPGA (0 or 1) response rate and PASI 75 response rate at Week 12 (ITT population, NRI)

	Q4W	Q2W	Etanercept	Placebo	Difference from placebo [95% CI], *P* value[a) b)]		Difference from etanercept [95% CI]	
					Q4W	Q2W	Q4W	Q2W
sPGA (0 or 1) response rate	72.9 (253/347)	83.2 (292/351)	36.0 (129/358)	2.4 (4/168)	70.5 [65.3, 75.7] *P* < 0.001	80.8 [76.3, 85.4] *P* < 0.001	36.9 [30.1, 43.7] *P* < 0.001	47.2 [40.8, 53.5] *P* < 0.001
PASI 75 response rate	77.5 (269/347)	89.7 (315/351)	41.6 (149/358)	2.4 (4/168)	75.1 [70.2, 80.1] *P* < 0.001	87.4 [83.4, 91.3] *P* < 0.001	35.9 [29.2, 42.6] *P* < 0.001	48.1 [42.1, 54.1] *P* < 0.001

% (n/N)

a) Cochran-Mantel-Haenszel test stratified by center

b) The primary and secondary endpoints were tested by pairwise comparisons in the following hierarchical order: ixekizumab regimens versus placebo in terms of the sPGA (0 or 1) response rate at Week 12 and PASI 75 response rate at Week 12 as the primary endpoints; ixekizumab regimens versus etanercept in terms of the above 2 primary endpoints; ixekizumab regimens versus placebo in terms of the sPGA (0) response rate at Week 12, PASI 90 response rate at Week 12, and PASI 100 response rate at Week 12 as the secondary endpoints; ixekizumab regimens versus etanercept in terms of the above 3 secondary endpoints; and ixekizumab regimens versus placebo in terms of the sPGA (0 or 1) response rate at Week 60 in the maintenance dosing period. For multiple pairwise comparisons between each ixekizumab regimen and placebo or etanercept, the *P* values were adjusted for multiplicity by a gatekeeping procedure based on the Bonferroni test at 2-sided significance level.

During the induction dosing period (up to Week 12), adverse events occurred in 58.8% (204 of 347) of subjects in the Q4W group, 61.7% (216 of 350) of subjects in the Q2W group, 59.1% (211 of 357) of subjects in the etanercept group, and 53.3% (89 of 167) of subjects in the placebo group. Major adverse events are shown in Table 35. No deaths were reported.

Serious adverse events occurred in 2.3% (8 of 347) of subjects in the Q4W group, 1.4% (5 of 350) of subjects in the Q2W group, 2.2% (8 of 357) of subjects in the etanercept group, and 1.2% (2 of 167) of subjects in the placebo group. A causal relationship to the study drug could not be ruled out for the events in 2 subjects in the Q4W group (angioedema and urinary tract infection in 1 subject each), 3 subjects in the etanercept group (injection site reaction/loss of consciousness, myocardial infarction, and cellulitis in 1 subject each), and 1 subject in the placebo group (erythrodermic psoriasis).

Adverse events leading to discontinuation occurred in 1.4% (5 of 347) of subjects in the Q4W group, 1.7% (6 of 350) of subjects in the Q2W group, 1.4% (5 of 357) of subjects in the etanercept group, and 0.6% (1 of 167) of subjects in the placebo group.

Adverse drug reactions occurred in 26.5% (92 of 347) of subjects in the Q4W group, 33.4% (117 of 350) of subjects in the Q2W group, 25.5% (91 of 357) of subjects in the etanercept group, and 18.0% (30 of 167) of subjects in the placebo group.

Table 35. Adverse events reported by ≥2% of subjects in any group (safety analysis set in the induction dosing period)

Event	Q4W (N = 347)	Q2W (N = 350)	Etanercept (N = 357)	Placebo (N = 167)
Injection site reaction	19 (5.5)	39 (11.1)	39 (10.9)	1 (0.6)
Nasopharyngitis	29 (8.4)	35 (10.0)	36 (10.1)	17 (10.2)
Upper respiratory tract infection	16 (4.6)	19 (5.4)	26 (7.3)	7 (4.2)
Headache	18 (5.2)	17 (4.9)	20 (5.6)	3 (1.8)
Injection site pain	6 (1.7)	13 (3.7)	4 (1.1)	2 (1.2)
Injection site erythema	9 (2.6)	12 (3.4)	18 (5.0)	2 (1.2)
Fatigue	6 (1.7)	9 (2.6)	4 (1.1)	2 (1.2)
Arthralgia	8 (2.3)	7 (2.0)	10 (2.8)	4 (2.4)
Pruritus	7 (2.0)	7 (2.0)	4 (1.1)	4 (2.4)
Nausea	5 (1.4)	7 (2.0)	1 (0.3)	2 (1.2)
Urinary tract infection	8 (2.3)	5 (1.4)	2 (0.6)	2 (1.2)
Psoriasis	6 (1.7)	4 (1.1)	7 (2.0)	5 (3.0)
Pain in extremity	2 (0.6)	3 (0.9)	1 (0.3)	4 (2.4)
Toothache	7 (2.0)	1 (0.3)	1 (0.3)	0
Type 2 diabetes mellitus	7 (2.0)	0	2 (0.6)	0

n (%)

Of 697 subjects on ixekizumab during the induction dosing period, 544 subjects (181 in the Q12W group, 187 in the Q4W group, 176 in the placebo group) were re-randomized at Week 12 to receive at least 1

dose of the study drug during the maintenance dosing period. The re-randomized subjects were included in the efficacy and safety analyses for the maintenance dosing period. During the maintenance dosing period, study treatment was discontinued in 4.4% (8 of 181) of subjects in the Q12W group, 8.0% (15 of 187) of subjects in the Q4W group, and 6.3% (11 of 176) of subjects in the placebo group. Main reasons for discontinuation included adverse events (3.3% [6 of 181] of subjects in the Q12W group, 3.2% [6 of 187] of subjects in the Q4W group, 2.3% [4 of 176] of subjects in the placebo group).

During the maintenance dosing period (from Week 12 to Week 60), adverse events occurred in 72.9% (132 of 181) of subjects in the Q12W group, 78.6% (147 of 187) of subjects in the Q4W group, and 61.9% (109 of 176) of subjects in the placebo group. Major adverse events are shown in Table 36. No deaths were reported.

Serious adverse events occurred in 7.7% (14 of 181) of subjects in the Q12W group, 5.9% (11 of 187) of subjects in the Q4W group, and 4.5% (8 of 176) of subjects in the placebo group. A causal relationship to the study drug could not be ruled out for the events in 5 subjects in the Q12W group (colitis ulcerative, prostate cancer, pneumonia pseudomonal, pustular psoriasis, and cholestasis in 1 subject each), 3 subjects in the Q4W group (cellulitis, dyspnoea, and pyogenic granuloma in 1 subject each), and 2 subjects in the placebo group (ischaemic stroke and Crohn's disease in 1 subject each).

Adverse events leading to discontinuation occurred in 3.9% (7 of 181) of subjects in the Q12W group, 3.2% (6 of 187) of subjects in the Q4W group, and 2.3% (4 of 176) of subjects in the placebo group. A causal relationship to the study drug could not be ruled out for the events in 2 subjects in the Q12W group (colitis ulcerative and cholestasis in 1 subject each), 4 subjects in the Q4W group (mycobacterium tuberculosis complex test positive in 3 subjects and injection site reaction in 1 subject), and 3 subjects in the placebo group (Crohn's disease in 2 subjects and double stranded DNA antibody positive in 1 subject).

Adverse drug reactions occurred in 24.9% (45 of 181) of subjects in the Q12W group, 33.7% (63 of 187) of subjects in the Q4W group, and 23.3% (41 of 176) of subjects in the placebo group.

Table 36. Adverse events reported by ≥2% of subjects in any group (safety analysis set in the maintenance dosing period)

Event	Q12W (N = 181)	Q4W (N = 187)	Placebo (N = 176)
Nasopharyngitis	24 (13.3)	32 (17.1)	20 (11.4)
Upper respiratory tract infection	21 (11.6)	25 (13.4)	14 (8.0)
Arthralgia	10 (5.5)	8 (4.3)	6 (3.4)
Bronchitis	10 (5.5)	7 (3.7)	3 (1.7)
Headache	8 (4.4)	12 (6.4)	7 (4.0)
Rhinitis	8 (4.4)	3 (1.6)	0
Urinary tract infection	7 (3.9)	5 (2.7)	3 (1.7)
Sinusitis	6 (3.3)	10 (5.3)	3 (1.7)
Back pain	6 (3.3)	9 (4.8)	1 (0.6)
Influenza	6 (3.3)	6 (3.2)	2 (1.1)
Diarrhoea	6 (3.3)	4 (2.1)	4 (2.3)
Fatigue	6 (3.3)	1 (0.5)	1 (0.6)
Psoriasis	5 (2.8)	3 (1.6)	4 (2.3)
Tonsillitis	5 (2.8)	2 (1.1)	0
Vomiting	5 (2.8)	2 (1.1)	4 (2.3)
Injection site reaction	4 (2.2)	15 (8.0)	0
Cough	4 (2.2)	4 (2.1)	1 (0.6)
Myalgia	4 (2.2)	4 (2.1)	0
Gastroenteritis viral	4 (2.2)	3 (1.6)	1 (0.6)
Injection site erythema	4 (2.2)	3 (1.6)	2 (1.1)
Oropharyngeal pain	4 (2.2)	3 (1.6)	1 (0.6)
Acne	4 (2.2)	2 (1.1)	0
Nausea	4 (2.2)	2 (1.1)	2 (1.1)
Blood creatine phosphokinase increased	4 (2.2)	1 (0.5)	3 (1.7)
Pharyngitis	3 (1.7)	11 (5.9)	1 (0.6)
Pyrexia	3 (1.7)	5 (2.7)	0
Tinea pedis	3 (1.7)	5 (2.7)	0
Oral candidiasis	3 (1.7)	4 (2.1)	0
Gastroenteritis	3 (1.7)	2 (1.1)	7 (4.0)
Folliculitis	2 (1.1)	5 (2.7)	1 (0.6)
Injection site pain	1 (0.6)	1 (0.5)	4 (2.3)
Laceration	0	4 (2.1)	2 (1.1)
Musculoskeletal pain	0	2 (1.1)	4 (2.3)
Tooth abscess	0	0	5 (2.8)

n (%)

7.2.3 Foreign phase III study (CTD 5.3.5.1.4, Study RHBC [ongoing since [redacted] 2012 (data cut-off on [redacted], 20[redacted]; up to Week 12)])

A randomized, double-blind, placebo- and etanercept-controlled, parallel-group study was conducted in 10 countries including the US, Germany, and Canada to investigate the efficacy and safety of ixekizumab in patients with moderate to severe plaque psoriasis vulgaris and patients with moderate to severe plaque psoriatic arthritis[14] (target sample size, 1225 subjects [350 in the active drug group, 175 in the placebo group]).

The study consisted of 2 periods, namely the induction dosing period up to Week 12 and the extension period from Week 12 to Week 264. In the induction dosing period, subjects received a starting dose of 160 mg of ixekizumab or placebo subcutaneously, followed by ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, or placebo subcutaneously, or etanercept 50 mg twice weekly subcutaneously. To ensure blindness for etanercept, placebo was administered twice weekly in the placebo group and the ixekizumab group. In the extension period, subjects received ixekizumab 80 mg Q4Wsubcutaneously.

All of the 1346 randomized subjects (386 in the Q4W group, 385 in the Q2W group, 382 in the etanercept group, 193 in the placebo group) were included in the ITT population. The efficacy analysis was performed based on the ITT population. Of the randomized subjects, 1341 subjects (382 in the Q4W group, 384 in the Q2W group, 382 in the etanercept group, 193 in the placebo group) were included in

[14] Patients with (a) chronic plaque psoriasis persistent for ≥6 months; (b) PASI score ≥12; (c) sPGA score ≥3; (d) psoriasis lesions involving ≥10% body surface area; and (e) psoriasis except for pustular psoriasis, erythrodermic psoriasis, and guttate psoriasis.

the safety analysis, and the remaining 5 subjects was excluded from the analysis because they did not receive the study drug. During the induction dosing period, study treatment was discontinued in 6.7% (26 of 386) of subjects in the Q4W group, 5.7% (22 of 385) of subjects in the Q2W group, 3.4% (13 of 382) of subjects in the etanercept group, 5.2% (10 of 193) of subjects in the placebo group. Main reasons for discontinuation included adverse events (2.3% [9 of 386] of subjects in the Q4W group, 2.1% [8 of 385] of subjects in the Q2W group, 1.0% [4 of 382] of subjects in the etanercept group, 1.0% [2 of 193] of subjects in the placebo group) and protocol deviations (2.1% [8 of 386] of subjects in the Q4W group, 1.8% [7 of 385] of subjects in the Q2W group, 0.8% [3 of 382] of subjects in the etanercept group, 0.5% [1 of 193] of subjects in the placebo group).

Table 37 shows the sPGA (0 or 1) response rate and PASI 75 response rate at Week 12 (the primary efficacy endpoints). Pairwise comparisons showed statistically significant differences between the placebo group and the Q4W group or Q2W group, demonstrating the superiority of ixekizumab Q4W and ixekizumab Q2W to placebo.

Table 37. sPGA (0 or 1) response rate and PASI 75 response rate at Week 12 (ITT population, NRI)

	Q4W	Q2W	Etanercept	Placebo	Difference from placebo [95% CI], *P* value[a), b)]		Difference from etanercept [95% CI]	
					Q4W	Q2W	Q4W	Q2W
sPGA (0 or 1) response rate	75.4 (291/386)	80.5 (310/385)	41.6 (159/382)	6.7 (13/193)	68.7 [63.1, 74.2] *P* < 0.001	73.8 [68.5, 79.1] *P* < 0.001	33.8 [27.2, 40.3] *P* < 0.001	38.9 [32.6, 45.2] *P* < 0.001
PASI 75 response rate	84.2 (325/386)	87.3 (336/385)	53.4 (204/382)	7.3 (14/193)	76.9 [71.8, 82.1] *P* < 0.001	80.0 [75.1, 85.0] *P* < 0.001	30.8 [24.6, 37.0] *P* < 0.001	33.9 [27.9, 39.9] *P* < 0.001

% (n/N)

a) Cochran-Mantel-Haenszel test stratified by center

b) The primary and secondary endpoints were tested by pairwise comparisons in the following hierarchical order: ixekizumab regimens versus placebo in terms of the sPGA (0 or 1) response rate at Week 12 and PASI 75 response rate at Week 12 as the primary endpoints; ixekizumab regimens versus etanercept in terms of the above 2 primary endpoints; ixekizumab regimens versus placebo in terms of the sPGA (0) response rate at Week 12, PASI 90 response rate at Week 12, and PASI 100 response rate at Week 12 as the secondary endpoints; and ixekizumab regimens versus etanercept in terms of the above 3 secondary endpoints. For multiple pairwise comparisons between each ixekizumab regimen and placebo or etanercept, the *P* values were adjusted for multiplicity by a gatekeeping procedure based on the Bonferroni test at 2-sided significance level.

During the induction dosing period (up to Week 12), adverse events occurred in 56.3% (215 of 382) of subjects in the Q4W group, 53.4% (205 of 384) of subjects in the Q2W group, 49.0% (187 of 382) of subjects in the etanercept group, and 36.3% (70 of 193) of subjects in the placebo group. Major adverse events are shown in Table 38. No deaths were reported.

Serious adverse events occurred in 1.6% (6 of 382) of subjects in the Q4W group, 2.3% (9 of 384) of subjects in the Q2W group, 1.3% (5 of 382) of subjects in the etanercept group, and 2.6% (5 of 193) of subjects in the placebo group. A causal relationship to the study drug could not be ruled out for the events in 1 subject in the Q4W group (pancreatitis acute), 4 subjects in the Q2W group (appendicitis in 1 subject; depression, bipolar disorder, and anxiety in 1 subject; arthritis in 1 subject; and Crohn's disease in 1 subject), and 1 subject in the placebo group (psoriasis, hyperkeratosis palmaris and plantaris, and skin bacterial infection).

Adverse events leading to discontinuation occurred in 2.1% (8 of 382) of subjects in the Q4W group, 2.3% (9 of 384) of subjects in the Q2W group, 1.0% (4 of 382) of subjects in the etanercept group, and 1.0% (2 of 193) of subjects in the placebo group.

Adverse drug reactions occurred in 21.7% (83 of 382) of subjects in the Q4W group, 26.8% (103 of 384) of subjects in the Q2W group, 22.3% (85 of 382) of subjects in the etanercept group, and 12.4% (24 of 193) of subjects in the placebo group.

Table 38. Adverse events reported by ≥2% of subjects in any group (up to Week 12, safety analysis set)

Event	Q4W (N = 382)	Q2W (N = 384)	Etanercept (N = 382)	Placebo (N = 193)
Injection site reaction	43 (11.3)	37 (9.6)	41 (10.7)	3 (1.6)
Nasopharyngitis	29 (7.6)	26 (6.8)	19 (5.0)	11 (5.7)
Headache	16 (4.2)	16 (4.2)	11 (2.9)	5 (2.6)
Arthralgia	10 (2.6)	13 (3.4)	7 (1.8)	4 (2.1)
Injection site erythema	5 (1.3)	12 (3.1)	11 (2.9)	0
Diarrhoea	3 (0.8)	11 (2.9)	6 (1.6)	2 (1.0)
Upper respiratory tract infection	8 (2.1)	8 (2.1)	8 (2.1)	5 (2.6)
Nausea	4 (1.0)	8 (2.1)	2 (0.5)	0
Injection site pain	3 (0.8)	8 (2.1)	5 (1.3)	3 (1.6)
Pruritus	9 (2.4)	7 (1.8)	4 (1.0)	1 (0.5)
Back pain	8 (2.1)	7 (1.8)	2 (0.5)	2 (1.0)
Cough	9 (2.4)	6 (1.6)	4 (1.0)	0
Hypertension	3 (0.8)	4 (1.0)	9 (2.4)	1 (0.5)

n (%)

7.2.4 Japanese long-term treatment study (CTD 5.3.5.2.1, Study RHAT [ongoing since July 2012 (data cut-off on [redacted], 20[redacted]; up to Week 52)])

An open-label uncontrolled study was conducted in Japan to investigate the efficacy and safety of ixekizumab in patients with moderate to severe plaque psoriasis vulgaris, patients with moderate to severe plaque psoriatic arthritis, patients with pustular psoriasis, and patients with erythrodermic psoriasis[15] (target sample size, 90 subjects).

The study consisted of 3 periods, namely the induction dosing period up to Week 12, maintenance dosing period from Week 12 to Week 52, and re-treatment period (dosing period differed from subject to subject). In the induction dosing period, subjects received a starting dose of 160 mg of ixekizumab subcutaneously, followed by 80 mg Q2W at and after Week 2. In the maintenance dosing period, subjects received ixekizumab 80 mg Q4W subcutaneously.

All of the 91 subjects who received at least 1 dose of the study drug and were assessed for the post-dose PASI score (78 patients with plaque psoriasis [including 11 patients with psoriatic arthritis], 5 patients with pustular psoriasis, and 8 patients with erythrodermic psoriasis) were included in the safety analysis set and the full analysis set (FAS). The FAS was used for the efficacy analysis. During the induction dosing period, study treatment was discontinued in 1.3% (1 of 78) of patients with plaque psoriasis due to adverse events. During the maintenance dosing period, study treatment was discontinued in 9.0% (7 of 78) of patients with plaque psoriasis. Main reasons for discontinuation included adverse events, physician's decision, and consent withdrawal (2.6% [2 of 78 subjects] for each reason).

The primary efficacy endpoint of the study was the PASI 75 response rate[16] at Week 12 in patients with plaque psoriasis. The PASI 75 response rate at Week 12 was 98.7% (77 of 78 subjects). The PASI 75 response rate at Week 52 was 92.3% (72 of 78 subjects). Table 39 shows the ACR20 response rate and patient-rated arthritis pain score (visual analog scale [VAS]), both of which were the efficacy endpoints for psoriatic arthritis; clinical global impression score and skin symptom assessment score[17] rated by the investigator, both of which were the efficacy endpoints for pustular psoriasis; and clinical global impression score rated by the investigator, which was the efficacy endpoint for erythrodermic psoriasis.

[15] Patients with psoriasis who were (a) patients with a diagnosis of chronic psoriasis for ≥6 months; (b) patients with plaque psoriasis who had a PASI score of ≥12 and sPGA score of ≥3 and whose lesions involved ≥10% body surface area; (c) patients with pustular psoriasis who have a confirmed diagnosis of pustular psoriasis based on the diagnostic criteria for generalized pustular psoriasis defined by the Ministry of Health, Labour and Welfare and the Japanese Dermatological Association; (d) patients with erythrodermic psoriasis who had erythema accompanied by inflammatory lesions involving ≥80% body surface area; and (e) patients without guttate psoriasis.

[16] Filled by NRI

[17] Sum of scores given by assessment on a 0-to-3-point scale for each of the areas affected by erythema, pustular erythema, and edema

Table 39. Week 12 and Week 52 efficacy endpoints in patients with psoriatic arthritis, erythrodermic psoriasis, and pustular psoriasis

	Baseline	Week 12 (induction dosing period)	Week 52 (maintenance dosing period)
Psoriatic arthritis (N = 11)			
ACR20 response rate[a) b)]		80.0 (4/5)	100.0 (5/5)
Arthritis pain score (VAS)[c)]			
Baseline	62.4 ± 23.79	15.1 ± 12.49	11.4 ± 8.88
Change from baseline	-	–47.3 ± 22.05	–51.0 ± 19.05
Pustular psoriasis (N = 5)			
Clinical global impression[d)]			
Remission		20.0 (1/5)	40.0 (2/5)
Improved		80.0 (4/5)	60.0 (3/5)
Unchanged		0 (0/5)	0 (0/5)
Worsened		0 (0/5)	0 (0/5)
Skin symptom score[c)]	2.8 ± 1.92	1.4 ± 1.52	0.8 ± 0.84
Change from baseline	-	–1.4 ± 0.55	–2.0 ± 1.41
Erythrodermic psoriasis (N = 8)			
Clinical global impression[d)]			
Remission		12.5 (1/8)	12.5 (1/8)
Improved		87.5 (7/8)	87.5 (7/8)
Unchanged		0 (0/8)	0 (0/8)
Worsened		0 (0/8)	0 (0/8)

% (n/N), or mean ± SD
a) Of 11 patients who had a diagnosis of psoriatic arthritis according to the CASPAR, 5 patients who had swollen and tender joint count ≥3 were included in the assessment.
b) Non-responder imputation (NRI)
c) Last observation carried forward (LOCF)
d) Observed

During the induction dosing period and maintenance dosing period (up to Week 52), adverse events occurred in 85.9% (67 of 78) of patients with plaque psoriasis, 100% (5 of 5) of patients with pustular psoriasis, and 87.5% (7 of 8) of patients with erythrodermic psoriasis. Major adverse events are shown in Table 40. No deaths were reported.

Serious adverse events occurred in 3.8% of patients with plaque psoriasis (3 of 78 patients; deep vein thrombosis/pulmonary embolism, sleep apnoea syndrome, and colon cancer in 1 patient each). A causal relationship to the study drug could not be ruled out for deep vein thrombosis/pulmonary embolism, and colon cancer.

Adverse events leading to discontinuation occurred in 3.8% (3 of 78) of patients with plaque psoriasis.

Adverse drug reactions occurred in 29.5% (23 of 78) of patients with plaque psoriasis, 60.0% (3 of 5) of patients with pustular psoriasis, and 25.0% (2 of 8) of patients with erythrodermic psoriasis.

Table 40. Adverse events reported by ≥3 subjects in any group (up to Week 52, safety analysis set)

Event	Patients with plaque psoriasis (N = 78)	Patients with pustular psoriasis (N = 5)	Patients with erythrodermic psoriasis (N = 8)
Nasopharyngitis	30 (38.5)	2 (40.0)	4 (50.0)
Eczema	11 (14.1)	0	0
Injection site reaction	8 (10.3)	0	0
Seborrhoeic dermatitis	8 (10.3)	0	0
Urticaria	6 (7.7)	1 (20.0)	1 (12.5)
Oropharyngeal pain	6 (7.7)	0	0
Dermatitis contact	6 (7.7)	0	0
Arthralgia	5 (6.4)	0	2 (25.0)
Diarrhoea	5 (6.4)	0	0
Alanine aminotransferase increased	5 (6.4)	0	0
Pruritus	4 (5.1)	0	2 (25.0)
Seasonal allergy	4 (5.1)	1 (20.0)	1 (12.5)
Tinea infection	4 (5.1)	0	0
Dry skin	4 (5.1)	0	0
Headache	3 (3.8)	1 (20.0)	1 (12.5)
Injection site pain	3 (3.8)	1 (20.0)	0
Gastroenteritis	3 (3.8)	0	0
Paronychia	3 (3.8)	0	0
Pharyngitis	3 (3.8)	0	0
Arthropod bite	3 (3.8)	0	0
Hypertriglyceridaemia	3 (3.8)	0	0
Dyshidrotic eczema	3 (3.8)	0	0

n (%)

7.2.5 Global phase III study (CTD 5.3.5.1.5, Study RHAP [ongoing since January 2013 (data cut-off on [redacted], 20[redacted]; up to Week 52)])

A randomized, double-blind, placebo- and adalimumab-controlled, parallel-group study was conducted in 15 countries including Japan, the US, Czech Republic, and Poland to investigate the efficacy and safety of ixekizumab in patients with active psoriatic arthritis[18] (target sample size, 412 subjects [103 per group]).

The study consisted of 3 periods, namely the double-blind period up to Week 24, extension period from Week 24 to Week 52, and long-term extension period from Week 52 to Week 156 (Figure 4). In the double-blind period, subjects received a starting dose of 160 mg of ixekizumab or placebo subcutaneously, followed by ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, placebo, or adalimumab 40 mg Q2W subcutaneously at and after Week 2. In the extension period, subjects treated with ixekizumab in the double-blind period received the study drug according to the same dosing regimen while subjects on placebo or adalimumab were re-randomized at a 1:1 ratio to receive ixekizumab Q4W or Q2W. Subjects on placebo in the double-blind period received ixekizumab 160 mg subcutaneously at Week 24, and subjects on adalimumab in the double-blind period received ixekizumab 80 mg subcutaneously at Week 32, both followed by ixekizumab 80 mg Q2W or Q4W subcutaneously according to the assigned regimen.

[18] Patients with psoriatic arthritis who had a confirmed diagnosis of psoriatic arthritis according to CASPAR; (a) who had swollen and tender joint count ≥3; and (b) who had inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs), DMARDs, or anti-TNFα antibody products.

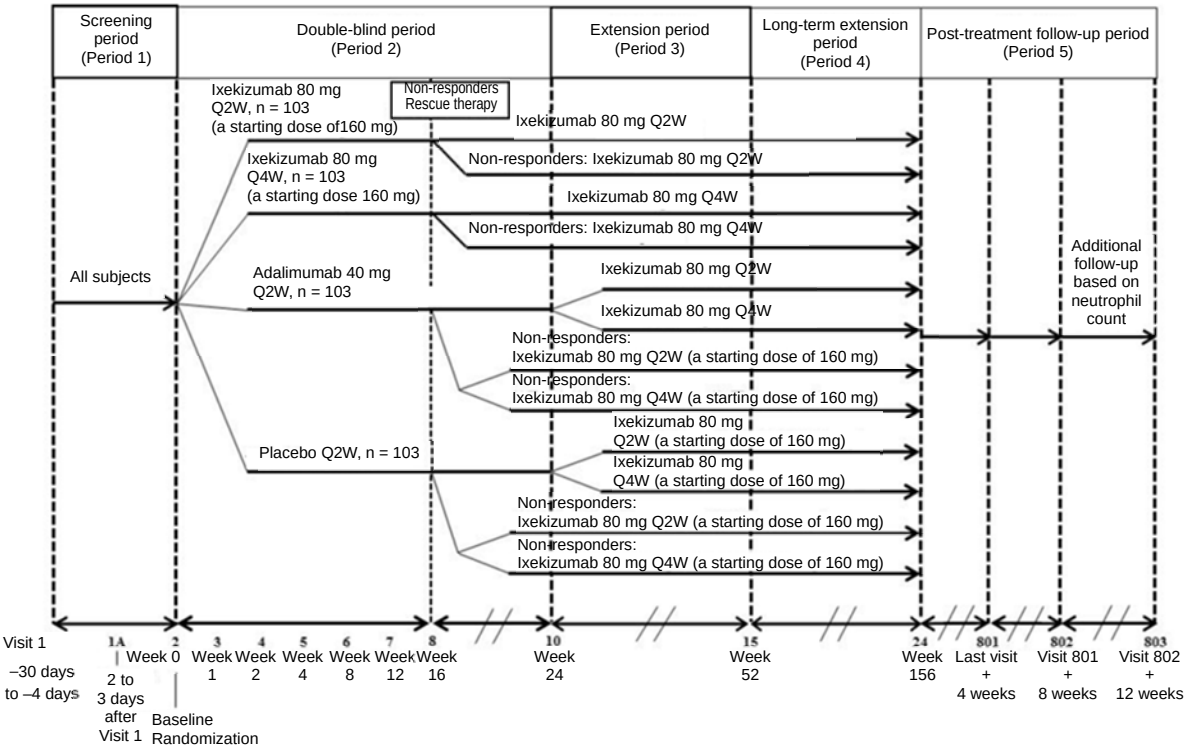

Figure 4. Randomization and dosing plan in Study RHAP

Among subjects on placebo or adalimumab during the double-blind period, those who had >20 % improvement in tender and swollen joint counts from baseline at Week 16 (non-responders) were re-randomized at a 1:1 ratio to receive ixekizumab 80 mg Q4W or Q2W. Subjects on placebo and adalimumab were to receive ixekizumab 160 mg subcutaneously at Week 16 and Week 24, respectively, followed by ixekizumab 80 mg Q2W or Q4W subcutaneously according to the assigned regimen.

All of the 417 randomized subjects (107 in the Q4W group, 103 in the Q2W group, 101 in the adalimumab group, 106 in the placebo group) were included in the ITT population. The efficacy analysis was performed based on the ITT population. Of these, 416 subjects (107 in the Q4W group, 102 in the Q2W group, 101 in the adalimumab group, 106 in the placebo group) were included in the safety analysis, and 1 subject who did not receive the study drug was excluded from the analysis. During the double-blind period, study treatment was discontinued in 8.4% (9 of 107) of subjects in the Q4W group, 5.8% (6 of 103) of subjects in the Q2W group, 4.0% (4 of 101) of subjects in the adalimumab group, 14.2% (15 of 106) of subjects in the placebo group. Main reasons for discontinuation included deviation from the inclusion criteria (2.8% [3 of 107] of subjects in the Q4W group, 2.9% [3 of 103] of subjects in the Q2W group, 1.0% [1 of 101] of subjects in the adalimumab group, 0.9% [1 of 106] of subjects in the placebo group) and adverse events (1.9% [2 of 107] of subjects in the Q4W group, 2.9% [3 of 103] of subjects in the Q2W group, 2.0% [2 of 101] of subjects in the adalimumab group, 1.9% [2 of 106] of subjects in the placebo group).

The ITT population included 12 Japanese subjects (2 in the Q4W group, 4 in the Q2W group, 2 in the adalimumab group, 4 in the placebo group). Study treatment was discontinued in 50.0% (1 of 2) of subjects in the Q4W group due to deviation from the inclusion criteria.

Table 41 shows the ACR20 response rate at Week 24 (the primary efficacy endpoint). Pairwise comparisons showed statistically significant differences between the placebo group and the Q4W group or Q2W group, demonstrating the superiority of ixekizumab Q4W and ixekizumab Q2W to placebo. Table 41 shows the ACR50 response rate and ACR70 response rate as the secondary endpoints.

Table 41. ACR20 response rate (primary endpoint), ACR50 response rate, and ACR70 response rate at Week 24 (ITT population, NRI)

	Q4W	Q2W	Adalimumab	Placebo	Difference from placebo [95% CI], *P* value[a), b)]	
					Q4W	Q2W
ACR20 response rate	57.9 (62/107)	62.1 (64/103)	57.4 (58/101)	30.2 (32/106)	27.8 [15.0, 40.6] $P < 0.001$	31.9 [19.1, 44.8] $P < 0.001$
ACR50 response rate	40.2 (43/107)	46.6 (48/103)	38.6 (39/101)	15.1 (16/106)	25.1 [13.6, 36.6]	31.5 [19.7, 43.3]
ACR70 response rate	23.4 (25/107)	34.0 (35/103)	25.7 (26/101)	5.7 (6/106)	17.7 [8.6, 26.8]	28.3 [18.2, 38.5]

% (n/N)

a) Logistic regression model using treatment group, geographic region, a history of DMARD therapy (not used, previously used, currently in use) as explanatory variables

b) The primary and secondary endpoints were tested by pairwise comparisons between ixekizumab regimens and placebo in the following hierarchical order: the ACR20 response rate at Week 24 as the primary endpoint; and change in health assessment questionnaire disability index (HAQ-DI) from baseline at Week 24, change in mTSS from baseline at Week 24, ACR20 response rate at Week 12, PASI 75 response rate at Week 12, and change in Leeds Enthesitis Index (LEI) score from baseline at Week 12, and change in Itch Numeric Rating Scale (Itch NRS) score from baseline at Week 12 as the secondary endpoints. For multiple pairwise comparisons between each ixekizumab regimen and placebo, the *P* values were adjusted for multiplicity by a graphical approach based on the Bonferroni test at 2-sided significance level.

A subgroup analysis was performed for the Japanese subgroup. ACR20 response at Week 24 was observed in 1 of 2 subjects in the Q4W group, 3 of 4 subjects in the Q2W group, 1 of 2 subjects in the adalimumab group, and 0 of 4 subjects in the placebo group. ACR50 response and ACR70 response at Week 24 were observed in 1 of 2 subjects and 1 of 2 subjects, respectively, in the Q4W group; 3 of 4 subjects and 2 of 4 subjects, respectively, in the Q2W group; 1 of 2 subjects and 1 of 2 subjects, respectively, in the adalimumab group; and 0 of 4 subjects and 0 of 4 subjects, respectively, in the placebo group.

Table 42 shows a change in van der Heijde modified Total Sharp Score (mTSS) from baseline at Week 24 (the secondary efficacy endpoint).

Table 42. Change in mTSS from baseline at Week 24 (ITT population)

	Q4W	Q2W	Adalimumab	Placebo	Difference from placebo [95% CI], *P* value	
					Q4W	Q2W
Baseline[a)]	19.2 ± 32.68 (100)	15.2 ± 28.85 (98)	15.9 ± 27.37 (95)	17.6 ± 28.62 (94)		
Week 24[a), f)]	16.7 ± 28.65 (76)	14.4 ± 30.71 (80)	14.9 ± 26.11 (79)	17.2 ± 24.53 (59)		
Change[a), g)]	0.1 ± 0.85 (82)	0.1 ± 0.57 (85)	0.1 ± 0.38 (83)	0.5 ± 1.10 (61)	–0.33 [−0.55, –0.10] $P = 0.004$[b), c)]	–0.41 [–0.63, −0.19] $P < 0.001$[b), c)]
Baseline[d)]	17.8 ± 28.36 (97)	15.2 ± 29.13 (96)	15.9 ± 27.37 (95)	17.8 ± 29.06 (91)		
Week 24[d), f)]	16.3 ± 26.75 (91)	14.7 ± 29.78 (91)	14.7 ± 25.09 (91)	17.6 ± 28.49 (89)		
Change[d), g)]	0.2 ± 0.91 (97)	0.1 ± 0.55 (96)	0.1 ± 0.58 (95)	0.5 ± 1.17 (91)	–0.32 [–0.56, –0.08][e)]	–0.42 [–0.67, –0.18][e)]

Mean ± SD (N)

a) Observed Cases (no missing data imputed)

b) Repeated measures mixed model on a hypothesis of unstructured covariance structure within subjects, using treatment group, geographic region, baseline value, a history of DMARD therapy (not used, previously used, currently in use), time point, and interaction between the time point and treatment group as explanatory variables

c) See Note b) in Table 41.

d) Tabulated from data collected in subjects for whom missing data (a change from baseline at Week 24) were imputed by linear extrapolation.

e) Analysis of the covariance model using treatment group, geographic region, baseline value, a history of DMARD therapy (not used, previously used, currently in use) as explanatory variables.

f) Tabulated from data collected in subjects with assessment results for all the joints which were necessary for mTSS assessment.

g) For subjects with assessment results for all the joints which were necessary for mTSS assessment, a change in mTSS from baseline at Week 24 was calculated according to the Van der Heijde algorithm.

During the double-blind period (up to Week 24), adverse events occurred in 66.4% (71 of 107) of subjects in the Q4W group, 65.7% (67 of 102) of subjects in the Q2W group, 64.4% (65 of 101) of subjects in the adalimumab group, and 47.2% (50 of 106) of subjects in the placebo group. Major adverse events are shown in Table 43. No deaths were reported.

Serious adverse events occurred in 5.6% (6 of 107) of subjects in the Q4W group, 2.9% (3 of 102) of subjects in the Q2W group, 5.0% (5 of 101) of subjects in the adalimumab group, and 1.9% (2 of 106) of subjects in the placebo group. A causal relationship to the study drug could not be ruled out for the events in 1 subject in the Q2W group (herpes zoster) and 1 subject in the adalimumab group (pneumonia mycoplasmal).

Adverse events leading to discontinuation occurred in 1.9% (2 of 107) of subjects in the Q4W group, 3.9% (4 of 102) of subjects in the Q2W group, 2.0% (2 of 101) of subjects in the adalimumab group, and 1.9% (2 of 106) of subjects in the placebo group.

Adverse drug reactions occurred in 29.9% (32 of 107) of subjects in the Q4W group, 36.3% (37 of 102) of subjects in the Q2W group, 20.8% (21 of 101) of subjects in the adalimumab group, and 11.3% (12 of 106) of subjects in the placebo group.

A subgroup analysis was performed for the Japanese subgroup in the double-blind period (up to Week 24). Adverse events occurred in 2 of 2 subjects in the Q4W group, 3 of 4 subjects in the Q2W group, 2 of 2 subjects in the adalimumab group, and 3 of 4 subjects in the placebo group. No deaths, serious adverse events, or adverse events leading to discontinuation were reported.

Adverse drug reactions occurred in 2 of 4 subjects in the Q2W group.

Table 43. Adverse events reported by ≥2% of subjects in any group (up to Week 24, safety analysis set)

Event	Q4W (N = 107)	Q2W (N = 102)	Adalimumab (N = 101)	Placebo (N = 106)
Injection site reaction	13 (12.1)	16 (15.7)	2 (2.0)	0
Injection site erythema	7 (6.5)	13 (12.7)	2 (2.0)	0
Diarrhoea	2 (1.9)	5 (4.9)	3 (3.0)	3 (2.8)
Nausea	0	5 (4.9)	4 (4.0)	2 (1.9)
Headache	4 (3.7)	4 (3.9)	3 (3.0)	1 (0.9)
Alanine aminotransferase increased	3 (2.8)	4 (3.9)	3 (3.0)	0
Muscle spasms	3 (2.8)	4 (3.9)	1 (1.0)	1 (0.9)
Nasopharyngitis	7 (6.5)	3 (2.9)	7 (6.9)	5 (4.7)
Upper respiratory tract infection	5 (4.7)	3 (2.9)	5 (5.0)	7 (6.6)
Bronchitis	3 (2.8)	3 (2.9)	4 (4.0)	3 (2.8)
Aspartate aminotransferase increased	2 (1.9)	3 (2.9)	2 (2.0)	0
Psoriatic arthropathy	3 (2.8)	2 (2.0)	3 (3.0)	1 (0.9)
Back pain	2 (1.9)	2 (2.0)	3 (3.0)	0
Hypertension	0	2 (2.0)	3 (3.0)	2 (1.9)
Sinusitis	1 (0.9)	1 (1.0)	2 (2.0)	3 (2.8)
Liver function test abnormal	0	1 (1.0)	4 (4.0)	2 (1.9)
Otitis media	0	1 (1.0)	0	3 (2.8)
Arthralgia	3 (2.8)	0	1 (1.0)	1 (0.9)
Urinary tract infection	2 (1.9)	0	4 (4.0)	2 (1.9)
Blood creatine phosphokinase increased	2 (1.9)	0	3 (3.0)	0
Injection site pain	2 (1.9)	0	1 (1.0)	3 (2.8)
Dyspepsia	1 (0.9)	0	0	3 (2.8)
Seminal vesicular cyst	0	1 (2.1)	0	0
Benign prostatic hyperplasia	0	0	1 (2.0)	1 (2.1)
Menopausal symptoms	0	0	1 (2.0)	0
Metrorrhagia	0	0	1 (2.0)	0
Biopsy prostate	0	0	0	1 (2.1)

n (%)

During the extension period (from Week 24 to Week 52), adverse events occurred in 55.7% (54 of 97) of subjects in the Q4W group, 56.3% (54 of 96) of subjects in the Q2W group, 40.8% (20 of 49) of subjects in the adalimumab/Q4W group, 43.8% (21 of 48) of subjects in the adalimumab/Q2W group, 62.2% (28 of 45) of subjects in the placebo/Q4W group, and 58.7% (27 of 46) of subjects in the placebo/Q2W group. Major adverse events are shown in Table 44 (tabulated from data collected in subjects who received ixekizumab during the double-blind period). No deaths were reported. Serious adverse events occurred in 4.1% (4 of 97) of subjects in the Q4W group. Any of the events were not related to the study drug.

Adverse events leading to discontinuation occurred in 1.0% (1 of 97) of subjects in the Q4W group.

Adverse drug reactions occurred in 12.4% (12 of 97) of subjects in the Q4W group and 18.8% (18 of 96) of subjects in the Q2W group.

A subgroup analysis was performed for the Japanese subgroup in the extension period (from Week 24 to Week 52). Adverse events occurred in 1 of 1 subject in the Q4W group and 3 of 4 subjects in the Q2W group. No deaths were reported. A serious adverse event occurred in 1 subject in the Q4W group (clavicle fracture), but a causal relationship of this event to the study drug was ruled out. No adverse events led to discontinuation.

An adverse drug reaction occurred in 1 of 4 subjects in the Q2W group.

Table 44. Adverse events reported by ≥2% of subjects in any group (Week 24 to Week 52, subjects on ixekizumab during the double-blind period)

Event	Q4W (N = 97)	Q2W (N = 96)
Nasopharyngitis	7 (7.2)	10 (10.4)
Injection site reaction	6 (6.2)	7 (7.3)
Upper respiratory tract infection	5 (5.2)	4 (4.2)
Back pain	5 (5.2)	1 (1.0)
Uterine leiomyoma	2 (2.1)	0
Conjunctivitis	3 (3.1)	2 (2.1)
Psoriatic arthropathy	3 (3.1)	1 (1.0)
Urinary tract infection	2 (2.1)	2 (2.1)
Fungal skin infection	2 (2.1)	2 (2.1)
Lymphadenopathy	2 (2.1)	1 (1.0)
Cystitis	2 (2.1)	1 (1.0)
Constipation	2 (2.1)	0
Hypertension	2 (2.1)	0
Pharyngitis	1 (1.0)	4 (4.2)
Rhinitis	1 (1.0)	2 (2.1)
Bronchitis	1 (1.0)	2 (2.1)
Headache	1 (1.0)	2 (2.1)
Benign prostatic hyperplasia	0	1 (1.0)
Circumcision	0	1 (1.0)
Oral candidiasis	0	2 (2.1)
Periodontitis	0	2 (2.1)
Joint injury	0	2 (2.1)
Interferon gamma release assay positive	0	2 (2.1)
Gamma-glutamyltransferase increased	0	2 (2.1)
Hyperlipidaemia	0	2 (2.1)

n (%)

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Efficacy on plaques

The applicant's explanation about the efficacy of ixekizumab on plaques in Japanese patients with psoriasis vulgaris or psoriatic arthritis:

The applicant considered it possible for the Japanese subjects to participate in Study RHAZ that investigated the efficacy of ixekizumab on plaques for the following reasons: (1) Pathology and symptoms of psoriasis were unlikely to have large ethnic differences; (2) no clinically relevant differences were recognized in any of the extrinsic ethnic factors such as diagnosis, therapeutic goal, and treatment algorithm for psoriasis between Japanese and non-Japanese patients; and (3) no clear ethnic differences were observed in the pharmacokinetics of ixekizumab [see Section "6.R.1 Ethnic differences in pharmacokinetics of ixekizumab"].

As shown in Table 45, a global phase III study in patients with plaque psoriasis including Japanese patients with psoriasis (Study RHAZ) demonstrated the superiority of ixekizumab at 80 mg Q2W and Q4W to placebo in terms of sPGA (0 or 1) response rate and PASI 75 response rate at Week 12 (both were the primary endpoints). In addition, the results of sPGA (0) response rate, PASI 90 response rate,

and PASI 100 response rate (all of which were the secondary endpoints) in the ixekizumab 80 mg Q2W and Q4W groups were higher than those in the placebo group. Furthermore, the foreign phase III studies (Studies RHBA and RHBC) yielded comparable results to those of the global study. The applicant, therefore, considers that the efficacy of ixekizumab on plaques has been demonstrated.

Table 45. Efficacy endpoints at Week 12 (Studies RHAZ, RHBA, and RHBC)

		Q4W	Q2W	Placebo	Difference from placebo [95% CI]	
					Q4W	Q2W
RHAZ	Overall study population					
	sPGA (0 or 1) response rate	76.4 (330/432)	81.8 (354/433)	3.2 (14/431)	73.1 [68.8, 77.5]	78.5 [74.5, 82.5]
	sPGA (0) response rate	34.5 (149/432)	37.0 (160/433)	0 (0/431)	34.5 [30.0, 39.0]	37.0 [32.4, 41.5]
	PASI 75 response rate	82.6 (357/432)	89.1 (386/433)	3.9 (17/431)	78.7 [74.7, 82.7]	85.2 [81.7, 88.7]
	PASI 90 response rate	64.6 (279/432)	70.9 (307/433)	0.5 (2/431)	64.1 [59.6, 68.7]	70.4 [66.1, 74.8]
	PASI 100 response rate	33.6 (145/432)	35.3 (153/433)	0 (0/431)	33.6 [29.1, 38.0]	35.3 [30.8, 39.8]
	Japanese subgroup					
	sPGA (0 or 1) response rate	66.7 (8/12)	100.0 (8/8)	0 (0/13)	66.7 [40.0, 93.3]	100.0 [100.0, 100.0]
	sPGA (0) response rate	33.3 (4/12)	62.5 (5/8)	0 (0/13)	33.3 [6.7, 60.0]	62.5 [29.0, 96.0]
	PASI 75 response rate	75.0 (9/12)	100.0 (8/8)	0 (0/13)	75.0 [50.5, 99.5]	100.0 [100.0, 100.0]
	PASI 90 response rate	58.3 (7/12)	75.0 (6/8)	0 (0/13)	58.3 [30.4, 86.2]	75.0 [45.0, 100.0]
	PASI 100 response rate	33.3 (4/12)	37.5 (3/8)	0 (0/13)	33.3 [6.7, 60.0]	37.5 [4.0, 71.0]
RHBA	sPGA (0 or 1) response rate	72.9 (253/347)	83.2 (292/351)	2.4 (4/168)	70.5 [65.3, 75.7]	80.8 [76.3, 85.4]
	sPGA (0) response rate	32.3 (112/347)	41.9 (147/351)	0.6 (1/168)	31.7 [26.6, 36.7]	41.3 [36.0, 46.6]
	PASI 75 response rate	77.5 (269/347)	89.7 (315/351)	2.4 (4/168)	75.1 [70.2, 80.1]	87.4 [83.4, 91.3]
	PASI 90 response rate	59.7 (207/347)	70.7 (248/351)	0.6 (1/168)	59.1 [53.8, 64.4]	70.1 [65.2, 75.0]
	PASI 100 response rate	30.8 (107/347)	40.5 (142/351)	0.6 (1/168)	30.2 [25.2, 35.2]	39.9 [34.6, 45.1]
RHBC	sPGA (0 or 1) response rate	75.4 (291/386)	80.5 (310/385)	6.7 (13/193)	68.7 [63.1, 74.2]	73.8 [68.5, 79.1]
	sPGA (0) response rate	36.0 (139/386)	40.3 (155/385)	0 (0/193)	36.0 [31.2, 40.8]	40.3 [35.4, 45.2]
	PASI 75 response rate	84.2 (325/386)	87.3 (336/385)	7.3 (14/193)	76.9 [71.8, 82.1]	80.0 [75.1, 85.0]
	PASI 90 response rate	65.3 (252/386)	68.1 (262/385)	3.1 (6/193)	62.2 [56.8, 67.5]	64.9 [59.7, 70.2]
	PASI 100 response rate	35.0 (135/386)	37.7 (145/385)	0 (0/193)	35.0 [30.2, 39.7]	37.7 [32.8, 42.5]

% (n/N)

As shown in Table 45, the Japanese subgroup and the overall study population yielded similar results in Study RHAZ for all the efficacy endpoints. In addition, in Japanese patients with psoriatic arthritis enrolled in Study RHAZ and the Japanese long-term treatment study (Study RHAT), percent change in PASI score (mean ± SD) from baseline at Week 12 was 89.5%[19] and 93.8% ± 9.2% (n = 11), respectively. In patients with psoriatic arthritis enrolled in a global phase III study (Study RHAP) who had skin symptom comparable to that in patients eligible for enrollment in Study RHAZ,[20] percent change in PASI score from baseline at Week 12 (least squares mean [95% CI]) was 89.7% [68.8, 110.5]. The study data showed improvement in skin symptom in patients with psoriatic arthritis, although the number of patients investigated was limited.

Based on the above results, ixekizumab is expected to show efficacy in the treatment of plaque lesions in Japanese patients with psoriasis vulgaris or psoriatic arthritis.

Because patient characteristics tended to differ between the overall study population and Japanese subgroup in Study RHAZ, PMDA asked the applicant to explain whether such differences affect the efficacy evaluation of ixekizumab.

The applicant's explanation:
Patient characteristics that tended to differ between the overall study population and Japanese subgroup included body weight (92.25 kg in the overall study population vs. 70.12 kg in the Japanese subgroup), baseline PASI score (20.15 in the overall study population vs. 24.54 in the Japanese subgroup), percentage of body surface area affected by psoriasis at baseline (27.7% in the overall study population vs. 37.8% in the Japanese subgroup), percentage of subjects with previous phototherapy (45.6% in the overall study population vs. 60.6% in the Japanese subgroup), and percentage of subjects with previous biologic therapy (40.3% in the overall study population vs. 24.2% in the Japanese subgroup). Table 46 shows subgroup analyses by these factors. The analyses revealed no clear differences among subgroups

[19] Data from 1 subject randomized to the ixekizumab 80 mg Q2W group in Study RHAZ
[20] Patients with psoriasis that was PASI score ≥12, sPGA score ≥3, and involved ≥10% body surface area

divided by any factor, and thus the differences in factor distribution were considered unlikely to affect efficacy evaluation.

Table 46. Subgroup analyses of PASI 75 response rate and sPGA (0 or 1) response rate at Week 12 (PPC)

		sPGA (0 or 1) response rate			PASI 75 response rate		
		Q4W	Q2W	Placebo	Q4W	Q2W	Placebo
Body weight	<80 kg	79.4 (281/354)	85.8 (338/394)	5.4 (14/258)	85.6 (303/354)	90.9 (358/394)	4.3 (11/258)
	≥80 kg and <100 kg	78.7 (344/437)	83.3 (354/425)	4.3 (12/280)	85.6 (374/437)	89.4 (380/425)	5.7 (16/280)
	≥100 kg	67.4 (248/368)	75.6 (264/349)	2.0 (2/251)	74.2 (273/368)	85.7 (299/349)	3.2 (8/251)
Baseline PASI score	<20	75.3 (528/701)	81.6 (616/755)	4.5 (22/490)	80.2 (562/701)	87.9 (664/755)	5.1 (25/490)
	≥20	74.6 (346/464)	82.1 (340/414)	3.0 (9/302)	83.8 (389/464)	90.1 (373/414)	3.3 (10/302)
Percentage of body surface area affected by psoriasis at baseline	<20%	75.3 (365/485)	81.4 (403/495)	3.7 (13/348)	79.8 (387/485)	88.9 (440/495)	5.5 (19/348)
	≥20%	74.9 (509/680)	82.0 (553/674)	4.1 (18/444)	82.9 (564/680)	88.6 (597/674)	3.6 (16/444)
Previous phototherapy	No	72.3 (467/646)	78.7 (515/654)	5.3 (25/473)	80.5 (520/646)	88.7 (580/654)	4.9 (23/473)
	Yes	78.4 (407/519)	85.6 (441/515)	1.9 (6/319)	83.0 (431/519)	88.7 (457/515)	3.8 (12/319)
Previous biologic therapy	No	77.6 (663/854)	82.6 (705/854)	5.0 (27/535)	83.1 (710/854)	88.4 (755/854)	5.2 (28/535)
	Yes	67.8 (211/311)	79.9 (251/315)	1.6 (4/257)	77.5 (241/311)	89.5 (282/315)	2.7 (7/257)

% (n/N)

PMDA accepted the above explanation and has concluded that ixekizumab is expected to have efficacy on plaques in Japanese patients with psoriasis vulgaris or psoriatic arthritis.

7.R.1.2 Efficacy on joint symptoms in patients with psoriatic arthritis

The applicant's explanation about the efficacy of ixekizumab on joint symptoms in patients with psoriatic arthritis:

When the clinical development was planned in Japan, the Japanese Dermatological Association reported that an estimated 0.1% of the population in Japan was affected by psoriasis and that approximately 1% of the affected people had psoriatic arthritis (*J Dermatol Sci.* 2003;31:59-64). The applicant, therefore, considered it difficult to conduct a confirmatory study enrolling a certain number of Japanese patients with psoriatic arthritis in Japan, and thus decided to include Japanese patients with psoriatic arthritis in Study RHAZ, Japanese long-term treatment study (Study RHAT), and Study RHAP in patients with psoriatic arthritis, thereby investigating the efficacy of ixekizumab on joint symptoms in Japanese patients with psoriatic arthritis.

Studies RHAZ and RHAT included 3 and 11 Japanese patients with psoriatic arthritis, respectively. All of the Japanese patients had a confirmed diagnosis of psoriatic arthritis according to the classification criteria for psoriatic arthritis (CASPAR). In Study RHAZ, 1 patient randomized to the Q2W group achieved ACR20 at Weeks 2, 4, 8, and 12. According to the efficacy data from Study RHAT, changes in the pain VAS score from baseline at Week 12 and Week 52 were –47.3 ± 22.1 (n = 11) and –51.0 ± 19.1 (n = 11), respectively, and ACR20 was achieved by 4 of 5 subjects at Week 12 and 5 of 5 subjects at Week 52. The results suggested that improvement in joint symptoms after treatment with ixekizumab [see Section "7.2.4 Japanese long-term treatment study (CTD 5.3.5.2.1, Study RHAT)"].

The primary endpoint of Study RHAP in patients with psoriatic arthritis was the ACR20 response rate at Week 24. Pairwise comparisons of the ACR20 response rate at Week 24 showed statistically significant differences between the placebo group and the Q4W group or Q2W group. In this study, the ACR20 response rate at Week 24 in the Japanese subgroup tended to be similar to that in the overall study population, although the number of Japanese patients was limited [see Section "7.2.5 Global phase III study (CTD 5.3.5.1.5, Study RHAP)].

Based on the above findings, ixekizumab is expected to have efficacy on joint symptoms in Japanese patients with psoriatic arthritis.

PMDA's view:
Given that the number of patients with psoriatic arthritis is limited in Japan, PMDA understands the difficulty of conducting a confirmatory study enrolling a certain number of Japanese patients with psoriatic arthritis to investigate the efficacy of ixekizumab on joint symptoms. On the basis of the following results and other findings, ixekizumab is expected to have efficacy on joint symptoms in Japanese patients with psoriatic arthritis. Because of a limited number of Japanese patients with psoriatic arthritis evaluated in the studies, however, the efficacy of ixekizumab on joint symptoms should be further investigated through a post-marketing surveillance study, etc.

- Findings in patients with psoriatic arthritis in Studies RHAZ and RHAT suggested a trend toward an improvement in joint symptoms.
- Data from Study RHAP in patients with psoriatic arthritis were analyzed for the ACR20 response rate at Week 24 (the primary endpoint), and the study demonstrated the superiority of ixekizumab Q4W and Q2W to placebo.
- An analysis of data from Japanese patients with psoriatic arthritis in Study RHAP also showed a trend toward an improvement in joint symptoms, though the number of patients evaluated in the study was limited.

7.R.1.3 Efficacy on pustular psoriasis and erythrodermic psoriasis

The applicant's explanation about the efficacy of ixekizumab in patients with pustular psoriasis and those with erythrodermic psoriasis:
Because patients with pustular psoriasis and those with erythrodermic psoriasis account for approximately 1% of patients with psoriasis overall, enrollment of such patients in clinical studies was assumed to be difficult. The applicant therefore planned to include these patients in Study RHAT, wherever possible, for efficacy and safety evaluation.

Because only small numbers of patients with pustular psoriasis and those with erythrodermic psoriasis were enrolled in Study RHAT, which was designed as an open-label uncontrolled study, there is a limitation to evaluating the efficacy of ixekizumab with data from such patients. However, patients receiving ixekizumab 80 mg Q2W subcutaneously showed improvements in both clinical global impression score and skin symptom assessment score at Week 12, and some responded to ixekizumab soon after the start of the treatment, despite the fact that all the patients enrolled in this study had previously used phototherapy or systemic therapy and that pustular psoriasis and erythrodermic psoriasis are serious refractory diseases. In addition, changes (mean ± SD) in skin symptom assessment score from baseline at Weeks 24, 36, and 52 in patients with pustular psoriasis were –2.0 ± 1.4, –2.2 ± 1.3, and –2.0 ± 1.4, respectively, showing a trend toward a decrease in skin symptom assessment score. All of the patients with erythrodermic psoriasis (100%, 8 of 8 subjects) reported remission or improvement in clinical global impression score. None of the patients with either form of psoriasis reported unchanged or worsened status for clinical global impression at and after Week 12, and the clinical global impression score was maintained almost consistently until Week 52 [see Section"7.2.4 Japanese long-term treatment study (CTD 5.3.5.2.1, Study RHAT)"]. In light of the above results, the applicant considers that ixekizumab is expected to show efficacy in patients with pustular psoriasis and those with erythrodermic psoriasis.

PMDA's view:
Given that the number of patients with pustular psoriasis or erythrodermic psoriasis is extremely limited, PMDA understands the difficulty of conducting a placebo-controlled comparative study only in patients with pustular psoriasis and those with erythrodermic psoriasis. It was unavoidable for the applicant to evaluate the efficacy and safety of ixekizumab in both patients with pustular psoriasis and those with erythrodermic psoriasis as a part of the evaluation in patients with various forms of psoriasis in Study RHAT. In light of data from patients with pustular psoriasis and those with erythrodermic psoriasis enrolled in Study RHAT, ixekizumab is expected to show efficacy in patients with these forms of psoriasis to some extent. Although no clear differences are noted in safety profile among forms of

psoriasis at present, the number of patients with pustular psoriasis or erythrodermic psoriasis evaluated is limited. Patients with pustular psoriasis and those with erythrodermic psoriasis are likely to be at a higher risk of serious infections than patients with other forms of psoriasis because the former patients are considered to be in poor general condition compared with patients with psoriasis vulgaris. Therefore, the applicant should continue to carefully investigate the safety and efficacy of ixekizumab in patients with pustular psoriasis and those with erythrodermic psoriasis through a post-marketing surveillance study and other means.

7.R.2 Safety

The applicant established the following pooled datasets: PPC which consists of the integrated data from Studies RHAZ, RHBA, and RHBC (for the induction dosing period [up to Week 12]); psoriasis placebo- and active-controlled integrated analysis set (PAC) which consists of the integrated data from Studies RHBA and RHBC (for the induction dosing period [up to Week 12]); psoriasis maintenance integrated analysis set (MPP) which consists of the integrated data from Studies RHAZ and RHBA (for the maintenance dosing period [from Week 12 to Week 60]); APS which consists of the integrated data from all the clinical studies in patients with psoriasis (Studies RHAG, RHAJ, RHAT, RHAZ, RHBA, RHBC, and RHBL); and J-APS which consists of the integrated data from 33 and 91 Japanese patients included in Study RHAZ and Study RHAT, respectively.

Based on the above pooled datasets, the applicant provided the following explanation about the safety of ixekizumab.

Table 47 shows safety summaries of ixekizumab in PPC, PAC, MPP, and APS.

Table 47. Safety summaries of ixekizumab in clinical studies in patients with psoriasis (PPC, PAC, MPP, and APS)

	PPC			PAC			
	Q4W (N = 1161)	Q2W (N = 1167)	Placebo (N = 791)	Q4W (N = 729)	Q2W (N = 734)	Etanercept (N = 739)	Placebo (N = 360)
Death	0	0	0	0	0	0	0
Any adverse event	683 (58.8)	681 (58.4)	370 (46.8)	419 (57.5)	424 (57.8)	399 (54.0)	160 (44.4)
Serious adverse events	26 (2.2)	20 (1.7)	12 (1.5)	14 (1.9)	14 (1.9)	14 (1.9)	7 (1.9)
Adverse events leading to discontinuation	24 (2.1)	25 (2.1)	9 (1.1)	14 (1.9)	15 (2.0)	9 (1.2)	3 (0.8)
Adverse drug reactions	285 (24.5)	347 (29.7)	103 (13.0)	174 (23.9)	220 (30.0)	176 (23.8)	54 (15.0)
Overall exposure duration (patient-years)	265.9	268.6	180.0	167.6	168.9	169.2	83.2

	MPP [a]			APS
	Q12W (N = 408)	Q4W (N = 416)	Placebo (N = 402)	Pooled ixekizumab (N = 4204)
Death	0	2	0	5
Any adverse event	300 (73.5) 106.2	330 (79.3) 95.6	233 (58.0) 123.8	3293 (78.3)
Serious adverse events	23 (5.6) 8.1	26 (6.3) 7.5	15 (3.7) 8.0	303 (7.2)
Adverse events leading to discontinuation	9 (2.2) 3.2	15 (3.6) 4.3	8 (2.0) 4.2	190 (4.5)
Adverse drug reactions	88 (21.6) 31.2	133 (32.0) 38.5	80 (19.9) 42.5	1436 (34.2)
Overall exposure duration (patient-years)	282.4	345.2	188.2	4729.7

n (%)

a) Top, number of subjects (%); bottom, incidence rate per 100 patient-years adjusted according to the overall exposure duration

Table 48 shows adverse events reported by ≥2% of subjects in any group in PPC. Events which occurred more frequently in the ixekizumab group than in the placebo group were injection site reaction, injection site erythema, nausea, and oropharyngeal pain, most of which were mild or moderate in severity.

Table 48. Adverse events reported by ≥2% of subjects in any group (PPC)

Event	Q4W (N = 1161)	Q2W (N = 1167)	Placebo (N = 791)
Nasopharyngitis	104 (9.0)	111 (9.5)	69 (8.7)
Injection site reaction	89 (7.7)	117 (10.0)	9 (1.1)
Headache	50 (4.3)	51 (4.4)	23 (2.9)
Upper respiratory tract infection	45 (3.9)	51 (4.4)	28 (3.5)
Injection site erythema	32 (2.8)	52 (4.5)	2 (0.3)
Pruritus	26 (2.2)	20 (1.7)	18 (2.3)
Arthralgia	22 (1.9)	29 (2.5)	17 (2.1)
Diarrhoea	18 (1.6)	25 (2.1)	8 (1.0)
Injection site pain	17 (1.5)	28 (2.4)	14 (1.8)
Nausea	15 (1.3)	23 (2.0)	5 (0.6)
Psoriasis (aggravated)	13 (1.1)	13 (1.1)	24 (3.0)

n (%)

Table 49 shows adverse events whose incidence rate was ≥5 per 100 patient-years in any treatment group in MPP. The incidence of injection site reaction tended to be higher in the ixekizumab Q4W group than in the placebo group. No serious adverse events occurred, and most of the events were mild or moderate in severity. Deaths occurred in 2 subjects in the Q4W group (death and myocardial infarction in 1 subject each). A causal relationship of the adverse event of death to the study drug was considered unknown, while myocardial infarction was considered causally related to the study drug. The incidences of serious adverse events are shown in Table 47. The events reported by ≥2 subjects in any group were fall (2 subjects in the Q4W group, 2 subjects in the placebo group), cholecystitis (2 subjects in the Q4W group), intervertebral disc protrusion (2 subjects in the Q12W group), and Crohn's disease (2 subjects in the placebo group). A causal relationship to the study drug was ruled out for all of these events except for Crohn's disease in 2 subjects in the placebo group.

Table 49. Adverse events with exposure-adjusted incidence rate of ≥5 per 100 patient-years in any group (MPP)

Event	Q12W (N = 408)	Q4W (N = 416)	Placebo (N = 402)
Total (patient-years)	282.4	345.2	188.2
Number of subjects with ≥1 adverse event	300 (73.5) 106.2	330 (79.3) 95.6	233 (58.0) 123.8
Nasopharyngitis	65 (15.9) 23.0	81 (19.5) 23.5	46 (11.4) 24.4
Upper respiratory tract infection	41 (10.0) 14.5	43 (10.3) 12.5	31 (7.7) 16.5
Headache	25 (6.1) 8.9	21 (5.0) 6.1	12 (3.0) 6.4
Arthralgia	24 (5.9) 8.5	21 (5.0) 6.1	13 (3.2) 6.9
Back pain	19 (4.7) 6.7	15 (3.6) 4.3	8 (2.0) 4.2
Sinusitis	17 (4.2) 6.0	18 (4.3) 5.2	10 (2.5) 5.3
Bronchitis	16 (3.9) 5.7	13 (3.1) 3.8	4 (1.0) 2.1
Influenza	14 (3.4) 5.0	13 (3.1) 3.8	6 (1.5) 3.2
Injection site reaction	11 (2.7) 3.9	27 (6.5) 7.8	2 (0.5) 1.1
Diarrhoea	10 (2.5) 3.5	12 (2.9) 3.5	12 (3.0) 6.4

Top, n (%)
Bottom, incidence rate per 100 patient-years adjusted according to the overall exposure duration

In APS, death occurred in 5 subjects (death, myocardial infarction, acute cardiac arrest, cerebrovascular accident, and cardio-respiratory arrest in 1 subject each). A causal relationship to the study drug was ruled out for all the events except for death and myocardial infarction. Serious adverse events occurred in 7.2% (303 of 4204) of subjects in APS. Major adverse events included cellulitis (0.3% [14 of 4204 subjects]), fall (0.2% [9 of 4204 subjects]); acute myocardial infarction and myocardial infarction (0.2%

[8 of 4204 subjects]); chronic obstructive pulmonary disease (0.2% [7 of 4204 subjects]); depression, inguinal hernia, and nephrolithiasis (0.1% [6 of 4202 subjects]); and angina pectoris, cholecystitis, coronary artery disease, suicide attempt, and type 2 diabetes mellitus (0.1% [5 of 4204 subjects]). Adverse events reported by ≥1% of subjects throughout the study period were analyzed for the incidence in each dosing period, and there was no increase over time in the incidences of the adverse events.

Safety analysis was performed for the Japanese subgroup. Adverse events occurred in 89.3% (108 of 121) of subjects in J-APS. Major adverse events included nasopharyngitis (40.5% [49 of 121 subjects]), eczema (13.2% [16 of 121 subjects]), diarrhoea (10.7% [13 of 121 subjects]), and urticaria and arthralgia (8.3% [10 of 121 subjects]). No deaths were reported. Serious adverse events occurred in 4.1% (5 of 121) of subjects in J-APS. The serious adverse events were pulmonary embolism and deep vein thrombosis (1 subject), sleep apnoea syndrome (1 subject), colon cancer (1 subject), bronchopneumonia (1 subject), and glomerulonephritis and colon cancer (1 subject). Adverse events leading to discontinuation occurred in 6.6% (8 of 121) of subjects. The events were neutropenia, allergic oedema, bronchopneumonia, tuberculin test positive, colon cancer, glomerulonephritis, pulmonary embolism, and pruritus generalised in 1 subject each (some subjects had more than 1 event).

The incidence of adverse events tended to be slightly higher in the Japanese subgroup than in the overall study population, and this trend was considered attributable to the high incidence of nasopharyngitis and urticaria. The applicant, however, considers that there are no safety concerns specific to Japanese patients with psoriasis because (1) the types of the events in the Japanese subgroup were generally similar to those in the overall study population and (2) most of the events were mild or moderate in severity.

To evaluate the safety of ixekizumab in clinical studies, PMDA investigated the following events in light of the pharmacological effect, etc. of ixekizumab.

7.R.2.1 Infections

The applicant's explanation about infections associated with ixekizumab:
IL-17 has been reported to induce secretion of chemokines such as IL-8, which recruits neutrophils into an inflammatory site (*Nat Biotechnol.* 2012;30:475-7). Inhibition of IL-17 potentially leads to neutropenia, thus increasing the risk of bacterial infection. In addition, patients with psoriasis are at an increased risk of serious infections because psoriasis is an immune-mediated disease (*J Am Acad Dermatol.* 2011;65:1135-44). In consideration of the above reports, the applicant investigated the risk of infection associated with ixekizumab.

Table 50 shows infections reported in clinical studies. Infections tended to be more common in the ixekizumab groups than in the control groups. Major adverse events included nasopharyngitis and upper respiratory tract infection. Most of the infection events reported were mild or moderate. Furthermore, no difference was observed in the incidence of serious infections between the placebo group and ixekizumab groups during the induction dosing period. There were no events reported by ≥2 subjects during the maintenance dosing period. The exposure-adjusted incidence rate per 100 patient-years in APS was 1.5, which was comparable to that in MPP.

Table 50. Incidences of infection-related adverse events (PPC, PAC, and MPP)

	PPC (induction dosing period)			PAC (induction dosing period)				MPP (maintenance dosing period)[a)]		
	Q4W (N = 1161)	Q2W (N = 1167)	Placebo (N = 791)	Q4W (N = 729)	Q2W (N = 734)	Etanercept (N = 739)	Placebo N = (360)	Q12W (N = 408)	Q4W (N = 416)	Placebo (N = 402)
Infections	318 (27.4)	315 (27.0)	181 (22.9)	191 (26.2)	190 (25.9)	159 (21.5)	74 (20.6)	206 (50.5) 72.9	240 (57.7) 69.5	143 (35.6) 76.0
Serious infections	8 (0.7)	5 (0.4)	3 (0.4)	5 (0.7)	2 (0.3)	3 (0.4)	2 (0.6)	3 (0.7) 1.1	6 (1.4) 1.7	3 (0.7) 1.6
Tuberculosis	0	1 (0.1)	0	0	1 (0.1)	0	0	0	2 (0.5) 0.6	0
Hepatitis viral	0	0	0	0	0	0	0	0	0	0
Staphylococcal infection	2 (0.2)	2 (0.2)	2 (0.3)	1 (0.1)	1 (0.1)	0	1 (0.3)	3 (0.7) 1.1	4 (1.0) 1.2	2 (0.5) 1.1
Herpes simplex and herpes zoster	15 (1.3)	7 (0.6)	6 (0.8)	11 (1.5)	5 (0.7)	7 (0.9)	1 (0.3)	9 (2.2) 3.2	8 (1.9) 2.3	7 (1.7) 3.7
Opportunistic infection	10 (0.9)	22 (1.9)	6 (0.8)	6 (0.8)	13 (1.8)	5 (0.7)	2 (0.6)	15 (3.7) 5.3	27 (6.5) 7.8	9 (2.2) 4.8

n (%)

a) Top, n (%); Bottom, incidence rate per 100 patient-years adjusted according to the overall exposure duration

One subject who tested positive for hepatitis B virus but did not meet the exclusion criteria[21)] was enrolled in a clinical study of ixekizumab. The subject did not experience hepatitis B reactivation.

In Study RHAZ, 1 subject in the Q2W/Q12W group was suspected of experiencing reactivation of tuberculosis. This subject was positive only on a QuantiFERON-TB Gold test (4.44 IE/mL compared with the reference value of <0.35) and thus was considered to have latent tuberculosis. The test was repeated after 286 days of treatment with ixekizumab, and the test result was 6.28 IE/mL. In response to the result, the study treatment was discontinued in the subject with suspected reactivation of tuberculosis at the discretion of the investigator. However, the observed data did not positively correlate with the activity of tuberculosis. There were neither clinical symptoms nor detailed test findings suggestive of reactivated tuberculosis. The protocols of clinical studies of ixekizumab, however, specified the exclusion of patients with active tuberculosis. The impact of ixekizumab on patients with active tuberculosis remains unknown.

The above clinical study data do not include findings suggesting that ixekizumab has a higher risk of serious infections than drugs in the same class, but infections tended to occur more frequently in the ixekizumab group than in the placebo and etanercept groups. In light of this finding, the applicant plans to include the following precautionary advice about the risk of infections in the package insert: (1)Patients should be closely monitored and examined before dosing; (2) ixekizumab should be contraindicated in patients with serious infections and active tuberculosis; (3) ixekizumab should be carefully administered to patients with a risk of tuberculosis or other infectious diseases; and (4) patients should be advised to consult their physician immediately if any sign or symptom of infection develops after administration of ixekizumab.

PMDA's view:
The incidence of serious infections in the ixekizumab group is comparable to that in the placebo group, but the incidence of infections in the ixekizumab group tended to be higher than that in the placebo group and the etanercept group. Furthermore, the pharmacological action of ixekizumab potentially contributes to an increased risk of serious infections. Precautionary advice therefore should be provided to healthcare professionals, as with other approved biological products for the treatment of psoriasis. Serious infections associated with ixekizumab should continue to be investigated through a post-marketing surveillance study. At the same time, dermatologists who are mainly engaged in the diagnosis and treatment of psoriasis should take sufficient safety measures in cooperation with physicians experienced in the diagnosis and treatment of serious infections so as to ensure prevention and early detection of serious infections [see Section "7.R.7 Post-marketing safety measures"].

One subject with suspected active or re-activated tuberculosis in Study RHAZ experienced no clear clinical symptoms. According to the applicant, the causal relationship of the event and the study drug

21) Patients with hepatitis B virus surface antigen positive or patients with anti-hepatitis B virus core antibody positive and hepatitis B virus surface antibody negative were excluded.

remained unknown. However, the number of such subjects evaluated in the clinical studies is not sufficient for evaluation of the risk of tuberculosis. Furthermore, the literature (*J Immunol.* 2010;184:4414-22) indicated that IL-17 produced by γδ-type T cells is involved in the formation of mature granuloma that plays a critical role in the prevention of tuberculosis infection. Given these findings, a relationship of ixekizumab with tuberculosis cannot be ruled out. In conclusion, precautionary advice about the risk of tuberculosis should be provided to healthcare professionals, as with other approved biological products for the treatment of psoriasis.

7.R.2.2 Fungal infections

The applicant's explanation about fungal infections such as Candida infection associated with ixekizumab:

IL-17A has been reported to be partly involved in the prevention of mucocutaneous candidiasis caused by *Candida albicans* (*Science.* 2011;332:65-8). The applicant investigated a risk of fungal infections such as Candida infection associated with ixekizumab.

Table 51 shows the incidences of Candida infection-related events reported in clinical studies. Adverse events related to Candida infection, especially oral candidiasis, tended to be more common in the Q2W group during the induction dosing period and in the Q4W and Q12W groups during the maintenance dosing period, compared with the placebo group. All of the adverse events related to Candida infection were non-serious, and none of them led to discontinuation. Such events were considered to be manageable with appropriate treatment. Deep mycosis did not occur. Precautionary advice about the risk of oral candidiasis will be included in the package insert.

Table 51. Incidences of adverse events related to Candida infection (PPC, PAC, and MPP)

	PPC (induction dosing period)			PAC (induction dosing period)				MPP (maintenance dosing period)[a)]		
	Q4W (N = 1161)	Q2W (N = 1167)	Placebo (N = 791)	Q4W (N = 729)	Q2W (N = 734)	Etanercept (N = 739)	Placebo (N = 360)	Q12W (N = 408)	Q4W (N = 416)	Placebo (N = 402)
Adverse events related to Candida infection	7 (0.6)	16 (1.4)	4 (0.5)	4 (0.5)	12 (1.6)	5 (0.7)	2 (0.6)	7 (1.7) 2.5	16 (3.8) 4.6	4 (1.0) 2.1
Vulvovaginal candidiasis	3 (0.8)	1 (0.2)	2 (0.9)	2 (0.9)	0	1 (0.1)	0	0	1 (0.8) 0.9	1 (0.7) 1.6
Oral candidiasis	2 (0.2)	8 (0.7)	0	1 (0.1)	5 (0.7)	1 (0.1)	0	6 (1.5) 2.1	7 (1.7) 2.0	1 (0.2) 0.5
Vulvovaginal mycotic infection	2 (0.5)	2 (0.5)	1 (0.4)	1 (0.4)	2 (0.8)	1 (0.4)	1 (1.0)	1 (0.7) 1.1	2 (1.6) 1.9	0
Skin candida	0	2 (0.2)	0	0	2 (0.3)	0	0	0	2 (0.5) 0.6	1 (0.2) 0.5
Oesophageal candidiasis	0	1 (0.1)	0	0	1 (0.1)	0	0	0	1 (0.2) 0.3	1 (0.2) 0.5
Oral fungal infection	0	1 (0.1)	0	0	1 (0.1)	0	0	0	1 (0.2) 0.3	0
Otitis externa candida	0	1 (0.1)	0	0	1 (0.1)	0	0	-	-	-
Intertrigo candidal	0	0	1 (0.1)	0	0	0	1 (0.1)	0	1 (0.2) 0.3	0

n (%)

a) Top, n (%); Bottom, incidence rate per 100 patient-years adjusted according to the overall exposure duration

PMDA's view:

Patients receiving ixekizumab should be monitored for superficial fungal infections such as Candida infection because (i) IL-17 plays a central role in mucosal defense against Candida (*Eur J Immunol.* 2012;42:2246-54), and (ii) ixekizumab clinical studies revealed a trend toward a higher incidence of Candida infection in the ixekizumab group than that in the placebo group. The applicant should also investigate fungal infections associated with ixekizumab through a post-marketing surveillance study and other means.

7.R.2.3 Neutropenia

The applicant's explanation about neutropenia associated with ixekizumab and its relationship with infections:

IL-17 plays a role in recruiting neutrophils through release of chemokines such as keratinocyte chemoattractant specifically acting on neutrophils (*J Immunol.* 2000;165:5814-21). In IL-17 knockout mice, baseline circulating neutrophil count fell within the normal range (*J Exp Med.* 2001;194:519-27), but direct bacterial challenge in IL-17 receptor negative homozygous mice decreased their recruitment

capability of neutrophils, resulting in a rapid decrease in the neutrophil count. In consideration of the report, the applicant investigated a risk of neutropenia associated with ixekizumab.

Table 52 shows neutropenia related-events occurring in clinical studies. Event grade was assessed based on hematology parameters. The incidence of Grade ≥2 (<1.5 × 10^9/L) neutrophil count decreased in the ixekizumab groups tended to be higher than that in the placebo group, but no clear differences were observed between the Q2W group and the Q4W group. The incidence of Grade ≥3 (<1.0 × 10^9/L) neutrophil count decreased was comparable to that in the placebo group during the induction dosing period, and the number of subjects with this event was limited. In APS, the incidence of Grade ≥2 neutrophil count decreased was 3.2% (133 of 4204 subjects). The percentage of subjects who experienced Grade ≥2 neutrophil count decreased twice consecutively was 0.5% (22 of 4204 subjects) in APS, and the percentage of subjects who experienced the event 3 times consecutively was 0.2% (7 of 4204 subjects). The incidence of Grade ≥3 neutrophil count decreased was 0.2% (9 of 4204 subjects), and the percentage of subject who experienced it twice consecutively was 0.02% (1 of 4204 subjects). The event was transient in most of the subjects.

The incidence of infection-related events occurring within 14 days before or after detection of Grade ≥2 neutrophil count decreased in PPC was 0.3% (4 of 1161 subjects) in the Q4W group, 0.2% (2 of 1167 subjects) in the Q2W group, and 0.3% (2 of 791 subjects) in the placebo group. The incidence of such events in PAC was 0.5% (4 of 729 subjects) in the Q4W group, 0.3% (2 of 734 subjects) in the Q2W group, 0.3% (2 of 739 subjects) in the etanercept group, and 0.3% (1 of 360 subjects) in the placebo group. The incidence of such events in MPP was 0.5% (2 of 408 subjects) in the Q12W group, 0.5% (2 of 416 subjects) in the Q4W group, and 0% (0 of 402 subjects) in the placebo group. The incidences of infection-related events associated with neutrophil count decreased were lower than those of overall infections. This does not suggest an increased risk of infections associated with neutrophil count decreased in patients receiving ixekizumab. Precautionary advice about the risk of neutrophil count decreased will be included in the package insert.

Table 52. Incidences of adverse events related to neutropenia (PPC, PAC, and MPP)

	PPC (induction dosing period)			PAC (induction dosing period)				MPP (maintenance dosing period)		
	Q4W (N = 1161)	Q2W (N = 1167)	Placebo (N = 791)	Q4W (N = 729)	Q2W (N = 734)	Etanercept (N = 739)	Placebo (N = 360)	Q12W (N = 408)	Q4W (N = 416)	Placebo (N = 402)
Neutropenia (preferred term)	3 (0.3)	4 (0.3)	1 (0.1)	2 (0.3)	3 (0.4)	8 (1.1)	1 (0.3)	1 (0.2) 0.4	3 (0.7) 0.9	0
Neutrophil count decreased (preferred term)	0	2 (0.2)	0	0	2 (0.3)	2 (0.3)	0	0	0	1 (0.2) 0.5
Grade ≥2 neutrophil count decreased	24 (2.1)	29 (2.5)	4 (0.5)	19 (2.6)	22 (3.0)	29 (4.0)	2 (0.6)	6 (1.5) 2.1	9 (2.2) 2.6	5 (1.3) 2.7
Grade ≥3 neutrophil count decreased	1 (0.1)	2 (0.2)	1 (0.1)	1 (0.1)	2 (0.3)	4 (0.5)	1 (0.3)	1 (0.2) 0.4	0	0

n (%)
a) Top, n (%); Bottom, incidence rate per 100 patient-years adjusted according to the overall exposure duration

PMDA's view:
The applicant should include precautionary advice about the risk of neutrophil count decreased associated with ixekizumab in the package insert and should continue to investigate the occurrence of this event and its relationship with infections through a post-marketing surveillance study, for the following reasons: (1) neutrophil count decreased is an event inferred from the pharmacological effect of ixekizumab; (2) the incidence of this event tended to be higher in the ixekizumab group than in the placebo group in clinical studies; and (3) it cannot be ruled out that neutrophil count decreased associated with ixekizumab potentially leads to infections.

7.R.2.4 Malignant tumors

The applicant's explanation about malignant tumor associated with ixekizumab:
Immunoregulation deficiency and chronic inflammation, which are considered to contribute to the pathogenesis of psoriasis, are potentially related to an increased risk of malignancies (*J Am Acad Dermatol.* 2008;58:1031-42). A retrospective cohort research in the UK revealed that the risk of lymphoma in patients with psoriasis was approximately 3-fold that in patients without psoriasis (*J Invest Dermatol.* 2006;126:2194-201). According to the database consisting of claim data for medical expenses

in the US, the incidence of malignant tumors overall in patients with psoriasis was 20% higher than that in the general population (*Br J Dermatol.* 2014,171:137-47). In addition, the publications has indicated a relationship of IL-17A to tumor growth (*J Immunol.* 2010;184:2281-8, *J Exp Med*. 2009;206:1457-64, and other reports). The applicant therefore investigated the risk of malignant tumors associated with ixekizumab.

Table 53 shows malignant tumors reported in clinical studies. The incidence of malignant tumor in the ixekizumab group was comparable to that in the placebo group or the etanercept group, without any dose-dependent increase. In APS, the incidence of malignant tumors was 1.1% (46 of 4204 subjects; non-melanoma skin cancers [NMSC] in 23 subjects and malignant tumors except for NMSC in 23 subjects), and the overall exposure duration-adjusted incidence rate per 100 patient-years was 1.0 (0.5 for NMSC and 0.5 for malignant tumors except for NMSC). Serious adverse events occurred in 0.4% (18 of 4204) of subjects. The events were prostate cancer in 3 subjects, lymphoma and large intestine carcinoma in 2 subjects each, and basal cell carcinoma, squamous cell carcinoma, breast cancer, invasive ductal breast carcinoma, lung neoplasm malignant, metastatic neoplasm, non-small cell lung cancer metastatic, rectal adenocarcinoma, renal cell carcinoma, small intestine adenocarcinoma, squamous cell carcinoma of lung, and synovial sarcoma in 1 subject each.

Table 53. Incidences of malignant tumors (PPC, PAC, and MPP)

	PPC (induction dosing period)			PAC (induction dosing period)				MPP (maintenance dosing period)[a)]		
	Q4W (N = 1161)	Q2W (N = 1167)	Placebo (N = 791)	Q4W (N = 729)	Q2W (N = 734)	Etanercept (N = 739)	Placebo (N = 360)	Q12W (N = 408)	Q4W (N = 416)	Placebo (N = 402)
Adverse events related to malignant tumor	3 (0.3)	3 (0.3)	2 (0.3)	0	3 (0.4)	1 (0.1)	0	5 (1.2) 1.8	1 (0.2) 0.3	1 (0.2) 0.5
NMSC	1 (0.1)	2 (0.2)	1 (0.1)	0	2 (0.2)	0	0	3 (0.7) 1.1	1 (0.2) 0.3	0
Malignant tumors except for NMSC	2 (0.2)	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	0	2 (0.5) 0.7	0	1 (0.2) 0.5

n (%)

a) Top, n (%); Bottom, incidence rate per 100 patient-years adjusted according to the overall exposure duration

An observational study in patients with psoriasis (*Arch Dermatol.* 2001;137:778-83) reported that the incidence rates of malignant tumors per 100 patient-years were 1.9 to 2.9, which was comparable to that in patients with psoriasis receiving ixekizumab. In addition, the incidence rates of malignant tumors except for NMSC per 100 patient-years in the PSOLAR (*Exp Dermatol.* 2014;23[Suppl 2]) and OBSERVE-5 registry (*J Am Acad Dermatol.* 2013;68:756-64) were 0.68 and 0.70, respectively, which were comparable to those in patients with psoriasis receiving ixekizumab.

The above comparisons of clinical study data and the published data did not suggest any increased risk of malignant tumors in patients receiving ixekizumab. The inclusion of special precautions in the package insert, etc. is considered unnecessary. The applicant, however, plans to monitor the development of malignant tumors in patients receiving ixekizumab in the post-marketing setting, because the number of subjects evaluated in clinical studies and the duration of evaluation were limited.

PMDA's view:

At present, the relationship of ixekizumab with malignant tumors remains unknown. However, the applicant should include precautionary advice about the risk of malignant tumors in the package insert, as with other approved biological products for psoriasis, because (1) the number of subjects evaluated in clinical studies and the duration of evaluation are not sufficient to evaluate the risk of malignant tumors; and (2) it cannot be ruled out that ixekizumab affects the host defense mechanism against malignant tumors, as with other approved biological products. In general, patients with psoriasis often have a previous history of phototherapy and therapy with immunosuppressive drugs. Especially, this may raise concerns about skin cancer. In light of the above situation, malignant tumors including skin cancer in patients with psoriasis receiving ixekizumab should continue to be investigated through a post-marketing surveillance study.

7.R.2.5 Allergic reaction/hypersensitivity and injection site reaction

The applicant's explanation about allergic reaction/hypersensitivity and injection site reaction associated with ixekizumab:

Table 54 shows allergic reaction/hypersensitivity-related adverse events reported in clinical studies. Allergic reaction/hypersensitivity-related adverse events tended to be more common in the ixekizumab groups than in other groups. In PPC, serious adverse events occurred in 5 subjects. The events were angioedema (Q4W group), drug hypersensitivity, hypersensitivity vasculitis, and urticaria (Q2W group), and drug eruption (placebo group). All of the events resolved or were resolving.

Anaphylactic reaction was reported in 2 subjects in APS. The events were both moderate in severity and resolved with medication.

Table 54 shows injection site reaction-related adverse events reported in clinical studies. Injection site reaction-related adverse events tended to be more common in the ixekizumab groups than that in the placebo group. The rate of episodes per 100 doses in PPC was 5.9 in the Q4W group, 5.9 in the Q2W group, and 0.76 in the placebo group. The rate of episodes per 100 doses in PAC was 6.3 in the Q4W group, 6.6 in the Q2W group, 3.3 in the etanercept group, and 0.71 events in the placebo group. The rate of episodes per 100 doses in MPP was 3.6 in the Q12W group, 3.4 in the Q4W group, and 1.2 in the placebo group. Injection site reaction-related adverse events tended to be more common in the ixekizumab groups than in the placebo group. Injection site reaction-related adverse events occurred in 15.2% (638 of 4204) of subjects in APS, but none of the events were serious. Most of the events were transient. In Study RHAZ, 1 subject experienced not only injection site reaction but also cellulitis, which was reported as a serious adverse event. In Study RHBC, 1 subject experienced injection site reaction initially and later generalized urticaria, which was considered a serious adverse event. Most of the injection site reactions reported were mild or moderate. No clinically relevant hypersensitivity occurred in patients who continued to receive ixekizumab even after experiencing injection site reaction.

Table 54. Incidences of adverse events related to allergic reaction/hypersensitivity and injection site reaction (PPC, PAC, and MPP)

	PPC (induction dosing period)			PAC (induction dosing period)				MPP (maintenance dosing period)[a)]		
	Q4W (N = 1161)	Q2W (N = 1167)	Placebo (N = 791)	Q4W (N = 729)	Q2W (N = 734)	Etanercept (N = 739)	Placebo (N = 360)	Q12W (N = 408)	Q4W (N = 416)	Placebo (N = 402)
Adverse events related to allergic reaction/ hypersensitivity	46 (4.0)	41 (3.5)	17 (2.1)	27 (3.7)	27 (3.7)	19 (2.6)	7 (1.9)	18 (4.4) 6.4	30 (7.2) 8.7	13 (3.2) 6.9
Serious adverse events related to allergic reaction/hypersensitivity	1 (0.1)	3 (0.3)	1 (0.1)	1 (0.1)	1 (0.1)	0	0	0	0	0
Adverse events related to injection site reaction	150 (12.9)	196 (16.8)	26 (3.3)	97 (13.3)	127 (17.3)	121 (16.4)	13 (3.6)	21 (5.1)	37 (8.9)	8 (2.0)
Serious adverse events related to injection site reaction	0	0	0	0	0	1 (0.1)	0	0	0	0

n (%)

a) Top, n (%); Bottom, incidence rate per 100 patient-years adjusted according to the overall exposure duration

As described above, the risk of serious adverse events related to allergic reaction/hypersensitivity and injection site reaction was not clearly increased in patients receiving ixekizumab, but serious adverse events occurred in ADA-positive patients, albeit a small number of affected patients. In light of the above findings, the "Contraindication" section of the package insert will state that ixekizumab is contraindicated in patients with a history of hypersensitivity to any of the components of Taltz (ixekizumab). In addition, the package insert will advise that ixekizumab should be discontinued immediately to take appropriate measures if any abnormalities are observed, because serious hypersensitivity reactions such as angioedema and urticaria were reported in clinical studies. It will also list injection site reaction as an adverse drug reaction and advice that appropriate measures should be taken if any injection site reaction occurs..

PMDA's view:

The applicant should provide precautionary advice about the risk of injection site reactions and serious hypersensitivity events such as anaphylaxis and should investigate such adverse events through a post-

marketing surveillance study, because (i) anaphylaxis occurred in clinical studies of ixekizumab and (ii) many subjects experienced injection site reactions, some of which were serious.

7.R.2.6 Inflammatory bowel disease (Crohn's disease, and colitis ulcerative)

The applicant's explanation about inflammatory bowel disease (Crohn's disease and colitis ulcerative) in patients receiving ixekizumab:
IL-17A-producing Th17 cells have been reported to play a critical pathogenetic role in psoriasis and inflammatory bowel disease (*Biomed Res Int.* 2013;2013:983902). A genetic study revealed a genetic relationship between psoriasis and autoimmune disease (*J Am Heart Assoc.* 2013;2:e000062). In addition, a report of a clinical study of an IL-17A inhibitor in patients with Crohn's disease suggested exacerbation of the primary disease (*Gastroenterology.* 2012;143:e26). The applicant therefore investigated a risk of inflammatory bowel disease associated with ixekizumab.

Table 55 shows inflammatory bowel disease reported in clinical studies. The incidence of inflammatory bowel disease in the ixekizumab group was not clearly different from that in the placebo group or the etanercept group, without any dose-dependent increase. Crohn's disease and colitis ulcerative occurred in 0.1% (4 of 4204) of subjects and 0.2% (9 of 4204) of subjects, respectively, in APS. Events related to Crohn's disease occurred in 4 subjects (anal abscess in 2 subjects, anal fistula in 1 subject, and rectal abscess in 1 subject). The incidence rate of inflammatory bowel disease per 100 patient-years was 0.1 for Crohn's disease and 0.2 for colitis ulcerative.

Serious adverse events related to inflammatory bowel disease occurred in 7 subjects (Crohn's disease in 3 subjects, colitis ulcerative in 2 subjects, anal fistula in 1 subject, and rectal abscess in 1 subject), and events leading to discontinuation occurred in 8 subjects (Crohn's disease and colitis ulcerative in 4 subjects each). Crohn's disease was reported in 4 subjects as an adverse event, and the 4 cases of Crohn's disease were newly diagnosed after enrollment. Of 3 subjects who had a diagnosis of Crohn's disease before the enrollment, none experienced exacerbation during the study. Colitis ulcerative was reported in 10 subjects as an adverse event. Of these, 6 subjects had newly diagnosed colitis ulcerative, and the remaining 4 subjects experienced an exacerbation of previously diagnosed colitis ulcerative. The 4 subjects were part of 11 subjects who had a previously diagnosed colitis ulcerative before enrollment.

Table 55. Incidences of inflammatory bowel disease (PPC, PAC, and MPP)

	PPC (induction dosing period)			PAC (induction dosing period)				MPP (maintenance dosing period)[a)]		
	Q4W (N = 1161)	Q2W (N = 1167)	Placebo (N = 791)	Q4W (N = 729)	Q2W (N = 734)	Etanercept (N = 739)	Placebo (N = 360)	Q12W (N = 408)	Q4W (N = 416)	Placebo (N = 402)
Adverse events related to autoimmune disease	1 (0.1)	4 (0.3)	0	0	3 (0.4)	0	0	3 (0.7) 1.1	1 (0.2) 0.3	3 (0.7) 1.6
Crohn's disease	1 (0.1)	1 (0.1)	0	0	1 (0.1)	0	0	0	0	3 (0.7) 1.6
Colitis ulcerative	0	2 (0.2)	0	0	1 (0.1)	0	0	2 (0.5) 0.7	1 (0.2) 0.3	0
Serious adverse events related to IBD										
Crohn's disease	1 (0.1)	1 (0.1)	0	0	1 (0.1)	0	0	0	1 (0.2) 0.3	2 (0.5) 1.1
Colitis ulcerative	0	0	0	0	0	0	0	1 (0.2) 0.4	0	0
Adverse events related to IBD leading to discontinuation										
Crohn's disease	1 (0.1)	1 (0.1)	0	0	1 (0.1)	0	0	0	0	2 (0.5) 1.1
Colitis ulcerative	0	1 (0.1)	0	0	0	0	0	1 (0.2) 0.4	0	0

n (%)
a) Top, n (%); Bottom, incidence rate per 100 patient-years adjusted according to the overall exposure duration

Although the incidence of inflammatory bowel disease in the ixekizumab group was low with any dosing regimen, the incidence rate per 100 patient-years was higher than that reported in a prospective observational study in female patients with psoriasis in the US (0.04 for Crohn's disease and 0.02 for colitis ulcerative, *Ann Rheum Dis.* 2013;72:1200-5). The published literature indicated that IL-17-producing Th17 cells play a critical role in antimicrobial immunity at epithelial and mucosal barriers by producing cytokines such as IL-22 (*Biomed Res Int.* 2013;2013:983902). On the basis of the above findings, the package insert will include precautionary advice about the risk of inflammatory bowel disease.

PMDA's view:
The package insert should include precautionary advice about the risk of inflammatory bowel disease, and a relationship of ixekizumab with exacerbation or new onset of inflammatory bowel disease should be further investigated through a post-marketing surveillance study and other means, for the following reasons:

- In clinical studies, new onset of Crohn's disease and exacerbation or new onset of colitis ulcerative occurred only in patients receiving ixekizumab.
- A study on the immunological mechanism indicated a relationship between IL-17A and the pathology of inflammatory bowel disease. A report of a clinical study of an IL-17A inhibitor in patients with Crohn's disease suggested exacerbation of the primary disease.

7.R.2.7 Cardiovascular events

The applicant's explanation about myocardial infarction, stroke, and vascular death in patients receiving ixekizumab:
More than one large-scale prospective cohort studies have reported that patients with psoriasis often have cardiovascular risk factors such as diabetes mellitus, hypertension, obesity, dyslipidaemia, smoking, and family history of cardiovascular diseases (*Br J Dermatol.* 2008;159:895-902, *Arch Dermatol.* 2009;145:379-82, *J Dermatol Sci.* 2011;63:40-6). The published literature has suggested that psoriasis is related to an increased risk of major atherothrombotic events such as myocardial infarction and ischaemic stroke (*J Am Heart Assoc.* 2013;2:e000062). In addition, although continuous IL-17 expression is observed in patients with psoriasis, the roles of IL-17 and Th17 cells in the pathogenesis of atherosclerosis remain unknown.

Table 56 shows major adverse cardiovascular events (MACEs) reported in clinical studies. The incidence of MACEs in the ixekizumab groups was comparable to that in the placebo group or the etanercept group, without any dose-dependent increase. MACEs occurred in 0.8% (31 of 4204) of subjects in APS. Vascular death occurred in 5 subjects. A causal relationship to the study drug could not be ruled out for the events of death and myocardial infarction in 1 subject each. Most of the subjects with MACEs had risk factors for MACEs such as a history and/or comorbidity of cardiovascular and cerebrovascular diseases and smoking. Table 56 shows the incidences of cardiovascular events except for MACEs. There were no differences in the incidences of those events among the treatment groups.

Table 56. Incidences of cardiovascular events (PPC, PAC, and MPP)

	PPC (induction dosing period)			PAC (induction dosing period)				MPP (maintenance dosing period)		
	Q4W (N = 1161)	Q2W (N = 1167)	Placebo (N = 791)	Q4W (N = 729)	Q2W (N = 734)	Etanercept (N = 739)	Placebo (N = 360)	Q12W (N = 408)	Q4W (N = 416)	Placebo (N = 402)
Overall exposure duration	265.9	268.6	180.0	167.6	168.9	169.2	83.2	282.4	345.2	188.2
MACE	2 (0.1) 0.8	0 0	1 (0.1) 0.6	1 (0.1) 0.6	0 0	1 (0.1) 0.6	1 (0.3) 1.2	0	3 (0.7) 0.9	1 (0.2) 0.5
Vascular death	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0	2 (0.5) 0.6	0
Nonfatal myocardial infarction	1 (0.1) 0.4	0 0	1 (0.1) 0.6	0 0	0 0	1 (0.1) 0.6	1 (0.3) 1.2	0	1 (0.2) 0.3	0
Nonfatal stroke	1 (0.1) 0.4	0 0	0 0	1 (0.1) 0.6	0 0	0 0	0 0	0	0	1 (0.2) 0.5
Cardiovascular events except for MACEs	3 (0.3) 1.1	0 0	1 (0.1) 0.6	1 (0.1) 0.6	0 0	2 (0.3) 1.2	1 (0.3) 1.2	3 (0.7) 1.1	2 (0.5) 0.6	1 (0.2) 0.5
Cardiogenic shock due to myocardial infarction	0	0	0	0	0	0	0	0	0	0
Resuscitated cardiac death	0	0	0	0	0	0	0	0	0	0
Hospitalisation due to angina unstable	0	0	0	0	0	0	0	0	0	0
Coronary revascularisation	1 (0.1) 0.4	0	1 (0.1) 0.6	0	0	1 (0.1) 0.6	1 (0.3) 1.2	3 (0.7) 1.1	1 (0.2) 0.3	0
Hospitalisation due to cardiac failure	0	0	0	0	0	0	0	0	1 (0.2) 0.3	0
Hospitalisation due to hypertension	0	0	0	0	0	0	0	0	0	0
Peripheral arterial event	0	0	0	0	0	0	0	0	0	0
Peripheral revascularisation	0	0	0	0	0	1 (0.1) 0.6	0	0	0	1 (0.2) 0.5
Serious arrhythmia	2 (0.2) 0.8	0	0	1 (0.1) 0.6	0	0	0	0	0	1 (0.2) 0.5

Top: n (%)
Bottom: Incidence rate per 100 patient-years adjusted according to the overall exposure duration

Table 57 summarizes MACEs and individual events by duration of ixekizumab exposure (approximately 6 months). The cardiovascular risk did not tend to increase with increasing duration of exposure.

Table 57. Incidence of MACEs by duration of exposure (APS)

Duration of exposure (days)	0-182	183-364	365-547	548-729	≥730
N	4030	3411	2083	969	282
MACE	13 (0.3)	8 (0.2)	7 (0.3)	3 (0.3)	0
Vascular death	2 (0.05)	2 (0.1)	1 (0.05)	0	0
Nonlethal myocardial infarction	7 (0.2)	5 (0.1)	5 (0.2)	3 (0.3)	0
Nonlethal cerebral infarction	4 (0.1)	1 (0.03)	1 (0.05)	0	0

n (%)

The incidence rates of MACEs per 100 patient-years in clinical studies of other biological products ranged from 0.44 to 0.51. The values were not clearly different from that (0.7) in patients receiving ixekizumab.

The applicant considers that the above results do not suggest an increased risk of MACEs in patients receiving ixekizumab.

PMDA's view:
At present, there are no data suggesting a clear relationship of ixekizumab with myocardial infarction, stroke, or vascular death. However, post-marketing information on the risk of cardiovascular events associated with ixekizumab should be collected including published literature.

7.R.2.8 Depression and suicide/self-injury

The applicant's explanation about adverse events related to depression and suicide/self-injury in patients receiving ixekizumab:
Due to its chronic pathology, psoriasis not only lowers patients' quality of life but also affects their emotional state, resulting in an increased risk of mental disorders including depression and suicidality (*J Am Acad Dermatol.* 1999;41:401-7 and other reports). A cohort study using electronic medical record

data between 1987 and 2002 reported that risks of depression, anxiety, and suicidality were increased by 39%, 31%, and 44%, respectively, in patients with psoriasis (*Arch Dermatol.* 2010;146:891-5). Table 58 shows the incidences of events related to depression and suicide/self-injury in clinical studies. The incidence of such events in the ixekizumab groups was comparable to that in the placebo group or the etanercept group. Depression-related events occurred in 1.3% (56 of 4204) of subjects in APS. The incidence of serious adverse events was 0.2% (7 of 4204 subjects; depression in 6 subjects, and depressed mood and mood swings in 1 subject each), and the incidence of events leading to discontinuation was 0.1% (3 of 4204 of subjects, depression in any subject). Suicide/self-injury-related events occurred in 0.1% (5 of 4204) of subjects in APS (suicide attempt in any subject). All of the events were considered serious adverse events. A causal relationship of the event to the study drug was ruled out in all of the 5 subjects. Of these, 2 subjects were found to have a history of past suicide attempt as a risk factor. All of the 5 subjects were found to have multiple risk factors such as a history of other mental disorders including mood disorder, anxiety disorder, alcohol disorder or other substance disorders, and the presence of critical and acute psychosocial incentive.

The effect of ixekizumab on new onset or exacerbation of depression and thoughts of death or suicide in PPC was evaluated using the quick inventory of depressive symptomatology 16 items self-report (QIDS-SR16).[22)] The percentage of subjects assessed as improved (post-dose score was lower than baseline score) was 4.3% (48 of 1129 subjects) in the Q4W group, 3.8% (43 of 1146 subjects) in the Q2W group, and 2.7% (21 of 767 subjects) in the placebo group. The percentage of subjects assessed as worsened (post-dose score was higher than baseline score) was 1.7% (19 of 1129 subjects) in the Q4W group, 1.5% (17 of 1146 subjects) in the Q2W group, and 2.2% (17 of 767 subjects) in the placebo group. The percentage of subjects assessed as unchanged (post-dose score was the same as baseline score) was 94.1% (1062 of 1129 subjects) in the Q4W group, 94.8% (1086 of 1146 subjects) in the Q2W group, and 95.0% (729 of 767 subjects) in the placebo group. The results in the ixekizumab groups were comparable to those in the placebo group.

Table 58. Incidences of adverse events related to depression and suicide/self-injury (PPC, PAC, and MPP)

	PPC (induction dosing period)			PAC (induction dosing period)				MPP (maintenance dosing period)[a)]		
	Q4W (N = 1161)	Q2W (N = 1167)	Placebo (N = 791)	Q4W (N = 729)	Q2W (N = 734)	Etanercept (N = 739)	Placebo (N = 360)	Q12W (N = 408)	Q4W (N = 416)	Placebo (N = 402)
Adverse events related to depression and suicide/self-injury	5 (0.4)	4 (0.3)	5 (0.6)	3 (0.4)	3 (0.4)	6 (0.8)	2 (0.6)	5 (1.2) 1.8	5 (1.2) 1.4	2 (0.5) 1.1
Depression	5 (0.4)	4 (0.3)	5 (0.6)	3 (0.3)	3 (0.4)	6 (0.8)	2 (0.6)	4 (1.0) 1.4	5 (1.2) 1.4	2 (0.5) 1.1
Depression	4 (0.3)	4 (0.3)	4 (0.5)	2 (0.3)	3 (0.4)	3 (0.4)	1 (0.3)	4 (1.0) 1.4	3 (0.7) 0.9	2 (0.5) 1.1
Depressed mood	0	0	1 (0.1)	0	0	1 (0.1)	1 (0.3)	0	0	0
Mood swings	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Suicide/self-injury	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	1 (0.1)	0	1 (0.2) 0.4	0	0
Suicide attempt	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	0	0	1 (0.2) 0.4	0	0
Suicidal ideation	0	0	0	0	0	1 (0.1)	0	0	0	0

n (%)
a) Top, n (%); Bottom, incidence rate per 100 patient-years adjusted according to the overall exposure duration

The incidence rate of depression-related events in the ixekizumab groups was comparable to the incidence rate based on historical data from the psoriasis patient population (3.2 per 100 patient-years). In addition, the incidence rate of events related to suicide/self-injury in the ixekizumab group was comparable to the incidence rate based on historical data from the psoriasis patient population (0.09 per 100 patient-years) (*Arch Dermatol.* 2010;146:891-5).

The applicant considers that the above findings do not suggest an increased risk of depression and suicide/self-injury in patients receiving ixekizumab.

22) QIDS-SR16 is a self-entry depression scale consisting of 16 questions. The severity of depression was assessed based on the total score. Subjects' total scores were classified into the following categories:
0 to 5 = none, 6 to 10 = mild, 11 to 15 = moderate, 16 to 20 = severe, and 21 to 27 = very severe

PMDA's view:
At present, there are no data suggesting a clear relationship of ixekizumab with adverse events related to depression and suicide/self-injury. However, post-marketing information on a risk of psychiatric disorders associated with ixekizumab should be collected including published literature, for the following reasons: (1) the number of subjects evaluated in clinical studies is not sufficient to assess a risk of adverse events related to depression and suicide/self-injury; and (2) an animal study indicated a relationship of IL-17 with depressed state (*Biol Psychiatry.* 2013;73:622-30, *PLoS One.* 2012;7:e42054).

Based on the above, patients treated with ixekizumab should be monitored for adverse events attributable to the immunosuppressive effect of the drug, especially, serious infections. In clinical studies, however, the incidence of such adverse events in the ixekizumab groups was comparable to that in the placebo group and was not higher than that in the etanercept group (active control). In light of the above findings, such adverse events are manageable with the same safety measures as those for other approved biological products. In addition, the safety data from the Japanese subgroup did not identify adverse events requiring special attention in Japanese patients with psoriasis. However, since clinical experience with the use of ixekizumab is limited at present, information should be collected through a post-marketing surveillance study, etc. to further clarify the safety profile of ixekizumab.

7.R.3 Dosage and administration

7.R.3.1 Rationale for dosage regimen (treatment duration and interval) in phase III studies

The applicant's explanation about the rationale for the dosage regimen employed in phase III studies:
In Study RHAJ, subjects received ixekizumab at a dose of 10 to 150 mg SC Q4W for 12 weeks, and the data obtained were analyzed for changes in the PASI 75 response rate and sPGA (0 or 1) response rate. Figure 5 shows changes over time in those measures. The analysis indicated that clinically significant response was achieved in the 75 mg Q4W and the 150 mg Q4W groups, and that the 150 mg Q4W regimen could possibly exhibit higher efficacy than other regimens. The conclusion was based on the following findings: (i) Statistically significant differences were observed at ixekizumab ≥25 mg compared with placebo; (ii) the data on the PASI 90 response rate, PASI 100 response rate, and sPGA (0) response rate at Week 12 (Table 59) showed that the response in the 25 mg Q4W group tended to be lower than that in the 75 mg Q4W group and the 150 mg Q4W group; and (iii) the PASI 75 response rate in the 75 mg Q4W group was comparable to that in the 150 mg Q4W group, but the PASI 90 response rate and sPGA (0) response rate at Week 12 in the 150 mg Q4W group were higher than those in the 75 mg Q4W group, with the response observed soon after the start of treatment. Furthermore, the appropriate ixekizumab concentration ranges only from approximately 80 to 120 mg/mL due to the limited stability of the solution; and the volume of dosing solution for 1 subcutaneous injection should be up to 1 mL. In consideration of the above findings, the 80 mg Q4W regimen was selected as the dose providing exposure equivalent to that with the 75 mg Q4W regimen, and the 80 mg Q2W regimen was selected as the dose providing the mean exposure equivalent to that with the 150 mg Q4W regimen.

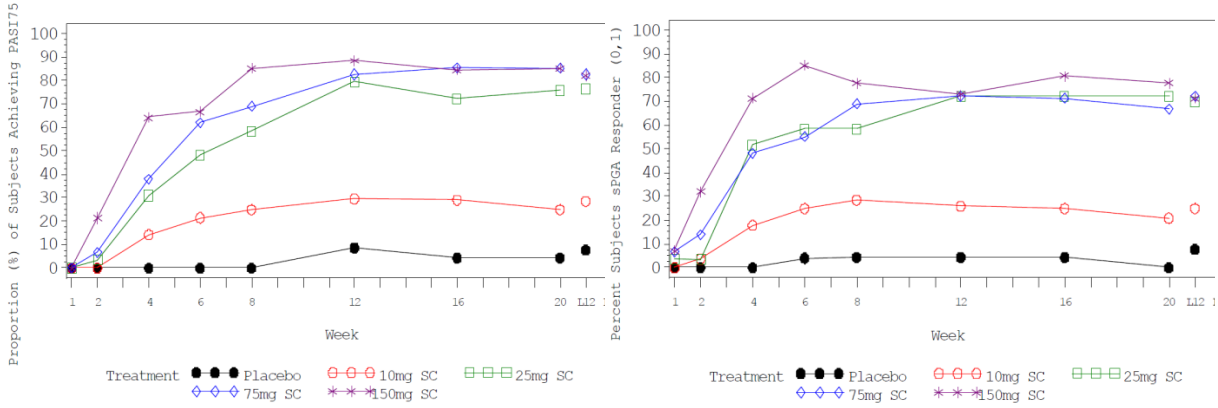

Figure 5. PASI 75 (left) and sPGA (0 or 1) (right) response rates in Study RHAJ (observed data, including LOCF data at Week 12 and Week 20)

Table 59. PASI 90, PASI 100, and sPGA (0) response rates at Week 12 (mITT population, LOCF)

	10 mg	25 mg	75 mg	150 mg	Placebo
PASI 90 response rate	17.9 (5/28)	50.0 (15/30)	58.6 (17/29)	71.4 (20/28)	0 (0/26)
PASI 100 response rate	0 (0/28)	16.7 (5/30)	37.9 (11/29)	39.3 (11/28)	0 (0/26)
sPGA (0) response rate	7.1 (2/28)	20.0 (6/30)	37.9 (11/29)	46.4 (13/28)	0 (0/26)

% (n/N)

The dosing schedule was determined as follows: A starting dose of 160 mg was selected because high response was observed at Week 2 in the 150 mg Q4W group in Study RHAJ; and simulations using the population pharmacokinetic analysis model based on data from Study RHAJ showed that the regimen with a starting dose of 160 mg allowed for steady state to be reached earlier than regimens without a starting dose of 160 mg (Figure 6). The induction dosing period up to 12 weeks was selected because serum ixekizumab concentrations were predicted to reach steady state by Week 12 following subcutaneous administration of ixekizumab as a starting dose of 160 mg (Week 0) followed by 80 mg Q2W or Q4W form Week 2 onward (Figure 6).

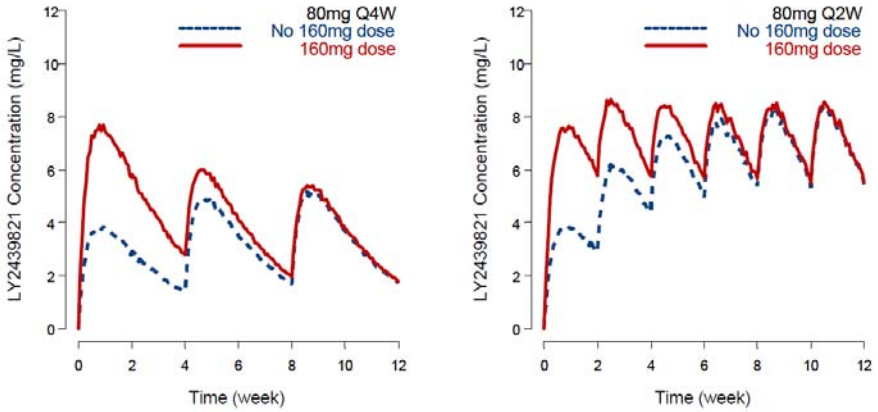

Figure 6. Changes over time in serum ixekizumab concentrations predicted by population pharmacokinetic analysis model based on data from Study RHAJ

(red solid line, regimen with a starting dose of 160 mg; blue wavy line, regimen with a starting dose of 80 mg)

The applicant considered that the extended dosing interval could possibly maintain the effect of ixekizumab in patients with improved skin symptoms after treatment with ixekizumab, for the following reasons: (i) In the phase I study (Study RHAG)[23)] and phase II study (Study RHAJ) in which ixekizumab was subcutaneously administered at 75 mg at Weeks 0, 2, 4, 8, 12, and 16, an improvement in skin symptoms observed at Week 12 was maintained until Week 20; and (ii) the therapeutic effect of ixekizumab in patients achieving an improvement in psoriasis symptoms at Week 12 could be continued for 12 weeks after the last dose. Based on the above results and from a viewpoint of the safety, a phase III study was designed to include the Q12W and Q4W regimens in the maintenance dosing period for subjects achieving an improvement in skin symptoms at Week 12. The purpose of this study was to investigate whether the response achieved during the induction dosing period could be sufficiently maintained with the exposure to ixekizumab at the minimum effective dose.

PMDA's view:

The applicant's explanation is generally acceptable. The study design is acceptable in that the efficacy and safety of ixekizumab in patients with psoriasis were to be evaluated for each of the induction dosing period and maintenance dosing period. The proposed dosage and administration is the regimen that provides exposure comparable to that with the regimen used in Study RHAJ. However, the population pharmacokinetic analysis revealed that the bioavailability of the proposed solution formulation which was used in the phase III studies (Studies RHAZ, RHBA, and RHBC) was higher than that of the

23) A placebo-controlled randomized dose-titration study (CTD 5.3.3.2.3) in which ixekizumab (5, 15, 50, or 150 mg) was subcutaneously administered, or ixekizumab (15 mg) was intravenously administered Q2W 3 times to patients with psoriasis vulgaris (n = 46).

lyophilized formulation used in Study RHAJ. The proposed dosage and administration should be evaluated carefully, taking data from the phase III studies into account.

7.R.3.2 Rationale for proposed dosage and administration

The proposed dosage and administration statement is "The usual adult dosage is 160 mg of Ixekizumab (Genetical Recombination) administered by subcutaneous injection at Week 0, followed by 80 mg once every 2 weeks from Week 2 to Week 12, and then 80 mg once every 4 weeks." The applicant explained the following rationale for the above proposal on the basis of the results of the placebo-controlled phase III studies (Studies RHAZ, RHBA, and RHBC):

Table 45 shows the results of efficacy endpoints in the induction dosing period for Studies RHAZ, RHBA, and RHBC. The Q2W group showed higher responses than the Q4W group in terms of all of the following endpoints: PASI 75 response rate, which indicates clinically significant improvement; PASI 90 response rate, which indicates more favorable improvement; PASI 100 response rate, which indicates remission; sPGA (0 or 1) response rate, which indicates the minimization of lesions or remission; and sPGA (0) response rate, which indicates clinically relevant remission. Similar trends were observed in the Japanese subgroup of Study RHAZ. In addition, subgroup analyses were performed for the efficacy endpoints at Week 12 using the pooled data from Studies RHAZ, RHBA, and RHBC. Subjects were divided into subgroups by patient characteristics, severity, and previous therapy. As shown in Table 46, the response in the Q2W group was consistently higher than that in the Q4W group for all the subgroups. Furthermore, Figure 7 and Table 60 show changes in the efficacy measures during the maintenance dosing period for each treatment group of the induction dosing period. The PASI 75, 90, and 100 response rates were all higher in patients treated with ixekizumab 80 mg Q2W during the induction dosing period than in patients treated with 80 mg Q4W during the induction dosing period at any time point of the maintenance dosing period. In addition, because biological products for psoriasis have become available in recent years, the therapeutic goal of psoriasis is changing from the conventional PASI 75 response to the PASI 90 response which is an index for more favorable improvement (*J Eur Acad Dermatol Venereol.* 2014;29:645-8). In addition, the remission of the skin lesion is associated with significant improvement in QOL (*J Am Acad Dermatol.* 2014;71:633-41). On the basis of the above findings, the applicant considered that the dosage and administration of ixekizumab used in the induction dosing period (80 mg Q2W) should be selected.

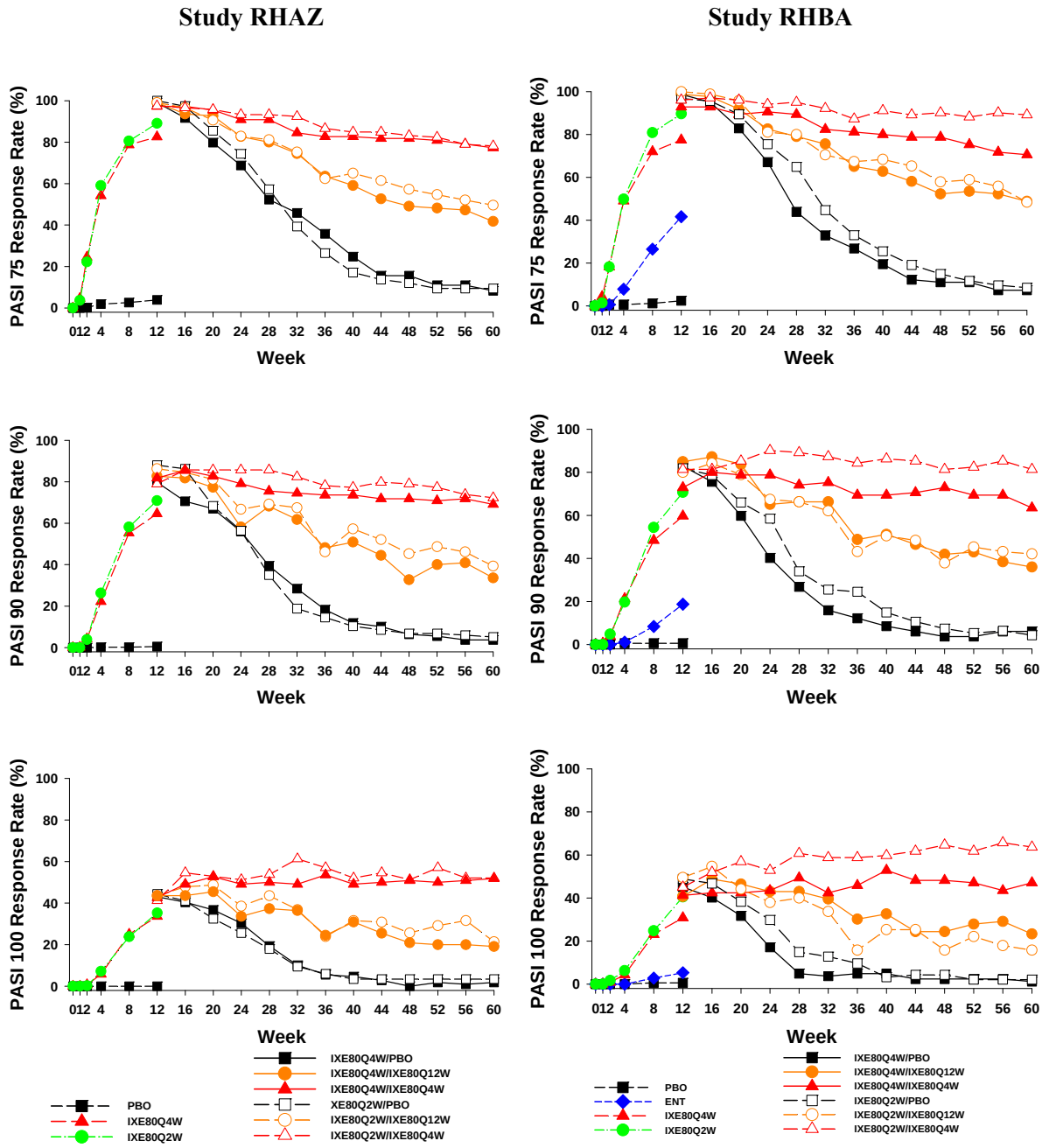

Figure 7. Changes over time in the PASI 75, 90, and 100 response rates by dosage regimen

Table 60. Results of efficacy endpoints at Week 60 by dosage regimen (Studies RHAZ and RHBA)

		Q2W/Q4W	Q4W/Q4W	Q2W/Q12W	Q4W/Q12W
Study RHAZ	PASI 75 response rate	78.2 (93/119)	77.3 (85/110)	49.6 (58/110)	41.8 (46/110)
	PASI 90 response rate	72.3 (86/119)	69.1 (76/110)	39.3 (46/110)	33.6 (37/110)
	PASI 100 response rate	52.1 (62/119)	51.8 (57/110)	21.4 (25/110)	19.1 (21/110)
Study RHBA	PASI 75 response rate	89.2 (91/102)	70.6 (60/85)	48.4 (46/95)	48.8 (42/86)
	PASI 90 response rate	81.4 (83/102)	63.5 (54/85)	42.1 (40/95)	36.0 (31/86)
	PASI 100 response rate	63.7 (65/102)	47.1 (40/85)	15.8 (15/95)	23.3 (20/86)

% (n/N)

The applicant considered that the 80 mg Q4W regimen should be selected to achieve the prolonged therapeutic effect of ixekizumab, taking account of the following results and findings: Analysis of the Week 60 data from Studies RHAZ and RHBA showed that the PASI 75 response rates were 45.8% (104 of 226 subjects) and 48.6% (88 of 181 subjects), respectively, in the Q12W group, and 77.7% (178 of 226 subjects) and 80.7% (151 of 187 subjects), respectively, in the Q4W group; and the sPGA (0 or 1) response rates were 37.4% (85 of 226 subjects) and 40.9% (74 of 181 subjects), respectively, in the

Q12W group, and 72.9% (167 of 226 subjects) and 74.9% (140 of 187 subjects), respectively, in the Q4W group. For the efficacy measures in the maintenance dosing period, the Q4W group showed a trend toward more favorable improvement than that in the Q12W group. Pooled analysis using MPP revealed that relapse (defined as sPGA score ≥3) occurred in 14.4% of subjects in the Q4W group and 46.8% of subjects in the Q12W group during the maintenance dosing period.

Some of the subjects on ixekizumab 80 mg Q2W in the induction dosing period who were assessed as responders at Week 12 and then were re-randomized to the Q4W group did not maintain the response with the Q4W maintenance regimen. [redacted].

PMDA's view:
The above explanation of the applicant is acceptable. On the basis of currently available clinical study data, the proposed dosage and administration (160 mg of ixekizumab by subcutaneous injection at Week 0, followed by 80 mg once every 2 weeks from Week 2 to Week 12 and then 80 mg once every 4 weeks) is allowed.

Some of the subjects treated with ixekizumab Q2W through Week 12 and then Q4W after Week 12 did not maintain the response. For this reason, [redacted] is an issue to be addressed in light of [redacted].

7.R.4 Indication

PMDA's view:
Ixekizumab should be indicated for patients who have had an inadequate response to the standard therapy for psoriasis such as phototherapy and systemic therapy with cyclosporine, etretinate, etc., or those who have had intolerance to these therapies, in light of the data submitted, reviews in Sections "7.R.1 Efficacy" and "7.R.2 Safety," and the following safety concerns: As with other approved biological products for psoriasis, ixekizumab may pose a concern about serious infections potentially leading to fatal outcome; and the safety in patients treated with ixekizumab for prolonged periods remains unclarified, including the risk of malignant tumor.

PMDA therefore has concluded that as with other approved biological products, the indication should be as follows: "Treatment of the following diseases in patients who have had an inadequate response to conventional therapies: Psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis."

7.R.5 Clinical positioning

7.R.5.1 Clinical positioning of ixekizumab relative to other approved biological products

The applicant's explanation about the clinical positioning of ixekizumab relative to other approved biological products in the treatment for psoriasis:
In recent years, biological products have become available as one of the therapeutic options for psoriasis, and consequently treatment for high therapeutic goals such as high PASI response (PASI 90 response rate) and remission (PASI 100 response rate or sPGA (0) response rate) is desired even in patients with severe psoriasis (*J Dtsch Dermatol Ges.* 2007;5:566-74). A report has shown that achievement of high PASI response and remission leads to an remarkable improvement in the QOL of patients (*J Am Acad Dermatol.* 2014;71:633-41). Pooled analysis using PPC showed that the sPGA (0) response rate and PASI 100 response rate for ixekizumab at Week 12 were 39.5% and 37.6%, respectively. Achievement of such high therapeutic goals at an early phase of treatment with ixekizumab is expected to improve the QOL of patients with psoriasis.

Table 61 shows efficacy data from pivotal clinical studies of ixekizumab and other approved biological products, namely adalimumab, infliximab, ustekinumab, and secukinumab. Although comparisons of studies of different designs require careful interpretation, ixekizumab was considered superior to other approved biological products in terms of improvements in skin symptoms evaluated at major time points. The efficacy of ixekizumab relative to other approved biological products on joint symptoms was assessed using data from foreign clinical studies. The ACR20 response rates for ixekizumab at Week 12

and Week 24 in Study RHAP were 57% and 58%, respectively, in the Q4W group and 60% and 62%, respectively, in the Q2W group, while the response rate was 65% for infliximab 5 mg/kg Q8W (Week 16), 58% for adalimumab 40 mg Q2W (Week 12), 50% for ustekinumab 90 mg Q12W (Week 24), and 58% for secukinumab 300 mg Q4W (Week 24). The efficacy of ixekizumab on joint symptoms was considered almost comparable to that of other biological products.

Safety analyses showed that the incidences of serious infections, neutropenia, hypersensitivity, cardiovascular events, injection site reaction, inflammatory bowel disease, and malignant tumor in the ixekizumab group did not largely exceed those in the etanercept group (active control). Comparison of major adverse events reported in clinical studies between ixekizumab and other approved biological products (Table 62) did not indicate any ixekizumab-specific events. Compared with other approved biological products, ixekizumab is considered to pose no safety concerns.

In light of the efficacy and safety of ixekizumab as demonstrated above and user convenience such as dosing frequency and dosing method, ixekizumab can serve as a first-line biological product for psoriasis.

Table 61. Efficacy of ixekizumab relative to other biological products in patients with psoriasis

	Ixekizumab	Secukinumab	Ustekinumab	Adalimumab	Infliximab
Study title	Global study (Study RHAZ)	Global study (Study A2302)	Japanese clinical study (Study JPN-02)	Japanese clinical study (Study M04-688)	Japanese clinical study (Study TA-650-15)
Proposed or approved dosage and administration	160 mg subcutaneously (SC) at Week 0 followed by 80 mg SC at Weeks 2, 4, 6, 8, and 10	150 mg or 300 mg SC at Weeks 0, 1, 2, 3, 4, and 8	45 mg SC at Weeks 0 and 4	80 mg SC Week 0,followed by 40 mg SC every 2 weeks	5 mg/kg SC at Weeks 0, 2, and 6
Endpoint	Week 12	Week 12	Week 12	Week 16	Week 10
PASI 75 response rate	89.1 (386/433)	150 mg: 71.6 (174/243)	59.4 (38/64)	62.8 (27/43)	68.6 (24/35)
		300 mg: 81.6 (200/245)			
	Placebo: 3.9 (17/431)	Placebo: 4.5 (11/246)	Placebo: 6.5 (2/31)	Placebo: 4.3 (2/46)	Placebo: 0 (0/19)
PASI 90 response rate	70.9 (307/433)	150 mg: 39.1 (95/243)	32.8 (21/64)	39.5 (17/43)	54.3 (19/35)
		300 mg: 59.2 (145/245)			
	Placebo: 0.5 (2/431)	Placebo: 1.2 (3/246)	Placebo: 3.2 (1/31)	Placebo: 0	Placebo: 0 (0/19)
PASI 100 response rate	35.3 (153/433)	150 mg: 12.8 (31/243)	-	-	-
		300 mg: 28.6 (70/245)			
	Placebo: 0	Placebo: 0.8 (2/246)	-	-	-
sPGA (0 or 1) response rate	81.8 (354/433)	150 mg: 51.2 (125/244)	-	-	-
		300 mg: 65.3 (160/245)			
	Placebo: 3.2 (14/431)	Placebo: 2.4 (6/246)	-	-	-
sPGA (0) response rate	37.0 (160/433)	150 mg: 16.4 (40/244)	-	-	-
		300 mg: 32.2 (79/245)			
	Placebo: 0	Placebo: 0.8 (2/246)	-	-	-

Table 62. Safety of xekizumab relative to other biological products in patients with psoriasis (Japanese and foreign clinical studies)

	Ixekizumab (N = 4204)	Secukinumab 150 mg (N = 1395)	Secukinumab 300 mg (N = 1410)	Ustekinumab (N = 2266)	Adalimumab (N = 1696)	Infliximab (N = 1564)
Any adverse event	3293 (78.3)	1066 (76.4)	1091 (77.4)	1676 (74.0)	1300 (76.7)	1371 (87.7)
Serious infections and infestations	69 (1.6)	12 (0.9)	16 (1.1)	15 (0.7)	21 (1.2)	26 (1.7)
Candida infection	128 (3.0)	21 (1.5)	41 (2.9)	-	-	-
Neutropenia	21 (0.5)	9 (0.65)	7 (0.47)	0	-	16 (1.0)
Leukopenia	15 (0.4)	8 (0.57)	8 (0.57)	-	-	-
Hypersensitivity	399 (9.5)	115 (8.2)	132 (9.4)	5 (0.2)	-	48 (3.1)
General disorders and administration site conditions	887 (21.1)	158 (11.3)	164 (11.6)	268 (11.8)	-	465 (29.7)
Cardiovascular events (incidence rate per 100 patient-years)	0.7	0.44	0.51	0.44	-	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	149 (3.5)	47 (3.4)	42 (3.0)	45 (2.0)	22 (1.3)	46 (2.9)
Pneumocystis pneumonia	0	-	-	-	-	-
Interstitial pneumonia	3 (0.1)	0	1 (0.07)	-	-	-
Crohn's disease	4 (0.1)	2 (0.1)	0	0	-	0
Colitis ulcerative	9 (0.2)	2 (0.1)	2 (0.1)	1 (<0.1)	-	0

n (%)
-: Unknown or not available

PMDA's view:
At present, ixekizumab should be considered to be one of biological products for psoriasis, because (1) no Japanese clinical studies were conducted to generate head-to-head data comparing the efficacy of ixekizumab with that of the biological products indicated for psoriasis; and (2) the current limited experience with ixekizumab precludes adequate assessment of the safety profile of ixekizumab relative to other approved biological products. The clinical positioning of ixekizumab will be discussed at related academic meetings or on other occasions, based on data from post-marketing surveillance and reports of studies conducted properly in and outside of Japan, in addition to currently available clinical study data.

PMDA asked the applicant to explain points to be considered for switching from other biological products to ixekizumab and vice versa.

The applicant's explanation:
There are no safety data from patients who switched directly from other biological products to ixekizumab, because the inclusion criteria allowed the participation of patients treated with other biological products in phase III studies only if the patients had a certain washout period. Furthermore, because use of other biological products was prohibited during the follow-up period after discontinuation of ixekizumab, there is no safety or efficacy data from patients who switched from ixekizumab to other biological products. In general, however, immunomodulation associated with biological products potentially causes serious infections. The package insert will include a precautionary statement that physicians should monitor patients carefully for any sign of infections after switching from other biological products to ixekizumab.

PMDA's view:
In light of the clinical study data and mechanism of action of ixekizumab, the drug is expected to be useful even in patients who have had inadequate response or intolerance to other approved biological products, but there are no data from patients who switched from other biological products to ixekizumab. Therefore, the package insert and other information materials should include a precautionary statement that physicians should pay attention to infections in patients who switch from other biological products to ixekizumab and vice versa. Furthermore, the applicant should collect information on switching from other biological products to ixekizumab through a post-marketing surveillance study, thereby evaluating the safety and efficacy of switching carefully. Findings should be communicated appropriately to healthcare professionals if they become available.

7.R.5.2 Concomitant use with conventional therapies

The applicant's explanation about the safety of ixekizumab used concomitantly with conventional therapies:

In Studies RHAZ, RHBA, and RHBC, the concomitant use of systemic therapy with cyclosporine, etc. or phototherapy were prohibited, but Study RHAP in patients with psoriatic arthritis allowed the use of concomitant DMARDs (e.g., methotrexate, leflunomide) in patients who had taken them at a constant dose for ≥8 weeks at baseline. The incidences of infections in patients receiving study drug with and without DMARD were 20.6% (27 of 131 subjects) and 34.6% (27 of 78 subjects), respectively, in the ixekizumab group; 25.4% (17 of 67 subjects) and 26.5% (9 of 34 subjects), respectively, in the adalimumab group; and 23.2% (16 of 69 subjects) and 29.7% (11 of 37 subjects), respectively, in the placebo group. The incidences of serious infections were 0.8% (1 of 131 subjects) and 2.6% (2 of 78 subjects), respectively, in the ixekizumab group; 3.0% (2 of 67 subjects) and 0% (0 of 34 subjects), respectively, in the adalimumab group; and 0% (0 of 69 subjects) and 0% (0 of 37 subjects), respectively, in the placebo group. Concomitant DMARDs did not increase the risk of infections. However, the number of subjects evaluated is limited, and thus risks associated with the concomitant use of ixekizumab with DMARDs cannot be assessed at present.

In light of the above, benefit-risk balance should be carefully assessed with due consideration of the safety of each therapy if ixekizumab is used in combination with other therapies. The package insert will therefore include a precautionary statement that the safety of ixekizumab used concomitantly with conventional systemic therapy or phototherapy has not been established. In addition, the package insert will include a precautionary statement that concomitant use of ixekizumab with other biological products should be avoided, because the safety of such concomitant use has not been established.

PMDA's view:

No sufficient data on the concomitant use of ixekizumab with other therapies were obtained from clinical studies of ixekizumab. Especially in patient treated with ixekizumab in combination with immunosuppressive systemic therapy, increased immunosuppression associated with the therapies may lead to infection or malignant tumor development. The concomitant use of ixekizumab with phototherapy may result in an increased risk of skin cancer. The package insert and other information materials should include precautionary advice about the concomitant use of ixekizumab with other therapies. Physicians should be advised to carefully monitor patients on such combination therapy. In addition, the package insert and other information materials should include a precautionary statement that concomitant use of ixekizumab with other biological products should be avoid because a report showed that the incidence of serious infections was increased in patients with rheumatoid arthritis receiving different biological products concomitantly, although no specific cases of concomitant use of ixekizumab with other biological products have been reported. Furthermore, the applicant should collect information on the concomitant use of ixekizumab with systemic therapy, phototherapy, or topical therapy through a post-marketing surveillance study, thereby evaluating the safety and efficacy of such combination therapy carefully. Findings should be communicated to healthcare professionals if they become available.

7.R.6 Self-administration

The applicant's explanation about the efficacy and safety of self-administered ixekizumab based on data from Japanese patients using self-administration in Studies RHAZ and RHAT:

Study RHAZ included 33 Japanese subjects (12 in the Q4W group, 8 in the Q2W group, 13 in the placebo group), of whom 25 subjects used self-administration[24)] (11 in the Q4W group, 8 in the Q2W group, 6 in the placebo group). A total of 22 subjects (88.0%) used self-administration ≥3 times. In Study RHAT, 7 of 78 patients with plaque psoriasis used self-administration. Table 63 shows the efficacy endpoints (PASI and sPGA) in the overall study population and patients using self-administration. Self-administration did not affect the efficacy.

[24)] The starting dose of the study drug was administered by a healthcare professional, and the subsequent doses were administered by the subjects on their own under supervision of a healthcare professional. Self-administration was allowed after the investigator judged the subject was capable of self-administration. Administration by a parent or a guardian was allowed for the subject who was not capable of self-administration.

Table 63. Comparison of efficacy between patients using self-administration and patients with plaque psoriasis (Study RHAT, induction dosing period and maintenance dosing period)

	Week 12		Week 52	
	Self-administration[a)] (N = 7)	Psoriasis[b)] (N = 77)	Self-administration[a)] (N = 6)	Psoriasis[b)] (N = 72)
PASI 75 response rate	100 (7/7)	100 (77/77)	100 (6/6)	100 (72/72)
PASI 90 response rate	100 (7/7)	84.4 (65/77)	100 (6/6)	87.5 (63/72)
PASI 100 response rate	42.9 (3/7)	32.5 (25/77)	83.3 (5/6)	52.8 (38/72)
sPGA (0 or 1) response rate	100 (7/7)	90.9 (70/77)	100 (6/6)	90.3 (65/72)
sPGA (0) response rate	42.9 (3/7)	36.4 (28/77)	83.3 (5/6)	56.9 (41/72)

% (n/N)
a) Subjects who received at least 1 dose using self-administration
b) Patients with plaque psoriasis

Safety analysis showed that adverse events occurred in 87.5% (14 of 16) of Japanese patients using self-administration in Study RHAZ (maintenance dosing period in which all the subjects received ≥3 doses of subcutaneous ixekizumab) and 85.7% (6 of 7) of Japanese patients using self-administration in Study RHAT. There was a limitation to the analysis of data from a small number of patients using self-administration. In a subgroup of Japanese patients using self-administration, injection site reaction occurred in 1 subject in the Q4W group during the induction dosing period in Study RHAZ and in 3 of 7 subjects (42.9%) in Study RHAT. Although the incidence of injection site reaction tended to be higher than that (10.3% [8 of 78 subjects]) in the overall patients with plaque psoriasis in Study RHAT, the severity was mostly mild.

Based on the above, the applicant considers that the efficacy and safety of self-administered ixekizumab in Japanese patients with psoriasis pose no particular concerns.

Education and training on self-administration in the post-marketing setting are considered necessary for healthcare professionals and patients. PMDA asked the applicant to explain the training and education.

The applicant's explanation:
A physician must decide the use of self-administration of ixekizumab only when a patient is confirmed to perform self-administration properly. Before that, the physician must carefully assess the appropriateness of use of self-administration by the patient, and provide the patient with adequate education and training to ensure that the patient understands risks associated with the use of ixekizumab and learns how to respond to such risks. In addition, the physician must instruct the patient to discontinue self-administration immediately if suspected adverse reactions to ixekizumab such as infections occur after self-administration or if self-administration cannot be continued. Then, appropriate measures such as careful follow-up should be taken under supervision of the physician.

The applicant will prepare explanatory materials for healthcare professionals about self-administration (e.g., a booklet and materials for patient education) and patient education materials describing procedures for self-administration.

PMDA's view:
Information on the safety and efficacy of self-administered ixekizumab does not suggest any particular concerns at present, but such information in Japanese patients with psoriasis is limited. Therefore, the safety and efficacy of self-administered ixekizumab should continue to be investigated in a post-marketing surveillance study. The management system that allows patients to start self-administration should be adequately established with reference to the situation for drugs in the same class available in Japan.

7.R.7 Post-marketing safety measures

PMDA's view:
The safety profile of ixekizumab is not largely different from those of other approved biological products. The data submitted has suggested no new safety concerns exceeding those of other approved biological products. However, a post-marketing surveillance study for long-term treatment should be conducted to collect information on the occurrence of adverse events such as serious infections and malignant tumor which are common concerns in patients treated with immunosuppressive drugs, because experience with

long-term use of ixekizumab is limited and the above information should be further collected as with other approved biological products.

Furthermore, ixekizumab should be used by physicians conversant with the diagnosis and treatment of psoriasis; and the physicians should treat adverse reactions, such as serious infections, in cooperation with other physicians with specialized knowledge and experience of treatment of infections. Post-marketing surveillance should confirm that such a system has been established in cooperation with other departments or institutions in routine clinical practice.

Furthermore, the applicant should ensure that healthcare professionals and patients are informed appropriately and promptly of the proper use of ixekizumab. To this end, the applicant should provide relevant materials to healthcare professionals such as physicians, prepare patient education materials in which risks associated with ixekizumab are described in an appropriate and easy-to-understand manner, and release post-marketing safety information on its website or by other media in a timely manner.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (5.3.5.1.2, 5.3.5.1.5, 5.3.5.2.1) were subjected to on-site GCP inspection in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection showed that the clinical studies as a whole were conducted in compliance with GCP. PMDA therefore concluded that there were no obstacles to conducting its review based on the application documents submitted. The following findings were noted in a study site (medical institution) and at the sponsor site, although they did not largely affect the overall evaluation of the study. These were notified to the head of the concerned medical institution, applicant, and sponsor (clinical trial in-country representative) individually as the findings requiring corrective action.

Findings requiring corrective action

Medical institution

- Protocol deviations (study drug administration error, insufficient confirmation of the exclusion criteria [washout period for the previous therapy and laboratory test values], failure to perform laboratory tests, non-compliance with provisions for rescue therapy)

Sponsor

- Failure to identify the protocol deviations (insufficient confirmation of the exclusion criteria [washout period for the previous therapy]) appropriately through monitoring

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that ixekizumab has efficacy in the treatment of patients with psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis who have had an inadequate to conventional therapies and that ixekizumab has acceptable safety in view of its benefits. PMDA considers that ixekizumab has clinical significance because it offers a new therapeutic option. The safety of ixekizumab, specifically adverse events such as serious infections associated with ixekizumab and long-term safety should be investigated in a post-marketing surveillance study.

PMDA has concluded that Taltz (ixekizumab) may be approved if the product is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

May 16, 2016

Product Submitted for Approval

Brand Name	Taltz 80 mg Syringe for SC Injection Taltz 80 mg Auto-Injector SC Injection
Non-proprietary Name	Ixekizumab (Genetical Recombination)
Applicant	Eli Lilly Japan K.K.
Date of Application	July 28, 2015

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, 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).

1.1 Efficacy, indication, and dosage and administration

PMDA's conclusion on the efficacy, indication, and dosage and administration of Taltz 80 mg Syringe for SC Injection and Taltz 80 mg Auto-Injector SC Injection ("Taltz") described in the Review Report (1) was supported by the expert advisors at the Expert Discussion.

1.2 Safety and draft risk management plan

PMDA's conclusion on the safety and post-marketing safety measures of Taltz (ixekizumab) described in the Review Report (1) was supported by the expert advisors at the Expert Discussion, and the following comment was raised from the expert advisor.

- In light of the potential immunological effect associated with ixekizumab-induced neutralization of IL-17A biological activity, adequate safety measures should be taken against serious infections including tuberculosis, as with the approved immunosuppressive biological products. In addition, the incidence of adverse events such as serious infections and malignant tumor in patients treated with ixekizumab for prolonged periods should be further investigated.

Based on the review presented in Section "7.R.7 Post-marketing safety measures" of the Review Report (1) and discussion at the Expert Discussion, PMDA has concluded that the current draft risk management plan of Taltz should include the safety and efficacy specifications as shown in Table 64, and that the applicant should implement additional pharmacovigilance activities and risk minimization activities as shown in Table 65.

Table 64. Safety and efficacy specifications in the draft risk management plan

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Serious infections • Serious hypersensitivity reactions • Neutrophil count decreased • Inflammatory bowel disease (Crohn's disease and colitis ulcerative)	• Malignant tumor • Immunogenicity	• None
Efficacy specifications		
• Efficacy of long-term treatment with Taltz in clinical use		

Table 65. Outline 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 • Specified drug use-results survey (long-term use) • Post-marketing clinical study (Study I1F-JE-RHAT)[a)]	• Early post-marketing phase vigilance • Preparation and distribution of proper use guide for healthcare professionals • Preparation and distribution of materials about self-administration for healthcare professionals and for patients • Ensuring that healthcare professionals are informed of proper use before delivery of the product

a) After approval of the product, Study I1F-JE- RHAT (ongoing) is to be modified to conduct a post-marketing clinical study in which patients will be treated with the product for 6 months and subsequently followed for up to 6 months.

In addition, PMDA instructed the applicant to conduct a post-marketing surveillance study to investigate the above specifications.

The applicant's explanation about a plan of the specified drug use-results survey (see Table 66):
The specified drug use-results survey will include patients with psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis who have had an inadequate response to conventional therapies with the target sample size of 700 patients (for the safety analysis) and the observation period of 52 weeks. To investigate the safety and efficacy of Taltz in clinical use, this survey will cover serious infections, fungal infections, tuberculosis, neutrophil count decreased, hypersensitivity, malignant tumor, and inflammatory bowel disease as the major survey items. After the end of the observation period, patients will be followed for serious infections and malignant tumor for up to 3 years after the first dose in order to further investigate the safety of long-term treatment.

Table 66. Outline of draft specified drug use-results surveys

Objective	To investigate the long-term safety and efficacy of Taltz in clinical use
Survey method	Continuous survey system
Patient population	Patients with psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis who have had an inadequate response to conventional therapies
Observation period	52 weeks (after end of the observation period, patients will be followed for up to 3 years after the first dose, irrespective of whether treatment is discontinued)
Planned sample size	700 patients (for the safety analysis)
Major survey items	• Key survey items: serious infections, fungal infections, tuberculosis, neutrophil count decreased, hypersensitivity, malignant tumor, and inflammatory bowel disease • Patient characteristics (disease type, severity, disease duration, complications, past history, etc.) • Previous treatment for psoriasis • Use of Taltz • Concomitant drugs or therapies • Laboratory tests • Adverse events • Efficacy evaluation

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved with the following condition for approval, after modifying the proposed indication, and dosage and administration statements as shown below. The re-examination period of the product is 8 years since it is a drug with a new active ingredient. The drug substance and the drug product are both classified as powerful drugs. The product is classified as a biological product.

Indication
Treatment of the following diseases in patients who have had an inadequate response to conventional therapies:
Psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis

Dosage and Administration
The usual adult dosage is 160 mg of Ixekizumab (Genetical Recombination) administered by subcutaneous injection at Week 0, followed by 80 mg once every 2 weeks from Week 2 to Week 12, and then 80 mg once every 4 weeks.

Condition of Approval
The applicant is required to develop appropriately implement a risk management plan.