Report on the Deliberation Results

February 28, 2019

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

Brand Name	Skyrizi 75 mg for S.C. Injection Syringe 0.83 mL
Non-proprietary Name	Risankizumab (Genetical Recombination) (JAN*)
Applicant	AbbVie GK
Date of Application	May 25, 2018

Results of Deliberation

In its meeting held on February 22, 2019, 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 product is classified as a biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Review Report

February 13, 2019
Pharmaceuticals and Medical Devices Agency

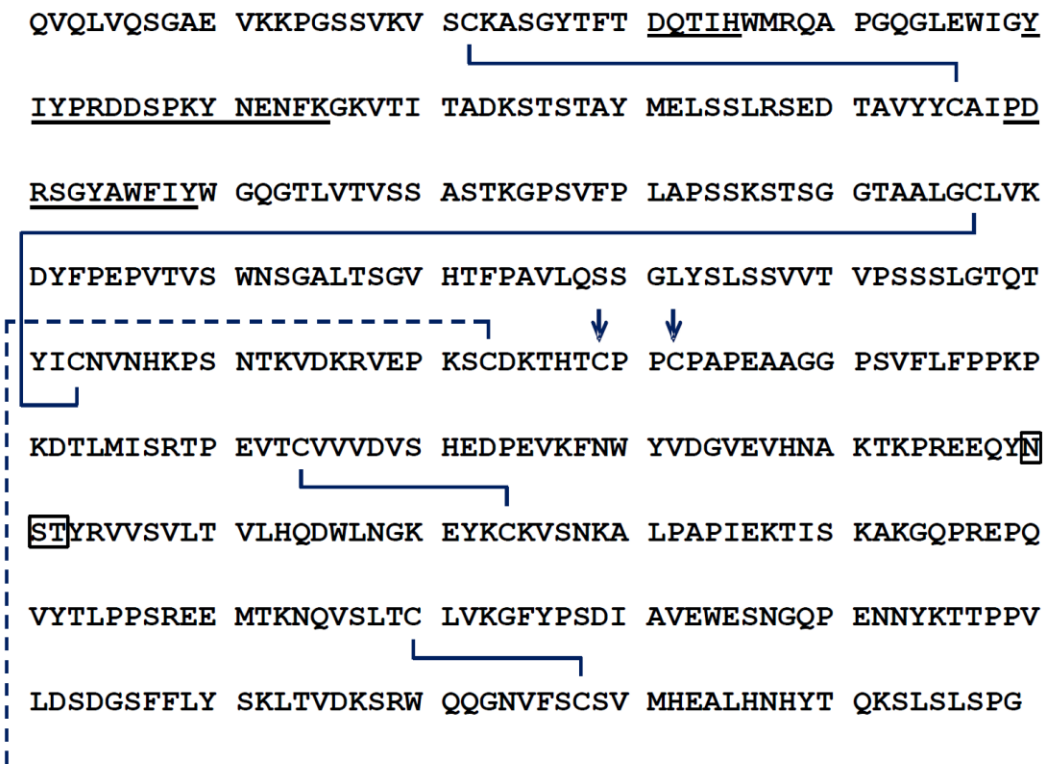
The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Skyrizi 75 mg for S.C. Injection Syringe 0.83 mL
Non-proprietary Name	Risankizumab (Genetical Recombination)
Applicant	AbbVie GK
Date of Application	May 25, 2018
Dosage Form/Strength	An injectable solution containing 75.0 mg of Risankizumab (Genetical Recombination) per syringe
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Risankizumab is a recombinant humanized monoclonal antibody composed of complementarity-determining regions derived from mouse anti-human interleukin-23 α subunit (p19) monoclonal antibody, human framework regions and human IgG1 constant regions, whose amino acid residues at position 237 and 238 in the H-chains are substituted by Ala each and C-terminus Lys is deleted in the H-chains. Risankizumab is produced in Chinese hamster ovary cells. Risankizumab is a glycoprotein (molecular weight: ca. 149,000) composed of 2 H-chains (γ1-chains) consisting of 449 amino acid residues each and 2 L-chains (κ-chains) consisting of 214 amino acid residues each.

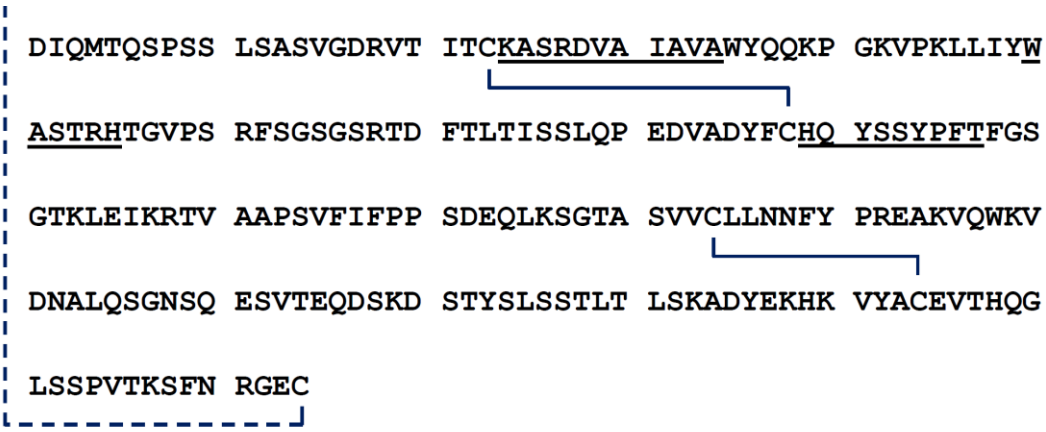
Structure

Amino acid sequence:

H-Chain



L-Chain



Complementarity-determining region (underlined parts in the figure)

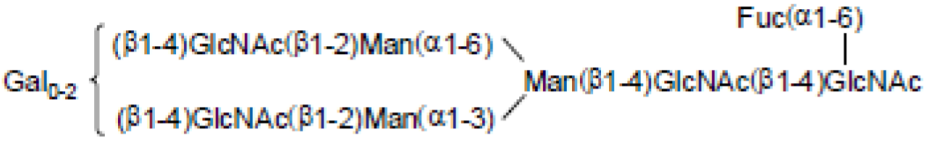
N-linked oligosaccharide binding site (square shapes in the figure)

Interchain disulfide bond (dotted line in the figure): C214 in L-chain - C223 in H-chain

Intrachain disulfide bonds (solid lines in the figure): C229 in H-chain - C229 in H-chain, C232 in H-chain - C232 in H-chain

Interchain disulfide bond between cysteine residues in the H-chain hinge region (↓)

Putative structure of the main carbohydrate chain



Molecular formula:

Risankizumab: $C_{6476}H_{9992}N_{1720}O_{2016}S_{44}$ (protein portion consisting of 4 chains)

H-Chain: $C_{2200}H_{3390}N_{580}O_{677}S_{16}$

L-Chain: $C_{1038}H_{1610}N_{280}O_{331}S_{6}$

Molecular weight: 145,609.80 (protein portion consisting of 4 chains)

Items Warranting Special Mention None

Reviewing Office Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis who 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 indications and dosage and administration shown below, with the following condition. Since the product may cause serious events such as infection, the risks and benefits of treatment with the product should be evaluated by closely monitoring the patients' condition prior to the administration. Post-marketing surveillance should be conducted to monitor the incidence of serious infections, malignant tumors, etc., and the information obtained through the surveillance should be provided to physicians and patients.

Indications

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 150 mg of risankizumab (genetical recombination) administered subcutaneously at Week 0, Week 4, and then at 12-week intervals. In addition, 75 mg per dose is allowed, depending on the patient's condition.

Approval Condition

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

Attachment

Review Report (1)

January 18, 2019

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

Product Submitted for Approval

Brand Name	Skyrizi 75 mg for S.C. Injection Syringe 0.83 mL
Non-proprietary Name	Risankizumab (Genetical Recombination)
Applicant	AbbVie GK
Date of Application	May 25, 2018
Dosage Form/Strength	An injectable solution containing 75.0 mg of Risankizumab (Genetical Recombination) per syringe
Proposed Indications	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

Proposed Dosage and Administration

The usual adult dosage is 150 mg of risankizumab (genetical recombination) administered subcutaneously at Week 0, Week 4, and then at 12-week intervals.

Table of Contents

List of Abbreviations

See Appendix.

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

Risankizumab (genetical recombination), the active ingredient of "Skyrizi 75 mg for S.C. Injection Syringe 0.83 mL," is a humanized Immunoglobulin G1 (IgG1) monoclonal antibody against human interleukin (IL)-23 p19 subunit, which was discovered by [redacted] and developed by [redacted] and the applicant (AbbVie GK).

Psoriasis is a chronic inflammatory skin disease with 0.1 to 0.2 million patients in Japan (*Clinical Dermatology Asset 10* [in Japanese]. Nakayama Shoten, Co., Ltd.; 2012). Psoriasis is characterized by clinical symptoms of erythematous plaques and epidermal hypertrophy and scales, and it is classified into the following subtypes: (1) psoriasis vulgaris, which accounts for approximately 90% of patients with psoriasis in Japan, (2) psoriatic arthritis (PsA), which is associated with systemic inflammatory arthritis, (3) generalized pustular psoriasis (GPP), which is accompanied by systemic symptoms such as systemic aseptic cysts and pyrexia, (4) erythrodermic psoriasis (EP), which is accompanied by systemic rash, diffuse flushing, and desquamation, and (5) guttate psoriasis, which presents as multiple small rashes all over the body.

Treatments of psoriasis include, depending on the range and severity of the skin lesion, topical treatment with corticosteroid, vitamin D_3 derivatives, etc., phototherapy, and systemic treatment with cyclosporine, etretinate, etc. For the treatment of patients who had an inadequate response to these treatments, the following drugs are approved in Japan: (1) guselkumab, an antibody that targets the same antigen (IL-23 p19) as risankizumab, (2) infliximab and adalimumab, anti-tumor necrosis factor (TNF)-α antibodies, (3) ustekinumab (UST), an anti-IL-12/23 antibody, (4) secukinumab and ixekizumab, anti-IL-17A antibodies, and (5) brodalumab, an anti-IL17 receptor A antibody.

IL-23, the target antigen of risankizumab, is a cytokine involved in the maintenance and activation of type 17 helper T cells, which are involved in autoimmune inflammatory diseases (*Nature.* 2003;421:744-8, *Immunol Rev*. 2004;202:96-105). IL-23 is overexpressed in psoriasis skin and in synovial cells of patients with PsA (*J Exp Med*. 2004;199:125-30, *Arthritis Res Ther.* 2012;14:R93). Risankizumab binds to IL-23 and thereby neutralizes the biological activity of IL-23. Therefore, risankizumab was developed as a therapeutic agent for psoriasis.

In Japan, clinical development of risankizumab as a drug for psoriasis was initiated in [redacted] 20[redacted] after the foreign phase II study had been completed, and a marketing application has now been submitted based on the results of Japanese clinical studies, etc. Outside Japan, clinical development of risankizumab for the treatment of psoriasis was started in [redacted] 20[redacted], and its marketing application is under review in the US and Europe as of January 2019.

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 substrate

Hybridomas were generated from cells obtained from mice that had been immunized with recombinant IL-23 consisting of mouse IL-23 p40 subunit and human IL-23 p19 subunit, and the optimum hybridoma clone was selected from among the hybridomas. The sequences of the variable regions of H- and L-chains obtained from the clone were humanized and separately introduced into different plasmids containing the constant region of human IgG1 (a mutation had been introduced into the plasmid for H-chain to eliminate the effector function of the fragment crystallizable [Fc] region). The expression constructs of H- and L-chains were thus constructed. These gene expression constructs were introduced into Chinese hamster ovary (CHO) cells to prepare the master cell bank (MCB) and working cell bank (WCB) that produce risankizumab, a monoclonal antibody originated from the thus appropriately selected clone.

MCB, WCB, and post production cell bank (PPCB) were subjected to characterization and purity tests in accordance with ICH Q5A (R1), Q5B, and Q5D Guidelines. Results demonstrated the genetic stability during the manufacturing period. Except for endogenous retroviruses-like particles commonly observed in rodent-derived cell lines, no viral or nonviral adventitious agents were detected within the range of the tests performed.

MCB and WCB are stored in the gas phase of liquid nitrogen. There is no plan to regenerate MCB, while WCB is regenerated as appropriate.

2.1.2 Manufacturing process

The manufacturing process of the drug substance comprises seed culture, expansion culture, manufacturing culture, harvesting, [redacted]chromatography, [redacted]treatment, [redacted]filtration, [redacted]chromatography, [redacted]chromatography, [redacted]filtration, ultrafiltration/diafiltration, formulation/filling, and storage/test.

[redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] are defined as critical steps.

The manufacturing process of the drug substance is validated at the commercial-scale production.

2.1.3 Safety evaluation of adventitious agents

In the manufacturing process of the drug substance, no raw materials of biological origin are used except for CHO cells, the host cells.

MCB, WCB, and PPCB have been subjected to purity tests [see Section 2.1.1]. The pre-harvest culture fluid obtained by commercial-scale production was subjected to a sterility testing, mycoplasma testing,

and *in vitro* adventitious virus testing. No contamination with either viral or nonviral adventitious agents was detected within the range of the tests performed. The sterility testing, mycoplasma testing, and *in vitro* adventitious virus testing of the pre-harvest culture fluid are included in the in-process control tests.

The purification process was subjected to viral clearance studies using model viruses. Results showed that the purification process has sufficient viral clearance (Table 1).

Table 1. Results of viral clearance studies

Purification process	Virus reduction factor (log_{10})			
	Xenotropic murine leukemia virus	Pseudorabies virus	Reovirus type 3	Minute virus of mice
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] treatment	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] filtration	[redacted]	[redacted]	[redacted]	[redacted]
Total virus reduction factor	≥19.06	≥16.94	≥10.56	≥10.18

[redacted]

2.1.4 Manufacturing process development

During the process of the drug substance development, changes were made to the manufacturing process. The main changes included [redacted], [redacted], [redacted], [redacted], and [redacted]. The drug product prepared from the drug substance manufactured by the pre-change manufacturing process was used in phase I and foreign phase II studies. The drug product prepared from the drug substance manufactured by the post-change manufacturing process was used in the Japanese phase II/III study and the phase III studies.

Pursuant to these changes in the manufacturing process, comparability of the quality attributes was evaluated. Results demonstrated the comparability of the pre-change and post-change drug substances.

The quality-by-design (QbD) approach was used in the development of the manufacturing process [see Section 2.3].

2.1.5 Characterization

2.1.5.1 Structure and characteristics

The drug substance was characterized as described in Table 2.

Table 2. Parameters used for characterization

Primary/higher-order structure	Amino acid sequence, molecular weight, disulfide bonds, free thiol group, posttranslational modification, secondary structure, tertiary structure, thermal stability
Physicochemical properties	Charge variants, hydrophobic variants, size variants
Carbohydrate structure	N-linked oligosaccharide profile
Biological properties	IL-23-binding activity, neutralization assay
	FcγR-binding activity (FcγRI, FcγRIIa, FcγRIIIa), FcRn-binding activity

In the drug substance, 2 amino acids within Fc region were substituted by other amino acids to eliminate the effector function of Fc region. Results confirmed that risankizumab has a lower binding activity to Fc γ receptor (FcγR) than wild-type IgG1.

2.1.5.2 Product-related substances/product-related impurities

Based on the characterization study results shown in Section 2.1.5.1, the following were identified as product-related substances: [redacted] variant at [redacted]terminal of [redacted] chain, [redacted] variant at [redacted]terminal of [redacted] chain caused by the difference in the site of [redacted] truncation, products formed by oxidation of [redacted] in L-chain and [redacted] in H-chain, [redacted]deamidated form, glycosylated form, deglycosylated form, and N-terminal glutamine variant. Size variants (high molecular weight species and low molecular weight species) were identified as product-related impurities. Size variants (high molecular weight species and low molecular weight species) are controlled by specifications established for the drug substance and for the drug product.

2.1.5.3 Process-related impurities

Host cell-derived deoxyribonucleic acid (DNA), host cell protein (HCP), Impurity 1, Impurity 2, Impurity 3, Impurity 4, Impurity 5, Impurity 6, and Impurity 7 were identified as process-related impurities. All of the process-related impurities were confirmed to be completely removed during the manufacturing process.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (peptide mapping), osmotic pressure, pH, purity (cation exchange chromatography, size exclusion chromatography, capillary sodium dodecyl sulfate [SDS] electrophoresis [redacted], HCP), bacterial endotoxin, microbial limit, bioactivity (neutralization assay), and assay (ultraviolet-visible spectrophotometry).

2.1.7 Stability of drug substance

Table 3 shows the main stability studies conducted on the drug substance.

Table 3. Summary of main stability studies of drug substance

Study	Number of batches	Storage conditions	Study period	Storage form
Long-term	2	−40 ± 10°C	36 months	[redacted]
	3		24 months	
	3		12 months[a)]	
Accelerated	8	[redacted]	12 months	
Stress	1	[redacted]	6 months	

a) The stability study is ongoing up to 60 months.

The long-term test showed no clear change in quality attributes throughout the test period.

The accelerated test showed the following results: an increasing tendency in the osmotic pressure; an increasing tendency in the amount of the high molecular weight species in size exclusion chromatography; an increasing tendency in [redacted] peak and protein content in cation exchange chromatography; a decreasing tendency in the sum of H- and L-chains in the capillary SDS electrophoresis (reduced); and a decreasing tendency in the main peak in capillary SDS electrophoresis (non-reduced).

The stress test showed the following results: an increase in both high and low molecular weight species in the size exclusion chromatography; an increase in acidic peaks in cation exchange chromatography; a decrease in the sum of H- and L-chains in the capillary SDS electrophoresis (reduced), and a decrease in the main peak in the capillary SDS electrophoresis (non-reduced).

Based on the above, the shelf life of 24 months has been proposed for the drug substance when stored at −40 ± 10°C [redacted].

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an aqueous injection containing 75.0 mg of risankizumab per syringe (0.83 mL). The drug product contains, as excipients, D-sorbitol, disodium succinate hexahydrate, succinic acid, polysorbate 20, and water for injection. The drug product is a combination product: a prefilled syringe with a needle, equipped with a safety device to prevent needle-stick injury after injection.

2.2.2 Manufacturing process

The manufacturing process of the drug product is comprised of thawing/sterile filtration of the drug substance, filling/capping, assembling/labeling/packaging, and testing/storage.

[redacted] and [redacted] processes are identified as the critical steps.

The manufacturing process of the drug product has been validated at commercial scale.

2.2.3 Manufacturing process development

During the process of the drug product development, changes were made to the manufacturing process of the drug substance [see Section 2.1.4], [redacted], [redacted], etc. The drug product prepared by the pre-change manufacturing process was used in phase I and foreign phase II studies. The drug product prepared by the post-change manufacturing process was used in the Japanese phase II/III study and the phase III studies.

Pursuant to these changes in the manufacturing process, comparability of the quality attributes was evaluated. Results demonstrated the comparability of the pre-change and post-change drug products.

The QbD approach was used in the development of the manufacturing process [see Section 2.3].

2.2.4 Control of drug product

The proposed specifications for the drug product include strength, description, identification ([redacted]), osmotic pressure, pH, purity (cation exchange chromatography, size exclusion chromatography, capillary SDS electrophoresis [[redacted]]), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, biological activity (neutralization assay), and assay (ultraviolet-visible spectrophotometry).

2.2.5 Stability of drug product

Table 4 shows the main stability studies of the drug product.

Table 4. Summary of the main stability studies of the drug product

Study	Number of batches	Storage conditions	Study period	Storage form
Long-term	3	5 ± 3°C	36 months	Glass syringe with a butyl bromide rubber plunger stopper and a stainless steel needle
	2		24 months[a)]	
	3		9 months[a)]	
Accelerated	5	25 ± 2°C, 60 ± 5% RH	12 months	
	3		9 months	
Stress	8	40 ± 2°C, 75 ± 5% RH	6 months	
Photostability	2	Integrated illuminance of ≥1.2 million lux▪h, an integrated near ultraviolet energy of ≥200 W▪h/m^2		

a) The stability study is ongoing up to 36 months.

The long-term test showed no clear change in quality attributes throughout the test period.

The accelerated and stress tests showed the following results: an increase in the amount of both high and low molecular weight species in size exclusion chromatography; an increase in [redacted] peak and insoluble particulate matter in cation exchange chromatography; a decrease in the sum of H- and L-chains in capillary SDS electrophoresis (reduced); and a decrease in the biological activity.

The photostability test showed that the drug product was photolabile.

Based on the above, the shelf-life of 24 months has been proposed for the drug product when stored at 2°C to 8°C protected from light in a glass syringe with a butylbromide rubber plunger stopper and a stainless steel needle.

2.3 QbD

The QbD approach was used in the development of the drug substance and the drug product. The quality control strategy was developed by doing the following:

- Identification of critical quality attributes (CQAs)
  The following CQAs were identified based on the information obtained during the developmental process, and relevant findings, regarding the quality attributes of the drug product, including product-related substances, product-related impurities, process-related impurities [see Sections 2.1.5.2 and 2.1.5.3], and the characteristics of the drug product:

- CQAs common to both the drug substance and drug product: IL-23 binding, high molecular weight species, low molecular weight species, [redacted]oxidation in the complementarity determining region, [redacted]oxidation at [redacted] binding site, bacterial endotoxins, bioburden, protein concentration, pH, osmotic pressure, polysorbate 20 content, description (transparency and color), and identification
- CQAs of the drug substance: Glycosylation, α-galactosylation, sialylated species, residual HCP, residual DNA, Impurity 2, Impurity 1, Impurity 3, Impurity 4, Impurity 5, Impurity 6, Impurity 7, adventitious viruses, and mycoplasmas
- CQAs of the drug product: Sterility, description (visible particulate matter), insoluble particulate matter, extractable volume, break-loose force, and gliding force

- Process characterization
  Process parameters were classified based on the effect on CQAs and on the process performance, together with the investigation of the control range of each process parameter.

- Establishment of the controlling methods
  Based on the knowledge on the process including the above process characterization, results of batch analysis, and results of stability studies, the methods for controlling the quality attributes of the drug product were established by the combination of process parameter control, in-process control, and specifications [see Sections 2.1.5.2 and 2.1.5.3 for the control of product-related impurities and process-related impurities].

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA has concluded that the quality of the drug substance and the drug product is controlled in an appropriate manner.

2.R.1 Novel excipients

The drug product contains disodium succinate hexahydrate, a novel excipient, in an amount exceeding the amount contained in already-approved subcutaneous drugs.

2.R.1.1 Specifications and stability

PMDA concluded that since disodium succinate hexahydrate meets the specifications for Japanese Pharmaceutical Excipients, there is no problem in the specifications and the stability of disodium succinate contained in the proposed product.

2.R.1.2 Safety

Based on the submitted data, PMDA concluded that disodium succinate hexahydrate is unlikely to pose any safety problem at the amount contained in the proposed product.

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

The applicant submitted the results from the following primary pharmacodynamic studies of risankizumab: *In vitro* studies on the binding to IL-23 and IL-12 and on the effects on IL-23- and IL-12-induced signaling and cytokine production; and an *in vivo s*tudy on the effect in a mouse model of auricular inflammation. No secondary pharmacology study or pharmacodynamic drug interaction study was conducted. No safety pharmacology study was conducted. Instead, the effect on the central nervous system, cardiovascular system, and respiratory system was investigated in a repeated-dose toxicity study in cynomolgus monkeys. Pharmacological parameters are expressed in mean values unless specified otherwise.

3.1 Primary pharmacodynamics

3.1.1 Binding to IL-23 and IL-12 (CTD 4.2.1.1-1, 4.2.1.1-2, and 4.2.1.1-6)

Binding of risankizumab to IL-23 of humans, cynomolgus monkeys, mice, and rats was investigated by surface plasmon resonance. Results showed that the dissociation constant (K_D) was ≤29 pmol/L in humans, <1 pmol/L in cynomolgus monkeys, and 15 nmol/L in mice. Binding to rat IL-23 was not observed at concentration of up to 1 μmol/L risankizumab.

Binding of risankizumab to human IL-12 was not observed at concentration of up to 1 μmol/L risankizumab.

3.1.2 Effect on IL-23- and IL-12-induced signaling and cytokine production (CTD 4.2.1.1-5 to 4.2.1.1-7)

Using DB cells, a cell line derived from human lymphoblasts, the effect of risankizumab on IL-23-induced STAT3 phosphorylation was investigated. Risankizumab inhibited human IL-23 (10 ng/mL)-induced phosphorylation of STAT3 with the 50% inhibitory concentration (IC_{50}) of 13 to 36 pmol/L.

Using mouse spleen cells, the effect of risankizumab on IL-17 production induced by recombinant human IL-23 (1 ng/mL) or endogenous human IL-23 (80 or 90 pg/mL) was investigated. Risankizumab inhibited IL-17 production induced by these human IL-23 samples with IC_{50} of 2 to 29.2 pmol/L (recombinant IL-23) and 1.3 to 3.7 pmol/L (endogenous IL-23). In the same experimental system, the applicant also investigated the effect of risankizumab on IL-17 production induced by recombinant monkey IL-23 (1 ng/mL), recombinant mouse IL-23 (0.25 ng/mL), and recombinant rat IL-23 (0.25 ng/mL). Risankizumab inhibited IL-17 production induced by monkey IL-23 with IC_{50} of 1.4 to 34.7 pmol/L, whereas risankizumab even at 33 nmol/L did not inhibit IL-17 production induced by mouse and rat IL-23.

Using phytohemagglutinin-induced human peripheral mononuclear cells, the effect of risankizumab on IL-12-induced interferon γ (IFNγ) production was investigated. Risankizumab up to 66 nmol/L did not inhibit IFNγ production induced by human IL-12 (0.1 ng/mL).

3.1.3 Effect on a mouse model of auricular inflammation (CTD 4.2.1.1-8)

A mouse model of auricular inflammation was generated by intradermal administration of human recombinant IL-23 to mouse auricle, to investigate the effect of risankizumab on auricular swelling and on cytokine production in the auricular tissue. Risankizumab (1 mg/kg) or the negative control (citrate buffer) was administered intraperitoneally 1 hour before the intradermal administration of IL-23. Compared with the negative control group, the risankizumab group showed inhibition of auricular swelling and inhibition of IL-17 and IL-22 production in the auricular tissue.

3.2 Safety pharmacology (CTD 4.2.3.2-1 and 4.2.3.2-2)

In the 4- and 26-week repeated-dose toxicity studies in cynomolgus monkeys [see Section 5.2], safety pharmacology parameters (effects on central nervous system, cardiovascular system, and respiratory system) were investigated. Animals received once-weekly administration of risankizumab for 4 weeks at 5 to 50 mg/kg (intravenous administration) or 20 mg/kg (subcutaneous administration), or once-weekly subcutaneous administration of risankizumab for 26 weeks at 5 to 50 mg/kg. The animals showed no risankizumab-associated changes in clinical signs, blood pressure, pulse rate, electrocardiogram, respiratory rate, or respiratory conditions.

3.R Outline of the review conducted by PMDA

PMDA asked the applicant to explain whether antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) activities of risankizumab may contribute to its therapeutic efficacy.

The applicant's explanation:

Although ADCC and CDC activities of risankizumab were not investigated, they are unlikely to contribute to its efficacy, for the following reasons:

- Risankizumab has mutations in amino acid residues at 2 sites in Fc region (Leu237Ala and Leu238Ala), which are reported to reduce ADCC and CDC activities. A surface plasmon resonance study showed that the binding affinity of risankizumab to Fcγ receptor was lower than that of wild-type IgG1 [see Section 2.1.5.1].

- The target of risankizumab is IL-23, a soluble cytokine not detected on the cell surface (*Immunity.* 2000;13:715-25).

PMDA's view:

The possibility that ADCC and CDC activities of risankizumab contribute to its therapeutic efficacy cannot be completely ruled out. However, the submitted data demonstrate its activity to inhibit the biological activity of IL-23, and risankizumab is thus expected to be effective against psoriasis, a disease for which IL-23 is considered to be a pathogenic factor.

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

The applicant submitted results of studies on subcutaneous and intravenous administration of risankizumab in cynomolgus monkeys, as data on the absorption and distribution. The serum risankizumab concentration was measured by enzyme-linked immunosorbent assay (lower limit of quantitation, 30.0 ng/mL), and anti-drug antibody (ADA) was measured by electrochemiluminescence immunoassay (detection limit, 19.5 or 31.8 ng/mL). Since risankizumab is a monoclonal antibody, it is considered to be degraded into peptides and amino acids which are then reused or excreted. No studies were therefore conducted on the metabolism or excretion of risankizumab. Pharmacokinetic parameters are expressed in mean ± standard deviation (SD), unless specified otherwise. The serum risankizumab concentration below the lower limit of quantitation was handled as 0 μg/mL.

4.1 Absorption

4.1.1 Single-dose study (CTD 4.2.2.2-1)

Table 5 shows pharmacokinetic parameters following a single subcutaneous or intravenous administration of risankizumab to female cynomolgus monkeys. The bioavailability following the subcutaneous administration was 71.8% ± 17.8%.

Table 5. Pharmacokinetic parameters following a single dose of risankizumab (female cynomolgus monkeys)

Route of administration	Dose (mg/kg)	No. of animals	C_{max} (μg/mL)	AUC_{inf} (μg▪h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL (mL/h/kg)	Vd_{ss} (mL/kg)
SC	1.5	3	16.1 ± 1.3	4460 ± 1110	48 [48, 72]	184 ± 24.4	-	-
IV	1.0	3	61.4 ± 8.2	4140 ± 410	2 [0.5, 2]	173 ± 12.9	0.24 ± 0.02	40.7 ± 2.8

Mean ± SD; t_{max} is expressed in median [minimum, maximum]; -, Not calculated or not applicable
SC, Subcutaneous administration; IV, Intravenous administration; Vd_{ss}, Volume of distribution at steady state

4.1.2 Repeated-dose studies (toxicokinetics) (CTD 4.2.3.2-1 and 4.2.3.2-2)

In the 4- and 26-week repeated dose toxicity studies in cynomolgus monkeys [see Section 5.2], toxicokinetics in once-week intravenous or subcutaneous administration of risankizumab was investigated. Table 6 shows pharmacokinetic parameters of risankizumab and occurrences of ADA. The risankizumab exposure increased roughly in proportion to dose, and showed no sex difference. Occurrence of ADA did not tend to affect the serum risankizumab concentration.

Table 6. Pharmacokinetic parameters in repeated once weekly administration of risankizumab to cynomolgus monkeys

Duration of treatment	Route of administration	Dose (mg/kg/week)	Measuring time point	Sex	No. of animals	C_{max} (μg/mL)	AUC_{168h} (μg•h/mL)	t_{max} (h)	No. of ADA-positive animals
4 weeks	IV	5	Day 1	M	3 each	108 ± 22	7980 ± 1350	0.083 [0.083, 8]	Male: 3 Female: 0
				F		92 ± 19	7380 ± 2100	0.083 [0.083, 8]	
			Week 4	M		139 ± 55	11,500 ± 4200	0.083 [0.083, 0.083]	
				F		98 ± 30	8780 ± 730	0.083 [0.083, 24]	
		20	Day 1	M		489 ± 66	36,600 ± 2400	0.083 [0.083, 8]	Male: 1 Female: 0
				F		615 ± 86	36,400 ± 5100	0.083 [0.083, 0.083]	
			Week 4	M		692 ± 86	55,300 ± 6300	0.083 [0.083, 0.083]	
				F		717 ± 165	61,600 ± 16,500	0.083 [0.083, 0.083]	
		50	Day 1	M	5 each	1030 ± 180	65,800 ± 10,200	0.083 [0.083, 0.083]	Male: 4 Female: 5
				F		1290 ± 230	78,900 ± 23,400	0.083 [0.083, 8]	
			Week 4	M		1630 ± 620	85,100 ± 21,400	0.083 [0.083, 8]	
				F		1580 ± 340	98,900 ± 31,000	0.083 [0.083, 24]	
	SC	20	Day 1	M	3 each	166 ± 53	19,200 ± 3200	48 [48, 48]	Male: 0 Female: 1
				F		119 ± 17	13,900 ± 600	72 [48, 72]	
			Week 4	M		225 ± 24	25,800 ± 5100	24 [24, 72]	
				F		214 ± 61	27,500 ± 5900	48 [24, 96]	
26 weeks	SC	5	Day 1	M	4 each	45 ± 8	5860 ± 984	60 [48, 96]	Male: 1 Female: 0
				F		42 ± 5	5530 ± 899	72 [72, 96]	
			Week 4	M		91 ± 20	12,600 ± 2750	48 [24, 72]	
				F		81 ± 15	12,100 ± 2460	36 [24, 48]	
			Week 26	M		88 ± 20	12,300 ± 3340	60 [48, 72]	
				F		89 ± 46	12,200 ± 5090	48 [24, 96]	
		20	Day 1	M		174 ± 11	22,000 ± 1440	84 [48, 96]	Male: 0 Female: 0
				F		170 ± 29	20,700 ± 4460	36 [24, 96]	
			Week 4	M		341 ± 41	46,100 ± 9990	60 [24, 72]	
				F		251 ± 66	33,200 ± 9760	48 [24, 48]	
			Week 26	M		320 ± 46	46,000 ± 7700	48 [24, 72]	
				F		221 ± 56	28,700 ± 9690	36 [24, 48]	
		50	Day 1	M	6 each	474 ± 51	58,700 ± 5790	48 [24, 72]	Male: 3 Female: 3
				F		440 ± 54	51,600 ± 5900	48 [24, 72]	
			Week 4	M		757 ± 101	102,000 ± 17,100	36 [24, 48]	
				F		559 ± 135	70,300 ± 12,300	48 [24, 48]	
			Week 26	M		731 ± 211	95,300 ± 29,300	24 [24, 48]	
				F		623 ± 76	77,200 ± 11,600	36 [24, 72]	

Mean ± SD; t_{max} is expressed in median [minimum, maximum]; IV, Intravenous administration; SC, Subcutaneous administration

4.2 Distribution

4.2.1 Placental transfer (CTD 4.2.3.5.3-1)

In an enhanced pre- and postnatal development study [see Section 5.5], toxicokinetics was investigated in pregnant cynomolgus monkeys following once weekly subcutaneous administration of risankizumab (5 or 50 mg/kg) from Gestation Day 20-22 until delivery. Table 7 shows the serum risankizumab concentration in maternal animals and the offspring. The exposure to risankizumab in the offspring increased with increasing exposure in the maternal animal. ADA was detected in 4 maternal animals and 1 pup in the 5 mg/kg group, and in 9 maternal animals in the 50 mg/kg group.

Table 7. Placental transfer in cynomolgus monkeys (serum risankizumab concentration in maternal animals and offspring)

Measuring time points	5 mg/kg (μg/mL)		50 mg/kg (μg/mL)	
	Maternal animals	Offspring	Maternal animals	Offspring
Gestation Day 20-22[a)]	29.9 ± 11.6 (22)		314 ± 122 (21)	
Gestation Day 132-134[a)]	98.8 ± 41.9 (18)		916 ± 335 (17)	
Postpartum/postnatal Day 14	20.5 ± 8.8 (16)	5.1 ± 4.1 (15)	121 ± 41.7 (13)	20.7 ± 10.7 (12)
Postpartum/postnatal Day 28	6.5 ± 3.4 (16)	2.0 ± 1.2 (15)	36.0 ± 12.0 (11)	13.0 ± 7.1 (12)
Postpartum/postnatal Day 91	0.1 ± 0.1 (16)	0.1 ± 0.0 (14)	0.8 ± 0.5 (11)	0.7 ± 0.4 (12)

Mean ± SD (number of animals)
a) At 24 hours after administration

4.R Outline of the review conducted by PMDA

Based on the submitted data of the non-clinical pharmacokinetic studies, PMDA concluded that the *in vivo* behavior of risankizumab has been elucidated to a certain extent, and that clinical use of risankizumab does not pose any concern from the pharmacokinetic point of view.

5. Toxicity and Outline of the Review Conducted by PMDA

The following toxicology studies of risankizumab were conducted: Repeated-dose toxicity studies, reproductive and developmental toxicity studies, local tolerance studies, and other toxicity studies (cross-reactivity studies). Cynomolgus monkeys were used in the studies because risankizumab binds to IL-23 of cynomolgus monkeys [see Section 3.1.1-2]. ADA was produced in some animals [see Section 4.1.2], but the exposure to risankizumab during the administration was considered to be sufficiently high to allow toxicological evaluation in all of the studies.

5.1 Single-dose toxicity

No single-dose toxicity study was conducted on risankizumab. Instead, acute toxicity was evaluated following the first dose in the repeated intravenous and subcutaneous dose toxicity studies in cynomolgus monkeys (CTD 4.2.3.2-1 and 4.2.3.2-2) (Table 8). Neither death nor any other toxic findings such as acute symptoms were observed.

Table 8. Outline of the toxicity evaluation following single-dose administration

Test system	Route of administration	Dose (mg/kg/week)	Main findings	Approximate lethal dose (mg/kg/week)	Attached document CTD
Male and female cynomolgus monkeys	IV, SC	IV: 0,[a)] 5, 20, 50 SC: 20	No toxic change	>50	4.2.3.2-1
Male and female cynomolgus monkeys	SC	0,[b)] 5, 20, 50	No toxic change	>50	4.2.3.2-2

a) 25 mmol/L succinic acid, 125 mmol/L sodium chloride, 0.02% Tween 20 (pH 6.5)
b) 4.4 mmol/L succinic acid, 275 mmol/L sorbitol, 0.02% Tween 20 (pH 5.5-6.1)

5.2 Repeated-dose toxicity

A 4-week intravenous and subcutaneous toxicity study and 26-week subcutaneous toxicity studies were conducted in cynomolgus monkeys (Table 9).

The 4-week intravenous and subcutaneous toxicity study (CTD 4.2.3.2-1) showed abnormalities in erythroid cells but no related abnormal findings. This finding was therefore considered to be of little toxicological significance.

A 26-week subcutaneous toxicity study (CTD 4.2.3.2-2) showed hypospermatogenesis. Therefore, another 26-week subcutaneous toxicity study was conducted in sexually matured male monkeys to evaluate testicular toxicity. No abnormality was observed in the testis. Based on these results, the testis of the animals that had hypospermatogenesis was subjected to histopathological re-examination. Results showed that the finding (hypospermatogenesis) was a histological manifestation associated with the process of testicular maturation in peripubertal cynomolgus monkeys (*Tox Pathol.* 2012;40:935-42). The no observed adverse effect level (NOAEL) in the 26-week subcutaneous toxicity study (CTD 4.2.3.2-2) was determined to be 50 mg/kg. $AUC_{0\text{-}12wk}$ (43,150 μg▪day/mL) at the NOAEL was approximately 61 times the $AUC_{4\text{-}16wk}$[1)] (704 μg▪day/mL) in Japanese patients with psoriasis who received subcutaneous risankizumab at the proposed clinical dosage.

Table 9. Outline of repeated-dose toxicity studies

Test system	Route of administration	Duration of treatment	Dose (mg/kg/week)	Main findings	NOAEL (mg/kg/week)	Attached document CTD
Male and female cynomolgus monkeys	IV, SC	4 weeks (once a week) + 8-week recovery period	IV: 0,[a)] 5, 20, 50 SC: 0,[a)] 20	IV: ≥5: Decreased hemoglobin and hematocrit 50: Decreased mean corpuscular volume SC: 20: Decreased hemoglobin, hematocrit, and mean corpuscular volume Recovery period: No abnormal findings	IV: 50 SC: 20	4.2.3.2-1
Male and female cynomolgus monkeys	SC	26 weeks (once a week) + 8-week recovery period	0,[b)] 5, 20, 50	≥5: Hypospermatogenesis 50: Decreased testis weight ≤50: No abnormalities in T lymphocyte function[d)] or lymphocyte subsets Recovery period: No abnormal findings	50	4.2.3.2-2
Male cynomolgus monkeys	SC	26 weeks (once a week) + 8-week recovery period	0,[c)] 50	None[e)] Recovery period: No abnormal findings	–	4.2.3.2-3

a) 25 mmol/L succinic acid, 125 mmol/L sodium chloride, 0.02% Tween 20 (pH 6.5)
b) 4.4 mmol/L succinic acid, 275 mmol/L sorbitol, 0.02% Tween 20 (pH 5.5-6.1)
c) 0.5 mmol/L succinic acid, 3.9 mmol/L disodium succinate hexahydrate, 275 mmol/L sorbitol, 0.2 g/L polysorbate 20 (pH 6.0 ± 0.5)
d) T-cell-dependent antibody production
e) Mainly fertility parameters (testicular size, serum testosterone concentration, sperm analysis) and spermatogenic cycle were evaluated.

5.3 Genotoxicity

Since risankizumab is a monoclonal antibody preparation, it is not considered to directly act on DNA or other chromosomal components. Therefore, no genotoxicity studies were conducted.

5.4 Carcinogenicity

Since risankizumab does not have any pharmacological activity either in mice or rats [see Sections 3.1.1 and 3.1.2], no carcinogenicity study in rodents was conducted.

1) The value was estimated by population pharmacokinetic (PPK) analysis of clinical study data including those of Japanese clinical studies [see Section 6.2.6.2]

The applicant explained that risankizumab is unlikely to be carcinogenic for the following reasons:
IL-23 enhances tumor formation by inducing inflammatory reaction and angiogenesis and by suppressing the immune reaction against tumor (*Biochem Biophys Res Commun*. 2017;482:1400-6, *Proc Natl Acad Sci USA*. 2010;107:8328-33, *Nature*. 2006;442:461-5). This mechanism of action suggests that risankizumab may suppress tumor formation. Repeated-dose toxicity studies in monkeys did not show any findings suggestive of carcinogenicity or any effect on the immune system [see Section 5.2].

5.5 Reproductive and developmental toxicity

An enhanced pre- and post-natal development study, including maternal function was conducted in cynomolgus monkeys, to investigate the reproductive and developmental toxicity of risankizumab, (Table 10).

The total number of abortions, still births, and early postnatal death, and the percentage of fetal death due to abortion or still birth were within the range of the historical data of the study facility and within the range of the spontaneous occurrence in cynomolgus monkeys (*Birth Defect Res B Dev Reprod Toxicol.* 2010;89:175-87). These results suggest that the relationship between risankizumab and fetal death is unlikely. The NOAEL in maternal animals and the offspring was determined to be 50 mg/kg. $AUC_{0\text{-}12wk}$ (61,500 µg▪day/mL) at the NOAEL was approximately 87 times the $AUC_{4\text{-}16wk}$[1)] (704 µg▪day/mL) in Japanese patients with psoriasis who received subcutaneous risankizumab at the proposed clinical dosage.

The 26-week repeated subcutaneous dose toxicity study did not show any effect on the reproductive organs of males and females [see Section 5.2], suggesting that risankizumab has little or no effect on fertility of males and females. Placental transfer of risankizumab was observed in cynomolgus monkeys [see Section 4.2.1].

Table 10. Outline of reproductive and developmental toxicity study

Type of study	Test system	Route of administration	Duration of treatment	Dose (mg/kg/week)	Main findings	NOAEL (mg/kg/week)	Attached document CTD
Study on pre- and post-natal development, including maternal function	Female cynomolgus monkeys	SC	Maternal animals: From Gestation Day 20 to 22 up to delivery, 22 doses at the maximum (once weekly)	0,[a] 5, 50	Maternal animals: 0: Abortion/still birth (3 of 21 animals) 5: Abortion/still birth (5 of 22 animals) 50: Abortion/still birth (6 of 21 animals) Pups[b]: Death: 0 (1 of 18 animals) 5 (2 of 17 animals) 50 (3 of 15 animals) ≤50: No effect on T lymphocyte function[c] or peripheral lymphocyte subsets	Maternal animals: 50 Pups: 50	4.2.3.5.3-1

a) 4.4 mmol/L succinic acid, 275 mmol/L sorbitol, 0.02% polysorbate 20 (pH 6.0)
b) The maternal animal of 1 pup in the 50 mg/kg group refused nursing. The pup was nursed by another maternal animal in the 5 mg/kg group from Postnatal Day 3.
c) T cell-dependent antibody production

5.6 Local tolerance

5.6.1 A single intramuscular and subcutaneous dose local tolerance studies in rabbits

Single intramuscular and subcutaneous dose local tolerance studies were conducted in New Zealand White rabbits (Table 11).

Table 11. Outline of local tolerance studies

Test system	Application site	Testing method	Main findings	Attached document CTD
Male rabbits (NZW)	Intramuscular	Single dose of 1 mL at 0[a] or 90[b] mg/mL	Not irritating	4.2.3.6-1
	Subcutaneous	Single dose of 1 mL at 0[a] or 90[b] mg/mL	Not irritating	

a) 3.9 mmol/L disodium succinate hexahydrate, 0.5 mmol/L succinic acid, 275 mmol/L sorbitol, 0.16 mmol/L polysorbate 20 (pH 6.0 ± 0.5)
b) 3.9 mmol/L disodium succinate hexahydrate, 0.5 mmol/L succinic acid, 225 mmol/L sorbitol, 0.16 mmol/L polysorbate 20 (pH 6.4, the same concentration as that used in the to-be-marketed formulation)

5.7 Other toxicity studies

5.7.1 Tissue cross-reactivity study

A tissue cross-reactivity study was conducted using normal human tissues (Table 12). Results showed staining of extracellular granular substances in the placenta, which was considered to be due to IL-23 expression, because IL-23 is expressed in decidual cells, cytotrophoblast, and syncytiotrophoblast of human placenta (*J Reprod Immunol.* 2010;87:21-7).

Table 12. Outline of tissue cross-reactivity study

Test system	Testing method	Main findings	Attached document CTD
Normal human tissues	Frozen sections were treated with risankizumab (1 or 10 μg/mL), and binding of risankizumab to tissues was detected by enzyme-linked immunosorbent assay (indirect method).	Staining was detected in extracellular granular substances in the placenta.	4.2.3.7.7-1

5.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that clinical use of risankizumab does not pose any specific problems from a toxicological point of view.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

The plasma risankizumab concentration was measured by enzyme-linked immunosorbent assay (lower limit of quantitation, 5 or 10 ng/mL), and the plasma ADA concentration was measured by electrochemiluminescence immunoassay (detection limit, 0.141 or 0.327 ng/mL).

6.2 Clinical pharmacology

The applicant submitted data of the following studies: A clinical study in healthy adults (Study M16-513 [CTD 5.3.3.1-1]) and clinical studies in patients with psoriasis (Studies 1311.1 [CTD 5.3.3.2-1], 1311.2 [CTD 5.3.5.1-1], M15-992 [CTD 5.3.5.1-5], M15-995 [CTD 5.3.5.1-6], M15-988 [CTD 5.3.5.1-8 and 5.3.5.1-8-2], M16-002 [CTD 5.3.5.1-2], M16-004 [CTD 5.3.5.1-3 and 5.3.5.1-3-2], M16-007 [CTD 5.3.3.2-2], M16-008 [CTD 5.3.5.1-4], M16-010 [CTD 5.3.5.1-7]). Also, the applicant submitted results of population pharmacokinetics (PPK) analysis, exposure-response analysis, etc. The dose of Skyrizi is expressed in the dose of risankizumab, and pharmacokinetic parameters in mean ± SD, unless specified otherwise. The plasma risankizumab concentration below the lower limit of quantitation was handled as 0 μg/mL.

In Studies 1311.1, 1311.2, and M16-513, 10 mg/mL vial formulation (intravenous administration) or 90 mg/mL prefilled syringe formulation (content 1.0 mL, subcutaneous administration) was used. In other studies, 90 mg/mL prefilled syringe formulation (content 0.83 mL), which is identical to the to-be marketed formulation, was used.

6.2.1 Phase I studies

6.2.1.1 Global study in healthy adults (CTD 5.3.3.1-1, Study M16-513 [August 2015 to June 2017])

A single dose of risankizumab was administered subcutaneously (18, 90, or 300 mg) to Japanese, Chinese, and Caucasian healthy adults, or administered intravenously (200, 600, or 1200 mg) to Japanese healthy adults. Table 13 shows pharmacokinetic parameters. The exposure to risankizumab (C_{max} and AUC_{inf}) increased roughly in proportion to dose over the dose range investigated. ADA was detected in 2 subjects (1 Japanese and 1 Chinese) in the 90 mg subcutaneous group and in 2 subjects (1 Caucasian and 1 Chinese) in the 300 mg subcutaneous group.

Table 13. Pharmacokinetic parameters following a single dose administration of risankizumab to Japanese and non-Japanese healthy adults (subcutaneous) and to Japanese healthy adults (intravenous)

Route of administration	Dose (mg)	Race	No. of subjects	C_{max} (μg/mL)	AUC_{inf} (μg▪day/mL)	t_{max} (day)	$t_{1/2}$ (day)	CL or CL/F (L/day)	Vd_β or Vd_β/F (L)
IV	200	Japanese	6 each	60.1 ± 8.6	998 ± 122	0.1 [0.1, 0.2]	31.2 ± 7.4	0.20 ± 0.02	9.41 ± 1.52
	600			225 ± 19	3620 ± 320	0.1 [0.1, 0.2]	30.7 ± 2.6	0.17 ± 0.01	7.43 ± 0.90
	1200			363 ± 55	7020 ± 1980	0.1 [0.1, 0.3]	32.7 ± 14.2	0.19 ± 0.06	8.94 ± 1.93
SC	18	Japanese		1.70 ± 0.51	84.7 ± 14.4	7.0 [7.0, 14.0]	32.5 ± 5.0	0.22 ± 0.04	10.3 ± 1.8
		Caucasian		1.04 ± 0.21	59.3 ± 10.7	7.0 [3.0, 28.1]	30.5 ± 8.9	0.31 ± 0.06	14.3 ± 3.0
		Chinese		1.91 ± 0.55	77.3 ± 17.2	7.0 [3.0, 7.0]	28.5 ± 3.8	0.24 ± 0.05	9.99 ± 2.02
	90	Japanese		9.08 ± 0.59	377 ± 23	7.0 [7.0, 7.0]	26.9 ± 1.5	0.24 ± 0.01	9.29 ± 0.48
		Chinese		6.81 ± 1.87	336 ± 75	5.0 [3.0, 7.0]	26.7 ± 3.7	0.28 ± 0.05	10.7 ± 1.4
	300	Japanese		22.3 ± 9.1	1100 ± 405	7.0 [7.0, 14.0]	29.7 ± 4.8	0.30 ± 0.11	13.2 ± 5.1
		Caucasian		20.4 ± 8.0	915 ± 305	7.0 [3.0, 7.0]	28.7 ± 3.8	0.36 ± 0.13	15.1 ± 5.6
		Chinese		19.5 ± 5.1	1030 ± 292	7.0 [3.0, 14.0]	33.8 ± 7.2	0.31 ± 0.09	15.1 ± 2.9

Mean ± SD, t_{max} is expressed in median [minimum, maximum].
IV, Intravenous administration; SC, Subcutaneous administration; CL/F, Apparent clearance; Vd_β, Volume of distribution in the terminal phase; Vd_β/F, Apparent volume of distribution in the terminal phase

6.2.1.2 Foreign study in patients with plaque psoriasis (CTD 5.3.3.2-1, Study 1311.1 [April 2012 to May 2014], Reference data)

A single dose of risankizumab (0.01-5 mg/kg) was administered intravenously or subcutaneously to non-Japanese patients with moderate to severe plaque psoriasis. Table 14 shows pharmacokinetic parameters and occurrences of ADA.

Table 14. Pharmacokinetic parameters following a single dose of risankizumab in patients with moderate to severe plaque psoriasis

Dose (mg/kg)	Route of administration	No. of patients	C_{max} (μg/mL)	AUC_{inf} (μg▪day/mL)	t_{max} (day)	$t_{1/2}$ (day)	CL or CL/F (L/day)	V_z or V_z/F (L)	No. of ADA-positive patients
0.01	IV	3 each	0.31 ± 0.03	2.99 ± 0.76	0.08 [0.07, 0.08]	19.6 ± 3.3	0.35 ± 0.15	9.34 ± 2.46	2
0.05			1.40 ± 0.38	17.0 ± 7.3	0.04 [0.04, 0.08]	22.8 ± 4.5	0.35 ± 0.15	10.8 ± 2.2	0
0.25			5.97 ± 0.64	85.6 ± 11.5	0.09 [0.08, 0.17]	22.8 ± 6.9	0.28 ± 0.05	9.58 ± 4.23	1
1			16.9 ± 12.0	224 ± 153	0.04 [0.04, 0.17]	27.8 ± 3.3	0.83 ± 0.91	36.0 ± 42.7	1
3			66.4 ± 6.2	955 ± 82	0.08 [0.04, 0.08]	19.0 ± 7.2	0.27 ± 0.01	7.50 ± 2.92	2
5			110 ± 10	1680 ± 381	0.08 [0.04, 0.08]	23.7 ± 8.0	0.24 ± 0.07	8.06 ± 3.18	0
0.25	SC	7	1.05 ± 0.47	45.5 ± 18.8	13.0 [2.0, 14.1]	23.4 ± 7.7	0.57 ± 0.34	18.0 ± 9.4	0
1		6	5.81 ± 0.97	227 ± 67	5.0 [2.0, 10.0]	27.9 ± 3.8	0.40 ± 0.15	15.7 ± 4.8	0

Mean ± SD. t_{max} is expressed in median [minimum, maximum].
IV, Intravenous administration; SC, Subcutaneous administration; CL/F, Apparent clearance; Vz (Vz/F), Volume of distribution in the terminal phase

6.2.2 Phase II studies

6.2.2.1 Foreign study in patients with plaque psoriasis (CTD 5.3.5.1-1, Study 1311.2 [February 2014 to July 2015], Reference data)

Non-Japanese patients with moderate to severe plaque psoriasis received risankizumab subcutaneously as a single dose (18 mg) or 3 times at Week 0, 4, and 16 (90 or 180 mg). Table 15 shows pharmacokinetic parameters. ADA was detected in 3 patients in the 18 mg group, 8 patients in the 90 mg group, and 9 patients in the 180 mg group.

Table 15. Pharmacokinetic parameters following subcutaneous administration of risankizumab to patients with moderate to severe plaque psoriasis

Dose (mg)	No. of patients	C_{max} (μg/mL) after the first dose	t_{max} (day) after the first dose	$AUC_{0\text{-}4wk}$ (μg•day/mL)	$AUC_{4\text{-}16wk}$ (μg•day/mL)	AUC_{inf} (μg•day/mL)	$C_{trough,\ 4wk}$ (μg/mL)	$C_{trough,\ 16wk}$ (μg/mL)
18	42	0.86 ± 0.64	7 [6, 28]	17.1 ± 9.5	-	39.1 ± 23.3	0.56 ± 0.37	-
90	41	5.16 ± 2.11	7 [6, 27]	101 ± 37[a)]	136 ± 65[b)]	-	2.71 ± 0.96[b)]	1.11 ± 0.69[c)]
180	42	10.1 ± 3.7	7 [6, 14]	201 ± 70[d)]	282 ± 141[d)]	-	5.78 ± 2.65 [e)]	1.83 ± 1.06[f)]

Mean ± SD. t_{max} is expressed in median [minimum, maximum].
a) n = 34, b) n = 40, c) n = 35, d) n = 39, e) n = 41, f) n = 37

6.2.2.2 Global study in patients with active PsA (CTD 5.3.5.1-2, Study M16-002 [May 2016 to August 2017])

Patients with active PsA, including Japanese patients, received risankizumab subcutaneously at 75 mg as a single dose or at 150 mg at Week 0 and 12 (Q12W group), at Week 0, 4, and 16 (LD Q12W group), or at 4-week intervals (Q4W group). Table 16 shows plasma risankizumab concentrations observed. ADA was detected in 3 of 19 patients in the 75 mg group, 2 of 39 patients in the 150 mg Q12W group, 9 of 42 patients in the 150 mg LD Q12W group, and 3 of 40 patients in the 150 mg Q4W group.

Table 16. Plasma risankizumab concentration following subcutaneous administration of risankizumab to patients with active PsA (μg/mL)

Treatment group	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28
75 mg	3.5 ± 1.3 (19)	1.6 ± 0.7 (19)	0.8 ± 0.4 (18)	0.5 ± 0.2 (19)	0.2 ± 0.1 (19)	0.1 ± 0.1 (18)	0.03, 0.17 (2)
150 mg Q12W	7.0 ± 2.3 (39)	3.6 ± 1.4 (39)	1.8 ± 1.0[a)] (38)	7.5 ± 2.0 (39)	3.8 ± 1.5 (39)	1.8 ± 0.8 (38)	0.7 ± 0.6 (8)
150 mg LD Q12W	7.2 ± 2.1[a)] (42)	11.5 ± 4.5 (42)	5.8 ± 2.4 (42)	3.0 ± 1.6[a)] (41)	8.1 ± 2.7 (40)	4.7 ± 1.9 (38)	3.0 ± 2.4 (8)
150 mg Q4W	6.6 ± 2.3[a)] (40)	10.4 ± 4.2[a)] (40)	12.1 ± 5.6[a)] (39)	13.3 ± 5.6[a)] (38)	12.8 ± 5.8 (38)	6.5 ± 3.9 (36)	2.4 ± 1.4 (5)

Mean ± SD or individual measured values (n), a) Trough level

6.2.3 Phase II/III study

6.2.3.1 Japanese study in patients with plaque psoriasis (CTD 5.3.5.1-3 and 5.3.5.1-3-2, Study M16-004 [December 2016 to June 2018])

Japanese patients with moderate to severe plaque psoriasis received risankizumab (75 or 150 mg) subcutaneously at Week 0 and 4, then at 12-week intervals. Table 17 shows the trough plasma concentration of risankizumab observed. ADA was detected in 14 of 58 patients in the 75 mg group and in 17 of 55 patients in the 150 mg group.

Table 17. Trough plasma concentration (μg/mL) of risankizumab following subcutaneous administration of risankizumab to Japanese patients with moderate to severe plaque psoriasis

Treatment group	Week 4	Week 16	Week 28	Week 40	Week 52
75 mg	3.5 ± 1.3 (56)	1.4 ± 0.8 (56)	1.3 ± 0.8 (56)	1.2 ± 1.0 (58)	1.1 ± 0.6 (56)
150 mg	6.7 ± 2.3 (54)	5.1 ± 2.2 (54)	2.2 ± 1.1 (54)	2.2 ± 1.3 (55)	2.1 ± 1.2 (54)

Mean ± SD (n)

6.2.4 Phase III studies

6.2.4.1 Japanese study in patients with GPP or EP (CTD 5.3.5.1-8 and 5.3.5.1-8-2, Study M15-988 [ongoing since January 2017 (data cut-off [redacted] 20[redacted]; data obtained up to Week 52)])

Japanese patients with GPP or EP received risankizumab (75 or 150 mg) subcutaneously at Week 0 and 4, then at 12-week intervals. Table 18 shows the trough plasma concentration of risankizumab observed. ADA was detected in 1 of 9 patients in the 75 mg group and in 3 of 8 patients in the 150 mg group.

Table 18. Trough plasma concentration of risankizumab following subcutaneous administration of risankizumab to Japanese patients with GPP or EP

Treatment group	Week 4	Week 16	Week 28	Week 52
75 mg	3.4 ± 0.7 (9)	1.0 ± 0.4 (8)	1.0 ± 0.5 (8)	0.7 ± 0.4 (8)
150 mg	7.3 ± 5.5 (8)	2.7 ± 2.7 (8)	2.9 ± 2.1 (6)	2.0 ± 1.3 (6)

Mean ± SD (n)

6.2.4.2 Global studies (CTD 5.3.5.1-4, Study M16-008 [February 2016 to September 2017]; CTD 5.3.5.1-5, Study M15-992 [ongoing since March 2016 (data cut-off [redacted] 20[redacted]; data obtained up to Week 52)]) and foreign studies (CTD 5.3.5.1-6, Study M15-995 [March 2016 to September 2017]; CTD 5.3.5.1-7, Study M16-010 [March 2016 to August 2017]; all are Reference data), in patients with plaque psoriasis

Table 19 shows the trough plasma concentration of risankizumab and occurrence of ADA following subcutaneous administration of risankizumab (150 mg) at Week 0 and 4, then at 12-week intervals to patients with moderate to severe plaque psoriasis (including Japanese patients).

Table 19. Trough plasma concentration of risankizumab (μg/mL) following subcutaneous administration of risankizumab (150 mg) to patients with moderate to severe plaque psoriasis

Study	Week 4	Week 16	Week 28	Week 40	Week 52	No. of ADA-positive patients
M16-008	6.0 ± 2.4 (297)	2.2 ± 1.2 (297)	2.0 ± 1.1 (293)	2.2 ± 1.7 (297)	1.9 ± 1.2 (289)	78/301
M15-992	5.7 ± 2.1 (177)	2.2 ± 1.5 (175)	1.8 ± 1.2 (173)	1.9 ± 1.7 (166)	1.9 ± 1.2 (156)	47/181
M15-995	6.0 ± 2.3 (293)	2.1 ± 1.3 (293)	1.9 ± 1.1 (288)	1.9 ± 1.1 (287)	2.0 ± 1.3 (276)	64/298
M16-010	5.9 ± 2.2 (298)	2.5 ± 1.4 (292)	2.2 ± 1.3 (284)	-	-	74/299

Mean ± SD (n); -, Not measured

6.2.5 Drug-drug interactions (CTD 5.3.3.2-2, Study M16-007 [September 2016 to September 2017], Reference data)

In a clinical study in non-Japanese patients with moderate to severe plaque psoriasis, the effect of risankizumab on the pharmacokinetics of caffeine (substrate of CYP1A2), warfarin (substrate of CYP2C9), omeprazole (substrate of CYP2C19), metoprolol (substrate of CYP2D6), and midazolam (substrate of CYP3A4) was investigated.[2)] Table 20 shows the pharmacokinetic parameters of each drug administered in combination with or without risankizumab. Risankizumab had no effect on the pharmacokinetics of drugs metabolized by their respective CYP isoforms.

[2)] The 5 types of substrates were administered as a single dose on Day 1, followed by subcutaneous administration of risankizumab 150 mg on Day 8, 36, 64 and 92, and by a single dose of the 5 types of substrates on Day 98. In this study, pharmacokinetics of each substrate on Day 1 and Day 98 were compared.

Table 20. Effect of risankizumab on pharmacokinetics of each substrate drug

Substrates	No. of patients	Substrate alone/ substrate + risankizumab	C_{max} (ng/mL) of substrate	AUC_{last} (ng▪h/mL) of substrate	Geometric mean ratio [90% CI] (substrate + risankizumab /substrate alone)	
					C_{max}	AUC_{last}
Caffeine 100 mg	21 each	Substrate alone	2700 (40)	20,900 (86)	1.09 [0.96, 1.23]	1.03 [0.89, 1.19]
		Substrate + risankizumab	2950 (77)	21,500 (185)		
S-Warfarin 10 mg		Substrate alone	534 (24)	15,800 (39)	0.92 [0.86, 0.98]	0.93 [0.89, 0.96]
		Substrate + risankizumab	490 (29)	14,600 (35)		
Omeprazole 20 mg		Substrate alone	226 (48)	464 (78)	0.85 [0.73, 0.99]	0.93 [0.82, 1.05]
		Substrate + risankizumab	192 (62)	431 (76)		
Metoprolol 50 mg		Substrate alone	32.0 (71)	177 (96)	0.97 [0.88, 1.07]	1.01 [0.93, 1.11]
		Substrate + risankizumab	31.0 (68)	179 (87)		
Midazolam 2 mg		Substrate alone	8.70 (34)	26.7 (40)	1.03 [0.96, 1.09]	1.01 [0.94, 1.09]
		Substrate + risankizumab	8.91 (33)	27.0 (43)		

Geometric mean (CV%)

6.2.6 PPK analysis and exposure-response analysis

6.2.6.1 PPK analysis using data of global studies and foreign clinical studies (CTD 5.3.3.5-1)

PPK analysis (NONMEM version 7.4) was conducted using plasma risankizumab concentration data (13,123 measuring points in 1899 subjects) obtained from a total of 7 global and foreign clinical studies[3)] in healthy subjects and patients with moderate to severe plaque psoriasis. The final model was described by a 2-compartment model with first-order absorption and elimination. The following parameters were identified as covariates[4)]: (1) Body weight, baseline serum albumin, serum creatinine, high-sensitivity C-reactive protein (CRP), and ADA titer for clearance (CL) of risankizumab, (2) body weight for volume of distribution of central compartment (V_c) and of peripheral compartment (V_p), and (3) manufacturing process of the drug product for absolute bioavailability (F).

6.2.6.2 PPK analysis including data of Japanese clinical studies (Studies M16-004 and M15-988) (CTD 5.3.3.5-2)

PPK analysis (NONMEM version 7.4.1) was conducted using plasma risankizumab concentration data (13,671 measuring points in 2083 subjects including 548 measuring points in 184 Japanese subjects)

3) Phase I studies (Studies 1311.1 and M16-513), phase II study (Study 1311.2), and phase III studies (Studies M15-992, M15-995, M16-008, and M16-010)

4) The following parameters were evaluated as potential covariates: (1) Age, body weight, sex, race, country, disease condition (healthy adult or patient with psoriasis), baseline serum albumin level, serum creatinine level, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, creatinine clearance, high-sensitivity CRP, baseline psoriasis area and severity index (PASI) score, ADA titer, presence or absence of ADA, presence or absence of ADA over time, presence or absence of neutralizing antibody, presence or absence of neutralizing antibody over time, and concomitant drugs (antihyperlipidemic drugs, antihypertensive agents, antidiabetic drugs, analgesic drugs, thyroid therapeutic drugs, and vitamins) for CL of risankizumab, (2) body weight, sex, patient population, age, and baseline serum albumin for Vc, (3) body weight for V_p, (4) body weight for inter-compartmental clearance (Q), (5) age, sex, and race for absorption rate constant (*K*a), and (6) manufacturing process of the drug product for absolute bioavailability (F).

obtained from a total of 9 Japanese and foreign clinical studies[5)] in healthy subjects, patients with moderate to severe plaque psoriasis, patients with GPP, or patients with EP. The final model was described by a 2-compartment model with first-order absorption and elimination, as was the case with the PPK analysis described in Section 6.2.6.1. The population pharmacokinetic parameters [95% confidence interval (CI)] in patients with psoriasis weighing 70 kg, estimated from the final model, were as follows: CL, 0.244 [0.236, 0.252] L/day; V_c, 4.87 [4.51, 5.23] L; V_p, 4.25 [4.08, 4.42] L; K_a, 0.230 [0.208, 0.252] day^{-1}; Q, 0.648 [0.602, 0.694] L/day; and F, 89.1% [85.8%, 91.7%]. Table 21 shows the estimated pharmacokinetic parameters of risankizumab at steady state (Week 16-28) in subcutaneous administration of risankizumab (75 or 150 mg) at Week 0, at Week 4, then at 12-week intervals. Figure 1 shows the effect of each covariate on C_{max} and AUC_{tau} at steady state following the subcutaneous administration of risankizumab at the proposed clinical dosage. C_{max} and AUC_{tau} tended to decrease in patients weighing >90 or >100 kg and AUC_{tau} in patients with ADA titer ≥128, compared with those in patients in the control group.[6)]

Table 21. Pharmacokinetic parameters of risankizumab at steady state, estimated from the final model

Treatment group	Race	No. of patients	C_{max} (μg/mL)	$AUC_{16\text{-}28wk}$ (μg▪day/mL)	C_{trough} (μg/mL)
150 mg	Non-Japanese	1130	12.4 ± 3.3	494 ± 176	2.02 ± 1.18
	Japanese	102	14.5 ± 3.4	559 ± 194	2.22 ± 1.26
75 mg	Japanese	64	8.32 ± 3.57	321 ± 174	1.32 ± 1.00

Mean ± standard deviation

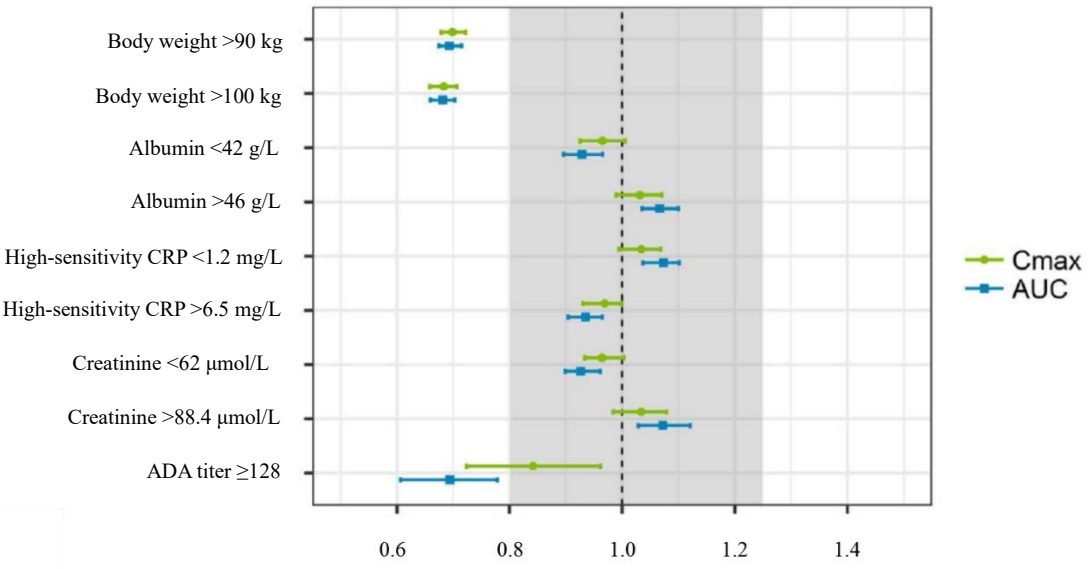


Figure 1. Effect of covariates on the exposure to risankizumab at steady state (ratio of risankizumab group to control group)

5) Phase I studies (Studies 1311.1 and M16-513), phase II study (Study 1311.2), phase II/III study (Study M16-004), and phase III studies (Studies M15-988, M15-992, M15-995, M16-008, and M16-010)

6) The control group included patients with the following characteristics to evaluate the effect of covariates: Body weight ≤90 kg or ≤100 kg; baseline serum albumin, 42 (first quartile) to 46 g/L (third quartile); baseline high sensitivity CRP, 1.2 (first quartile) to 6.5 mg/L (third quartile); baseline serum creatinine, 62 (first quartile) to 88.4 (third quartile) μmol/L, and ADA titer, negative or <128

6.2.6.3 Exposure-response analysis (CTD 5.3.4.2-3)

The exposure-response relationship was investigated using the data of efficacy endpoints (achievement rates of psoriasis area and severity index [PASI] 75, PASI 90, PASI 100, and static physician global assessment [sPGA] [0/1]) and the plasma risankizumab concentration obtained from Japanese and foreign clinical studies[7] in patients with moderate to severe plaque psoriasis, patients with GPP, or patients with EP. Figure 2 shows the relationship between the mean plasma risankizumab concentration (C_{ave}) from Week 0 to 16 and efficacy endpoints (achievement rates of PASI 90, PASI 100, and sPGA [0/1]), and estimated C_{ave} in patient subgroups classified by body weight. Results suggested that the efficacy of risankizumab decreased in some patients weighing >90 kg who received 75 mg. In patients receiving 150 mg at Week 0, at Week 4, then at 12-week intervals, no clinically significant difference was observed in efficacy endpoints between subgroups classified by body weight.

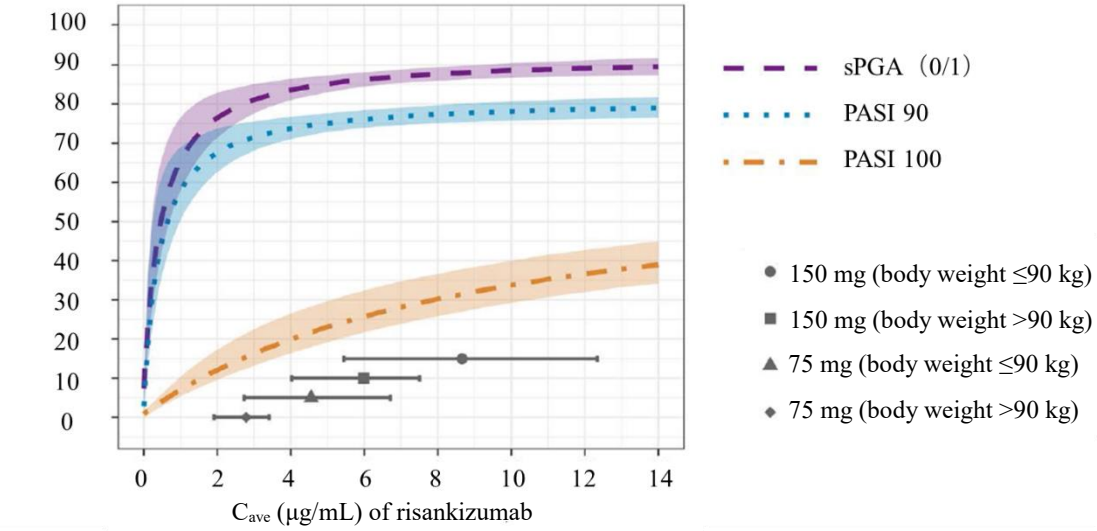


Figure 2. Exposure-response relationship in the efficacy of risankizumab in Japanese patients with psoriasis, and estimated C_{avg}

6.R Outline of the review conducted by PMDA

6.R.1 Dosage regimen in Japanese clinical studies (Studies M16-004 and M15-988)

The applicant's explanation about the dosage regimen in clinical studies of risankizumab:

In the global and foreign phase III studies[8] that were planned and conducted ahead of Japanese clinical studies, risankizumab 150 mg was administered subcutaneously at Week 0 and 4, then at 12-week intervals, for the following reasons:

- In the phase II study (Study 1311.2) in patients with moderate to severe plaque psoriasis, risankizumab was administered subcutaneously at 18 mg as a single dose or at 90 or 180 mg 3 times at Week 0, 4, and 16. As for efficacy, the achievement rate of PASI 90 was the highest in the

[7] Phase II study (Study 1311.2), phase II/III study (Study M16-004), phase III studies (Studies M15-988, M15-992, M15-995, M16-008, and M16-010)

[8] Studies M15-992, M15-995, M16-008, and M16-010

180 mg group (32.6% [14 of 43] of patients in the 18 mg group, 73.2% [30 of 41] of patients in the 90 mg group, 81.0% [34 of 42] of patients in the 180 mg group). As for safety, no dose-dependent adverse events were reported within the dosage range investigated.

- Exposure-response analysis was conducted using the efficacy endpoints and plasma risankizumab concentration data obtained from the phase I study (Study 1311.1) and the phase II study (Study 1311.2) in patients with moderate to severe plaque psoriasis. A simulation with this model was conducted to estimate the achievement rates of PASI 90 and PASI 100 following subcutaneous administration of risankizumab to patients with psoriasis vulgaris at each dose at Week 0, 4, and 16, and at 150 mg at different intervals (8, 12, or 16-week intervals) (Tables 22 and 23). The simulation predicted that the efficacy of risankizumab reached a plateau following the subcutaneous administration of 150 mg risankizumab at Week 0, Week 4, then at 12-week intervals, and that a further increase in dose or a decrease in the interval would provide only a marginal increase in efficacy.

Table 22. Estimated achievement rates of PASI 90 and PASI 100 following administration of risankizumab at Week 0, 4, and 16 to patients with plaque psoriasis

Dose (mg)	PASI 90 achievement rate (%)			PASI 100 achievement rate (%)		
	Week 12	Week 16	Week 28	Week 12	Week 16	Week 28
18	58 [49, 66]	63 [56, 70]	65 [57, 73]	34 [25, 42]	39 [32, 48]	43 [35, 50]
90	66 [58, 73]	72 [64, 78]	75 [67, 82]	43 [34, 52]	51 [42, 59]	54 [47, 63]
150	68 [61, 76]	75 [68, 81]	78 [71, 84]	46 [38, 53]	54 [47, 62]	58 [50, 67]
180	68 [61, 76]	75 [68, 81]	79 [72, 85]	46 [39, 53]	55 [46, 62]	59 [51, 67]
300	71 [63, 78]	78 [72, 84]	81 [75, 88]	48 [41, 57]	58 [51, 66]	62 [55, 70]

Median [90% predicated range]

Table 23. Estimated achievement rates of PASI 90 and PASI 100 following administration of risankizumab 150 mg at Week 0, 4, then at 8-, 12- or 16-week intervals

Dosage regimen	PASI 90 achievement rate (%)		PASI 100 achievement rate (%)	
	Week 16	Week 52	Week 16	Week 52
Week 0 and 4, then at 8-week intervals	79 [70, 85]	79 [71, 85]	58 [51, 67]	59 [50, 68]
Week 0 and 4, then at 12-week intervals	75 [68, 81]	77 [70, 84]	54 [45, 62]	57 [50, 65]
Week 0 and 4, then at 16-week intervals	74 [66, 81]	73 [66, 80]	53 [46, 61]	52 [44, 59]

Median [90% predicated range]

For the Japanese clinical studies (Studies M15-988 and M16-004), the applicant considered that the dosage regimen should be "subcutaneous administration of risankizumab 150 mg at Week 0 and 4, then at 12-week intervals," as were the cases with global and foreign phase III studies, for the following reason.

- Table 13 shows pharmacokinetic parameters following a single subcutaneous administration of risankizumab (18, 90, or 300 mg) to Japanese and non-Japanese subjects in Study M16-513 in healthy adults [see Section 6.2.1.1], suggesting a tendency of higher exposure in Japanese subjects than in Caucasian subjects. However, the safety profile in Japanese subjects was favorable within the dose range investigated.

The applicant also selected 75 mg per dose in addition to 150 mg per dose, to confirm the dose-response relationship in the Japanese population.

PMDA accepted the applicant's explanation.

6.R.2 ADA

The applicant's explanation about the occurrences of ADA and the effect of ADA on the pharmacokinetics, efficacy, and safety of risankizumab:

Table 24 shows changes over time in the trough plasma risankizumab concentration in patients with and without ADA in each treatment group in the pooled population of the Japanese phase II/III study (Study M16-004) and 4 global and foreign phase III studies (Studies M15-992, M15-995, M16-008, and M16-010) in patients with plaque psoriasis. The time-course of trough plasma risankizumab concentrations in ADA-positive subjects with antibody titer of <128 and in neutralizing antibody-positive subjects were similar to those in ADA-negative subjects. There were extremely few ADA-positive subjects with antibody titer of ≥128, precluding the evaluation in this subpopulation. In PPK analysis using the data of 9 clinical studies[5)] including those of Japanese studies [see Section 6.2.6.2], ADA titer was identified as a covariate for CL of risankizumab and, in patients with antibody titer of ≥128, CL increased and steady state AUC_{tau} tended to decrease compared to ADA-negative patients and in patients with antibody titer of <128. These results suggest that occurrence of ADA will not generally have any clinically significant effect on the pharmacokinetics of risankizumab.

Table 24. Changes over time in trough plasma risankizumab concentration (μg/mL) in patients with plaque psoriasis in clinical studies, classified by the presence or absence of ADA

Study	Treatment group	ADA	Week 4	Week 16	Week 28	Week 40	Week 52
Study M16-004	75 mg	ADA-positive (antibody titer ≥128)	-	-	-	-	-
		ADA-positive (antibody titer <128)	3.7 ± 1.6 (9)	1.6 ± 0.8 (9)	1.6 ± 0.9 (10)	1.3 ± 0.8 (8)	1.4 ± 0.8 (7)
		ADA-negative	3.5 ± 1.2 (47)	1.4 ± 0.8 (47)	1.2 ± 0.8 (46)	1.2 ± 1.0 (50)	1.0 ± 0.6 (49)
		Neutralizing antibody-positive	2.89, 6.30 (2)	1.16, 2.51 (2)	1.6 ± 0.8 (6)	1.4 ± 0.8 (7)	1.1 ± 0.1 (3)
	150 mg	ADA-positive (antibody titer ≥128)	-	0.69 (1)	-	-	-
		ADA-positive (antibody titer <128)	5.7 ± 2.7 (11)	1.9 ± 1.3 (11)	1.9 ± 1.0 (13)	2.3 ± 2.5 (9)	1.4 ± 0.7 (5)
		ADA-negative	7.0 ± 2.2 (43)	2.7 ± 1.3 (42)	2.4 ± 1.1 (41)	2.2 ± 0.9 (46)	2.1 ± 1.3 (49)
		Neutralizing antibody-positive	1.83, 2.77 (2)	2.3 ± 2.3 (3)	1.5 ± 0.9 (6)	1.5 ± 1.2 (6)	1.4 ± 0.7 (5)
Pooled population of 4 global and foreign phase III studies	150 mg	ADA-positive (antibody titer ≥128)	3.04, 3.12 (2)	0.4 ± 0.8 (9)	0.4 ± 0.6 (9)	<0.005, 0.825 (2)	0.2 ± 0.3 (3)
		ADA-positive (antibody titer <128)	5.7 ± 2.3 (50)	2.1 ± 1.3 (193)	1.8 ± 1.2 (189)	1.9 ± 2.1 (120)	1.7 ± 1.3 (121)
		ADA-negative	5.7 ± 2.3 (377)	2.3 ± 1.4 (853)	2.1 ± 1.2 (837)	2.0 ± 1.3 (626)	2.0 ± 1.2 (597)
		Neutralizing antibody-positive	5.9 ± 2.3 (22)	1.9 ± 1.2 (62)	1.6 ± 1.2 (66)	1.5 ± 1.8 (53)	1.3 ± 1.2 (35)

Mean ± SD or measured values (n); -, Not applicable

Table 25 shows the efficacy of risankizumab administered subcutaneously at the proposed dosage in the pooled populations of Study M16-004 and 4 global and foreign phase III studies, classified by the presence or absence of ADA. Because of the extremely small number of ADA-positive patients with antibody titer of ≥128, the efficacy in this subpopulation could not be evaluated.

Table 25. Efficacy of risankizumab in clinical studies in patients with plaque psoriasis, classified by presence or absence of ADA (non-responder imputation [NRI])

		Week 16				Week 52[a)]			
			ADA-positive				ADA-positive		
		ADA-negative	ADA titer <128	ADA titer ≥128	Neutralizing antibody positive	ADA-negative	ADA titer <128	ADA titer ≥128	Neutralizing antibody positive
Study M16-004	PASI 90 achievement rate	80.5 (33/41)	61.5 (8/13)	0 (0/1)	75.0 (3/4)	97.4 (37/38)	81.3 (13/16)	100 (1/1)	90.9 (10/11)
	sPGA (0/1) achievement rate	97.6 (40/41)	84.6 (11/13)	0 (0/1)	75.0 (3/4)	97.4 (37/38)	87.5 (14/16)	100 (1/1)	100 (11/11)
Pooled population of 4 global and foreign phase III studies	PASI 90 achievement rate	73.9 (782/1058)	75.7 (174/230)	38.5 (5/13)	69.9 (72/103)	82.7 (377/456)	77.9 (106/136)	50.0 (3/6)	75.6 (59/78)
	sPGA (0/1) achievement rate	84.7 (896/1058)	86.1 (198/230)	53.8 (7/13)	81.6 (84/103)	84.4 (385/456)	88.2 (120/136)	33.3 (2/6)	85.9 (67/78)

% (n/N)

a) The rates in the pooled population of 4 global and foreign phase III studies were calculated from the data of Studies M15-995 and M16-008.

Table 26 shows the incidences of all adverse events, hypersensitivity reactions, and injection site reactions observed in the pooled population of Study M16-004 and 4 global and foreign phase III studies, classified by the presence or absence of ADA. ADA had no clear effect on the safety.

Table 26. Safety in patients with plaque psoriasis, classified by the presence or absence of ADA, in clinical studies of risankizumab

		ADA-negative	ADA-positive		
			ADA titer <128	ADA titer ≥128	Neutralizing antibody positive
Study M16-004	All adverse events	79.1 (102/129)	75.7 (28/37)	100 (1/1)	70.4 (19/27)
	Hypersensitivity reactions[a)]	11.6 (15/129)	8.1 (3/37)	0 (0/1)	3.7 (1/27)
	Injection site reactions[b)]	0 (0/129)	2.7 (1/37)	0 (0/1)	3.7 (1/27)
Pooled population of 4 global and foreign phase III studies	All adverse events	73.6 (893/1213)	78.4 (279/356)	85.7 (18/21)	77.4 (171/221)
	Hypersensitivity reactions[a)]	6.4 (78/1213)	7.6 (27/356)	19 (4/21)	7.7 (17/221)
	Injection site reaction[b)]	3.5 (42/1213)	4.5 (16/356)	4.8 (1/21)	5.0 (11/221)

% (n/N)

a) Events classified as "Hypersensitivity" in Standardised Medical dictionary for regulatory activities (MedDRA) queries (SMQ)

b) Events classified as "Injection Site Reactions" according to the MedDRA Query defined by the applicant.

Because of the limited number of ADA-positive patients, it is practically impossible to draw a conclusion on the effect of ADA and neutralizing antibodies on the efficacy and safety of risankizumab. However, the available results do not suggest any clear effect of ADA or neutralizing antibodies on the efficacy or safety of risankizumab.

PMDA's view:

Due to the limited number of ADA-positive subjects, it is difficult to draw any conclusion on the effect of ADA and neutralizing antibodies on the efficacy and safety of risankizumab. However, since PPK analysis suggested a decrease in the exposure to risankizumab as a result of the occurrence of high-titer ADA, the possible effects of ADA on the pharmacokinetics and efficacy of risankizumab cannot be ruled out. Using the package insert, the applicant should appropriately disseminate

information on the occurrence of ADA in clinical studies of risankizumab, the effect of ADA on risankizumab exposure, the efficacy and safety, etc. The applicant should monitor occurrence of ADA after the market launch and provide new findings without delay to healthcare professionals.

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

The applicant submitted pivotal efficacy and safety evaluation data, in the form of results data from 5 studies shown in Table 27.

Table 27. Submitted pivotal data

Phase	Study (data category)	Region	Patient population	No. of patients	Outline of dosage regimen (subcutaneous administration in all patients)	Main endpoints
II	M16-002 (evaluation)	Global	Patients with active PsA	(a) 20 (b) 39 (c) 42 (d)42 (e) 42	(a) Risankizumab (75 mg) at Week 0 (b) Risankizumab (150 mg) at Week 0 and 12 (c) Risankizumab (150 mg) at Week 0, 4, and 16 (d) Risankizumab (150 mg) at 4-week intervals (e) Placebo	Efficacy Safety
II/III	M16-004 (evaluation)	Japan	Patients with moderate to severe plaque psoriasis	(a) 58 (b) 55 (c) 58	(a) Risankizumab (75 mg) at Week 0 and 4, then at 12-week intervals (b) Risankizumab (150 mg) at Week 0 and 4, then at 12-week intervals (c) Placebo[a)]	Efficacy Safety
III	M15-988 (evaluation)	Japan	Patients with GPP or EP	GPP: (a) 4, (b) 4 EP: (a) 5, (b) 4	(a) Risankizumab (75 mg) at Week 0 and 4, then at 12-week intervals[b)] (b) Risankizumab (150 mg) at Week 0 and 4, then at 12-week intervals	Efficacy Safety
	M16-008 (evaluation)	Global	Patients with moderate to severe plaque psoriasis	(a) 304 (b) 100 (c) 102	(a) Risankizumab (150 mg) at Week 0 and 4, then at 12-week intervals (b) UST at Week 0 and 4, then at 12-week intervals[c)] (c) Placebo[d)]	Efficacy Safety
	M15-992 (evaluation)	Global	Patients with moderate to severe plaque psoriasis	(a) 407 (b) 100	Risankizumab 150 mg (a) or placebo (b) at Week 0 and 4, followed by risankizumab 150 mg at Week 16[e)]	Efficacy Safety

a) Placebo was administered at Week 0 and 4, followed by administration of risankizumab (75 or 150 mg) at Week 16, 28, and 40.
b) If response was inadequate, risankizumab (150 mg) was administered at 12-week intervals from Week 16.
c) 45 mg if the body weight at the screening was ≤100 kg, 90 mg if >100 kg
d) Placebo was administered at Week 0 and 4, followed by administration of risankizumab (150 mg) at Week 16, 28, and 40.
e) Administration after Week 16:
Risankizumab 150 mg or placebo at 12-week intervals if sPGA score was 0 or 1 at Week 28.
Risankizumab 150 mg at 12-week intervals if sPGA score was ≥2 at Week 28.

7.1 Phase II study

7.1.1 Global study in patients with active PsA (CTD 5.3.5.1-2, Study M16-002 [May 2016 to August 2017])

A placebo-controlled, randomized, double-blind, parallel-group study in patients with active PsA[9)] (target sample size, 180 patients [20 in the 75 mg group, 40 in each of other groups]) was conducted to

9) Main inclusion criteria: Patients who met all of the following:
(a) diagnosed with PsA according to "Classification criteria for psoriatic arthritis" (CASPAR) criteria (patients who have inflammatory joint disease [arthritis, spondylitis, or enthesitis] and have a total score of ≥3 points in the following: (1) currently suffering from psoriasis [2 points] or has a past or family history of psoriasis [1 point]; (2) psoriatic nail lesion [1 point]; (3) rheumatoid factor negative [1 point]; (4) dactylitis [1 point]; and (5) new bone formation near the hand or foot joint revealed by radiography [1 point])
(b) PsA symptoms for ≥6 months,
(c) tender joint count and swollen joint count are both ≥5, and
(d) inadequately responsive or intolerant to treatment with nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic agents, or TNF inhibitors.

investigate the efficacy and safety of risankizumab in 11 countries or regions including Japan, the US, Poland, and Germany.

The study drug was administered at the following dosage:

- 75 mg group: Subcutaneous administration of risankizumab (75 mg) at Week 0
- 150 mg Q12W group: Subcutaneous administration of risankizumab (150 mg) at Week 0 and 12
- 150 mg LD Q12W group: Subcutaneous administration of risankizumab (150 mg) at Week 0, 4, and 16
- 150 mg Q4W group: Subcutaneous administration of risankizumab (150 mg) at 4-week intervals
- Placebo group: Subcutaneous administration of placebo at 4-week intervals

Of 185 randomized patients (20 in the 75 mg group, 39 in the 150 mg Q12W group, 42 in the 150 mg LD Q12W group, 42 in the 150 mg Q4W group, 42 in the placebo group), all of patients who received at least 1 dose of the study drug were included in the full analysis set (FAS) and the safety analysis population, and FAS was handled as the population for efficacy analysis. Study discontinuation occurred in 10.0% (2 of 20) of patients in the 75 mg group, 5.1% (2 of 39) of patients in the 150 mg Q12W group, 7.1% (3 of 42) of patients in the 150 mg LD Q12W group, 9.5% (4 of 42) of patients in the 150 mg Q4W group, and 2.4% (1 of 42) of patients in the placebo group. The main reasons for the discontinuation were adverse events (10.0% [2 of 20] of patients in the 75 mg group, 4.8% [2 of 42] of patients in the 150 mg Q4W group, 2.4% [1 of 42] of patients in the placebo group) and subjects' request (2.6% [1 of 39] of patients in the 150 mg Q12W group, 4.8% [2 of 42] of patients in the 150 mg LD Q12W group, 4.8% [2 of 42] of patients in the 150 mg Q4W group).

The Japanese subpopulation in FAS consisted of 14 patients (3 in the 75 mg group, 3 in the 150 mg Q12W group, 2 in the 150 mg LD Q12W group, 3 in the 150 mg Q4W group, 3 in the placebo group), and none of them discontinued the treatment.

Table 28 shows an American college of rheumatology (ACR) 20 response rate at Week 16, the primary efficacy endpoint. The paired comparison between the placebo group and the combined 150 mg LD Q12W/Q4W group was conducted as the primary comparison.

Table 28. ACR20 response rate at Week 16 (FAS, NRI)

		75 mg	150 mg Q12W	150 mg LD Q12W	150 mg Q4W	150 mg LD Q12W/150 mg Q4W combined	Placebo
Entire population	ACR 20 response rate	65.0 (13/20)	59.0 (23/39)	61.9 (26/42)	57.1 (24/42)	59.5 (50/84)	35.7 (15/42)
	Difference from placebo[a] [90% CI][a]	28.5 [7.7, 49.4]	23.1 [5.7, 40.4]	26.4 [9.8, 43.0]	21.8 [4.6, 39.1]	24.0 [9.3, 38.7]	
Japanese subpopulation	ACR 20 response rate	100 (3/3)	33.3 (1/3)	100 (2/2)	100 (3/3)	100 (5/5)	0 (0/3)

% (n/N)

a) Estimate by Cochran-Mantel-Haenszel method, stratified by prior treatment with TNF inhibitor and concomitant methotrexate (MTX) use

Adverse events were observed in 65.0% (13 of 20) of patients in the 75 mg group, 69.2% (27 of 39) of patients in the 150 mg Q12W group, 52.4% (22 of 42) of patients in the 150 mg LD Q12W group, 64.3% (27 of 42) of patients in the 150 mg Q4W group, and 73.8% (31 of 42) of patients in the placebo group. Table 29 shows the main adverse events.

No death occurred. Serious adverse events were observed in 15.0% (3 of 20) of patients in the 75 mg group, 5.1% (2 of 39) of patients in the 150 mg Q12W group, 7.1% (3 of 42) of patients in the 150 mg Q4W group, and 4.8% (2 of 42) of patients in the placebo group. A causal relationship to the study drug could not be ruled out in 1 patient in the 75 mg group (influenza/sepsis/urinary tract infection), 2 patients in the 150 mg Q12W group (alanine aminotransferase [ALT] increased/aspartate aminotransferase [AST] increased/blood bilirubin increased, and rotator cuff syndrome), and 1 patient in the 150 mg Q4W group (anaphylactic reaction). Adverse events leading to treatment discontinuation were observed in 5.0% (1 of 20) of patients in the 75 mg group, 7.1% (3 of 42) of patients in the 150 mg Q4W group, and 4.8% (2 of 42) of patients in the placebo group. Adverse drug reactions were observed in 20.0% (4 of 20) of patients in the 75 mg group, 20.5% (8 of 39) of patients in the 150 mg Q12W group, 16.7% (7 of 42) of patients in the 150 mg LD Q12W group, 19.0% (8 of 42) of patients in the 150 mg Q4W group, and 19.0% (8 of 42) of patients in the placebo group.

Table 29. Adverse events reported by ≥2 patients in any group (safety analysis population)

Event	75 mg (N = 20)	150 mg Q12W (N = 39)	150 mg LD Q12W (N = 42)	150 mg Q4W (N = 42)	Placebo (N = 42)
Viral upper respiratory tract infection	4 (20.0)	9 (23.1)	5 (11.9)	7 (16.7)	2 (4.8)
Headache	1 (5.0)	3 (7.7)	1 (2.4)	3 (7.1)	3 (7.1)
Cough	0	1 (2.6)	1 (2.4)	3 (7.1)	2 (4.8)
Fatigue	0	1 (2.6)	1 (2.4)	3 (7.1)	0
Upper respiratory tract infection	1 (5.0)	2 (5.1)	3 (7.1)	2 (4.8)	5 (11.9)
Back pain	1 (5.0)	0	2 (4.8)	2 (4.8)	1 (2.4)
Psoriatic arthritis	0	0	1 (2.4)	2 (4.8)	0
Vomiting	0	1 (2.6)	0	2 (4.8)	0
Injection site erythema	0	1 (2.6)	0	2 (4.8)	0
Oral herpes	0	1 (2.6)	0	2 (4.8)	0
Spinal pain	0	1 (2.6)	0	2 (4.8)	0
Asthenia	0	0	0	2 (4.8)	0
Sinusitis	0	2 (5.1)	2 (4.8)	1 (2.4)	0
Influenza	1 (5.0)	2 (5.1)	1 (2.4)	1 (2.4)	0
Bronchitis	1 (5.0)	1 (2.6)	1 (2.4)	1 (2.4)	3 (7.1)
Psoriasis	0	0	0	1 (2.4)	3 (7.1)
Oropharyngeal pain	0	0	0	1 (2.4)	2 (4.8)
ALT increased	1 (5.0)	3 (7.7)	1 (2.4)	0	1 (2.4)
AST increased	1 (5.0)	2 (5.1)	1 (2.4)	0	0
Abdominal pain	0	2 (5.1)	1 (2.4)	0	1 (2.4)
Hypertension	0	1 (2.6)	1 (2.4)	0	3 (7.1)
Pharyngitis	0	2 (5.1)	0	0	1 (2.4)
Rotator cuff syndrome	0	2 (5.1)	0	0	0
Pain in extremity	0	0	0	0	3 (7.1)

n (%)

In the Japanese subpopulation, adverse events were observed in 2 patients in the 75 mg group (viral upper respiratory tract infection and haematuria in 1 patient each), 1 patient in the 150 mg Q12W group (stomatitis), 1 patient in the 150 mg LD Q12W group (viral upper respiratory tract

infection/back pain/cough), 3 patients in the 150 mg Q4W group (influenza, upper respiratory tract infection/periodontitis/trichophytosis/acne, and dry skin), and 1 patient in the placebo group (paronychia/upper respiratory tract infection/dry skin/hypertension).

There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation. An adverse drug reaction was observed in 1 patient in the 75 mg group (haematuria).

7.2 Phase II/III study

7.2.1 Japanese study in patients with plaque psoriasis (CTD 5.3.5.1-3 and 5.3.5.1-3-2, Study M16-004 [December 2016 to June 2018])

A placebo-controlled, randomized, double-blind, parallel-group study in Japanese patients with moderate to severe plaque psoriasis[10] (target sample size, 168 patients [56 in the 75 mg group, 56 in the 150 mg group, 28 in the placebo/75 mg group, 28 in the placebo/150 mg group]) was conducted to investigate the efficacy and safety of risankizumab.

The study consisted of 2 periods (Part A, up to Week 16; Part B, from Week 16 to 52). In Part A, risankizumab (75 mg or 150 mg) or placebo was administered subcutaneously at Week 0 and 4. In Part B, patients received subcutaneous risankizumab at 12-week intervals: (a) patients who had received risankizumab in Part A were treated with the same dose, and (b) patients who had received placebo in Part A were treated with 75 or 150 mg.

All of the 171 randomized patients (58 in the 75 mg group, 55 in the 150 mg group, 58 in the placebo group [sum of the placebo/75 mg group and placebo/150 mg group]) were included in the Intent-to-treat (ITT) population of Part A. Among the patients in the ITT, all of patients who received at least 1 dose of the study drug were included in the safety analysis population. The ITT population was handled as the population for efficacy analysis. In Part A, treatment discontinuation occurred in 6.9% (4 of 58) of patients in the placebo group. The reason for the discontinuation was adverse events in all of them.

Table 30 shows a PASI 90 achievement rate at Week 16, the primary efficacy endpoint. The paired comparison between the placebo group and the 75 mg group and between the placebo group and the 150 mg group showed a statistically significant difference, demonstrating the superiority of both 75 and 150 mg to placebo.

[10] Main inclusion criteria: Patients with psoriasis who met all of the following: (a) chronic plaques lasting for ≥6 months, (b) PASI score ≥12, (c) sPGA score ≥3, and (d) psoriatic lesion ≥10% of body surface area (BSA).

Table 30. PASI 90 achievement rate at Week 16 (ITT population, NRI)

	75 mg	150 mg	Placebo
PASI 90 achievement rate	75.9 (44/58)	74.5 (41/55)	1.7 (1/58)
Difference from placebo[a)] [95% CI][a)] *P* value[b)]	73.6 [62.2, 85.0] *P* < 0.001	72.4 [60.6, 84.1] *P* < 0.001	

% (n/N)

a) Estimate by Cochran-Mantel-Haenszel method stratified by presence/absence of PsA at baseline and body weight

b) Significance level 5% (two-sided), Cochran-Mantel-Haenszel test stratified by presence/absence of PsA at baseline and body weight. Multiplicity of test adjusted by the closed testing procedure

In Part A, adverse events were observed in 51.7% (30 of 58) of patients in the 75 mg group, 56.4% (31 of 55) of patients in the 150 mg group, and 56.9% (33 of 58) of patients in the placebo group. Table 31 shows main adverse events.

No death occurred. Serious adverse events were observed in 3.4% (2 of 58) of patients in the 75 mg group, 3.6% (2 of 55) of patients in the 150 mg group, and 1.7% (1 of 58) of patients in the placebo group. A causal relationship to the study drug could not be ruled out in 1 patient in the 75 mg group (hypotension), 1 patient in the 150 mg group (acute myocardial infarction), and 1 patient in the placebo group (pneumonia bacterial). Adverse events leading to treatment discontinuation were observed in 3.4% (2 of 58) of patients in the 75 mg group, 1.8% (1 of 55) of patients in the 150 mg group, and 6.9% (4 of 58) of patients in the placebo group. Adverse drug reactions were observed in 17.2% (10 of 58) of patients in the 75 mg group, 12.7% (7 of 55) of patients in the 150 mg group, and 6.9% (4 of 58) of patients in the placebo group.

Table 31. Adverse events reported by ≥2 patients in any group (Part A, safety analysis population)

Event	75 mg (N = 58)	150 mg (N = 55)	Placebo (N = 58)
Nasopharyngitis	3 (5.2)	10 (18.2)	8 (13.8)
Arthralgia	0	2 (3.6)	1 (1.7)
Folliculitis	2 (3.4)	1 (1.8)	1 (1.7)
Back pain	2 (3.4)	1 (1.8)	1 (1.7)
Conjunctivitis	2 (3.4)	1 (1.8)	0
Hyperlipidaemia	2 (3.4)	1 (1.8)	0
Diarrhoea	0	1 (1.8)	2 (3.4)
Gastroenteritis	0	1 (1.8)	2 (3.4)
Psoriasis	3 (5.2)	0	9 (15.5)
Diabetes mellitus	3 (5.2)	0	1 (1.7)
Hepatic function abnormal	2 (3.4)	0	0
Pharyngitis	2 (3.4)	0	0
Skin papilloma	2 (3.4)	0	0
Cough	2 (3.4)	0	0
Tinea pedis	1 (1.7)	0	2 (3.4)
Inflammation	0	0	2 (3.4)
Upper respiratory tract infection	0	0	2 (3.4)
Dermal cyst	0	0	2 (3.4)

n (%)

Of 167 patients who had completed Part A (58 in the 75 mg group, 55 in the 150 mg group, 54 in the placebo group), 164 patients who received at least 1 dose of the study drug in Part B (56 in the 75 mg group, 54 in the 150 mg group, 27 in the placebo/75 mg group, 27 in the placebo/150 mg group) were included in the safety analysis population in Part B. Treatment discontinuation in Part B occurred in 3.7% (1 of 27) of patients (adverse event) in the placebo/150 mg group.

In Part B, adverse events were observed in 62.5% (35 of 56) of patients in the 75 mg group, 57.4% (31 of 54) of patients in the 150 mg group, 66.7% (18 of 27) of patients in the placebo/75 mg group, and 85.2% (23 of 27) of patients in the placebo/150 mg group. Table 32 shows the main adverse events.

No death occurred. Serious adverse events were observed in 1.8% (1 of 56) of patients in the 75 mg group, 1.9% (1 of 54) of patients in the 150 mg group, and 7.4% (2 of 27) of patients in the placebo/75 mg group. A causal relationship to the study drug could not be ruled out in 1 patient in the 150 mg group (rectal polyp) and 1 patient in the placebo/75 mg group (rectal cancer). Adverse events leading to treatment discontinuation were observed in 3.7% (1 of 27) of patients in the placebo/150 mg group. Adverse drug reactions were observed in 10.7% (6 of 56) of patients in the 75 mg group, 13.0% (7 of 54) of patients in the 150 mg group, 25.9% (7 of 27) of patients in the placebo/75 mg group, and 22.2% (6 of 27) of patients in the placebo/150 mg group.

Table 32. Adverse events reported by ≥2 patients in any group (Part B, safety analysis population)

Event	75 mg (N = 56)	150 mg (N = 54)	Placebo/75 mg (N = 27)	Placebo/150 mg (N = 27)
Nasopharyngitis	12 (21.4)	11 (20.4)	8 (29.6)	8 (29.6)
Dental caries	1 (1.8)	4 (7.4)	0	1 (3.7)
Tinea pedis	0	3 (5.6)	0	1 (3.7)
Blood triglycerides increased	0	3 (5.6)	0	0
Influenza	3 (5.4)	2 (3.7)	1 (3.7)	1 (3.7)
Folliculitis	2 (3.6)	2 (3.7)	0	0
Rib fracture	0	2 (3.7)	0	1 (3.7)
Insomnia	0	2 (3.7)	0	0
Leukopenia	0	2 (3.7)	0	0
Haemorrhoids	0	2 (3.7)	0	0
Weight increased	3 (5.4)	1 (1.9)	0	1 (3.7)
Back pain	2 (3.6)	1 (1.9)	2 (7.4)	1 (3.7)
Urticaria	2 (3.6)	1 (1.9)	1 (3.7)	1 (3.7)
Vomiting	0	1 (1.9)	0	2 (7.4)
Asthma	0	1 (1.9)	2 (7.4)	0
Pharyngitis	3 (5.4)	0	1 (3.7)	1 (3.7)
Hepatic function abnormal	3 (5.4)	0	0	0
Gingivitis	2 (3.6)	0	0	0
Benign prostatic hyperplasia	2 (3.6)	0	0	0
Arthralgia	0	0	3 (11.1)	3 (11.1)
Asteatosis	0	0	2 (7.4)	0
Oral herpes	0	0	0	2 (7.4)

n (%)

7.3 Phase III studies

7.3.1 Japanese study in patients with GPP or EP (CTD 5.3.5.1-8 and 5.3.5.1-8-2, Study M15-988 [ongoing since January 2017 (data cut-off [redacted] 20[redacted]; data collected up to Week 52)])

A randomized, open-label, parallel-group study in patients with GPP[11] or EP[12] (target sample size, 16 patients [8 each of GPP and EP]) was conducted to investigate the efficacy and safety of risankizumab.

[11] Main inclusion criteria: Patients who met all of the following: (a) Diagnosis of GPP ≥60 days before based on GPP diagnostic criteria of Japanese dermatological association (JDA), (b) area of pustular erythema ≥10% of BSA, (c) JDA severity index score <14, and (d) eligible for systemic therapy or phototherapy

Risankizumab (75 or 150 mg) was administered subcutaneously at Week 0 and 4, then at 12-week intervals. Patients who received 75 mg but did not achieve clinical efficacy against GPP/EP were allowed to increase the dose to 150 mg after Week 16.

Of 17 randomized patients (4 in the GPP 75 mg group, 4 in the GPP 150 mg group, 5 in the EP 75 mg group, 4 in the EP 150 mg group), all of patients who received at least 1 dose of the study drug were included in the ITT population and the safety analysis population, and the ITT population was handled as the population for efficacy analysis. Treatment discontinuation occurred in 1 patient in the GPP 75 mg group (patient's request) and in 2 patients in the GPP 150 mg group (adverse event in one patient and patient's request in the other).

Clinical efficacy against GPP/EP at Week 16, the primary efficacy endpoint, was achieved in all patients in all treatment groups (4 of 4 patients in the GPP 75 mg group, 4 of 4 patients in the GPP 150 mg group, 5 of 5 patients in the EP 75 mg group, 4 of 4 patients in the EP 150 mg group; ITT population, non-responder imputation [NRI]).

Adverse events were observed in all patients except in 2 patients in the EP 75 mg group. Main adverse events were viral upper respiratory tract infection (1 patient in the GPP 75 mg group, 1 patient in the GPP 150 mg group, 3 patients in the EP 75 mg group, 3 patients in the EP 150 mg group), constipation (1 patient in the GPP 150 mg group, 1 patient in the EP 75 mg group), hepatic function abnormal (1 patient in the GPP 75 mg group, 1 patient in the GPP 150 mg group), otitis media (2 patients in the EP 150 mg group), dehydration (2 patients in the GPP 150 mg group), acne (1 patient in the GPP 150 mg group, 1 patient in the EP 150 mg group), and rash (1 patient in the GPP 75 mg group, 1 patient in the GPP 150 mg group).

No death occurred. Serious adverse events were observed in 2 patients in the GPP 150 mg group, 1 patient in the EP 75 mg group, and 1 patient in the EP 150 mg group. Their causal relationship to the study drug was ruled out. Adverse events leading to treatment discontinuation were observed in 2 patients in the GPP 150 mg group. Adverse drug reactions were observed in 2 patients in the GPP 75 mg group, 1 patient in the GPP 150 mg group, and 2 patients in the EP 150 mg group.

7.3.2 Global study in patients with plaque psoriasis (CTD 5.3.5.1-4, Study M16-008 [February 2016 to September 2017])

A placebo-controlled, randomized, double-blind, parallel-group study in patients with moderate to severe plaque psoriasis[10)] (target sample size, 500 patients [300 in the 150 mg group, 100 each in the placebo and UST groups]) was conducted to investigate the efficacy and safety of risankizumab in 8 countries or regions including Japan, the US, and Canada.

[12)] Main inclusion criteria: Patients who met both of the following: (a) Diagnosis of EP with area of pustular erythema ≥80% of BSA, and (b) eligible for systemic therapy or phototherapy

The study consisted of 2 periods (Part A, up to Week 16; Part B, Week 16 to 52), In Part A, risankizumab (150 mg), UST,[13,14] or placebo was administered subcutaneously at Week 0 and 4. In Part B, (a) patients who had received risankizumab 150 mg or UST in Part A were treated with the same drug at the same dose at 12-week intervals, and (b) patients who had received placebo in Part A were treated with risankizumab 150 mg at 12-week intervals.

A total of 506 randomized patients in Part A (304 in the 150 mg group, 102 in the placebo group, 100 in the UST group) were included in the ITT population. Of the patients in the ITT population, all who received at least 1 dose of the study drug were included in the safety analysis population. The ITT population was handled as the population for efficacy analysis.

In Part A, treatment discontinuation occurred in 1.6% (5 of 304) of patients in the 150 mg group, 3.9% (4 of 102) of patients in the placebo group, and 1.0% (1 of 100) of patients in the UST group. The main reasons for the discontinuation were patient's request (1.0% [1 of 102] of patients in the placebo group, 1.0% [1 of 100] of patients in the UST group), adverse events (0.3% [1 of 304] of patients in the 150 mg group, 2.0% [2 of 102] of patients in the placebo group), and lost to follow-up (1.0% [3 of 304] of patients in the 150 mg group, 1.0% [1 of 102] of patients in the placebo group).

A PASI 90 achievement rate and sPGA (0/1) achievement rate at Week 16 were defined as the co-primary efficacy endpoints. Table 33 shows the results. The paired comparison between the placebo group and the 150 mg group, which was conducted as the main comparison, revealed a statistically significant difference in both primary endpoints, demonstrating the superiority of 150 mg to placebo. Table 34 shows the results in the Japanese subpopulation.

Table 33. PASI 90 achievement rate and sPGA (0/1) achievement rate at Week 16 (ITT population, NRI)

	150 mg	Placebo	UST
PASI 90 achievement rate	75.3 (229/304)	4.9 (5/102)	42.0 (42/100)
Difference from placebo[a)] [95% CI][a)] *P* value[b)]	70.3 [64.0, 76.7] *P* < 0.001		
sPGA (0/1) achievement rate	87.8 (267/304)	7.8 (8/102)	63.0 (63/100)
Difference from placebo[a)] [95% CI][a)] *P* value[b)]	79.9 [73.5, 86.3] *P* < 0.001		

% (n/N)
a) Estimate by Cochran-Mantel-Haenszel method stratified by body weight and prior treatment with TNF inhibitor
b) Significance level 5% (two-sided), Cochran-Mantel-Haenszel test stratified by body weight and prior treatment with TNF inhibitor

13) The 45 mg dose was administered to patients weighing ≤100 kg at screening, and the 90 mg dose to patients weighing >100 kg.
14) All Japanese patients weighed ≤100 kg and therefore received the 45 mg dose.

Table 34. PASI 90 achievement rate and sPGA (0/1) achievement rate at Week 16 (Japanese subpopulation, NRI)

	150 mg	Placebo	UST
PASI 90 achievement rate	77.4 (24/31)	0 (0/9)	40.0 (4/10)
Difference from placebo[a)] [95% CI][a)]	76.0 [59.2, 92.9]		
sPGA (0/1) achievement rate	90.3 (28/31)	0 (0/9)	90.0 (9/10)
Difference from placebo[a)] [95% CI][a)]	87.2 [73.3, 101.1]		

% (n/N)

a) Estimate by Cochran-Mantel-Haenszel method stratified by body weight and prior treatment with TNF inhibitor

In Part A, adverse events were observed in 49.7% (151 of 304) of patients in the 150 mg group, 51.0% (52 of 102) of patients in the placebo group, and 50.0% (50 of 100) of patients in the UST group. Table 35 shows main adverse events observed.

No death occurred. Serious adverse events were observed in 2.3% (7 of 304) of patients in the 150 mg group, 2.9% (3 of 102) of patients in the placebo group, and 8.0% (8 of 100) of patients in the UST group. A causal relationship to the study drug could not be ruled out in 1 patient in the 150 mg group (drug-induced liver injury) and 3 patients in the UST group (sinusitis, post herpetic neuralgia, and suicidal ideation). Adverse events leading to treatment discontinuation were observed in 0.7% (2 of 304) of patients in the 150 mg group, 3.9% (4 of 102) of patients in the placebo group, and 2.0% (2 of 100) of patients in the UST group. Adverse drug reactions were observed in 11.8% (36 of 304) of patients in the 150 mg group, 13.7% (14 of 102) of patients in the placebo group, and 11.0% (11 of 100) of patients in the UST group.

Table 35. Adverse events reported by ≥3% of patients in any group (Part A, safety analysis population)

Event	150 mg (N = 304)	Placebo (N = 102)	UST (N = 100)
Viral upper respiratory tract infection	20 (6.6)	6 (5.9)	6 (6.0)
Upper respiratory tract infection	17 (5.6)	2 (2.0)	6 (6.0)
Fatigue	9 (3.0)	1 (1.0)	3 (3.0)
Headache	9 (3.0)	2 (2.0)	2 (2.0)
Arthralgia	8 (2.6)	4 (3.9)	2 (2.0)
Pruritus	3 (1.0)	0	3 (3.0)
Injection site reaction	0	0	3 (3.0)
Psoriasis	0	6 (5.9)	1 (1.0)

n (%)

In the Japanese subpopulation of Part A, adverse events were observed in 64.5% (20 of 31) of patients in the 150 mg group, 77.8% (7 of 9) of patients in the placebo group, and 40.0% (4 of 10) of patients in the UST group. Main adverse events observed were viral upper respiratory tract infection (16.1% [5 of 31] of patients in the 150 mg group, 11.1% [1 of 9] of patients in the placebo group, 20.0% [2 of 10] of patients in the UST group), eczema (12.9% [4 of 31] of patients in the 150 mg group), arthropod bite (9.7% [3 of 31] of patients in the 150 mg group), and psoriasis (33.3% [3 of 9] of patients in the placebo group).

No death occurred. Serious adverse events were observed in 20.0% (2 of 10) of patients in the UST group. Of these, a causal relationship between sinusitis and the study drug could not be ruled out.

Adverse events leading to treatment discontinuation were observed in 3.2% (1 of 31) of patients in the 150 mg group and in 11.1% (1 of 9) of patients in the placebo group. Adverse drug reactions were observed in 12.9% (4 of 31) of patients in the 150 mg group, 33.3% (3 of 9) of patients in the placebo group, and 20.0% (2 of 10) of patients in the UST group.

Of 496 patients who completed Part A (299 in the 150 mg group, 98 in the placebo group, 99 in the UST group), 493 patients (297 in the 150 mg group, 97 in the placebo/150 mg group, 99 in the UST group) who received at least 1 dose of the study drug in Part B, were included in the safety analysis population of Part B. In Part B, treatment discontinuation occurred in 2.7% (8 of 297) of patients in the 150 mg group, 2.1% (2 of 97) of patients in the placebo/150 mg group, and 5.1% (5 of 99) of patients in the UST group. Main reasons for the discontinuation were lost to follow-up (1.7% [5 of 297] of patients in the 150 mg group, 1.0% [1 of 97] of patients in the placebo/150 mg group, 2.0% [2 of 99] of patients in the UST group) and patient's request (0.7% [2 of 297] of patients in the 150 mg group, 1.0% [1 of 97] of patients in the placebo/150 mg group, 1.0% [1 of 99] of patients in the UST group).

In Part B, adverse events were observed in 61.3% (182 of 297) of patients in the 150 mg group, 67.0% (65 of 97) of patients in the placebo/150 mg group, and 66.7% (66 of 99) of patients in the UST group. Table 36 shows main adverse events observed.

No death occurred. Serious adverse events were observed in 5.4% (16 of 297) of patients in the 150 mg group, 3.1% (3 of 97) of patients in the placebo/150 mg group, and 4.0% (4 of 99) of patients in the UST group. A causal relationship to the study drug could not be ruled out in 1 patient in the 150 mg group (pyelonephritis/sepsis) and in 1 patient in the placebo/150 mg group (cellulitis/osteomyelitis/wound complication). There were no adverse events leading to treatment discontinuation. Adverse drug reactions were observed in 12.5% (37 of 297) of patients in the 150 mg group, 11.3% (11 of 97) of patients in the placebo/150 mg group, 15.2% (15 of 99) of patients in the UST group.

Table 36. Adverse events reported by ≥3% of patients in any group (Part B, safety analysis population)

Event	150 mg (N = 297)	Placebo/150 mg (N = 97)	UST (N = 99)
Viral upper respiratory tract infection	40 (13.5)	15 (15.5)	18 (18.2)
Upper respiratory tract infection	30 (10.1)	8 (8.2)	11 (11.1)
Arthralgia	8 (2.7)	4 (4.1)	4 (4.0)
Gastroenteritis	6 (2.0)	1 (1.0)	3 (3.0)
Headache	5 (1.7)	3 (3.1)	5 (5.1)
Bronchitis	4 (1.3)	2 (2.1)	3 (3.0)
Urinary tract infection	3 (1.0)	0	5 (5.1)
Gastrooesophageal reflux disease	3 (1.0)	0	3 (3.0)
Hypertension	2 (0.7)	3 (3.1)	1 (1.0)
Nasopharyngitis	2 (0.7)	3 (3.1)	1 (1.0)
Insomnia	1 (0.3)	3 (3.1)	0

n (%)

In the Japanese subpopulation of Part B, adverse events were observed in 70.0% (21 of 30) of patients in the 150 mg group, 75.0% (6 of 8) of patients in the placebo/150 mg group, and 80.0% (8 of 10) of

patients in the UST group. The main adverse event observed was viral upper respiratory tract infection (30.0% [9 of 30] of patients in the 150 mg group, 25.0% [2 of 8] of patients in the placebo/150 mg group, 60.0% [6 of 10] of patients in the UST group).

No death occurred. Serious adverse events were observed in 3.3% (1 of 30) of patients in the 150 mg group (mitral valve incompetence/Prinzmetal angina), but their causal relationship to the study drug was ruled out. There were no adverse events leading to treatment discontinuation. Adverse drug reactions were observed in 23.3% (7 of 30) of patients in the 150 mg group, 25.0% (2 of 8) of patients in the placebo/150 mg group, and 30.0% (3 of 10) of patients in the UST group.

7.3.3 Global study in patients with plaque psoriasis (CTD 5.3.5.1-5, Study M15-992 [ongoing since March 2016 (data cut-off [redacted] 20[redacted]; data collected up to Week 52)])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients with moderate to severe plaque psoriasis[10] (target sample size, 500 patients [400 in the 150 mg group, 100 in the placebo group]), to investigate the efficacy and safety of risankizumab in 9 countries or regions including Japan, the US, Canada, and Korea.

Figure 3 shows the study design. During the treatment period up to Week 28, patients subcutaneously received (a) risankizumab 150 mg at Week 0, 4 and 16 or (b) placebo at Week 0 and 4 and risankizumab 150 mg at Week 16. From Week 28, patients received, depending on sPGA score at Week 28, risankizumab 150 mg or placebo subcutaneously at 12-week intervals under blinded or unblinded conditions. If patients receiving the study drug under blinded conditions were found to have a sPGA score of 3 (moderate) or 4 (severe) on or after Week 32, they received risankizumab 150 mg) at 12-week intervals under unblinded conditions.

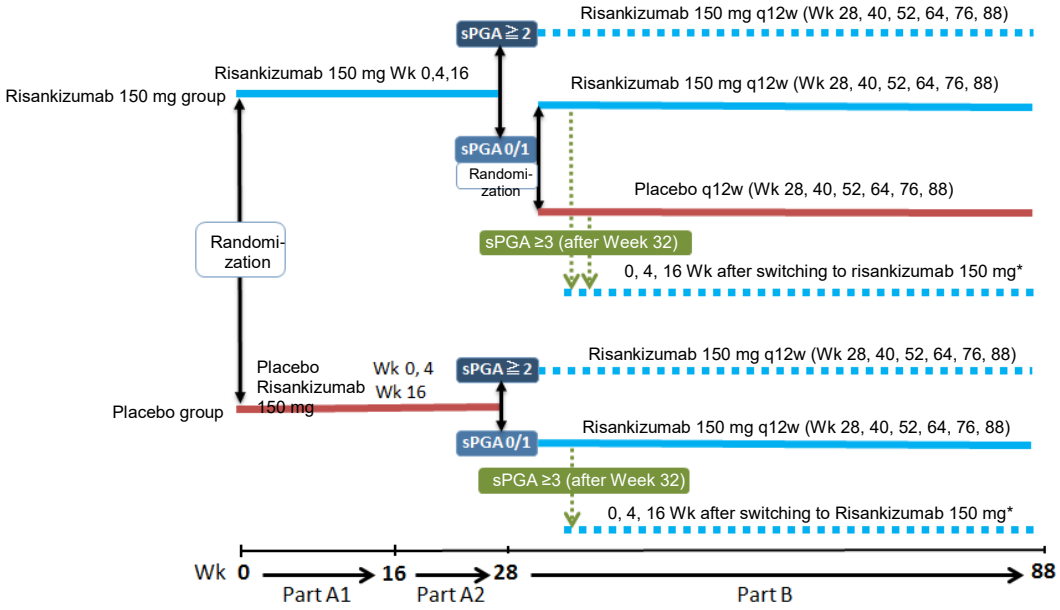


Figure 3. Study design and administration schedule in Study M15-992

Solid lines, blinded; dotted lines, unblinded; Wk, week; q12w, administration at 12-week intervals

* Risankizumab was administered (1) at Week 0, 4, and 16 after switching in patients who switched to risankizumab between Week 32 and 70, (2) at Week 0 and 4 after switching in patients who switched between Week 71 and 82, and (3) at Week 0 after switching in patients who switched at or after Week 83.

During the first 16-week period, all of the 507 randomized patients (407 in the 150 mg group, 100 in the placebo group) were included in the ITT population. Of these, all patients who received at least 1 dose of the study drug were included in the safety analysis population. The ITT population was handled as the population for efficacy analysis.

During the first 16-week period, treatment discontinuation occurred in 1.0% (4 of 407) of patients in the 150 mg group and in 3.0% (3 of 100) of patients in the placebo group. The reasons for the discontinuation were lost to follow-up (0.5% [2 of 407] of patients in the 150 mg group, 1.0% [1 of 100] of patients in the placebo group), adverse events (0.2% [1 of 407] of patients in the 150 mg group, 1.0% [1 of 100] of patients in the placebo group), and patient's request (0.2% [1 of 407] of patients in the 150 mg group, 1.0% [1 of 100] of patients in the placebo group).

A PASI 90 achievement rate and sPGA (0/1) achievement rate at Week 16 were defined as the co-primary efficacy endpoints. Table 37 shows the results. The paired comparison between the placebo group and the 150 mg group revealed a statistically significant difference in both primary endpoints, demonstrating the superiority of 150 mg to placebo. Table 38 shows the results in the Japanese subpopulation.

Table 37. PASI 90 and sPGA (0/1) achievement rates at Week 16 (ITT population, NRI)

	150 mg	Placebo
PASI 90 achievement rate	73.2 (298/407)	2.0 (2/100)
Difference from placebo[a)] [95% CI][a)] *P* value[b)]	70.8 [65.7, 76.0] *P* < 0.001	
sPGA (0/1) achievement rate	83.5 (340/407)	7.0 (7/100)
Difference from placebo[a)] [95% CI][a)] *P* value[b)]	76.5 [70.4, 82.5] *P* < 0.001	

% (n/N)
a) Estimate by Cochran-Mantel-Haenszel method stratified by body weight and prior treatment with TNF inhibitor
b) Significance level 5% (two-sided), Cochran-Mantel-Haenszel test stratified by body weight and prior treatment with TNF inhibitor

Table 38. PASI 90 and sPGA (0/1) achievement rates at Week 16 (ITT population, Japanese subpopulation, NRI)

	150 mg	Placebo
PASI 90 achievement rate	83.3 (10/12)	0 (0/2)
Difference from placebo[a)] [95% CI][a)]	73.7 [35.8, 111.6]	
sPGA (0/1) achievement rate	83.3 (10/12)	0 (0/2)
Difference from placebo[a)] [95% CI][a)]	73.7 [35.8, 111.6]	

% (n/N)
a) Estimate by Cochran-Mantel-Haenszel method stratified by body weight and prior treatment with TNF inhibitor

During the first 16-week period, adverse events were observed in 45.5% (185 of 407) of patients in the 150 mg group and in 48.0% (48 of 100) of patients in the placebo group. Table 39 shows main adverse events observed.

No death occurred. Serious adverse events were observed in 2.0% (8 of 407) of patients in the 150 mg group and in 8.0% (8 of 100) of patients in the placebo group. A causal relationship to the study drug

could not be ruled out in 1 patient in the placebo group (liver injury). Adverse events leading to treatment discontinuation were observed in 0.5% (2 of 407) of patients in the 150 mg group and in 4.0% (4 of 100) of patients in the placebo group. Adverse drug reactions were observed in 8.1% (33 of 407) of patients in the 150 mg group and in 7.0% (7 of 100) of patients in the placebo group.

Table 39. Adverse events reported by ≥3% of patients in either group (up to Week 16, safety analysis population)

Event	150 mg (N = 407)	Placebo (N = 100)
Viral upper respiratory tract infection	21 (5.2)	5 (5.0)
Headache	14 (3.4)	0
Upper respiratory tract infection	6 (1.5)	5 (5.0)
Arthralgia	7 (1.7)	3 (3.0)
Hypertension	2 (0.5)	3 (3.0)
Psoriasis	2 (0.5)	5 (5.0)

n (%)

Among the patients in the Japanese subpopulation, adverse events were observed during the first 16-week period in 41.7% (5 of 12) of patients in the 150 mg group and in 50.0% (1 of 2) of patients in the placebo group. The main adverse event was viral upper respiratory tract infection (25.0% [3 of 12] of patients in the 150 mg group).

Neither death nor serious adverse events occurred. An adverse event leading to treatment discontinuation was observed in 1 patient in the placebo group. Adverse drug reactions were observed in 16.7% (2 of 12) of patients in the 150 mg group.

A total of 500 patients who received at least 1 dose of risankizumab during the entire study period were included in the "entire risankizumab population." The incidence of adverse events in this population was 77.4% (387 of 500) of patients. Table 40 shows the main adverse events observed.

Death occurred in 2 patients (death, hepatic cancer metastatic/intestinal adenocarcinoma), but a causal relationship to the study drug was ruled out in both patients. Serious adverse events were observed in 7.0% (35 of 500) of patients; a causal relationship to the study drug could not be ruled out in 3 patients (arthralgia, sepsis, and meningitis bacterial in 1 patient each). Adverse events leading to treatment discontinuation were observed in 1.6% (8 of 500) of patients, and adverse drug reactions were observed in 15.4% (77 of 500) of patients.

Table 40. Adverse events reported by ≥3% of patients (up to Week 52, entire risankizumab population)

Event	Number of patients receiving risankizumab (N = 500)
Viral upper respiratory tract infection	97 (19.4)
Upper respiratory tract infection	53 (10.6)
Arthralgia	28 (5.6)
Headache	26 (5.2)
Back pain	18 (3.6)
Influenza	16 (3.2)
Urinary tract infection	15 (3.0)
Diarrhoea	15 (3.0)

n (%)

In the Japanese subpopulation of the "entire risankizumab population," adverse events were observed in 69.2% (9 of 13) of patients. The main adverse event was viral upper respiratory tract infection (46.2% [6 of 13] of patients).

No death occurred. Serious adverse events were observed in 7.7% (1 of 13, intracardiac thrombus/myocardial infarction) of patients, but their causal relationship to the study drug was ruled out. There were no adverse events leading to treatment discontinuation. Adverse drug reactions were observed in 23.1% (3 of 13) of patients.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

The applicant's explanation:

The efficacy of risankizumab was evaluated focusing on the data of the Japanese clinical studies (Studies M16-004 and M15-988). The data of the global studies that included Japanese patients were also evaluated, because there is no clinically significant difference between Japan and other countries in the diagnosis of psoriasis or in the extrinsic ethnic factors such as treatment policy, nor are there any clear ethnic differences in the pharmacokinetics of risankizumab [see Section 6.2].

7.R.1.1 Efficacy against plaques

The applicant's explanation about the efficacy of risankizumab against plaques in Japanese patients with psoriasis vulgaris or PsA:

Paired comparisons in Study M16-004 showed a statistically significant difference in the PASI 90 achievement rate at Week 16, the primary efficacy endpoint, between the placebo and 75 mg groups and between the placebo and 150 mg groups, demonstrating the superiority of 75 mg and 150 mg to placebo (Table 30). The results of secondary endpoints and other efficacy endpoints showed a tendency of a greater improvement up to Week 16 in the risankizumab group than in the placebo group, and demonstrated the lasting efficacy throughout the treatment period (Table 41). Table 42 shows the results of the analysis of subgroups classified by patient characteristics in Study M16-004, and no clear difference was observed in the efficacy of risankizumab among each subpopulation.

Table 41. Changes over time in efficacy, assessed by each endpoint (Study M16-004, ITT population, NRI)

		75 mg	150 mg	Placebo/75 mg	Placebo/150 mg
sPGA (0/1) achievement rate					
	Week 16	86.2 (50/58)	92.7 (51/55)	10.3 (6/58)	
	Week 52	84.5 (49/58)	94.5 (52/55)	96.3 (26/27)	88.9 (24/27)
sPGA (0) achievement rate					
	Week 16	29.3 (17/58)	38.2 (21/55)	0 (0/58)	
	Week 52	50.0 (29/58)	47.3 (26/55)	48.1 (13/27)	63.0 (17/27)
PASI 75 achievement rate					
	Week 16	89.7 (52/58)	94.5 (52/55)	8.6 (5/58)	
	Week 52	94.8 (55/58)	96.4 (53/55)	100 (27/27)	88.9 (24/27)
PASI 90 achievement rate					
	Week 4	1.7 (1/58)	7.3 (4/55)	0 (0/58)	
	Week 8	36.2 (21/58)	49.1 (27/55)	0 (0/58)	
	Week 12	55.2 (32/58)	67.3 (37/55)	0 (0/58)	
	Week 16	75.9 (44/58)	74.5 (41/55)	1.7 (1/58)	
	Week 52	86.2 (50/58)	92.7 (51/55)	81.5 (22/27)	85.2 (23/27)
PASI 100 achievement rate					
	Week 4	0 (0/58)	0 (0/55)	0 (0/58)	
	Week 8	3.4 (2/58)	12.7 (7/55)	0 (0/58)	
	Week 12	22.4 (13/58)	25.5 (14/55)	0 (0/58)	
	Week 16	22.4 (13/58)	32.7 (18/55)	0 (0/58)	
	Week 52	43.1 (25/58)	41.8 (23/55)	40.7 (11/27)	44.4 (12/27)

% (n/N)

Table 42. sPGA (0/1) and PASI 90 achievement rates at Week 16, classified by patient characteristics (Study M16-004, ITT population, NRI)

		sPGA (0/1) achievement rate			PASI 90 achievement rate		
		75 mg	150 mg	Placebo	75 mg	150 mg	Placebo
Entire population		86.2 (50/58)	92.7 (51/55)	10.3 (6/58)	75.9 (44/58)	74.5 (41/55)	1.7 (1/58)
Sex	Male	85.4 (41/48)	92.0 (46/50)	11.1 (5/45)	75.0 (36/48)	72.0 (36/50)	2.2 (1/45)
	Female	90.0 (9/10)	100 (5/5)	7.7 (1/13)	80.0 (8/10)	100 (5/5)	0 (0/13)
Age (years)	<40	87.5 (7/8)	88.9 (8/9)	11.1 (1/9)	75.0 (6/8)	66.7 (6/9)	0 (0/9)
	≥40 and <65	84.6 (33/39)	90.9 (30/33)	4.9 (2/41)	74.4 (29/39)	69.7 (23/33)	0 (0/41)
	≥65	90.9 (10/11)	100 (13/13)	37.5 (3/8)	81.8 (9/11)	92.3 (12/13)	12.5 (1/8)
Body weight	≤70.8 kg	96.6 (28/29)	97.0 (32/33)	12.5 (3/24)	89.7 (26/29)	78.8 (26/33)	0 (0/24)
	>70.8 kg	75.9 (22/29)	86.4 (19/22)	8.8 (3/34)	62.1 (18/29)	68.2 (15/22)	2.9 (1/34)
Body mass index	<25	92.6 (25/27)	94.1 (32/34)	17.4 (4/23)	77.8 (21/27)	79.4 (27/34)	0 (0/23)
	≥25 and <30	90.0 (18/20)	100 (7/7)	4.3 (1/23)	85.0 (17/20)	42.9 (3/7)	4.3 (1/23)
	≥30	63.6 (7/11)	85.7 (12/14)	8.3 (1/12)	54.5 (6/11)	78.6 (11/14)	0 (0/12)
Diagnosis of psoriatic arthritis	Yes	100 (5/5)	100 (3/3)	0 (0/3)	80.0 (4/5)	100 (3/3)	0 (0/3)
	No	84.9 (45/53)	92.3 (48/52)	10.9 (6/55)	75.5 (40/53)	73.1 (38/52)	1.8 (1/55)
Baseline PASI score	≤22.8	91.7 (22/24)	96.9 (31/32)	10.0 (3/30)	79.2 (19/24)	81.3 (26/32)	0 (0/30)
	>22.8	82.4 (28/34)	87.0 (20/23)	10.7 (3/28)	73.5 (25/34)	65.2 (15/23)	3.6 (1/28)
Baseline sPGA score	<4	88.2 (45/51)	93.5 (43/46)	9.3 (5/54)	78.4 (40/51)	76.1 (35/46)	1.9 (1/54)
	4	71.4 (5/7)	88.9 (8/9)	25.0 (1/4)	57.1 (4/7)	66.7 (6/9)	0 (0/4)
Percentage of lesion area at baseline	<20%	100 (11/11)	100 (13/13)	5.6 (1/18)	90.9 (10/11)	84.6 (11/13)	0 (0/18)
	≥20%	83.0 (39/47)	90.5 (38/42)	12.5 (5/40)	72.3 (34/47)	71.4 (30/42)	2.5 (1/40)
Baseline DLQI score	<10	85.7 (18/21)	92.9 (26/28)	6.1 (2/33)	71.4 (15/21)	75.0 (21/28)	0 (0/33)
	≥10	86.5 (32/37)	92.6 (25/27)	16.0 (4/25)	78.4 (29/37)	74.1 (20/27)	4.0 (1/25)
Prior systemic treatment[a)]	Yes	90.3 (28/31)	88.6 (31/35)	8.8 (3/34)	80.6 (25/31)	71.4 (25/35)	2.9 (1/34)
	No	81.5 (22/27)	100 (20/20)	12.5 (3/24)	70.4 (19/27)	80.0 (16/20)	0 (0/24)
Prior treatment with biological products[b)]	Yes	75.0 (6/8)	93.8 (15/16)	7.1 (1/14)	87.5 (7/8)	81.3 (13/16)	0 (0/14)
	No	88.0 (44/50)	92.3 (36/39)	11.4 (5/44)	74.0 (37/50)	71.8 (28/39)	2.3 (1/44)

% (n/N)
a) MTX, cyclosporine
b) Etanercept, infliximab, adalimumab, UST, secukinumab, brodalumab, ixekizumab, etc.

A paired comparison in the global phase III studies in patients with plaque psoriasis (Studies M15-992 and M16-008, both included Japanese patients) showed a statistically significant difference in both primary efficacy endpoints (sPGA [0/1] and PASI 90 achievement rates at Week 16) between the placebo and 150 mg groups, demonstrating superiority of 150 mg to placebo (Tables 33 and 37).

Secondary and other efficacy endpoints also showed a tendency of greater improvement in the 150 mg group than in the placebo group. Results in the Japanese subpopulation were similar to those in the entire population (Table 43).

Table 43. Results of each efficacy endpoint at Week 16 (Studies M15-992 and M16-008, ITT population, NRI)

			150 mg	Placebo	Difference from placebo [95% CI]
Study M16-008					
	Entire population				
		sPGA (0/1) achievement rate (*)	87.8 (267/304)	7.8 (8/102)	79.9 [73.5, 86.3]
		sPGA (0) achievement rate	36.8 (112/304)	2.0 (2/102)	34.7 [28.6, 40.8]
		PASI 75 achievement rate	89.1 (271/304)	8.8 (9/102)	80.2 [73.8, 86.7]
		PASI 90 achievement rate (*)	75.3 (229/304)	4.9 (5/102)	70.3 [64.0, 76.7]
		PASI 100 achievement rate	35.9 (109/304)	0 (0/102)	35.5 [30.0, 41.0]
	Japanese subpopulation				
		sPGA (0/1) achievement rate	90.3 (28/31)	0 (0/9)	87.2 [73.3, 101.1]
		sPGA (0) achievement rate	38.7 (12/31)	0 (0/9)	38.2 [18.7, 57.6]
		PASI 75 achievement rate	90.3 (28/31)	0 (0/9)	87.2 [73.3, 101.1]
		PASI 90 achievement rate	77.4 (24/31)	0 (0/9)	76.0 [59.2, 92.9]
		PASI 100 achievement rate	32.3 (10/31)	0 (0/9)	31.5 [12.6, 50.4]
Study M15-992					
	Entire population				
		sPGA (0/1) achievement rate (*)	83.5 (340/407)	7.0 (7/100)	76.5 [70.4, 82.5]
		sPGA (0) achievement rate	46.4 (189/407)	1.0 (1/100)	44.8 [39.5, 50.0]
		PASI 75 achievement rate	88.7 (361/407)	8.0 (8/100)	80.6 [74.5, 86.6]
		PASI 90 achievement rate (*)	73.2 (298/407)	2.0 (2/100)	70.8 [65.7, 76.0]
		PASI 100 achievement rate	47.2 (192/407)	1.0 (1/100)	45.5 [40.3, 50.8]
	Japanese subpopulation				
		sPGA (0/1) achievement rate	83.3 (10/12)	0 (0/2)	73.7 [35.8, 111.6]
		sPGA (0) achievement rate	33.3 (4/12)	0 (0/2)	25.8 [−15.1, 66.6]
		PASI 75 achievement rate	91.7 (11/12)	0 (0/2)	81.9 [46.5, 117.3]
		PASI 90 achievement rate	83.3 (10/12)	0 (0/2)	73.7 [35.8, 111.6]
		PASI 100 achievement rate	33.3 (4/12)	0 (0/2)	25.8 [−15.1, 66.6]

% (n/N); *, Primary endpoints

Table 44 shows the results of each efficacy endpoint at Week 16 in the population with psoriatic lesion at ≥3% of body surface area (BSA) at baseline, in the global phase II study (Study M16-002) in patients with active PsA. Results showed improvement even in patients with PsA, albeit in the study including only a limited number of patients.

Table 44. Results of each efficacy endpoint at Week 16 (Study M16-002, population with psoriatic lesion at ≥3% of BSA at baseline, NRI)

	75 mg	150 mg Q12W	150 mg LD Q12W	150 mg Q4W	150 mg LD Q12W/Q4W combined	Placebo
sPGA (0/1) achievement rate	88.9 (8/9)	78.3 (18/23)	85.0 (17/20)	81.3 (13/16)	83.3 (30/36)	33.3 (7/21)
sPGA (0) achievement rate	55.6 (5/9)	39.1 (9/23)	50.0 (10/20)	50.0 (8/16)	50.0 (18/36)	9.5 (2/21)
PASI 75 achievement rate	66.7 (6/9)	73.9 (17/23)	70.0 (14/20)	75.0 (12/16)	72.2 (26/36)	9.5 (2/21)
PASI 90 achievement rate[a)]	55.6 (5/9)	52.2 (12/23)	66.7 (12/18)	58.3 (7/12)	63.3 (19/30)	9.5 (2/21)
PASI 100 achievement rate[a)]	55.6 (5/9)	34.8 (8/23)	50.0 (9/18)	33.3 (4/12)	43.3 (13/30)	9.5 (2/21)

% (n/N)

a) If the area of psoriatic lesion decreased to <3% of BSA after baseline, missing data were not imputed.

The applicant considers that the above results demonstrate the efficacy of risankizumab against plaques in Japanese patients with psoriasis vulgaris or PsA.

PMDA accepted the above explanation of the applicant and concluded that risankizumab has efficacy against plaques in Japanese patients with psoriasis vulgaris or PsA.

7.R.1.2 Efficacy against joint symptoms of PsA

The applicant's explanation about the efficacy of risankizumab against the joint symptoms of PsA:
No confirmatory study in Japanese patients with PsA could be conducted because of the limited number of patients with PsA in Japan. Instead, the effect of risankizumab on the joint symptoms of PsA was evaluated in the global phase II study (Study M16-002) in patients with active PsA (including Japanese patients) and in the Japanese phase II/III study (Study M16-004) in patients with plaque psoriasis.

Table 28 shows an ACR 20 response rate at Week 16, the primary endpoint, in Study M16-002. Table 45 shows results of the efficacy endpoints in patients in Study M16-002 and in patients in Study M16-004 who were diagnosed with PsA according to classification criteria for psoriatic arthritis (CASPAR) and had ≥3 swollen or tender joints at baseline.

Table 45. Results of efficacy endpoints related to joint symptoms of psoriatic arthritis

		Study M16-004				Study M16-002	
		75 mg	150 mg	Placebo/ 75 mg	Placebo/ 150 mg	150 mg LD Q12W	Placebo
ACR 20 response rate (NRI)							
	Week 16	40.0 (2/5)	33.3 (1/3)	0 (0/3)		61.9 (26/42)	35.7 (15/42)
	Week 52	60.0 (3/5)	0 (0/3)	100 (1/1)	100 (2/2)	-	-
Change in tender joint count from baseline (LOCF)							
	Week 16	−9.8 ± 2.5 (5)	−7.2 ± 3.8 (3)	−8.1 ± 4.1 (3)		−9.6 ± 1.7 (41)	−7.9 ± 1.7 (42)
	Week 52	−12.6 ± 1.7 (5)	−15.3 ± 2.5 (3)	−17.9 ± 3.6 (1)	−16.5 ± 3.0 (2)	-	-
Change in swollen joint count from baseline (LOCF)							
	Week 16	−4.2 ± 1.1 (5)	−9.3 ± 1.6 (3)	−8.7 ± 1.6 (3)		−7.8 ± 0.9 (41)	−7.1 ± 0.9 (42)
	Week 52	−7.2 ± 1.8 (5)	−8.5 ± 2.7 (3)	−11.1 ± 3.8 (1)	−10.3 ± 3.0 (2)	-	-
Change in pain VAS from baseline (LOCF)							
	Week 16	−35.0 ± 12.3 (5)	−13.6 ± 21.6 (3)	19.7 ± 22.6 (3)		−17.6 ± 3.6 (41)	−3.5 ± 3.6 (42)
	Week 52	−38.4 ± 11.4 (5)	−43.3 ± 20.2 (3)	−18.0 ± 27.7 (1)	−44.9 ± 22.2 (2)	-	-

Response rate, % (n/N); Change, Least squares mean ± standard error (n); -, Not tested

The above results demonstrated the efficacy of risankizumab against joint symptoms in Japanese patients with PsA.

PMDA's view:
PMDA understands that, due to the extremely limited number of patients with PsA in Japan, it is practically impossible to conduct a study to confirm the efficacy of risankizumab in a sufficiently large

number of Japanese patients with PsA. However, risankizumab is expected to be effective for joint symptoms in Japanese patients with PsA, because risankizumab was shown to have efficacy against joint symptoms in Study M16-002, and because risankizumab tended to improve joint symptoms in Study M16-004 as well, although there were only a limited number of patients showing joint symptoms in these studies. Because of the extremely limited number of Japanese patients evaluated in these studies, information on the efficacy of risankizumab in patients with PsA should be collected as much as possible in the post-marketing surveillance, etc.

7.R.1.3 Efficacy against GPP and EP

The applicant's explanation about the efficacy of risankizumab in patients with GPP or EP:

In Study M15-988, clinical efficacy against GPP/EP at Week 16, the primary efficacy endpoint, was achieved in all patients [see Section 7.3.1]. Clinical efficacy against GPP/EP was achieved in all patients except in 3 patients who discontinued the treatment before Week 52 (1 in the GPP 75 mg group, 2 in the GPP 150 mg group). Table 46 shows a PASI 90 achievement rate, a secondary endpoint.

Table 46. PASI 90 achievement rate at Week 16 and 52 (Study M15-988, ITT population, NRI)

	GPP		EP	
	75 mg	150 mg	75 mg	150 mg
Week 16	100 (4/4)	75.0 (3/4)	60.0 (3/5)	100 (4/4)
Week 52	75.0 (3/4)	50.0 (2/4)	80.0 (4/5)	100 (4/4)

% (n/N)

The applicant thus considers that risankizumab is expected to be effective in patients with GPP or EP.

PMDA's view:

PMDA understands that, due to the extremely limited number of patients with GPP or EP in Japan, it is practically impossible to conduct a study to confirm the efficacy of risankizumab in a sufficiently large number of Japanese patients with GPP or EP. In Study M15-988, clinical efficacy against GPP/EP and PASI 90 were achieved in most of the patients, and therefore risankizumab is expected to have a level of efficacy in Japanese patients with GPP or EP. Because of the extremely limited number of Japanese patients with GPP or EP evaluated in these studies, information on the efficacy of risankizumab in these patient groups should be collected as much as possible in the post-marketing surveillance, etc.

7.R.2 Safety

The applicant explained the safety of risankizumab, based on the result of the analysis[15] of the pooled data of the double-blind period (up to Week 16) in randomized, double-blind studies[16] (hereinafter referred to as "pooled population of 4 Japanese and foreign placebo-controlled studies") and the pooled data of clinical studies in patients with plaque psoriasis[17] (hereinafter referred to as "pooled population of 6 Japanese and foreign studies").

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15) For the safety in the adalimumab group in Study M16-010, see Section 7.R.5.1.
16) Studies M15-992, M15-995, M16-004, and M16-008. Patients receiving risankizumab 75 mg were included only in Study M16-004.
17) Studies M15-992, M15-995, M16-004, M15-997, M16-008, and M16-010

The applicant's explanation:

Table 47 shows the safety summary in the pooled population of 4 Japanese and foreign placebo-controlled studies and in the pooled population of 6 Japanese and foreign studies. Tables 48 and 49 show main adverse events. No clear difference was observed in the safety summary, or types or incidence of adverse events, between treatment groups.

Table 47. Summary of safety in clinical studies in patients with psoriasis

	Pooled population of 4 Japanese and foreign placebo-controlled studies					Pooled population of 6 Japanese and foreign studies			
	Japanese subpopulation			Entire population		Japanese subpopulation		Entire population	
	75 mg	150 mg	Placebo	150 mg	Placebo	75 mg	150 mg	150 mg	UST
N	58	98	69	1060	358	85	134	1672	199
Total duration of exposure (100 patient-years)	17.7	29.9	21.2	325.8	109.8	79.6	130.6	1758.5	202.1
All adverse events	29 (50.0) 288.1	56 (57.1) 314.4	41 (59.4) 334.9	501 (47.3) 290.1	178 (49.7) 293.3	64 (75.3) 226.1	109 (81.3) 244.3	1257 (75.2) 245.4	157 (78.9) 281.0
Serious adverse events	2 (3.4) 11.3	2 (2.0) 6.7	1 (1.4) 4.7	23 (2.2) 9.5	13 (3.6) 15.5	5 (5.9) 6.3	6 (4.5) 6.1	112 (6.7) 9.6	18 (9.0) 10.9
Adverse events leading to treatment discontinuation	2 (3.4) 11.3	2 (2.0) 6.7	6 (8.7) 28.3	6 (0.6) 2.5	13 (3.6) 11.8	2 (2.4) 2.5	3 (2.2) 2.3	31 (1.9) 2.2	4 (2.0) 2.0
Adverse drug reactions	10 (17.2) 73.4	13 (13.3) 60.2	9 (13.0) 51.9	105 (9.9) 51.6	36 (10.1) 49.2	21 (24.7) 33.9	34 (25.4) 45.9	342 (20.5) 43.4	52 (26.1) 55.4
Death	0 0	0 0	0 0	1 (<0.1) 0.3	0 0	0 0	0 0	5 (0.3) 0.3	0 0

Upper row, n (%)
Lower row, Number of events per 100 patient-years adjusted for the total duration of exposure

Table 48. Adverse events reported by ≥2% of patients in any group (pooled population of 4 Japanese and foreign placebo-controlled studies)

	Japanese subpopulation			Entire population	
	75 mg (N = 58)	150 mg (N = 98)	Placebo (N = 69)	150 mg (N = 1060)	Placebo (N = 358)
Nasopharyngitis	3 (5.2)	10 (10.2)	8 (11.6)	16 (1.5)	9 (2.5)
Viral upper respiratory tract infection	0	8 (8.2)	1 (1.4)	51 (4.8)	13 (3.6)
Eczema	1 (1.7)	4 (4.1)	0	7 (0.7)	1 (0.3)
Arthropod bite	1 (1.7)	3 (3.1)	0	8 (0.8)	0
Arthralgia	0	3 (3.1)	2 (2.9)	23 (2.2)	11 (3.1)
Gastroenteritis	0	3 (3.1)	2 (2.9)	10 (0.9)	5 (1.4)
Back pain	2 (3.4)	2 (2.0)	1 (1.4)	13 (1.2)	2 (0.6)
Hyperlipidaemia	2 (3.4)	2 (2.0)	0	4 (0.4)	1 (0.3)
Hepatic function abnormal	2 (3.4)	2 (2.0)	0	2 (0.2)	0
Oedema peripheral	1 (1.7)	2 (2.0)	1 (1.4)	5 (0.5)	3 (0.8)
Diarrhoea	0	2 (2.0)	2 (2.9)	15 (1.4)	7 (2.0)
Pruritus	0	2 (2.0)	0	11 (1.0)	4 (1.1)
Sinusitis	0	2 (2.0)	0	10 (0.9)	1 (0.3)
Folliculitis	2 (3.4)	1 (1.0)	1 (1.4)	12 (1.1)	1 (0.3)
Conjunctivitis	2 (3.4)	1 (1.0)	0	7 (0.7)	1 (0.3)
Headache	0	1 (1.0)	0	33 (3.1)	6 (1.7)
Psoriasis	3 (5.2)	0	13 (18.8)	2 (0.2)	24 (6.7)
Diabetes mellitus	3 (5.2)	0	1 (1.4)	0	1 (0.3)
Cough	2 (3.4)	0	0	12 (1.1)	0
Pharyngitis	2 (3.4)	0	0	4 (0.4)	3 (0.8)
Skin papilloma	2 (3.4)	0	0	4 (0.4)	1 (0.3)
Upper respiratory tract infection	0	0	2 (2.9)	34 (3.2)	11 (3.1)

n (%)

Table 49. Adverse events reported by ≥3% of patients in any group (pooled population of 6 Japanese and foreign studies)

	Japanese subpopulation		Entire population	
	75 mg (N = 85)	150 mg (N = 134)	150 mg (N = 1672)	UST (N = 199)
Nasopharyngitis[a)]	22 (25.9)	46 (34.3)	308 (18.4)	5 (2.5)
Tinea pedis	1 (1.2)	9 (6.7)	22 (1.3)	0
Arthralgia	3 (3.5)	8 (6.0)	91 (5.4)	8 (4.0)
Dental caries	1 (1.2)	8 (6.0)	22 (1.3)	1 (0.5)
Eczema	2 (2.4)	7 (5.2)	25 (1.5)	2 (1.0)
Influenza	4 (4.7)	6 (4.5)	49 (2.9)	5 (2.5)
Folliculitis	4 (4.7)	6 (4.5)	35 (2.1)	6 (3.0)
Diarrhoea	0	5 (3.7)	52 (3.1)	10 (5.0)
Back pain	6 (7.1)	4 (3.0)	60 (3.6)	8 (4.0)
Hyperlipidaemia	3 (3.5)	4 (3.0)	22 (1.3)	1 (0.5)
Urticaria	3 (3.5)	4 (3.0)	18 (1.1)	1 (0.5)
Arthropod bite	2 (2.4)	4 (3.0)	17 (1.0)	1 (0.5)
Dermatitis contact	1 (1.2)	4 (3.0)	27 (1.6)	3 (1.5)
Contusion	0	4 (3.0)	16 (1.0)	1 (0.5)
Hepatic function abnormal	5 (5.9)	3 (2.2)	3 (0.2)	0
Weight increased	3 (3.5)	3 (2.2)	13 (0.8)	1 (0.5)
Blood creatine phosphokinase increased	2 (2.4)	3 (2.2)	20 (1.2)	7 (3.5)
Gastroenteritis	1 (1.2)	3 (2.2)	42 (2.5)	6 (3.0)
Nausea	1 (1.2)	3 (2.2)	26 (1.6)	7 (3.5)
Diabetes mellitus	4 (4.7)	2 (1.5)	17 (1.0)	2 (1.0)
Skin papilloma	3 (3.5)	2 (1.5)	13 (0.8)	1 (0.5)
Bronchitis	0	2 (1.5)	34 (2.0)	7 (3.5)
Pharyngitis	5 (5.9)	1 (0.7)	22 (1.3)	3 (1.5)
Psoriasis	3 (3.5)	1 (0.7)	15 (0.9)	4 (2.0)
Hypertension	2 (2.4)	1 (0.7)	55 (3.3)	8 (4.0)
Headache	1 (1.2)	1 (0.7)	76 (4.5)	13 (6.5)
Upper respiratory tract infection	0	1 (0.7)	188 (11.2)	26 (13.1)
Urinary tract infection	0	0	39 (2.3)	10 (5.0)
Viral upper respiratory tract infection	0	0	27 (1.6)	42 (21.1)

n (%)
a) Including events classified as nasopharyngitis in the UST group.

Death occurred in 4 patients receiving 150 mg in the pooled population of 6 Japanese and foreign studies (death, acute myocardial infarction, hepatic cancer metastatic/intestinal adenocarcinoma, and seizure in 1 patient each). Their causal relationship to the study drug was ruled out. Death after discontinuation or completion of the study was observed in 1 patient receiving 150 mg (death), but its causal relationship to the study drug was ruled out. No death occurred in patients who participated in other studies (i.e., studies other than the 6 Japanese and foreign studies).

Table 47 shows the incidence of serious adverse events in the pooled population of 6 Japanese and foreign studies. Serious adverse events reported by ≥3 patients in any group of the entire population were basal cell carcinoma in 0.4% (7 of 1672) of patients receiving 150 mg, cellulitis and sepsis in 0.3% each (5 of 1672) of patients receiving 150 mg, squamous cell carcinoma of skin and coronary artery disease in 0.2% each (4 of 1672) of patients receiving 150 mg, and acute myocardial infarction, cardiac failure congestive, and pneumonia in 0.2% each (3 of 1672) of patients receiving 150 mg. Table 47 shows the incidence of serious adverse events observed in the Japanese subpopulation: rectal cancer, loss of consciousness, dermal cyst, psoriasis, and hypotension in 1.2% each (1 of 85) of patients receiving 75 mg; and acute myocardial infarction, intracardiac thrombus/myocardial infarction, mitral valve incompetence/Prinzmetal angina, rectal polyp, bursitis infective, and

erythrodermic psoriasis in 0.7% each (1 of 134) of patients receiving 150 mg. A causal relationship to the study drug could not be ruled out for rectal cancer, hypotension, acute myocardial infarction, rectal polyp, and bursitis infective.

Incidences of adverse events in clinical studies in patients with PsA, GPP, or EP are shown in Sections 7.1.1 and 7.3.1.

Taking account of the pharmacological action of risankizumab and of the disease characteristics in patients with psoriasis, PMDA conducted detailed reviews on the following adverse events.

7.R.2.1 Infection

The applicant's explanation about the incidences of infection during the treatment with risankizumab:
Table 50 shows the incidences of infection in the pooled population of 4 Japanese and foreign placebo-controlled studies and in the pooled population of 6 Japanese and foreign studies. Reactivation of asymptomatic hepatitis B was observed in 1 patient in the 150 mg group of Study M16-008, but the incidence was within the range of reactivation rate of hepatitis B predicted among the general population.

Table 50. Incidences of adverse events related to infection

	Pooled population of 4 Japanese and foreign placebo-controlled studies					Pooled population of 6 Japanese and foreign studies			
	Japanese subpopulation			Entire population		Japanese subpopulation		Entire population	
	75 mg	150 mg	Placebo	150 mg	Placebo	75 mg	150 mg	150 mg	UST
N	58	98	69	1060	358	85	134	1672	199
Total duration of exposure (100 patient-years)	17.7	29.9	21.2	325.8	109.8	79.6	130.6	1758.5	202.1
Infection	2 (3.4) 11.3	2 (2.0) 6.7	6 (8.7) 28.3	21 (2.0) 8.0	9 (2.5) 8.2	3 (3.5) 5.5	11 (8.2) 10.4	91 (51.4) 6.3	7 (3.5) 5.9
Category									
Serious infection[a)]	0 0	0 0	1 (1.4) 4.7	4 (0.4) 1.8	2 (0.6) 1.8	0 0	1 (0.7) 0.8	22 (1.3) 1.5	4 (2.0) 2.5
Tuberculosis[a)]	0 0	0 0	0 0	0 0	1 (0.3) 0.9	0 0	0 0	6 (0.4) 0.4	0 0
Fungal infection[a)]	2 (3.4) 11.3	2 (2.0) 6.7	4 (5.8) 18.9	18 (1.7) 5.8	5 (1.4) 4.6	3 (3.5) 3.8	12 (9.0) 9.2	63 (3.8) 4.2	2 (1.0) 1.0
Opportunistic infection[a)]	0 0	0 0	0 0	0 0	0 0	0 0	1 (0.7) 0.8	6 (0.4) 0.4	2 (1.0) 1.0
Herpes zoster[a)]	0 0	0 0	1 (1.4) 4.7	1 (<0.1) 0.3	1 (0.3) 0.9	1 (1.2) 1.3	1 (0.7) 0.8	7 (0.4) 0.4	3 (1.5) 1.5
Main events (PT)									
Tinea pedis	1 (1.7) 5.6	1 (1.0) 3.3	2 (2.9) 9.4	3 (0.3) 0.9	2 (0.6) 1.8	1 (1.2) 1.3	9 (6.7) 6.9	22 (1.3) 1.3	0 0
Herpes zoster	0 0	0 0	1 (1.4) 4.7	1 (<0.1) 0.3	1 (0.3) 0.9	0 0	1 (0.7) 0.8	7 (0.4) 0.4	2 (1.0) 1.0
Onychomycosis	0 0	0 0	1 (1.4) 4.7	1 (<0.1) 0.3	1 (0.3) 0.9	0 0	0 0	6 (0.4) 0.3	0 0
Latent tuberculosis	0 0	0 0	0 0	0 0	0 0	0 0	0 0	6 (0.4) 0.3	0 0
Body tinea	0 0	0 0	0 0	3 (0.3) 1.2	1 (0.3) 0.9	0 0	0 0	5 (0.3) 0.5	0 0
Tinea versicolour	1 (1.7) 5.6	0 0	0 0	3 (0.3) 0.9	0 0	1 (1.2) 1.3	0 0	5 (0.3) 0.3	0 0
Cellulitis	0 0	0 0	0 0	2 (0.2) 0.6	1 (0.3) 0.9	0 0	0 0	5 (0.3) 0.3	0 0
Fungal infection	0 0	0 0	0 0	2 (0.2) 0.6	0 0	0 0	1 (0.7) 0.8	5 (0.3) 0.3	0 0
Sepsis	0 0	0 0	0 0	1 (<0.1) 0.3	0 0	0 0	0 0	5 (0.3) 0.3	0 0

Upper row: n (%)
Lower row, Number of events per 100 patient-years adjusted for the total duration of exposure
a) Events classified according to MedDRA Query defined by the applicant

In Study M16-002 in patients with active PsA, the incidence of adverse events related to infection was 3.5% (5 of 143) of patients (2 in the 75 mg group, 3 in the 150 mg group). By category, they were serious infection in 1.4% (2 of 143) of patients (75 mg group), fungal infection in 1.4% (2 of 143) of patients (150 mg Q4W group), and herpes zoster in 0.7% (1 of 143) of patients (150 mg Q4W group). In Study M15-988 in patients with GPP or EP, the incidence of adverse events related to infection was 5.9% (1 of 17) of patients (EP 75 mg group, urinary tract infection).

These results showed that the incidence of serious infection was similar in the 150 mg group and the placebo group. There were no particular safety concerns regarding tuberculosis, opportunistic infection, fungal infection, or herpes zoster. However, immunological changes caused by psoriasis and treatment of psoriasis may increase the risk of infection (*J Am Acad Dermatol*. 2011;65:1135-44), and immunomodulatory agents are known to possibly increase the risk of infection. Therefore, a precautionary statement will be provided regarding the occurrence of serious infection, and the risk of infection in long-term use of risankizumab will be continuously investigated in the post-marketing clinical studies.

PMDA's view:

Currently there are no data suggestive of any clear relationship between risankizumab treatment and infection. However, serious infection and latent tuberculosis were observed among patients in the risankizumab group in clinical studies, and the incidence of serious infection in the risankizumab group was comparable to that in the UST group. Taking account of these findings, the applicant, as the marketing authorization holder, should alert physicians to possible risk of serious infection associated with risankizumab and also take appropriate measures for early detection of infection, as are the cases with other approved biological products for psoriasis. Incidence of serious infection during risankizumab treatment should be investigated continuously after the market launch [see Section 7.R.6].

7.R.2.2 Malignant tumor

The applicant's explanation about the incidence of malignant tumor associated with risankizumab:

Table 51 shows the incidences of malignant tumor in the pooled population of 4 Japanese and foreign placebo-controlled studies and in the pooled population of 6 Japanese and foreign studies.

Table 51. Incidence of adverse events related to malignant tumor

	Pooled population of 4 Japanese and foreign placebo-controlled studies					Pooled population of 6 Japanese and foreign studies			
	Japanese subpopulation			Entire population		Japanese subpopulation		Entire population	
	75 mg	150 mg	Placebo	150 mg	Placebo	75 mg	150 mg	150 mg	UST
N	58	98	69	1060	358	85	134	1672	199
Total duration of exposure (100 patient-years)	17.7	29.9	21.2	325.8	109.8	79.6	130.6	1758.5	202.1
Malignant tumor (including malignancies)	0 0	0 0	0 0	6 (0.6) 1.8	1 (0.3) 0.9	1 (1.2) 1.3	1 (0.7) 0.8	27 (1.6) 1.8	1 (0.5) 0.5
Category									
Malignancies[a)]	0 0	0 0	0 0	6 (0.6) 1.8	1 (0.3) 0.9	1 (1.2) 1.3	1 (0.7) 0.8	27 (1.6) 1.8	1 (0.5) 0.5
Malignant tumor[b)]	0 0	0 0	0 0	5 (0.5) 1.5	1 (0.3) 0.9	1 (1.2) 1.3	0 0	21 (1.3) 1.4	1 (0.5) 0.5
Non-melanoma skin cancer[c)]	0 0	0 0	0 0	3 (0.3) 0.9	1 (0.3) 0.9	0 0	0 0	12 (0.7) 0.9	0 0
Malignant tumor other than non-melanoma skin cancer[d)]	0 0	0 0	0 0	2 (0.2) 0.6	0 0	1 (1.2) 1.3	0 0	9 (0.5) 0.6	1 (0.5) 0.5
Main events (PT)									
Basal cell carcinoma	0 0	0 0	0 0	1 (<0.1) 0.3	0 0	0 0	0 0	8 (0.5) 0.5	0 0
Squamous cell carcinoma of skin	0 0	0 0	0 0	2 (0.2) 0.6	1 (0.3) 0.9	0 0	0 0	4 (0.2) 0.3	0 0
Malignant melanoma in situ	0 0	0 0	0 0	1 (<0.1) 0.3	0 0	0 0	0 0	2 (0.1) 0.1	0 0
Prostatic specific antigen increased	0 0	0 0	0 0	1 (<0.1) 0.3	0 0	0 0	0 0	2 (0.1) 0.1	0 0
Prostate cancer	0 0	0 0	0 0	0 0	0 0	0 0	0 0	2 (0.1) 0.1	1 (0.5) 0.5
Acanthosis nigricans	0 0	0 0	0 0	0 0	0 0	0 0	0 0	2 (0.1) 0.1	0 0

Upper row, n (%)

Lower row, Number of events per 100 patient-years adjusted for the total duration of exposure

a) Events classified as "Malignancies" (SMQ)

b) Events classified as "Malignant tumours" (SMQ)

c) Events classified as "Skin malignant tumours" (SMQ) except for those classified as "Melanoma" according to MedDRA query defined by the applicant

d) Events identified by search for "malignant tumors," except for those identified by the search for "non-melanoma skin cancer"

In Study M16-002 in patients with active PsA, the incidence of adverse events related to malignant tumor was 0.7% (1 of 143) of patients in the 75 mg group (ovarian cancer stage IV). In Study M15-988 in patients with GPP or EP, the incidence of adverse events related to malignant tumor was 5.9% (1 of 17) of patients in the GPP 150 mg group (gastric cancer).

In clinical studies of drugs in the same class (inhibitors of IL-17, IL-12/23, and IL-23), the incidence of malignant tumor was 0.81 events per 100 patient-years with brodalumab, 0.97 events per 100 patient-years with ixekizumab, 0.96 events per 100 patient-years with secukinumab, 1.30 events per 100 patient-years with UST, and 0.93 events per 100 patient-years with guselkumab, and the incidence of malignant tumor other than non-melanoma skin cancer was 0.49 events per 100 patient-years with ixekizumab, 0.48 events per 100 patient-years with secukinumab, 0.34 events per 100 patient-years with UST, and 0.31 events per 100 patient-years with guselkumab. Although there are limitations to the inter-study comparison, there was no clear difference in the incidence between these clinical studies and the clinical studies of risankizumab.

Based on the above, the applicant considers that risankizumab treatment does not increase the risk of malignant tumor.

PMDA's view:
A causal relationship between risankizumab and development of malignant tumor is unclear from the data currently available. However, given the mechanism of action of risankizumab, the possibility of risankizumab increasing the risk of malignant tumor cannot be excluded. Caution should be provided regarding the risk of malignant tumor in the package insert, etc., as are the cases with other biological products against psoriasis. Also, incidences of malignant tumor should be investigated continuously after the market launch, including the incidences during the long-term administration [see Section 7.R.6].

7.R.2.3 Cardiovascular events

The applicant's explanation about the incidences of cardiovascular events associated with risankizumab:
Table 52 shows the incidences of cardiovascular events in the pooled population of 4 Japanese and foreign placebo-controlled studies and in the pooled population of 6 Japanese and foreign studies.

Table 52. Incidence of adverse events related to cardiovascular events

	Pooled population of 4 Japanese and foreign placebo-controlled studies					Pooled population of 6 Japanese and foreign studies			
	Japanese subpopulation			Entire population		Japanese subpopulation		Entire population	
	75 mg	150 mg	Placebo	150 mg	Placebo	75 mg	150 mg	150 mg	UST
N	58	98	69	1060	358	85	134	1672	199
Total duration of exposure (100 patient-years)	17.7	29.9	21.2	325.8	109.8	79.6	130.6	1758.5	202.1
Cardiovascular endpoints confirmed	0 0	1 (1.0) 3.3	0 0	3 (0.3) 1.2	4 (1.1) 4.6	0 0	2 (1.5) 2.8	22 (1.3) 2.1	0 0
Category									
Main cardiovascular events in a broad sense[a)]	0 0	1 (1.0) 3.3	0 0	2 (0.2) 0.6	1 (0.3) 0.9	0 0	1 (0.7) 0.8	11 (0.7) 0.8	0 0
Main cardiovascular events[b)]	0 0	1 (1.0) 3.3	0 0	1 (<0.1) 0.3	1 (0.3) 0.9	0 0	1 (0.7) 0.8	7 (0.4) 0.5	0 0
Other cardiovascular events[c)]	0 0	0 0	0 0	1 (<0.1) 0.3	3 (0.8) 2.7	0 0	2 (1.5) 1.5	13 (0.8) 0.8	0 0
Main events									
Arrhythmia	0 0	0 0	0 0	0 0	1 (0.3) 0.9	0 0	1 (0.7) 0.8	8 (0.5) 0.5	0 0
Cardiac failure congestive	0 0	0 0	0 0	0 0	0 0	0 0	1 (0.7) 0.8	5 (0.3) 0.3	0 0
Nonfatal myocardial infarction	0 0	1 (1.0) 3.3	0 0	1 (<0.1) 0.3	0 0	0 0	1 (0.7) 0.8	4 (0.2) 0.3	0 0
Death caused by cardiovascular events	0 0	0 0	0 0	0 0	0 0	0 0	0 0	3 (0.2) 0.2	0 0
Coronary arterial revascularization	0 0	0 0	0 0	0 0	0 0	0 0	0 0	3 (0.2) 0.2	0 0
Hospitalization due to unstable angina	0 0	0 0	0 0	1 (<0.1) 0.3	0 0	0 0	0 0	2 (0.1) 0.1	0 0

Upper row, n (%)
Lower row, Number of events per 100 patient-years adjusted for total duration of exposure

a) Events identified by the independent review panel as nonfatal myocardial infarction, nonfatal cerebrovascular disorder, sudden death, death of unknown cause, cardiovascular death (including suspicious death and unevaluable death), hospitalization due to unstable angina, or coronary arterial revascularization.
b) Events identified by the independent review panel as nonfatal myocardial infarction, nonfatal cerebrovascular disorder, sudden death, death of unknown cause, or cardiovascular death (including suspicious death and unevaluable death).
c) Events identified by the independent review panel as clinically significant arrhythmia, cardiac failure, hypertensive emergency, or thrombotic events (deep vein thrombosis, transient ischaemic attack, pulmonary embolism, and other nonfatal vascular infarction [those designated]).

In Study M16-002 in patients with active PsA, the incidence of adverse events related to cardiovascular endpoints was 1.4% (2 of 143) of patients (1 patient each in the 75 mg group and the 150 mg Q4W group: acute myocardial infarction/cardiac failure congestive/coronary artery occlusion in one patient, and cerebrovascular accident in the other). In Study M15-988 in patients with GPP or EP, there were no adverse events related to cardiovascular endpoints confirmed.

In clinical studies of drugs in the same class (inhibitors of IL-17, IL-12/23, and IL-23), the incidence of main cardiovascular events was 0.70 events per 100 patient-years with brodalumab, 0.72 events per 100 patient-years with ixekizumab, 0.37 events per 100 patient-years with secukinumab, 0.61 events per 100 patient-years with UST, and 0.84 events per 100 patient-years with guselkumab. Although there are limitations to the inter-study comparison, there were no clear difference in the incidence between these clinical studies and the clinical studies of risankizumab. According to the report from Psoriasis Longitudinal Assessment and Registry (PSOLAR), the incidence of the main cardiovascular events in patients with psoriasis treated with drugs other than biological products was 0.47 events per 100 patient-years (*J Drugs Dermatol*. 2015;14:706-14), which was comparable to the incidence observed in the clinical studies of risankizumab.

The above results suggest that risankizumab does not increase the risk of cardiovascular events.

PMDA's view:
Currently there are no data suggestive of any clear relationship between risankizumab and cardiovascular events. However, incidences of cardiovascular events associated with risankizumab should be continuously investigated after the market launch.

7.R.2.4 Hypersensitivity-related events and injection site reaction

The applicant's explanation about the incidences of hypersensitivity-related events and injection site reaction:
Table 53 shows the incidence of hypersensitivity-related events and injection site reaction in the pooled population of 4 Japanese and foreign placebo-controlled studies and in the pooled population of 6 Japanese and foreign studies. No serious events were observed in any of the groups.

Table 53. Incidence of adverse events related to hypersensitivity and injection site reaction

	Pooled population of 4 Japanese and foreign placebo-controlled studies					Pooled population of 6 Japanese and foreign studies			
	Japanese subpopulation			Entire population		Japanese subpopulation		Entire population	
	75 mg	150 mg	Placebo	150 mg	Placebo	75 mg	150 mg	150 mg	UST
N	58	98	69	1060	358	85	134	1672	199
Total duration of exposure (100 patient-years)	17.7	29.9	21.2	325.8	109.8	79.6	130.6	1758.5	202.1
Hypersensitivity-related events	3 (5.2) 16.9	5 (5.1) 16.7	2 (2.9) 9.4	29 (2.7) 9.8	9 (2.5) 10.9	9 (10.6) 12.6	20 (14.9) 15.3	118 (7.1) 8.6	9 (4.5) 5.4
Category									
Hypersensitivity[a)]	3 (5.2) 16.9	5 (5.1) 16.7	2 (2.9) 9.4	29 (2.7) 9.8	9 (2.5) 10.9	9 (10.6) 12.6	20 (14.9) 15.3	118 (7.1) 8.6	9 (4.5) 5.4
Anaphylactic reaction[b)]	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Main events (PT)									
Dermatitis contact	1 (1.7) 5.6	0 0	0 0	6 (0.6) 1.8	2 (0.6) 2.7	1 (1.2) 1.3	4 (3.0) 3.1	27 (1.6) 1.9	3 (1.5) 1.5
Eczema	1 (1.7) 5.6	4 (4.1) 13.4	0 0	7 (0.7) 2.1	1 (0.3) 0.9	2 (2.4) 2.5	7 (5.2) 5.4	25 (1.5) 1.5	2 (1.0) 1.5
Urticaria	0 0	0 0	1 (1.4) 4.7	6 (0.6) 2.5	2 (0.6) 1.8	3 (3.5) 3.8	4 (3.0) 3.1	18 (1.1) 1.5	1 (0.5) 0.5
Dermatitis	0 0	0 0	0 0	5 (0.5) 1.5	2 (0.6) 1.8	1 (1.2) 1.3	1 (0.7) 0.8	17 (1.0) 1.0	1 (0.5) 0.5
Rash	0 0	0 0	0 0	2 (0.2) 0.6	0 0	0 0	1 (0.7) 0.8	8 (0.5) 0.5	0 0
Injection site reaction[c)]	0 0	1 (1.0) 3.3	0 0	13 (1.2) 5.8	3 (0.8) 4.6	0 0	1 (0.7) 0.8	60 (3.6) 5.5	7 (3.5) 4.5
Main events (PT)									
Injection site erythema	0 0	0 0	0 0	5 (0.5) 1.8	0 0	0 0	0 0	28 (1.7) 2.3	1 (0.5) 1.0
Injection site pruritus	0 0	0 0	0 0	3 (0.3) 1.2	0 0	0 0	0 0	8 (0.5) 0.7	0 0
Injection site pain	0 0	0 0	0 0	2 (0.2) 0.6	3 (0.8) 2.7	0 0	0 0	8 (0.5) 0.5	1 (0.5) 0.5
Injection site swelling	0 0	0 0	0 0	2 (0.2) 0.9	1 (0.3) 0.9	0 0	0 0	6 (0.4) 0.5	0 0
Injection site reaction	0 0	0 0	0 0	1 (<0.1) 0.3	0 0	0 0	0 0	6 (0.4) 0.5	5 (2.5) 3.0

Upper row, n (%)
Lower row, Number of events per 100-patient years adjusted for the total duration of exposure
a) Events classified as "Hypersensitivity" (SMQ)
b) Events classified as "Anaphylactic reaction" (SMQ)
c) Events included in MedDRA Query defined by the applicant.

In Study M16-002 in patients with active PsA, the incidence of adverse events related to hypersensitivity was 0.7% (1 of 143) of patients (150 mg Q4W group, anaphylactic reaction), and the incidence of adverse events related to injection site reaction was 3.5% (5 of 143) of patients (2 in the 150 mg Q12W group, 3 in the 150 mg Q4W group). In Study M15-988 in patients with GPP or EP, the incidence of hypersensitivity-related events was 23.5% (4 of 17) of patients (2 in the GPP 75 mg group, 1 in the GPP 150 mg group, 1 in the EP 75 mg group). No injection site reaction was observed.

In Studies M15-992, M15-995, M15-997, M16-004, M16-008, and M16-010, injection site reaction was evaluated using case reports on local tolerability. Table 54 shows the incidence of adverse events related to injection site reaction. No clear difference was observed between the placebo group and the risankizumab group.

Table 54. Incidence of adverse events related to injection site reaction described in case reports on local tolerability

	Pooled population of 4 Japanese and foreign placebo-controlled studies					Pooled population of 6 Japanese and foreign studies			
	Japanese subpopulation			Entire population		Japanese subpopulation		Entire population	
	75 mg	150 mg	Placebo	150 mg	Placebo	75 mg	150 mg	150 mg	UST
N	58	98	69	1060	358	85	134	1672	199
Swelling	0	0	0	2 (0.2)	2 (0.6)	0	0	10 (0.6)	3 (1.5)
Induration	0	0	0	0	1 (0.3)	0	0	6 (0.4)	1 (0.5)
Pyrexia	0	0	0	1 (<0.1)	2 (0.6)	0	0	10 (0.6)	1 (0.5)
Redness	0	0	0	13 (1.2)	3 (0.8)	0	0	30 (1.8)	8 (4.1)
Pain	0	0	0	3 (0.3)	2 (0.6)	0	0	12 (0.7)	4 (2.0)
Other	0	0	0	10 (0.9)	4 (1.1)	0	0	23 (1.4)	4 (2.0)

n (%). Patients who had at least 1 episode of injection site reaction are included."

PMDA's view:

Since hypersensitivity and injection site reaction were observed following the administration of risankizumab, a precautionary statement should be included in the package insert. Also, because risankizumab is a biological product, incidences of hypersensitivity-related events and injection site reaction should be investigated continuously after the market launch.

7.R.2.5 Psychoneurological events

The applicant's explanation about incidence of psychoneurological events associated with risankizumab:

Table 55 shows the incidence of psychoneurological events in the pooled population of 4 Japanese and foreign placebo-controlled studies and in the pooled population of 6 Japanese and foreign studies. There was no case of completed suicide.

Table 55. Incidence of adverse events related to psychoneurological events

	Pooled population of 4 Japanese and foreign placebo-controlled studies					Pooled population of 6 Japanese and foreign studies			
	Japanese subpopulation			Entire population		Japanese subpopulation		Entire population	
	75 mg	150 mg	Placebo	150 mg	Placebo	75 mg	150 mg	150 mg	UST
N	58	98	69	1060	358	85	134	1672	199
Total duration of exposure (100 patient-years)	17.7	29.9	21.2	325.8	109.8	79.6	130.6	1758.5	202.1
Depression, suicidal ideation and attempt	0 0	0 0	0 0	4 (0.4) 1.2	3 (0.8) 2.7	0 0	1 (0.7) 0.9	21 (1.3) 1.3	4 (2.0) 2.5
Category									
Depression[a)]	0 0	0 0	0 0	3 (0.3) 0.9	2 (0.6) 1.8	0 0	1 (0.7) 0.9	20 (1.2) 1.1	3 (1.5) 2.0
Suicidal ideation and attempt[b)]	0 0	0 0	0 0	1 (<0.1) 0.3	1 (0.3) 0.9	0 0	0 0	2 (0.1) 0.1	1 (0.5) 0.5
Main event (PT)									
Depression	0 0	0 0	0 0	1 (<0.1) 0.3	2 (0.6) 1.8	0 0	1 (0.7) 0.9	16 (1.0) 0.9	2 (1.0) 1.5
Depressed mood	0 0	0 0	0 0	2 (0.2) 0.6	0 0	0 0	0 0	3 (0.2) 0.2	0 0

Upper row, n (%)
Lower row, Number of events per 100 patient-years adjusted for total duration of exposure
a) Events classified as "Depression (excl suicide and self-injury)" in SMQ
b) Events classified as "Suicide/self-injury" in SMQ

In Study M16-002 in patients with active PsA, the incidence of adverse events related to psychoneurological events was 1.4% (2 of 143) of patients (2 patients in the 150 mg Q12W group: depression in one patient and depressed mood in the other). In Study M15-988 in patients with GPP or EP, the incidence of adverse events related to psychoneurological events was 5.9% (1 of 17) of patients (GPP 150 mg group; depression).

These results showed that the incidence of adverse events related to depression, suicidal ideation or attempt did not tend to increase in the risankizumab group compared to the placebo group. The applicant therefore considers that risankizumab does not increase the risk of depression, suicidal ideation or attempt.

PMDA's view:
Patients with psoriasis often also have mental disorder such as depression (*Dermatol Res Pract.* 2015;2015:409637, *Clin Dermatol*. 2013;31:47-56). Serious psychoneurological events (depression in 2 patients, suicidal attempt in 1 patient) occurred in the risankizumab group although their causal relationship to the study drug was ruled out. It is therefore necessary to continuously investigate the effect of risankizumab on depression and other events related to suicide after the market launch.

7.R.2.6 Neutropenia

The applicant's explanation about the incidence of neutropenia-related events associated with risankizumab:
Grade 3 neutrophil count decreased was observed in <0.1% (1 of 1060) of patients in the 150 mg group and in 0.3% (1 of 358) of patients in the placebo group in the pooled population of 4 Japanese and foreign placebo-controlled studies; and in 0.2% (3 of 1672) of patients in the 150 mg group in the pooled population of 6 Japanese and foreign studies. No serious infection was observed in these patients.

Changes over time in neutrophil count from baseline were investigated in Studies M15-995 and M16-008. Results showed a slight decrease in neutrophil count in the risankizumab group compared to the placebo group, but the decrease was within the range of the reference level, suggesting no significant clinical effect.

PMDA's view:
Currently no data suggest that risankizumab increases the risk of decreased neutrophil count. However, IL-23 is involved in the growth and maintenance of IL-17-producing T cells (*J Immunol.* 2007;179:8274-9), and IL-17A is involved in the growth and maturation of neutrophils (*Immunol Res.* 2012;52:34-41). Therefore, occurrences of adverse drug reactions related to the decreased neutrophil count following risankizumab treatment should be investigated continuously after the market launch.

PMDA's view on the safety of risankizumab, based on its views in Sections 7.R.2.1 to 6:
Given the submitted data of clinical studies and the pharmacological action of risankizumab, there is no serious concern about the safety of risankizumab in patients with psoriasis. Therefore, the observed adverse events can be controlled appropriately by issuing precautions similar to those for the approved biological drugs. However, since serious adverse events including serious infection occurred in clinical studies, and since the risk of infection, etc., caused by the long-term suppression of IL-23 signaling is unclear currently, information on the safety of risankizumab, including the long-term safety, should be continuously collected after the market launch.

The above conclusion by PMDA will be finalized, taking account of comments raised in the Expert Discussion.

7.R.3 Dosage and administration

The applicant's explanation about the proposed dosage and administration based on the results of clinical studies submitted as evaluation data:
Paired comparisons in the Japanese phase II/III study (Study M16-004) showed a statistically significant difference in the PASI 90 achievement rate at Week 16, the primary efficacy endpoint, between the placebo and 75 mg groups and between the placebo and 50 mg groups, demonstrating the superiority of 75 and 150 mg to placebo. There was no clear difference in the safety between 75 mg and 150 mg, but the 150 mg dose is considered more appropriate for psoriasis vulgaris, for the following reasons:

- Improvement in each efficacy endpoint was achieved more rapidly in the 150 mg group than in the 75 mg group (Table 41).
- In the 75 mg group, efficacy tended to be lower in patients weighing >90 kg than in patients weighing ≤90 kg, whereas no such tendency was observed in the 150 mg group (Table 56).

Table 56. Efficacy at Week 16, classified by body weight (Study M16-004, ITT population, NRI)

	75 mg		150 mg		Placebo	
	≤90 kg (N = 50)	>90 kg (N = 8)	≤90 kg (N = 48)	>90 kg (N = 7)	≤90 kg (N = 49)	>90 kg (N = 9)
PASI 90 achievement rate	78.0 (39)	62.5 (5)	72.9 (35)	85.7 (6)	2.0 (1)	0
PASI 100 achievement rate	26.0 (13)	0	33.3 (16)	28.6 (2)	0	0
sPGA (0) achievement rate	34.0 (17)	0	37.5 (18)	42.9 (3)	0	0
sPGA (0/1) achievement rate	90.0 (45)	62.5 (5)	93.8 (45)	85.7 (6)	10.2 (5)	11.1 (1)

% (n)

For the treatment of PsA, GPP, and EP as well, risankizumab was shown to have efficacy in each clinical study at the same dosage regimen as used in the 150 mg group of studies in patients with psoriasis vulgaris, although the efficacy of PsA, GPP, and EP was evaluated in only a limited number of patients due to the small number of patients with these diseases in Japan. The above results suggested that PsA, GPP, and EP are treatable using the same dosage regimen as used for the treatment of psoriasis vulgaris.

Based on the above, the applicant considered that the dosage and administration for risankizumab should be as follows: 150 mg of risankizumab administered subcutaneously at Week 0, Week 4, and then at 12-week intervals.

PMDA's view:
Based on the currently available clinical study data, PMDA considers that the proposed dosage and administration (150 mg of risankizumab administered subcutaneously at Week 0, Week 4, and then at 12-week intervals) is acceptable.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.4 Indications

PMDA's view:
Reviews of the submitted data and in Sections 7.R.1 and 7.R.2 confirmed the safety and efficacy of risankizumab in patients with psoriasis vulgaris, PsA, GPP, and EP. Risankizumab therefore can be positioned as one of the treatment options for these patients. Thus, risankizumab should be indicated for "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," as proposed by the applicant.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.5 Clinical positioning

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

The applicant's explanation about the efficacy and safety of risankizumab in patients with psoriasis relative to the approved biological products:

In the global study and the foreign phase III studies (M15-995, M16-008, and M16-010) in patients with moderate to severe plaque psoriasis, the UST group and the adalimumab group were included as the active comparator groups. Table 57 shows a PASI 90 achievement rate at Week 16 and 52 in these studies.

Table 57. PASI 90 achievement rate over time
(Studies M15-995, M16-008, and M16-010, ITT population, NRI)

		150 mg	UST	Adalimumab	Placebo
Study M15-995					
	Week 16	74.8 (220/294)	47.5 (47/99)	-	2.0 (2/98)
	Week 52	80.6 (237/294)	50.5 (50/99)	-	85.1 (80/94)[a)]
Study M16-008					
	Week 16	75.3 (229/304)	42.0 (42/100)	-	4.9 (5/102)
	Week 52	81.9 (249/304)	44.0 (44/100)	-	78.4 (76/97)[a)]
Study M16-010					
	Week 16	72.4 (218/301)	-	47.4 (144/304)	-

% (n/N)
a) Placebo/risankizumab group

The outline of the safety profile and the incidences of adverse events, confirmed by the detailed investigations, are presented in Section 7.R.2 and Table 58. No clear difference in the safety profile was observed among risankizumab, UST, and adalimumab.

Table 58. Summary of safety in Study M16-010 (safety analysis population, up to Week 16)

	150 mg	Adalimumab
N	301	304
Total duration of exposure (100 patient years)	93.3	95.0
All adverse events	168 (55.8) 407.3	173 (56.9) 460.0
Serious adverse events	10 (3.3) 11.8	9 (3.0) 14.7
Adverse events leading to treatment discontinuation	4 (1.3) 4.3	6 (2.0) 6.3
Adverse drug reactions	55 (18.3) 114.7	61 (20.1) 150.5
Death	1 (0.3) 1.1	2 (0.7)[a)] 2.1
Infection[b)]	4 (1.3) 4.3	7 (2.3) 10.5
Serious infection[b)]	1 (0.3) 1.1	1 (0.3) 2.1
Malignant tumor[c)]	2 (0.7) 2.1	1 (0.3) 1.1
Cardiovascular events confirmed[d)]	2 (0.7) 2.1	2 (0.7) 2.1
Hypersensitivity-related events[e)]	10 (3.3) 12.9	9 (3.0) 11.6
Injection site reaction[b)]	7 (2.3) 8.6	17 (5.6) 48.4
Psychoneurological events[f)]	1 (0.3) 2.1	1 (0.3) 2.1
Neutrophil count decreased[g)]	0	1 (0.3) 1.1

Upper row, n (%)
Lower row, Number of events per 100 patient-years adjusted for total duration of exposure

a) Gallbladder cancer and abdominal abscess/sepsis in 1 patient each. The causal relationship of abdominal abscess/sepsis to the study drug was ruled out
b) Events classified as "Infection" by the MedDRA query defined by the applicant.
c) Events classified as "Malignancies" or "Malignant tumours" by SMQ
d) Events identified by the independent review panel as nonfatal myocardial infarction, nonfatal cerebrovascular disorder, sudden death, death of unknown cause, cardiovascular death (including suspicious death and unevaluable death), hospitalization due to angina unstable, or coronary arterial revascularization, and events identified by the independent review panel as clinically significant arrhythmia, cardiac failure, hypertensive emergency, thrombotic events (deep vein thrombosis, transient ischaemic attack, pulmonary embolism, or other nonfatal vascular infarction [those designated]).
e) Events classified as "Hypersensitivity" or "Anaphylactic reaction" by SMQ
f) Events classified as "Depression (excl suicide and self-injury)" or "Suicide/self-injury" by SMQ
g) Grade ≥3

PMDA's view:

Given the pharmacological action of risankizumab and its efficacy and safety profiles obtained so far, the clinical positioning of risankizumab will be similar to that of approved biological products used for psoriasis. The clinical positioning of risankizumab will be discussed by relevant academic societies, based on the information to be obtained after the market launch.

PMDA asked the applicant to explain points to remember in switching from other biological products to risankizumab or vice versa.

The applicant's explanation:

In Study M16-010,[18] patients in the adalimumab group who did not achieve PASI 50 at Week 16 and some of patients who achieved PASI 50 but did not achieve PASI 90 at Week 16 switched the study drug from adalimumab to risankizumab 150 mg (adalimumab/150 mg group). Tables 59 and 60 show PASI 90 and sPGA (0/1) achievement rates, and the safety summary, at Week 44. There was no particular concern about the efficacy or safety of risankizumab in patients inadequately responsive to adalimumab.

Table 59. PASI 90 and sPGA (0/1) achievement rates at Week 44 (Study M16-010, ITT population, NRI)

	150 mg	Adalimumab/150 mg		Adalimumab/adalimumab	
		Patients who had not achieved PASI 50[a)]	Patients who had achieved PASI 50 but not PASI 90[a)]	Patients who had achieved PASI 50 but not PASI 90[a)]	Patients who had achieved PASI 90[a)]
PASI 90 achievement rate	75.7 (228/301)	60.5 (23/38)	66.0 (35/53)	21.4 (12/56)	75.7 (109/144)
sPGA (0/1) achievement rate	77.7 (234/301)	63.2 (24/38)	73.6 (39/53)	33.9 (19/56)	79.9 (115/144)

% (n/N); a) At Week 16

Table 60. Safety summary (Study M16-010, after Week 16, safety analysis population)

	150 mg (N = 294)	Adalimumab/150 mg		Adalimumab/adalimumab	
		Patients who had not achieved PASI 50[a)] (N = 38)	Patients who had achieved PASI 50 but not PASI 90[a)] (N = 53)	Patients who had achieved PASI 50 but not PASI 90[a)] (N = 56)	Patients who had achieved PASI 90[a)] (N = 144)
All adverse events	63.9 (188)	60.5 (23)	75.5 (40)	66.1 (37)	68.1 (98)
Serious adverse events	4.1 (12)	10.5 (4)	5.7 (3)	3.6 (2)	3.5 (5)
Adverse events leading to treatment discontinuation	1.7 (5)	2.6 (1)	0	5.4 (3)	0.7 (1)
Adverse drug reactions	22.4 (66)	21.1 (8)	30.2 (16)	21.4 (12)	19.4 (28)
Death	0	0	0	0	0

% (n), a) At Week 16

Tables 61 and 62 show PASI 90 and sPGA (0/1) achievement rates and safety summary at Week 12 in patients who, after receiving UST in Study M16-008 or Study M15-995 (a foreign study with the same design as that of Study M16-008), proceeded to Study M15-997.[19]

[18] Foreign, active-controlled, randomized, double-blind, parallel-group study in patients with plaque psoriasis. Patients were randomized at baseline to the 150 mg group (administered at Week 0, 4, 16, 28, and 40) or to the adalimumab group (80 mg at Week 0, 40 mg at Week 1 and at 2-week intervals thereafter). Among patients randomized to the adalimumab group, those who did not achieve PASI 50 at Week 16 switched to risankizumab 150 mg (administered at Week 16, 20, and 32), those who achieved PASI 50 but not PASI 90 at Week 16 were re-randomized to risankizumab 150 mg (administered at Week 16, 20, and 32) or continued to receive adalimumab (40 mg at 2-week intervals), and those who achieved PASI 90 at Week 16 continued to receive adalimumab.

[19] An open-label, long-term treatment study enrolling patients who had completed Study M15-992, M15-995, M16-004, M16-008, or M16-010. Risankizumab (150 mg) was administered at 12-week intervals.

Table 61. PASI 90 and sPGA (0/1) achievement rates at Week 12 of risankizumab administration in patients who had received UST in the preceding study (Study M15-997, ITT population, LOCF)

	Patients who had not achieved PASI 50 (N = 11)	Patients who had achieved PASI 50 but not PASI 90 (N = 78)	Patients who had achieved PASI 90 (N = 80)
PASI 90 achievement rate	25.0 (1/4[a)])	48.6 (17/35[a)])	97.6 (41/42[a)])
sPGA (0/1) achievement rate	75.0 (3/4[a)])	74.3 (26/35[a)])	95.2 (40/42[a)])

% (n/N)

a) The population who were assessed for efficacy at 12 weeks after the start of risankizumab therapy

Table 62. Safety summary in patients who had received UST in the preceding study (Study M15-997, safety analysis population, data cut-off September 2017)

	Patients who had not achieved PASI 50 (N = 11)	Patients who had achieved PASI 50 but not PASI 90 (N = 78)	Patients who had achieved PASI 90 (N = 80)
All adverse events	9.1 (1)	17.9 (14)	17.5 (14)
Serious adverse events	0	1.3 (1)	1.3 (1)
Adverse events leading to treatment discontinuation	0	1.3 (1)	0
Adverse drug reactions	0	3.8 (3)	3.8 (3)
Death	0	0	0

% (n)

The above results showed a favorable benefit-risk balance in switching from adalimumab or UST to risankizumab, suggesting no particular problem about the switching. No data are available on the safety and efficacy after switching from risankizumab to other biological products.

PMDA's view:

So far, no data have shown particular problems in switching from other biological products to risankizumab. However, there are only limited data available on the switching, and immunomodulation associated with the administration of biological products generally has a possibility of causing serious infection. Therefore, the applicant should advise, through the package insert, etc. healthcare professionals to pay attention to the occurrence of serious infection when switching from other biological products to risankizumab, or vice versa, as is the case with approved biological products for psoriasis. Also, information on the switching from other biological products should be collected after the market launch, and such information should be provided appropriately to healthcare professionals.

7.R.5.2 Concomitant use with conventional treatments

The applicant's explanation about the safety in concomitant use of risankizumab with conventional treatments:

Judging from the experience in the clinical studies, risankizumab is expected to be used as a monotherapy for the treatment of psoriasis vulgaris, and not in combination with other systematic treatment or phototherapy. Some patients are expected to use topical corticosteroid in combination with risankizumab, but such concomitant use is unlikely to pose any safety problem.

Concomitant methotrexate (MTX) was used in more than half of patients with PsA in Study M16-002. The incidence of adverse events, serious adverse events, and serious infection was similar in patients

receiving risankizumab + MTX and those receiving risankizumab alone, showing no clear difference in safety between the 2 treatment regimens (see below).

Adverse events: 61.0% (50 of 82) of patients receiving risankizumab + MTX
63.9% (39 of 61) of patients receiving risankizumab alone
Serious adverse events: 3.7% (3 of 82) of patients receiving risankizumab + MTX
8.2% (5 of 61) of patients receiving risankizumab + alone
Serious infection: 0% (0 of 82) of patients receiving risankizumab + MTX
3.3% (2 of 61) of patients receiving risankizumab + alone

In patients with GPP or EP, risankizumab may be used in combination with non-biological systemic treatments (cyclosporine and etretinate), and concomitant use of cyclosporine or etretinate was allowed in Study M15-988. Concomitant use of these systemic treatments did not pose any problem, albeit investigated in only a limited number of patients (adverse events, GPP [5 of 5 patients receiving risankizumab + systemic treatment, 3 of 3 patients receiving risankizumab alone], EP [4 of 5 patients, 3 of 4 patients]; serious adverse events, GPP [0 of 5 patients, 2 of 3 patients], EP [1 of 5 patients, 1 of 4 patients]).

Thus, as for concomitant use with conventional treatments, the safety of risankizumab in combination with systemic treatments with immunosuppressive effect (similar to risankizumab), phototherapy, or other biological products remains to be established, as are the cases with conventional biological products. Therefore, a precautionary statement will be included in the package insert.

PMDA's view:
No sufficient data are available on the concomitant use of risankizumab with other treatments in clinical studies of risankizumab. In particular, concomitant use of risankizumab with immunosuppressive systemic treatments may cause infection and malignant tumor as a result of enhanced immunosuppressive effect, and concomitant use of risankizumab with phototherapy may increase the risk of skin cancer. Therefore, the applicant should advise, via the package insert, etc., healthcare professionals to exercise caution when using risankizumab in combination with other treatments, in the same manner as with other biological products against psoriasis, as proposed by the applicant. Patients using risankizumab in combination with other treatments should be closely monitored for their clinical conditions. Also, the applicant should advise, via the package insert, etc., healthcare professionals to avoid concomitant use of other biological products. Information on the safety of risankizumab in combination with other psoriasis treatments should be collected continuously after the market launch, and the information obtained should be provided appropriately to healthcare professionals.

7.R.6 Post-marketing safety measures

In order to confirm the safety and efficacy of risankizumab in the post-marketing setting (including the long-term safety and efficacy), the applicant plans to conduct, as post-marketing clinical studies, Study M15-997 (an open-label study in patients who have completed any of Studies M15-992, M15-995,

M16-004, M16-008, and M16-010) and Study M15-988, in addition to the usual pharmacovigilance activities.

PMDA's view:
As reviewed in Section 7.R.2, the safety profile of risankizumab is acceptable, judging from the data of the clinical studies. However, the safety and efficacy of risankizumab (including the long-term safety and efficacy) should be further investigated, because (1) serious events (e.g., serious infection) were observed in clinical studies and (2) risankizumab is expected to be administered over a long-term period, and the risk of infection, malignant tumor, etc., caused by the long-term suppression of IL-23 signaling pathway is currently unknown. It is therefore acceptable to investigate the long-term safety and efficacy of risankizumab in post-marketing clinical studies (which are to be switched from pre-marketing clinical studies) as proposed by the applicant, in addition to the usual pharmacovigilance activities.

Risankizumab should be used by a physician who has sufficient knowledge of risankizumab and expertise in the treatment of psoriasis. Adverse drug reactions such as serious infection should be addressed in coordination with a physician with sufficient knowledge and experience in the treatment of infection.

The above conclusion of PMDA and the necessity of further safety measures will be discussed at the Expert Discussion.

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 a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. 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 (CTD 5.3.5.1-3, CTD 5.3.5.1-4, CTD 5.3.5.1-5, and CTD 5.3.5.1-8) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that risankizumab has efficacy in the treatment of patients with psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis who had an inadequate response to conventional therapies, and that risankizumab has acceptable safety in view of its benefits. Risankizumab provides one of the options for the treatment of psoriasis and thus has a clinical significance. It is essential to take safety measures similar to those taken for other biological products used for psoriasis. Incidences of serious infection and other adverse events, including those occurring during long-term treatment, should be further investigated in the post-marketing surveillance, etc.

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

10. Other

The methods for efficacy assessment in clinical studies of risankizumab and the definitions of the endpoints are shown below.

<table>
<tr><th>Item</th><th>Definition</th></tr>
<tr><td>ACR 20 response rate</td><td>Percentage of patients who showed a ≥20% decrease from baseline in tender joint count among 68 joints and in swollen joint count among 66 joints, and also showed a ≥20% improvement from baseline in ≥3 of items among the following: (a) pain assessment by the patient using VAS, (b) overall assessment by the patients by VAS, (c) overall assessment by the physician using VAS, (d) assessment of the activity of daily living by the patient using Stanford Health Assessment Questionnaire Disability Index (HAQ-DI), and (e) CRP.</td></tr>
<tr><td>CGI-GI score</td><td>Overall improvement from the time of enrollment, assessed by the physician according to the following rating scale: 0 (not assessed), 1 (markedly improved), 2 (significantly improved), 3 (slightly improved), 4 (unchanged), 5 (slightly worsened), 6 (significantly worsened), and 7 (markedly worsened)</td></tr>
<tr><td>Clinical efficacy against EP</td><td>CGI-GI score 3 (slightly improved) or greater</td></tr>
<tr><td>Assessment of overall GPP improvement</td><td>Overall assessment of improvement according to the following criteria
<table>
<tr><th></th><th>Change in total JDA score</th><th></th><th>Other criteria</th></tr>
<tr><td>Markedly improved</td><td>Decrease by ≥3 points</td><td>or</td><td>No or few generalized GPP symptoms</td></tr>
<tr><td>Slightly improved</td><td>Decrease by 1 or 2 points</td><td>or</td><td>≥30% decrease in the area of pustular erythema
or
clinically significant improvement in ≥2 of other severity assessment parameters (area of erythema, area of edema, white blood cell count, CRP, pyrexia, serum albumin)</td></tr>
<tr><td>Marginally improved</td><td>0 (no change)</td><td>and</td><td>≥20% decrease in the area of pustular erythema
or
clinically significant improvement in ≥1 of other severity assessment parameters (area of erythema, area of edema, white blood cell count, CRP, pyrexia, serum albumin)</td></tr>
<tr><td>Unchanged</td><td>0 (no change)</td><td>and</td><td>Failure to meet other criteria of “mild improvement”</td></tr>
<tr><td>Worsened</td><td>Increase by ≥1 point</td><td>-</td><td>-</td></tr>
</table></td></tr>
<tr><td>Clinical efficacy against GPP</td><td>“Marginally improved” or greater in the assessment of overall GPP improvement</td></tr>
<tr><td>Total JDA score</td><td>Cutaneous symptoms (area of pustular erythema, area of erythema, and area of edema) are rated on a score of 0 to 3, and each of systemic symptoms/laboratory findings (pyrexia, white blood cell count, CRP, and serum albumin) is rated on a score of 0 to 2.
The severity of the symptoms is defined as mild if the total score is 1 to 6, moderate if 7 to 10, and severe if 11 to 17.</td></tr>
<tr><td>sPGA score</td><td>The physician rates erythema, induration, and scale formation in all psoriatic lesions on a score of 0 to 4. The severity of the symptoms is determined according to the mean of the three scores, as follows: 0, eradicated (mean score 0); 1, almost eradicated (mean score >0 and <1.5); 2, mild (mean score ≥1.5 and <2.5); 3, moderate (mean score ≥2.5 and <3.5); and 4, severe (mean score ≥3.5).</td></tr>
<tr><td>sPGA (0/1) achievement rate</td><td>Percentage of patients with sPGA of 0 or 1</td></tr>
<tr><td>PASI score</td><td>The whole body is divided into 4 parts: Head, trunk, upper limbs, and lower limbs, and each part is scored for (a) erythema, (b) infiltration/thickening, and (c) scales on a 5-point scale: 0 (none), 1 (mild), 2 (moderate), 3 (severe), and 4 (very severe). The sum of scores are multiplied by the percentage of the diseased area relative to BSA and by the percentage of each part (10% [head], 20% [upper limbs], 30% [trunk], 40% [lower limbs]) to obtain PASI score (maximum, 72.0).</td></tr>
<tr><td>PASI 50, 75, and 90 achievement rates</td><td>Percentage of patients who showed a ≥50%, ≥75%, or ≥90% decrease in PASI score from baseline</td></tr>
</table>

Review Report (2)

February 8, 2019

Product Submitted for Approval

Brand Name	Skyrizi 75 mg for S.C. Injection Syringe 0.83 mL
Non-proprietary Name	Risankizumab (Genetical Recombination)
Applicant	AbbVie GK
Date of Application	May 25, 2018

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. 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 and indications

The expert advisers at Expert Discussion supported PMDA's conclusion on the efficacy and indications of risankizumab described in Review Report (1).

1.2 Dosage and administration

The expert advisers at Expert Discussion largely supported PMDA's conclusion on the dosage and administration of risankizumab described in Review Report (1). The expert advisers also raised the following comment:

> Japanese clinical studies showed favorable treatment outcome in the 75 mg group. Therefore, it is also acceptable to offer patients the option of 75 mg dose, which can be chosen according to the patient's condition, for example, as a dose to be increased to, or decreased from, 150 mg.

PMDA's view:

Results of Study M16-004 showed that, in the 75 mg group, the clinical effect tended to be slow to become manifest compared to the 150 mg group, but the efficacy after Week 28 of administration was similar in both groups (Figure 4). PMDA considers that physician should be allowed to select the dose of risankizumab based on the comprehensive evaluation of the patient's condition because, together with the comments raised in the Expert Discussion, risankizumab is used by physicians with sufficient

knowledge of risankizumab and experience in the treatment of psoriasis. Based on the above, the dosage and administration of risankizumab should be "The usual adult dosage is 150 mg of risankizumab (genetical recombination) administered subcutaneously at Week 0, Week 4, and then at 12-week intervals. In addition, 75 mg per dose is allowed, depending on the patient's condition."

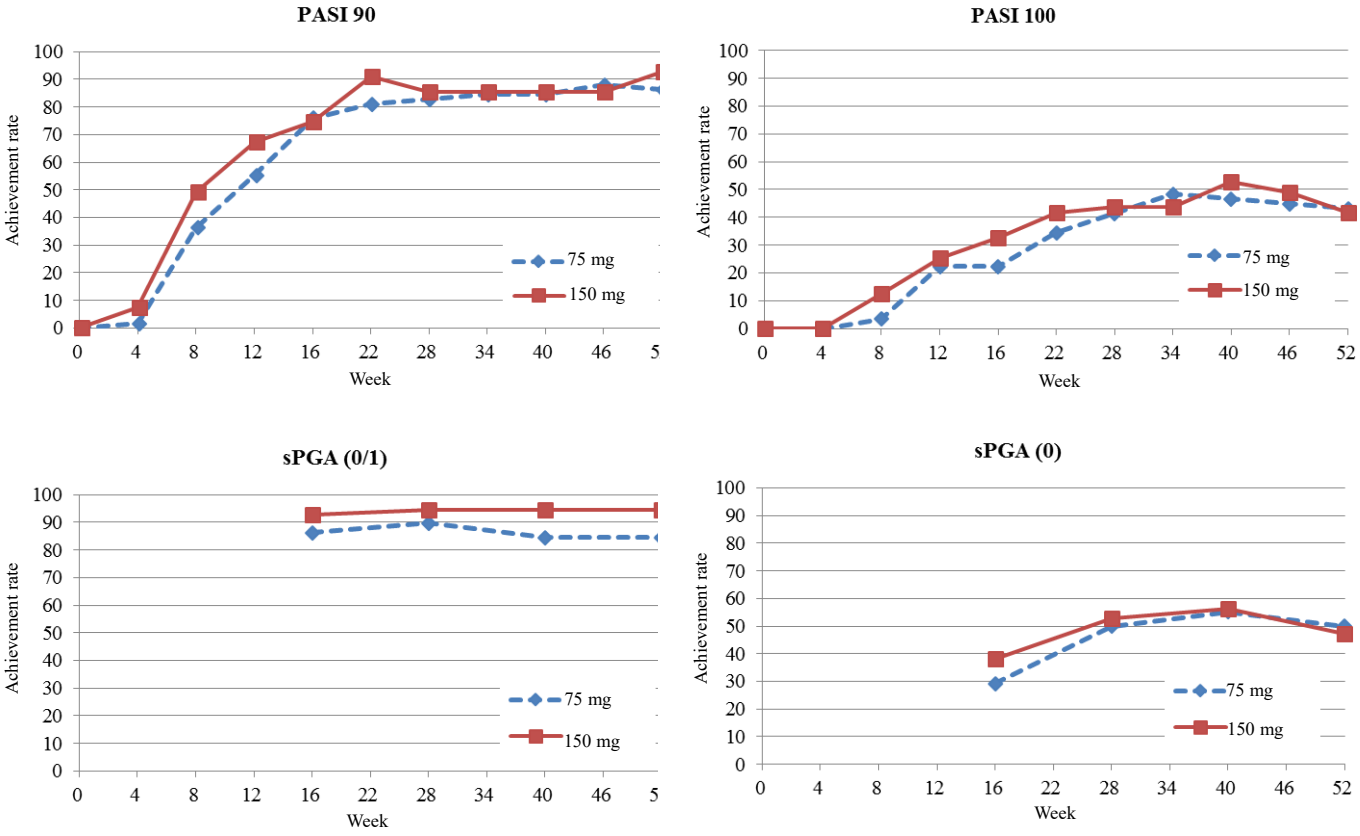

Figure 4. Changes over time in each efficacy endpoint
(Study M16-004, ITT population, NRI)

1.3 Safety and risk management plan (draft)

The expert advisers at Expert Discussion supported PMDA's conclusion on the safety of risankizumab and on the post-marketing safety measures described in Review Report (1).

In review of the discussion presented in Section "7.R.6 Post-marketing safety measures" in the Review Report (1) and the comments raised in the Expert Discussion, PMDA has concluded that the risk management plan (draft) for risankizumab should include the safety and efficacy specifications presented in Table 63, and that the applicant should conduct additional pharmacovigilance activities, surveillance and a study on the efficacy, and additional risk minimization activities presented in Table 64. Based on the above, PMDA instructed the applicant to conduct post-marketing surveillances, etc., to investigate these items.

Table 63. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Serious infection • Serious hypersensitivity	• Cardiovascular events • Malignant tumor • Immunogenicity • Decrease in neutrophil count	• None
Efficacy specification		
• None		

Table 64. Summary of additional pharmacovigilance activities, efficacy surveillance/study, and additional risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy surveillance/study	Additional risk minimization activities
• Early post-marketing phase vigilance • Post-marketing clinical study[a)] • Post-marketing clinical study[b)]	• None	• Disseminate data gathered during early post-marketing phase vigilance • Prepare and distribute "information materials for healthcare professionals (guideline for proper use)" • Make sure to provide information on proper use prior to risankizumab delivery

a) To be conducted after the approval of risankizumab by switching Study M15-997 to a post-marketing clinical study based on the approved dosage and administration.
b) To be conducted after the approval of risankizumab by switching Study M15-988 to a post-marketing clinical study based on the approved dosage and administration.

The applicant explained the plan to conduct post-marketing clinical studies to be switched from clinical studies, in patients with plaque psoriasis who have had an inadequate response to conventional therapies, patients with GPP, and patients with EP, to investigate the long-term safety and efficacy of risankizumab (Tables 65 and 66).

Table 65. Outline of post-marketing clinical study (to be switched from Study M15-997) (draft)

Objective	To evaluate the long-term safety and efficacy of risankizumab in patients with plaque psoriasis
Population	Patients with plaque psoriasis who had an inadequate response to conventional therapies and have completed any of the following preceding studies: M15-992, M15-995, M16-004, M16-008, and M16-010
Treatment duration	Approximately 60 to 120 weeks (156 weeks as Study M15-997; 196 to 244 weeks including the treatment duration in the preceding study)
Planned sample size	1971 at the maximum (including 210 Japanese patients)
Main survey items	Efficacy (PASI, sPGA, etc.) Safety (adverse events, vital sign, laboratory values, etc.)

Table 66. Outline of post-marketing clinical study (to be switched from M15-988) (draft)

Objective	To evaluate the long-term safety and efficacy of risankizumab in Japanese patients with GPP or EP
Population	Japanese patients with GPP or EP who participated in Study M15-988
Treatment duration	Approximately 56 to 72 weeks (160 weeks as Study M15-988)
Planned sample size	12 at the maximum (4 patients with GPP, 8 patients with EP)
Main survey items	Efficacy (clinical efficacy for GPP/EP, PASI, etc.) Safety (adverse events, vital signs, laboratory tests, etc.)

PMDA accepted these plans. The information obtained through these activities should be provided appropriately and promptly to healthcare professionals, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the dosage and administration as shown below, with the following approval condition.

Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is classified as a biological product. The drug product and its drug substance are both classified as powerful drugs.

Indications

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 150 mg of risankizumab (genetical recombination) administered subcutaneously at Week 0, Week 4, and then at 12-week intervals. In addition, 75 mg per dose is allowed, depending on the patient's condition.

(The underlined words are added to the proposed text.)

Approval Condition

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

Appendix

List of Abbreviations

ACR	American college of rheumatology
ADA	Anti-drug antibody
Adalimumab	Adalimumab (Genetical Recombination)
ADCC	Antibody-dependent cellular cytotoxicity
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma/serum concentration-time curve
AUC_{inf}	AUC up to infinity
AUC_{last}	AUC up to the last time point with a measurable concentration after dosing
AUC_{tau}	AUC over a dosing interval
Brodalumab	Brodalumab (Genetical Recombination)
BSA	Body surface area
CASPAR	Classification criteria for psoriatic arthritis
CDC	Complement-dependent cytotoxicity
CGI-GI	Clinical global impression-global improvement
CHO	Chinese hamster ovary
CI	confidence interval
CL	Clearance
C_{max}	Maximum plasma/serum concentration
CQA	Critical quality attribute
CRP	C-reactive protein
C_{trough}	Trough plasma concentration
DLQI	Dermatology life quality index
DNA	Deoxyribonucleic acid
EP	Erythrodermic psoriasis
FAS	Full analysis set
Fc	Fragment, crystallizable
FcRn	Neonatal Fc receptor
FcγR	Fc γ receptor
GCP	Good clinical practice
GPP	Generalized pustular psoriasis
Guselkumab	Guselkumab (Genetical Recombination)
HCP	Host cell protein
IC_{50}	50% inhibitory concentration
IFNγ	Interferon γ
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IL	Interleukin
Infliximab	Infliximab (Genetical Recombination)
ITT	Intent-to-treat
Ixekizumab	Ixekizumab (Genetical Recombination)
JDA	Japanese dermatological association
K_D	Dissociation constant
LOCF	Last observation carried forward
MCB	Master cell bank
MedDRA	Medical dictionary for regulatory activities
MTX	Methotrexate

NRI	Non-responder imputation
PASI	Psoriasis area and severity index
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPCB	Post production cell bank
PPK	Population pharmacokinetics
PsA	Psoriatic arthritis
PT	Preferred term
QbD	Quality by design
RH	Relative humidity
Risankizumab	Risankizumab (Genetical Recombination)
SDS	Sodium dodecyl sulfate
Secukinumab	Secukinumab (Genetical Recombination)
Skyrizi	Skyrizi for Subcutaneous Injection 75 mg syringe 0.83 mL
SMQ	Standardised MedDRA queries
sPGA	Static physician global assessment
$t_{1/2}$	Elimination half-life
t_{max}	Time to reach maximum plasma/serum concentration
TNF	Tumor necrosis factor
UST	Ustekinumab (Genetical Recombination)
VAS	Visual analogue scale
Vd	Volume of distribution
WCB	Working cell bank