Report on the Deliberation Results

August 10, 2017

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

Brand Name	Kevzara 150 mg Syringe for SC Injection
	Kevzara 200 mg Syringe for SC Injection
	Kevzara 150 mg Auto-injector for SC Injection
	Kevzara 200 mg Auto-injector for SC Injection
Non-proprietary Name	Sarilumab (Genetical Recombination) (JAN*)
Applicant	Sanofi K.K.
Date of Application	October 7, 2016

Results of Deliberation

In its meeting held on July 27, 2017, 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, and the re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Condition of Approval

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

**Japanese Accepted Name (modified INN)*

Review Report

July 18, 2017
Pharmaceuticals and Medical Devices Agency

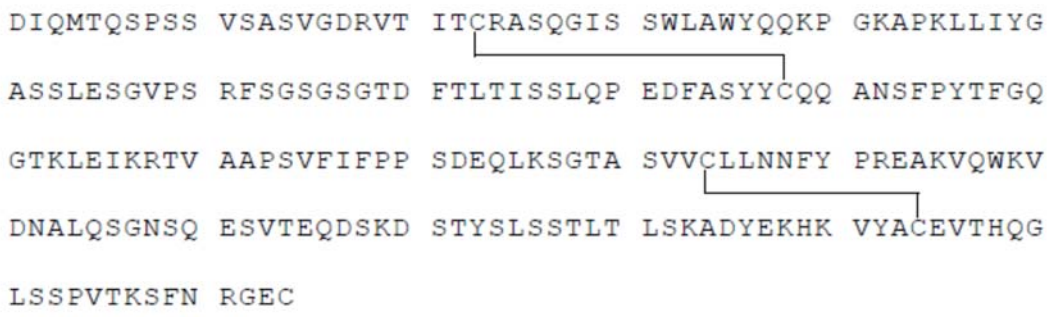
The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Kevzara 150 mg Syringe for SC Injection Kevzara 200 mg Syringe for SC Injection Kevzara 150 mg Auto-injector for SC Injection Kevzara 200 mg Auto-injector for SC Injection
Non-proprietary name	Sarilumab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	October 7, 2016
Dosage Form/Strength	Solution for injection in a syringe, each containing 150 or 200 mg of Sarilumab (Genetical Recombination)
Application Classification	Prescription drug (1) Drug(s) with a new active ingredient
Definition	Sarilumab is a recombinant human IgG1 monoclonal antibody against human interleukin-6 receptor α subunit. Sarilumab is produced in Chinese hamster ovary cells. Sarilumab is a glycoprotein (molecular weight: ca. 150,000) composed of 2 H-chains (γ1-chains) consisting of 446 amino acid residues each and 2 L-chains (κ-chains) consisting of 214 amino acid residues each.

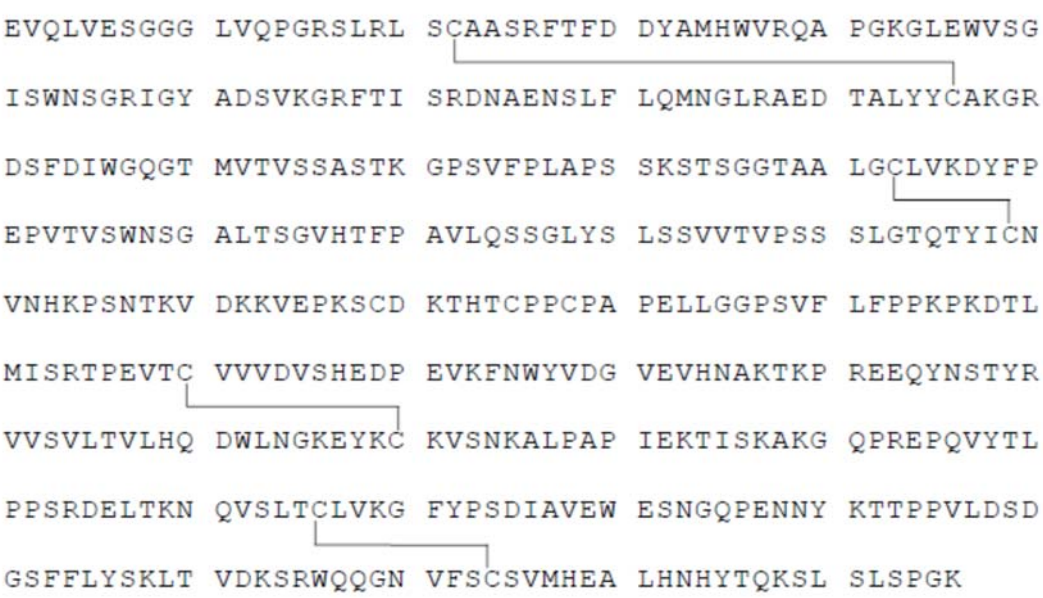
Structure

Amino acid sequence:

L chain



H chain



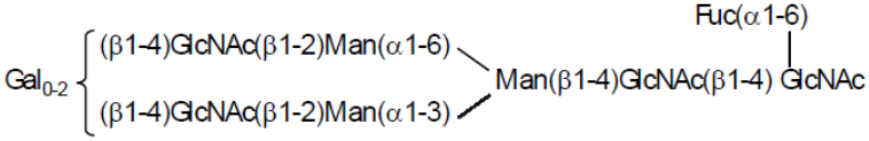
N296 in H chain: Glycosylation site

K446 in H chain: Partial processing

C214 in L chain - C219 in H chain, C225 in H chain - C225 in H chain, C228 in H chain - C228 in H chain: Disulfide bonds

Solid lines in the figure: Intrachain disulfide bonds in H chains and L chains

Estimated structure of main carbohydrate chain



Gal, Galactose; GlcNAc, N-acetylglucosamine; Man, Mannose; Fuc, Fucose

Molecular formula: (Sarilumab) $C_{6388}H_{9886}N_{1718}O_{1998}S_{44}$
(L chain) $C_{1022}H_{1581}N_{273}O_{334}S_{6}$
(H chain) $C_{2172}H_{3366}N_{586}O_{665}S_{16}$

Molecular weight: (Sarilumab) 144,130.02 (protein moiety consisting of 4 chains)
(L chain) 23,228.51
(H chain) 48,840.53

Reviewing Office Office of New Drug IV

Results of Review

PMDA has concluded that the product has efficacy in the treatment of patients with rheumatoid arthritis who have had an inadequate response to conventional treatments, and that the product has acceptable safety in view of the benefits (see Attachment).

As a result of its review, PMDA has concluded that Kevzara may be approved for the indication and dosage and administration shown below, with the following condition. The product may cause serious adverse events such as infections. Healthcare professionals should be reminded to carefully monitor patient condition and weigh the risk and benefit before deciding to use Kevzara and to take other safety measures as practiced for the conventional biological products for RA. Post-marketing surveillance must be designed to trace the occurrence of adverse events including serious infections and malignant tumors. New findings should be communicated to healthcare professionals and patients.

Indication

Rheumatoid arthritis in patients who have had an inadequate response to conventional treatments

Dosage and Administration

The usual adult dosage is 200 mg of sarilumab (genetical recombination) subcutaneously injected once every 2 weeks. The dose should be reduced to 150 mg according to the patient's condition.

Condition of Approval

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

Attachment

Review Report (1)

June 23, 2017

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.

Product Submitted for Approval

Brand Name	Kevzara 150 mg Syringe for SC Injection Kevzara 200 mg Syringe for SC Injection Kevzara 150 mg Auto-injector for SC Injection Kevzara 200 mg Auto-injector for SC Injection
Non-proprietary Name	Sarilumab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	October 7, 2016
Dosage Form/Strength	Solution for injection in a syringe, each containing 150 or 200 mg of Sarilumab (Genetical Recombination)
Proposed Indication	Rheumatoid arthritis in patients who have had an inadequate response to conventional treatments

Proposed Dosage and Administration

The usual adult dosage is 200 mg of sarilumab (genetical recombination) subcutaneously injected once every 2 weeks. The dose may be adjusted to 150 mg according to the patient's body weight.

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List of Abbreviations

ADA	anti-drug antibody
adalimumab	adalimumab (genetical recombination)
ADCC	antibody-dependent cell-mediated cytotoxicity
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
CAL	cells at the limit of *in vitro* cell age used for production
CDC	complement-dependent cytotoxicity
cDMARDs	conventional disease modifying anti-rheumatic drugs
CI	confidence interval
CL	total body clearance for intravenous administration
CL/F	total body clearance for extravascular administration
C_{max}	maximum serum concentration
CRP	C-reactive protein
C_{trough}	trough concentration
ELISA	enzyme-linked immunosorbent assay
etanercept	etanercept (genetical recombination)
Fc	fragment crystallizable
IC_{50}	half maximal inhibitory concentration
Ig	immunoglobulin
IL	Interleukin
IL-6Rα	interleukin-6 receptor α-subunit
infliximab	infliximab (genetical recombination)
ITT/mITT	intent-to-treat/modified intent-to-treat
K_D	equilibrium dissociation constant
Kevzara	Kevzara 150 mg Syringe for SC Injection, Kevzara 200 mg Syringe for SC Injection, Kevzara 150 mg Auto-injector for SC Injection, and Kevzara 200 mg Auto-injector for SC Injection
KLH	keyhole limpet hemocyanin
LLN	lower limit of normal
LOCF	last observation carried forward
[redacted]	[redacted]
MCB	master cell bank
MedDRA	medical dictionary for regulatory activities
MMRM	mixed model for repeated measures
MTX	methotrexate
NMSC	non-melanoma skin cancers
NRI	non-responder imputation
q2w	once every 2 weeks
QbD	quality by design
qw	once every week
RA	rheumatoid arthritis
sarilumab	sarilumab (genetical recombination)
SDS	sodium dodecyl sulfate
SEC	size exclusion chromatography
STAT	signal transducer and activator of transcription
$t_{1/2}$	half-life
t_{max}	time of occurrence of maximum serum concentration
tocilizumab	tocilizumab (genetical recombination)
ULN	upper limit of normal
V_{ss}	volume of distribution at steady-state
WCB	working cell bank

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

Sarilumab (genetical recombination) is the active ingredient of "Kevzara 150 mg Syringe for SC Injection, Kevzara 200 mg Syringe for SC Injection, Kevzara 150 mg Auto-injector for SC Injection, and Kevzara 200 mg Auto-injector for SC Injection." Sarilumab is a human immunoglobulin (Ig) G1 monoclonal antibody against human interleukin-6 (IL-6) receptor discovered by Regeneron Pharmaceuticals, Inc.

Rheumatoid arthritis (RA) is an inflammatory disease characterized by persistent synovitis and progressive joint destruction in multiple joints. Available drugs for RA are conventional disease modifying anti-rheumatic drugs (cDMARDs) such as methotrexate (MTX) used for disease control including the inhibition of progression of joint destruction in drug therapy for early-stage RA. Biological products such as tumor necrosis factor (TNF) inhibitors are also used in patients who have not responded adequately to these treatments.

IL-6 is a cytokine involved in inflammatory response, cell differentiation/proliferation, and immune response control (*Arthritis Res Ther*. 2006;8[Suppl 2]:S2:1-6). The concentration of IL-6 in serum and synovial fluid is higher in patients with RA than in healthy individuals. IL-6 is expressed in most synovial cells, and increased soluble interleukin-6 receptor α-subunit (IL-6Rα) is shown in patients with inflammatory diseases including RA (*Arthritis Res Ther*. 2006;8[Suppl 2]:S4:1-5). Based on these findings, IL-6 is recognized as one of the main cytokines involved in RA and other inflammatory diseases. Sarilumab, in expectation of its effects by inhibiting IL-6 signaling, has been developed as a medication for RA.

Outside Japan, the clinical development of sarilumab for patients with RA started in [redacted] 20[redacted]. Approval was granted in Canada in January 2017 and in the US in May 2017. In Europe, the regulatory review is ongoing as of June 2017.

In Japan, the clinical development of sarilumab in patients with RA began in [redacted] 20[redacted] after the start of a foreign Phase III studies. With data that incorporate the foreign study results, the applicant recently submitted an application for marketing approval of Kevzara in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E5 guidelines ("Ethnic Factors in the Acceptability of Foreign Clinical Data," PMSB/ELD Notification No. 672 dated August 11, 1998).

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

2.1 Drug substance

2.1.1 Preparation and control of cell substrate

Cells producing anti-human IL-6Rα antibodies were generated by [redacted] to [redacted] transgenic mice. Hybridoma cells were generated using these production cells, and appropriate clones were selected [redacted]. A gene expression construct was developed by inserting gene fragments encoding the variable regions of heavy and light chains prepared

using these clones into plasmids encoding the constant regions of heavy and light chains of human IgG1. The gene expression construct was introduced into a Chinese hamster ovary cell line, and clones appropriate for production of sarilumab were selected as the source for the preparation of the master cell bank (MCB) and working cell banks (WCBs).

The characterization and purity testing of the MCB, WCBs, and cells at the limit of *in vitro* cell age used for production (CALs) were conducted according to ICH Q5A (R1), Q5B, and Q5D guidelines. Genetic stability during the production period was demonstrated, and neither adventitious viruses nor non-viral adventitious agents were detected in the tests performed, other than endogenous retrovirus-like particles commonly found in rodent-derived cell lines.

The MCB and WCBs are stored in liquid nitrogen vapor phase. The regeneration of the MCB is not planned, while WCBs will be regenerated as required.

2.1.2 Manufacturing process

Manufacturing process of the drug substance consists of expansion culture, production culture, harvest/filtration, [redacted], viral filtration, [redacted], dispensing/storage, and formulation/testing/storage. The obtained drug substance is dispensed into [redacted] vessels and stored at [redacted]°C to [redacted]°C. In the formulation/testing/storage process, 2 different types of the drug substance specific to 2 different formulations of the drug product (150 and 200 mg) are manufactured and controlled separately.

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

Process validation is conducted for the manufacturing process of the drug substance on a commercial scale.

2.1.3 Safety evaluation of adventitious agents

No biologically-derived raw materials are used in the manufacturing process for the drug substance except Chinese hamster ovary cell (host cell) line. However, [redacted] is used for manufacturing of [redacted] (a material of the culture media during the preparation of MCB and WCBs), and [redacted] is used for manufacturing of [redacted]. These materials have been confirmed to meet the Standard for Biological Ingredients.

Purity tests were performed on the MCB, WCBs, and CALs [see Section "2.1.1 Preparation and control of cell substrate"]. Mycoplasma testing, bioburden, *in vitro* adventitious virus testing, and murine minute virus testing were performed on the unprocessed bulks after production culture. No contamination with viral or non-viral adventitious agents was detected in the performed tests. These tests of the unprocessed bulks have been specified as in-process control tests.

Viral clearance in the purification process was evaluated using model viruses. The purification process was found to have a certain capacity to remove viruses (Table 1).

Table 1. Results of viral clearance studies

Manufacturing process	Viral clearance factor (log_{10})				
	X-MuLV	MMV	PRV	EMCV	Reo3
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Viral filtration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall reduction factor	>18.0	>12.1	>19.9	>9.4	>16.3

X-MuLV, Xenotropic murine leukemia virus; MMV, Murine minute virus; PRV, Pseudorabies virus; EMCV, Encephalomyocarditis virus; Reo-3, Reovirus type 3
[redacted]

2.1.4 Manufacturing process development

The following major changes were made in the manufacturing method for the drug substance during development (4 different methods are referred to as Non-clinical Study Method, Method S1, Method S2, and Proposed Method): Phase I studies used the drug product derived from the drug substance made by Method S1, S2 or Proposed Method. Phase II studies used the drug product derived from Method S2-drug substance. Phase III studies used the drug product derived from the drug substance made by Method S2 or Proposed Method.

- From Non-clinical Study Method to Method S1: Changes of [redacted] and [redacted], etc.
- From Method S1 to Method S2: Changes of [redacted], [redacted], and [redacted], etc.
- From Method S2 to Proposed Method: Changes of [redacted], [redacted] and [redacted], [redacted] and [redacted] processes, etc.

The comparability of the quality attributes was evaluated at the time of the changes of the manufacturing method. When Method S2 was modified to Proposed Method, a clinical study begun [see Section "6.1.1 Comparison of pharmacokinetics between different formulations"], which demonstrated the comparability between the pre-change and post-change drug substances.

The concept of quality by design (QbD) was employed for manufacturing process development [see Section "2.3 QbD"].

2.1.5 Characterization

2.1.5.1 Structure and characteristics

Characterization was performed according to Table 2.

Table 2. Characterization parameters

Primary structure	Amino acid sequence, post-translational modification (, , , , and)
Higher order structure	Secondary and tertiary structures, disulfide bonds, free thiol groups
Physicochemical properties	Molecular weight, , molecular variants
Carbohydrate structure	Monosaccharide composition, carbohydrate profile, glycosylation site
Biological properties	Complex formation with IL-6Rα
	Affinity to IL-6Rα
	Activity of IL-6 signaling inhibition
	ADCC and CDC activities

A study on biological properties conducted using revealed that sarilumab forms predominantly a complex with IL-6Rα at the ratio of or , and value of sarilumab against IL-6Rα was calculated through a analysis. In addition, sarilumab was found to inhibit dose-dependently the activation of signal transducer and activator of transcription 3 (STAT3) by human IL-6 in HepG2 cells, the proliferation of DS-1 cells after stimulation by human IL-6, and the activation of STAT3 by human IL-6 in HEK293 cells in the presence of extracellular domain of human IL-6Rα [see Section "3.1.4 Effect on IL-6 signaling"]. Sarilumab demonstrated to have neither antibody-dependent cell-mediated cytotoxicity (ADCC) nor complement-dependent cytotoxicity (CDC) activity [see Section "3.1.2 Study on effector function"].

2.1.5.2 Product-related substances/Product-related impurities

Based on the data obtained by the characterization described in Section "2.1.5.1 Structure and characteristics," and were identified as product-related substances, and and were identified as product-related impurities. The product-related impurities are appropriately controlled by specifications of .

2.1.5.3 Process-related impurities

Process-related impurities identified include , , , host cell-derived proteins, host cell-derived DNAs, , , (, , , and), , , , endotoxins, and bioburden. All process-related impurities were demonstrated to be adequately removed through the manufacturing process. Endotoxins are controlled by the drug substance and drug product specifications, and bioburden is controlled by the drug substance specification.

2.1.6 Control of drug substance

The proposed specification for the drug substance include content, description, identification (peptide map,), glycan analysis, osmolality, pH, , purity (size exclusion chromatography [SEC], sodium dodecyl sulfate [SDS] capillary gel electrophoresis [reduced and non-reduced]), charge heterogeneity ( ), bacterial endotoxins, bioburden, , potency ( ), and assay (ultraviolet-visible spectrophotometry). In the course of the regulatory review, and were added.

2.1.7 Stability of drug substance

Table 3 outlines the major stability studies of the drug substance. These studies were conducted on the drug substance produced by Proposed Method.

Table 3. Outline of major stability studies of the drug substance

Study	Number of batches	Storage condition	Duration	Storage form
Long-term testing	3[a)]	[redacted]°C	[redacted] months	[redacted] container
Accelerated testing	3[a)]	[redacted]°C	[redacted] months	
Stress testing	1[b)]	[redacted]°C	[redacted] months	
Photostability testing	1[b)]	Overall illumination ≥1.2 million lux·hr and integrated near ultraviolet energy ≥200 W·hr/m^2		

[a)] Three lots of the drug substance for 150 mg formulation and 3 lots of the drug substance for 200 mg formulation.
[b)] One lot of the drug substance for 150 mg formulation and 1 lot of the drug substance for 200 mg formulation.

The long-term testing showed no significant changes in quality attributes throughout the study period.

The accelerated testing showed trends towards [redacted], [redacted], and [redacted].

The stress testing showed [redacted] and [redacted] in addition to the same changes seen in the accelerated testing.

Photostability data showed that [redacted].

Based on the above, a shelf-life of [redacted] months has been proposed for the drug substance when stored at [redacted]°C to [redacted]°C [redacted] in a [redacted] container.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

One of the product forms is a pre-filled syringe. It is a glass syringe (1 mL) with a needle filled with a drug solution containing 150 or 200 mg of sarilumab per 1.14 mL. Another one is an auto-injector product, which is the combination of a pre-filled syringe product and an auto-injector. The drug product contains L-histidine, L-histidine hydrochloride hydrate, L-arginine hydrochloride, sucrose, polysorbate 20, and water for injection as excipients.

2.2.2 Manufacturing process

The manufacturing process for the drug product consists of dissolution of the drug substance, mixing, prefiltration, sterile filtration, filling/stoppering, assembling/labeling of syringe, storage/testing, labeling/packaging/storage/testing processes. [redacted] and [redacted] are defined as critical steps. Process validation has been conducted for the manufacturing process for the drug product on a commercial scale.

2.2.3 Manufacturing process development

The major changes in the manufacturing method of the drug product during development are shown below (3 different manufacturing methods are referred to as Method A, Method B, and Proposed

Method). Phase I studies used the drug product produced by [redacted]. Phase II studies used the drug product produced by Method [redacted], and Phase III studies Method [redacted] or Proposed Method.

- From Method A to Method B: Changes of [redacted] and [redacted], etc.

- From Method B to Proposed Method: Changes of [redacted] and [redacted], etc.

The comparability of the quality attributes was evaluated at the time of these changes. When Method B was modified to Proposed Method, clinical studies began [see Section "6.1.1 Comparison of pharmacokinetics between different formulations"]. Study results demonstrated the comparability between the pre-change and post-change drug products.

2.2.4 Control of drug product

The proposed specification for the drug product include content, description, identification ([redacted]), pH, purity (SEC, SDS, capillary gel electrophoresis [reduced and non-reduced]), charge heterogeneity ([redacted]), bacterial endotoxins, extractable volume ([redacted]), foreign insoluble matter, insoluble particulate matter, sterility, potency ([redacted]), and assay (ultraviolet-visible spectrophotometry).

2.2.5 Stability of drug product

Table 4 outlines the major stability studies of the drug product. These studies were conducted on the drug product manufactured by Proposed Method.

Table 4. Outline of major stability studies of the drug product

Study	Formulation specification	Number of batches	Storage condition	Duration	Storage form[a)]
Long-term testing	150 mg	3	5 ± 3°C	[redacted] months	Glass syringe
	200 mg	3		[redacted] months[b)]	
Accelerated testing	150 mg	3	[redacted]°C	[redacted] months	
	200 mg	3		[redacted] months	
Stress testing	150 mg	1	[redacted]°C	[redacted] months	
	200 mg	1		[redacted] months	
Photostability testing	150 mg	1	Overall illumination ≥1.2 million lux·hr and integrated near ultraviolet energy ≥200 W·hr/m^2		
	200 mg	1			

[a)] Some of the stability studies (long-term, accelerated, stress, and photostability testing) were also conducted on the auto-injector product, which shares the same primary container with the syringe product.
[b)] A [redacted]-month stability test is ongoing.

The long-term testing showed no significant changes in quality attributes throughout the study period.

The accelerated testing showed [redacted].

The stress testing showed [redacted] in addition to the same changes as seen in the accelerated testing.

The drug product was unstable to light in the photostability study.

Based on the above, a shelf-life of 30 months has been proposed for the drug product (150 and 200 mg formulations) when stored at 2°C to 8°C protected from light in a paper carton.

2.3 QbD

The QbD approach has been employed for the manufacturing process development of the drug substance to establish quality control strategies including the identification of critical quality attributes and critical process parameters shown below.

- Identified critical quality attributes: [redacted]
- Identified critical process parameters: [redacted]

2.R Outline of the review conducted by PMDA

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

2.R.1 Novel excipient

The drug product contains polysorbate 20, of which amount is higher than that ever used in subcutaneous formulations.

2.R.1.1 Specifications and stability

PMDA has concluded that polysorbate 20 in the drug product complies with the relevant monograph in the Japanese Pharmaceutical Excipients, and therefore acceptable in terms of the specification or stability.

2.R.1.2 Safety

Based on the review on the data submitted, PMDA concluded that a polysorbate 20-related safety issue is unlikely to arise.

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

The applicant submitted the data on primary pharmacodynamics, i.e., the results from *in vitro* studies evaluating binding characteristics to IL-6Rα, effector function, and effects on IL-6/IL-6Rα binding and IL-6 signaling and the results from *in vivo* studies evaluating activity in mouse acute inflammation model and activity in mouse collagen-induced arthritis model. Data on secondary pharmacodynamics submitted were the results from *in vitro* studies evaluating the effect on IL-6 signaling and the results from *in vivo* study evaluating activities in human tumor xenograft-transplanted mice. Although no safety pharmacology studies were conducted, effects of sarilumab on central nervous, cardiovascular, and

respiratory systems were evaluated in 13- and 26-week repeated-dose toxicity studies in cynomolgus monkeys.

Unless otherwise specified, human IL-6 and human IL-6Rα were used in the studies described in this section. Pharmacodynamic parameter values are expressed as a mean value.

3.1 Primary pharmacodynamics

3.1.1 Binding characteristics to IL-6Rα (CTD 4.2.1.1-1 and 4.2.1.1-2)

Binding affinities of sarilumab to the monomeric extracellular domain of human, cynomolgus monkey, and mouse sIL-6Rα were evaluated by surface plasmon resonance. Sarilumab bound to human and cynomolgus monkey sIL-6Rα with an equilibrium dissociation constant (K_D) value of 54 and 123 pmol/L, respectively, but not to mouse sIL-6Rα.

Binding characteristics of sarilumab to IL-6Rα on the surface of peripheral-blood mononuclear cells isolated from whole blood of humans, rhesus monkeys, marmosets, sheep, dogs, rabbits, minipigs, guinea pigs, hamsters, rats, and mice were evaluated by flow cytometry. Chimeric antibodies having the variable region of sarilumab bound to peripheral-blood mononuclear cells of humans, rhesus monkeys, and marmosets, but not to those of the other animal species.

3.1.2 Effector function (CTD 4.2.1.1-3)

ADCC and CDC activities of sarilumab were evaluated. The results showed that sarilumab has neither ADCC (concentration of sarilumab, 0.169 pmol/L to 10 nmol/L) nor CDC (concentration of sarilumab, 0.845 pmol/L to 50 nmol/L) activity in cells (KG-1, XG-1, and HepG2 cells) expressing different levels of IL-6Rα.

3.1.3 Effect on human IL-6/IL-6Rα binding (CTD 4.2.1.1-4)

Inhibition of IL-6/IL-6Rα binding by sarilumab was evaluated by enzyme-linked immunosorbent assay (ELISA). Sarilumab inhibited binding between immobilized IL-6 and IL-6Rα fused with human fragment crystallizable (Fc) (100 pmol/L) with a half maximal inhibitory concentration (IC_{50}) of 108 pmol/L.

Inhibition of IL-6/IL-6Rα binding by sarilumab was evaluated by surface plasmon resonance. Sarilumab (333 nmol/L) was added to the extracellular region of IL-6Rα fixed on a sensor tip until saturation, and IL-6 (200 nmol/L) was added. IL-6 did not bind to IL-6Rα.

3.1.4 Effect on IL-6 signaling (CTD 4.2.1.1-4 and -5)

Effects of sarilumab on STAT3 activation by IL-6 (50 pmol/L) in HepG2 cells and proliferation of DS-1 cells induced by IL-6 (1 pmol/L) were evaluated. Sarilumab inhibited STAT3 activation and cell proliferation with an IC_{50} of approximately 150 and 140 pmol/L, respectively.

The effect of sarilumab on STAT3 activation by IL-6 (12.5 nmol/L) in HEK293 cells was evaluated in the presence of sIL-6Rα (1 nmol/L). When sarilumab was premixed with sIL-6Rα, sarilumab inhibited STAT3 activation with an IC_{50} of 860 pmol/L.

3.1.5 Activity in mouse acute inflammation model (CTD 4.2.1.1-6)

To evaluate the activity of sarilumab in mice, *Il6*$^{hu/hu}$*Il6ra*$^{hu/hu}$ mice were generated by substituting mouse *Il6* locus with the exon of human *IL6* gene and the extracellular part of mouse *Il6ra* gene with corresponding human *IL6RA* gene fragment. In these mice, effect of sarilumab (0.015-15 mg/kg) on turpentine oil-induced acute systemic inflammation was evaluated. Sarilumab dose-dependently suppressed an increase in circulating serum amyloid A, which is related to the severity of inflammation. Circulating human IL-6 tended to increase.

3.1.6 Activity in mouse acute inflammation model using analogous mouse antibodies (CTD 4.2.1.1-7 to 4.2.1.1-10)

Because sarilumab does not bind to mouse IL-6Rα, analogous anti-mouse IL-6Rα antibodies were created. The analogous antibodies bound to mouse sIL-6Rα (K_D, 193 pmol/L) and inhibited the binding between immobilized human IL-6 and mouse IL-6Rα (10 nmol/L) with an IC_{50} of 4 nmol/L. The analogous antibodies also inhibited the proliferation of B9 cells induced by human and mouse IL-6 stimulation (both at 0.5 pmol/L) with an IC_{50} of approximately 60 and 110 pmol/L, respectively.

In female wild-type C57BL/6 mice and wild-type CD-1 mice, the effect of the analogous mouse antibodies (5 or 25 mg/kg in C57BL/6 mice, 0.015-15 mg/kg in CD-1 mice) on turpentine oil-induced acute systemic inflammation was evaluated. The analogous mouse antibodies (5 or 25 mg/kg in C57BL/6 mice, 5 or 15 mg/kg in CD-1 mice) suppressed an increase in circulating serum amyloid A and tended to increase circulating IL-6.

3.1.7 Activity in mouse collagen-induced arthritis model using analogous mouse antibodies (CTD 4.2.1.1-11)

The effect of the analogous mouse antibodies (10 or 30 mg/kg) on collagen-induced arthritis was evaluated in male DBA/1J mice. The analogous mouse antibodies inhibited arthritis and bone erosion in the model animals.

3.2 Secondary pharmacodynamics

3.2.1 Effect on IL-6 signaling in tumor cells (CTD 4.2.1.2-1)

The effect of sarilumab (10 μg/mL) on phosphorylation of STAT3 was evaluated in tumor cells (prostate cancer-derived DU145 and PC3 cells; lung cancer-derived NCI-H1975, NCI-H1650, A549, and Calu3 cells). Sarilumab inhibited STAT3 phosphorylation in DU145, NCI-H1650, A549, and Calu3 cells in the presence of IL-6 (10 ng/mL).

3.2.2 Effect on tumor growth (CTD 4.2.1.2-1)

The effect of sarilumab (25 mg/kg) on tumors was evaluated in male C.B.-17 severe combined immunodeficient mice transplanted with DU145, NCI-H1650, A549, and Calu3 cells. Sarilumab inhibited the growth of all these tumor cells. DU145 tumor cells were used to evaluate the effects of sarilumab on STAT3 phosphorylation as well as on cleaved caspase-3, Ki67, and PECAM-1 by an immunohistochemical analysis. An inhibition of STAT3 phosphorylation and an enhanced staining of cleaved caspase-3 were observed in mice treated with sarilumab.

3.3 Safety pharmacology (CTD 4.2.3.2-5 and 4.2.3.2-6)

To evaluate the safety pharmacology parameters, 13- and 26-week repeated-dose toxicity studies were conducted in cynomolgus monkeys. No sarilumab-related effects were observed on clinical signs, body temperature, heart rate, blood pressure, electrocardiographic parameters, or respiratory status in cynomolgus monkeys receiving sarilumab at 1, 5, 15, or 50 mg/kg twice a week subcutaneously for 13 weeks or at 0.5, 5, 15, or 50 mg/kg once a week intravenously for 26 weeks.

3.R Outline of the review conducted by PMDA

Based on the data submitted, PMDA has concluded that the data demonstrate sarilumab's inhibitory effect on IL-6Rα-mediated biological activity of IL-6 and that sarilumab is expected to be effective against RA of which development may attribute to IL-6.

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

The submitted data on absorption and distribution included the results from intravenous and subcutaneous infusion studies of sarilumab in cynomolgus monkeys. Serum sarilumab concentrations of cynomolgus monkeys were determined by ELISA (lower limit of quantification, 156.5 ng/mL). Anti-drug antibody (ADA) was detected by electrochemiluminescence-based bridging immunoassay (sensitivity, 26.9 ng/mL) or ELISA (sensitivity, 5270 ng/mL).

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

4.1 Absorption

4.1.1 Single-dose study (CTD 4.2.2.2-1 to 4.2.2.2-6)

Table 5 shows the pharmacokinetic parameters following a single dose of sarilumab in cynomolgus monkeys. There were no clear sex differences. The incidence of ADA following a single dose of sarilumab 5 mg/kg in cynomolgus monkeys was 90% (18 of 20 males, 18 of 20 females).

Table 5. Pharmacokinetic parameters following a single dose of sarilumab in cynomolgus monkeys

Route of administration	Dose (mg/kg)	Sex	Number of animals	C_{max} (μg/mL)	AUC_{inf} (mg·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL or CL/F (mL/h/kg)
Intravenous	1	Male	3	38.3	1.74	0.417	32.7	0.580
		Female	3	41.3	1.57	0.761	25.5	0.675
	5	Male	5	260	22.2	0.407	36.0[a)]	0.230
		Female	5	228	21.9	1.22	34.8[a)]	0.233
	15	Male	3	479	87.2	0.344	76.8[a)]	0.175
		Female	3	588	70.9	2.84	63.1[a)]	0.212
Subcutaneous	1	Male	3	9.82	1.20	35	29.1	0.841
		Female	3	11.5	1.37	48	30.9	0.826
	5	Male	3	54.8	14.3	88	50.2[a)]	0.357
		Female	3	61.0	11.9	56	21.0[a)]	0.448
	5 (Method S2)	Male	5	67.7	15.9	96.0	30.4[a)]	0.318
		Female	5	78.7	15.9	72.0	22.5[a)]	0.322
	5 (Method S2)	Male	5	58.1	15.4	115	48.5[a)]	0.334
		Female	5	61.8	13.6	62.4	28.5[a)]	0.386
	5 (Proposed Method)	Male	5	51.9	12.1	76.8	35.7[a)]	0.423
		Female	5	49.8	10.8	72.0	46.4[a)]	0.496
	15	Male	3	183	75.0	152	69.8[a)]	0.214
		Female	3	170	49.5	72	47.2[a)]	0.310

Mean
[a)] The value in the terminal phase of biphasic elimination

4.1.2 Repeated-dose study (toxicokinetics) (CTD 4.2.3.2-3 to 4.2.3.2-6)

The repeated-dose toxicokinetics in animals receiving sarilumab once a week (intravenously) or twice a week (subcutaneously) were evaluated based on the data from 5-, 13-, and 26-week intravenous dose toxicity studies [see Sections "5.2.1 Five-week repeated intravenous dose toxicity study," "5.2.2 Thirteen-week repeated intravenous dose toxicity study," and "5.2.4 Twenty-six-week repeated intravenous dose toxicity study"] and a 13-week subcutaneous dose toxicity study [see Section "5.2.3 Thirteen-week repeated subcutaneous dose toxicity study"] in cynomolgus monkeys. The pharmacokinetic parameters of sarilumab were as shown in Table 6. The exposure was higher after repeated administrations than after the first dose in animals receiving ≥5 mg/kg/week. The ADA positivity rate decreased with increasing dose, with no ADAs being detected at higher doses (Table 6). The presence of ADAs was associated with decreased exposure to sarilumab.

Table 6. Pharmacokinetic parameters and immunogenicity following repeated doses of sarilumab in cynomolgus monkeys

Route of administration	Treatment duration	Dose (mg/kg)	Number of animals (male/female)	C_{max} (μg/mL)	Estimated $AUC_{0\text{-}168h}$ (mg·h/mL)	ADA positivity (%) and number of animals (male/female)
Intravenous	5 weeks	5	5/5	127 ± 21 (Week 1) 197 ± 62 (Week 5)	8.72 ± 0.95 (Week 1) 16.8 ± 8.0 (Week 5)	20 (0/2)
		10	5/5	273 ± 29 (Week 1) 344 ± 121 (Week 5)	20.4 ± 2.3 (Week 1) 28.1 ± 19.4 (Week 5)	30 (2/1)
		40	5/5	1180 ± 333 (Week 1) 1570 ± 348 (Week 5)	75.2 ± 12.2 (Week 1) 160 ± 37 (Week 5)	0
	13 weeks	1	6/6	28.3 ± 2.5 (Week 1) 10.2 ± 8.8 (Week 13)	1.48 ± 0.25 (Week 1) 0.389 ± 0.721 (Week 13)	92 (6/5)
		10	6/6	259 ± 29 (Week 1) 521 ± 158 (Week 13)	22.2 ± 5.4 (Week 1) 61.6 ± 14.5 (Week 13)	0
		50	6/6	1140 ± 292 (Week 1) 2190 ± 457[a)] (Week 13)	114 ± 12 (Week 1) 258 ± 49[a)] (Week 13)	0
	26 weeks	0.5	6/6	12.2 ± 1.7 (Week 1) 4.90 ± 4.11[a)] (Week 25)	0.644 ± 0.069 (Week 1) 0.172 ± 0.289[a)] (Week 25)	100 (6/6)
		5	6/6	145 ± 35 (Week 1) 203 ± 119 (Week 25)	12.1 ± 2.8 (Week 1) 22.9 ± 19.1 (Week 25)	42 (4/1)
		15	6/6	390 ± 157 (Week 1) 715 ± 420[a)] (Week 25)	32.8 ± 4.9 (Week 1) 88.6 ± 49.9[a)] (Week 25)	8 (1/0)
		50	6/6	1360 ± 182 (Week 1) 3110 ± 334 (Week 25)	134 ± 44 (Week 1) 381 ± 30 (Week 25)	0

Administration route	Treatment duration	Dose (mg/kg)	Number of animals (male/female)	C_{trough} (μg/mL)	ADA positivity (%) and number of animals (male/female)
Subcutaneous	13 weeks	1	6/6	3.94 ± 1.39 (Week 1 [after the first dose]) 1.11 ± 1.60 (Week 12 [after the 23th dose])	100 (6/6)
		5	6/6	32.1 ± 4.7 (Week 1 [after the first dose]) 150 ± 114 (Week 12 [after the 23th dose])	33 (1/3)
		15	6/6	128 ± 27 (Week 1 [after the first dose]) 837 ± 210 (Week 12 [after the 23th dose])	0
		50	6/6	385 ± 113 (Week 1 [after the first dose]) 2460 ± 438 (Week 12 [after the 23th dose])	0

Mean ± SD
[a)] In 5 males and 6 females.

4.2 Distribution

4.2.1 Placental transfer (CTD 4.2.3.5.3-1)

The toxicokinetics in animals receiving once-weekly intravenous doses of sarilumab 5, 15, or 50 mg/kg from Gestation Day 20 to the day of natural delivery (near Gestation Day 165) was evaluated based on the data from a study on embryo-fetal development and pre- and postnatal development, including maternal function in pregnant cynomolgus monkeys [see Section "5.5.2 Study on embryo-fetal development and pre- and postnatal development in cynomolgus monkey"]. Serum sarilumab concentrations in maternal animals and offspring are shown in Table 7. Exposure to sarilumab in serum of the newborns depended on the maternal exposure. ADAs were detected in 2 maternal animals in the

5 mg/kg group, but not detected in maternal animals in the 15 and 50 mg/kg groups or in any of the offspring.

Table 7. Data on placental transfer in cynomolgus monkeys (serum sarilumab concentrations in maternal animals and offspring)

	5 mg/kg (μg/mL)		15 mg/kg (μg/mL)		50 mg/kg (μg/mL)	
	Maternal animals	Offspring	Maternal animals	Offspring	Maternal animals	Offspring
Gestation Day 20[a)]	167 ± 29 (12)		495 ± 141 (12)		1620 ± 186 (12)	
Gestation Day 146[b)]	310 ± 64 (9)		922 ± 112 (8)		3050 ± 493 (7)	
Lactation Day 7	66.9 ± 48.6 (8)	54.7 ± 40.9 (7)	311 ± 54 (4)	521 ± 179 (5)	1390 ± 389 (7)	1440 ± 630 (5)
Lactation Day 30	15.7 ± 16.4 (7)	9.18 ± 7.58 (7)	154 ± 121 (6)	129 ± 32 (5)	482 ± 119 (5)	339 ± 215 (5)

(Number of animals).
[a)] After the first dose, [b)] After the 19th dose

4.R Outline of the review conducted by PMDA

Based on the submitted non-clinical pharmacokinetic data, PMDA has concluded that a certain level of understanding can be achieved on the *in vivo* behavior of sarilumab.

5. Toxicity and Outline of the Review Conducted by PMDA

The toxicity data submitted included, the results from repeated-dose toxicity studies, reproductive and developmental toxicity studies, and other toxicity studies (a tissue cross-reactivity study etc.). Because sarilumab binds to IL-6Rα of cynomolgus monkeys but does not bind to IL-6Rα of rats and mice [see Section "3.1.1 Binding characteristics to IL-6Rα"], toxicity studies of sarilumab were conducted in cynomolgus monkeys. Although exposure to sarilumab decreased due to ADA formation in some animals [see Section "4.1.2 Repeated-dose study (toxicokinetics)"], no ADAs were detected in higher dose groups. Therefore, exposure to sarilumab was considered adequate for toxicity assessment during the treatment period in all of the *in vivo* studies. Some data on the reproductive and developmental toxicity were obtained from studies using analogous mouse antibodies.

Unless otherwise specified, [redacted]% sucrose, [redacted]% polysorbate 20, and [redacted] mmol/L histidine (pH 6.0) were used as the vehicle for sarilumab and analogous mouse antibodies.

5.1 Single-dose toxicity

No single dose toxicity studies of sarilumab were conducted. According to the data on post first dose in the repeated-dose toxicity studies in cynomolgus monkeys (5-, 13-, and 26-week intravenous dose toxicity studies and a 13-week subcutaneous dose toxicity study [CTD 4.2.3.2-3 to 4.2.3.2-6]), an intravenous or subcutaneous dose of sarilumab at up to 50 mg/kg was well tolerated, and caused no deaths. The approximate lethal dose for intravenous or subcutaneous administration was determined to be >50 mg/kg.

5.2 Repeated-dose toxicity

In cynomolgus monkeys, 5-, 13-, and 26-week intravenous dose toxicity studies and a 13-week subcutaneous dose toxicity study were conducted. According to the applicant, although some changes (decreased in neutrophil count and serum fibrinogen, etc.) were observed, they were expected from the

mechanism of action of sarilumab. The applicant considers these changes have limited toxicological significance because of their reversibility and no associated increase in the incidence of infections, etc. In the 26-week intravenous dose toxicity study, the no observed adverse effect level (NOAEL) was determined to be 50 mg/kg/week, and the estimated area under the serum concentration-time curve $(AUC)_{0\text{-}14\ days}$[1)] (762.08 mg·h/mL) in animals receiving sarilumab once a week for 2 weeks was 54.3-fold the estimated $AUC_{0\text{-}14\ days}$ (14.04 mg·h/mL) in Japanese patients with RA receiving multiple subcutaneous sarilumab 200 mg once every 2 weeks [see Section "6.2.2 Population pharmacokinetic analysis"].

5.2.1 Five-week repeated intravenous dose toxicity study (CTD 4.2.3.2-3)

Sarilumab was intravenously administered at 0 (vehicle), 5, 10, or 40 mg/kg to male and female cynomolgus monkeys once a week for 5 weeks. A 9-week recovery period was scheduled after the last dose. There were neither treatment-related deaths nor effects of sarilumab on clinical signs, body weight, cardiovascular parameters, or histopathological findings. Decreases or decreasing trends of neutrophil count and serum fibrinogen and C-reactive protein (CRP) concentrations were observed in animals receiving ≥5 mg/kg, but these changes were reversible. The NOAEL was determined to be 40 mg/kg/week.

5.2.2 Thirteen-week repeated intravenous dose toxicity study (CTD 4.2.3.2-4)

Sarilumab was intravenously administered at 0 (vehicle), 1, 10, or 50 mg/kg to male and female cynomolgus monkeys once a week for 13 weeks. An 8-week recovery period was scheduled after the last dose. There were neither treatment-related deaths nor effects of sarilumab on clinical signs, body weight, cardiovascular parameters, or histopathological findings. Decreases or decreasing trends of neutrophil count and serum fibrinogen and CRP concentrations were observed in animals receiving ≥1 mg/kg, but these changes were reversible. The NOAEL was determined to be 50 mg/kg/week.

5.2.3 Thirteen-week repeated subcutaneous dose toxicity study (CTD 4.2.3.2-5)

Sarilumab was subcutaneously administered at 0 (vehicle), 1, 5, 15, or 50 mg/kg to male and female cynomolgus monkeys twice a week for 13 weeks. A 12-week recovery period was scheduled after the last dose. There were neither treatment-related deaths nor effects of sarilumab on clinical signs, body weight, or cardiovascular parameters. Decreases in white blood cell count, neutrophil count, and serum fibrinogen and CRP concentrations and mild to moderate perivascular mixed inflammatory cell infiltration at the injection site were observed in animals receiving ≥1 mg/kg, but these changes were reversible. The NOAEL was determined to be 100 mg/kg/week.

5.2.4 Twenty-six-week repeated intravenous dose toxicity study (CTD 4.2.3.2-6)

Sarilumab was intravenously administered at 0 (vehicle), 0.5, 5, 15, or 50 mg/kg to male and female cynomolgus monkeys once a week for 26 weeks A 12-week recovery period was scheduled after the last dose. During the study, keyhole limpet hemocyanin (KLH)-specific IgM and IgG antibody responses, peripheral blood leukocyte immunophenotyping, and serum concentrations of IL-6 and endogenous immunoglobulins were determined to evaluate immunotoxicity. There were neither treatment-related

[1)] Calculated by doubling the $AUC_{0\text{-}168h}$ in the 50 mg/kg group (males and females are pooled) at the final week of once-weekly treatment.

deaths nor effects of sarilumab on clinical signs, body weight, cardiovascular parameters, or histopathological findings. Decreases in neutrophil count and serum fibrinogen concentrations, an increase in serum IL-6 concentrations, and a trend towards decreased IgG antibody titer during T-cell dependent antibody responses against KLH were observed in animals receiving ≥5 mg/kg, but these changes were reversible. The applicant explained that the toxicological significance of the trend towards decreased IgG antibody titer is limited because the values were within the range of baseline or control group data, and the incidence of histopathological changes or infections in immune tissues did not increase. The NOAEL was determined to be 50 mg/kg/week.

5.3 Genotoxicity

No genotoxicity studies were conducted because sarilumab is an antibody preparation and is not considered to directly interact with DNAs or other chromosome components.

5.4 Carcinogenicity

Because sarilumab does not bind to mouse or rat IL-6Rα, carcinogenicity studies in rodents were not conducted. Some articles suggest a tumorigenic potential of IL-6Rα inhibition (*Cancer Res.* 1992;52:6020-4, *Cancer Res*. 1992;52:5412-5). However, the applicant has a view that the carcinogenic risk of sarilumab is limited, based on sarilumab's inhibitory effects on STAT3 phosphorylation and tumor growth suggested in *in vitro* and *in vivo* studies in human tumor cells [see Section "3.2 Secondary pharmacodynamics"] and because of no findings suggestive of carcinogenic potential or immunotoxic effects of sarilumab in the 26-week repeated intravenous dose toxicity study [see Section "5.2.4 Twenty-six-week repeated intravenous dose toxicity study"].

5.5 Reproductive and developmental toxicity

A study on embryo-fetal development and pre- and postnatal development, including maternal function was conducted in cynomolgus monkeys. In addition, a study on fertility and early embryonic development to implantation and a study in juvenile animals were conducted in mice using analogous mouse antibodies. In the study on embryo-fetal development and pre- and postnatal development, including maternal function in cynomolgus monkeys, the NOAELs for maternal animals and offspring were determined to be 50 mg/kg/week. At that time, the estimated $AUC_{0\text{-}14\ days}$[2)] (792.910 mg·h/mL) in maternal animals receiving sarilumab once a week for 2 weeks was 56.5-fold the estimated $AUC_{0\text{-}14\ days}$ (14.04 mg·h/mL) in Japanese patients with RA receiving multiple subcutaneous administration of 200 mg of sarilumab once every 2 weeks.

5.5.1 Study on fertility and early embryonic development to implantation in mice (CTD 4.2.3.5.1-1)

Analogous mouse antibody was subcutaneously administered twice a week to male and female mice at 0 (vehicle), 10, 25, or 100 mg/kg from 4 weeks prior to mating and throughout the mating period until necropsy for males (7-8 weeks), and from 2 weeks prior to mating and throughout the mating period until Gestation Day 7 for females (approximately 4 weeks). There were no treatment-related deaths. Although degeneration of implantation site was observed in females receiving 100 mg/kg, toxicological

2) Calculated by doubling the $AUC_{0\text{-}168h}$ in the 50 mg/kg group at the final week of once-weekly treatment.

significance of this change was considered to be limited because no effects were observed on reproductive function or fertility. Based on the above, the NOAEL was determined to be 200 mg/kg/week for paternal and maternal general toxicity, reproductive functions, and early embryonic development.

5.5.2 Study on embryo-fetal development and pre- and postnatal development in cynomolgus monkey (CTD 4.2.3.5.3-1)

Sarilumab was intravenously administered once a week to at 0 (vehicle), 5, 15, or 50 mg/kg to pregnant cynomolgus monkeys from Gestation Day 20 to the day of natural delivery (near Gestation Day 165). In maternal animals, neither treatment-related deaths nor effects on maintenance of pregnancy were observed. There were neither treatment-related deaths nor effects of sarilumab on functional development (e.g., pupillary reflex), morphological development (e.g., external organ measurements), skeletal, necropsy, and histopathological changes, or lymphocyte or monocyte subsets in peripheral blood in offspring. The NOAELs for maternal animals and offspring were determined to be 50 mg/kg/week.

5.5.3 Nine-week repeated subcutaneous dose toxicity study in juvenile mice (CTD 4.2.3.5.4-2)

The analogous mouse antibody was subcutaneously administered once a week at 0 (vehicle), 20, 60, or 200 mg/kg to male and female mice from 14 days after birth for 9 weeks. There were no treatment-related deaths. Observed changes included a trend towards decreased IgG antibody titer during T-cell dependent antibody responses against KLH, subepidermal and dermal inflammation at the injection site, and hyperplasia of lymphoid tissue in axillary lymph nodes in animals receiving ≥20 mg/kg; slightly enhanced hematopoiesis in the bone marrow of the femur and sternum in animals receiving ≥60 mg/kg; and alopecia, erosion, and nodule at the injection site in animals receiving 200 mg/kg. These changes were reversible. The applicant had a view that hyperplasia of lymphoid tissue in lymph nodes and enhanced hematopoiesis in the bone marrow, etc. are secondary changes caused by local inflammation at the injection site rather than changes suggestive of toxicity to blood and lymphoreticular system. The NOAEL was determined to be 200 mg/kg/week.

5.6 Local tolerance

No local tolerance studies of sarilumab were conducted because it was evaluated in repeated-dose toxicity studies. In the 26-week repeated intravenous dose toxicity study, no abnormalities were observed at the injection site. In the 13-week repeated subcutaneous dose toxicity study, mild to moderate perivascular mixed inflammatory cell infiltration was observed in the dermis or beneath the epidermis, the incidence and severity of which were not increased with increasing dose of sarilumab. This change reversed during a 12-week recovery period.

5.7 Other toxicity studies

5.7.1 Tissue cross-reactivity study in human and cynomolgus monkeys (CTD 4.2.3.7.7-1)

Normal tissue cross-reactivity of sarilumab between humans and cynomolgus monkeys was examined. A cross-reactivity was found in the tissues tested, and the similar staining patterns were observed. The applicant explained that although binding was detected also in cell membranes of the mammary gland

epithelium in monkeys, its toxicological significance is limited because no effects on the mammary gland attributed to sarilumab were observed in the repeated-dose toxicity studies.

5.7.2 Thirteen-week repeated subcutaneous dose toxicity study in cynomolgus monkeys for comparative evaluation between different formulations (CTD 4.2.3.7.7-2)

Male and female cynomolgus monkeys received subcutaneously sarilumab prepared using Proposed Method [3)] at 0 (vehicle), 5, or 50 mg/kg or sarilumab prepared using an early developmental manufacturing method[4)] at 50 mg/kg twice a week for 13 weeks [for manufacturing processes, see Section "2.1.4 Manufacturing process development"]. No sarilumab-related deaths were observed in either group. Based on these results and other toxicity findings, the 2 kinds of sarilumab, each produced by different methods, were determined to have similar toxicity profiles.

5.R Outline of the review conducted by PMDA

Based on the data submitted, PMDA concluded that no particular concern about clinical use of sarilumab was suggested from a toxicological viewpoint.

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 following studies were conducted for comparison of pharmacokinetics between different formulations: A foreign clinical study in healthy adult subjects (Study TDU11373 [CTD5.3.3.1-1, reference data]) and foreign clinical studies in patients with RA (Studies PKM12058 [CTD 5.3.3.2-5, evaluation data] and MSC12665 [CTD 5.3.5.2-4, reference data]).

Serum sarilumab concentrations were determined by ELISA (lower limit of quantification, 294-313 ng/mL). ADA was detected by electrochemiluminescence-based bridging immunoassay (sensitivity, 63.5-116.3 ng/mL). Neutralizing antibody was detected by competitive ligand-binding assay (sensitivity, 150 ng/mL).

Unless otherwise specified, the doses of Kevzara are expressed as sarilumab equivalent, and pharmacokinetic parameter values are expressed as mean ± SD.

6.1.1 Comparison of pharmacokinetics between different formulations (CTD5.3.3.1-1, Study TDU11373 [July to December 2010]; CTD 5.3.3.2-5, Study PKM12058 [May to September 2011]; CTD 5.3.5.2-4, Study MSC12665 [March 2014 to February 2015])

In foreign clinical studies conducted to compare the different formulations, healthy adult subjects received a single subcutaneous dose of 100 mg of the formulation prepared using Method B (produced from Method S2 drug substance) or the formulation in vials prepared using Proposed Method. Patients with RA received a single subcutaneous dose of 200 mg of the formulation prepared using Method B

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3) The drug substance prepared using Proposed Method and vehicle containing 5% sucrose, 0.2% polysorbate 20, [redacted] mmol/L histidine, and [redacted] mmol/L arginine (pH 6.0) were used.

4) The drug substance prepared using Method S1 and vehicle containing [redacted]% sucrose, [redacted]% polysorbate 20, and [redacted] mmol/L histidine (pH 6.0) were used.

(produced from Method S2 drug substance) or the formulation prepared using Proposed Method. Patients with RA received multiple subcutaneous doses of 150 or 200 mg of the formulation (pre-filled syringe [PFS] or auto-injector [AI] formulation) prepared using Proposed Method once every 2 weeks. The obtained pharmacokinetic parameters are shown in Table 8.

Table 8. Pharmacokinetic parameters obtained in foreign clinical studies conducted to compare different formulations

Study	Formulation	Dose	C_{max} (μg/mL)	AUC_{last} (μg·day/mL)	AUC_{tau} (μg·day/mL)	Geometric mean ratio[a)]	
						C_{max}	AUC_{last} or AUC_{tau}
TDU11373	Method B Formulation	100 mg	7.88 ± 3.27 (14)	47.5 ± 23.5 (14)		0.91 [0.55, 1.51][b)]	0.86 [0.43, 1.71][b)]
	Proposed Method Formulation in vial	100 mg	7.77 ± 3.65 (14)	45.0 ± 22.7 (14)			
PKM12058	Method B Formulation	200 mg	15.8 ± 7.02 (15)	153 ± 92.5 (15)		1.18 [0.83, 1.66][b)]	1.21 [0.82, 1.79][b)]
	Proposed Method Formulation (PFS)	200 mg	17.9 ± 9.98 (16)	178 ± 146 (16)			
MSC12665	Proposed Method Formulation (PFS)	150 mg	24.2 ± 14.8 (44)		220 ± 130 (40)	0.94 [0.77, 1.16][c)]	0.99 [0.80, 1.22][c)]
	Proposed Method Formulation (AI)		21.7 ± 12.9 (45)		205 ± 126 (44)		
	Proposed Method Formulation (PFS)	200 mg	39.4 ± 22.3 (46)		405 ± 244 (38)	1.34 [1.08, 1.66][c)]	1.21 [0.96, 1.51][c)]
	Proposed Method Formulation (AI)		50.4 ± 33.8 (36)		455 ± 294 (36)		

Mean ± SD (number of subjects).
[a)] Ratio relative to the formulation prepared using Method B (Studies TDU11373 and PKM12058) or to the formulation prepared using Proposed Method (PFS) (Study MSC12665).
[b)] 95% confidence interval (CI); [c)] 90% CI

6.2 Clinical pharmacology

The applicant submitted evaluation data including the results from Japanese clinical studies (Studies TDU13402 [CTD 5.3.3.2-1], PDY14191 [CTD 5.3.4.2-1], EFC14059 [CTD 5.3.5.1-1], and LTS13618 [CTD 5.3.5.2-1]), foreign clinical studies (Study 6R88-RA-1309 [CTD 5.3.4.2-3], Study EFC11072 Part A [CTD 5.3.5.1-2] and Study EFC11072 Part B [CTD 5.3.5.1-3], and Study EFC10832 [CTD 5.3.5.1-4]), a population pharmacokinetic analysis, and an exposure-response analysis (CTD 5.3.3.5-1 to 5.3.3.5-5). In addition, the applicant submitted reference data, including the results from a drug-drug interaction study (Study INT12684 [CTD 5.3.3.4-1]).

6.2.1 Studies in patients with RA

6.2.1.1 Japanese Phase I studies (CTD 5.3.3.2-1, Study TDU13402 [May to December 2013]; CTD 5.3.4.2-1, Study PDY14191 [May 2015 to March 2016])

Patients with RA received a single subcutaneous dose of 50, 100, or 200 mg of sarilumab in combination with MTX or received a single subcutaneous dose of 150 mg of sarilumab alone in Japanese clinical studies. Table 9 shows pharmacokinetic data, indicating a more than dose-proportional increase in exposure.

Table 9. Pharmacokinetic parameters in Japanese patients with RA after a single dose of sarilumab

Study	Dose	Number of subjects	C_{max} (μg/mL)	AUC_{last} (μg·day/mL)	t_{max}[a] (day)	$t_{1/2}$[b] (day)
TDU13402	50 mg	4	1.36 ± 0.411	4.69 ± 2.43	3.00 [2.00, 3.00]	
	100 mg	6	4.54 ± 2.97	33.0 ± 30.4	3.00 [3.00, 7.00]	1.62[c]
	200 mg	6	27.7 ± 12.6	339 ± 173	3.00 [2.00, 7.00]	3.49 ± 1.35[d]
PDY14191	150 mg	15	15.4 ± 6.17	164 ± 84.8	3.91 [2.08, 7.04]	2.34 ± 0.334

Mean ± SD
[a] Median [minimum, maximum]; [b] Half-life ($t_{1/2}$) in terminal-phase; [c] n = 1; [d] n = 5

6.2.1.2 Foreign Phase I study (CTD 5.3.4.2-3, Study 6R88-RA-1309 [March 2014 to April 2015])

Table 10 shows the data of pharmacokinetic parameters following a single subcutaneous dose of 150 or 200 mg of sarilumab combined with MTX in the foreign clinical study in patients with RA.

Table 10. Pharmacokinetic parameters in non-Japanese patients with RA after a single dose of sarilumab

Dose	Number of subjects	C_{max} (μg/mL)	AUC_{last} (μg·day/mL)	t_{max}[a] (day)	$t_{1/2}$[b] (day)
150 mg	26	13.9 ± 9.28	106 ± 91.9	3.02 [2.00, 6.16]	1.70 ± 0.457
200 mg	26	21.6 ± 11.7	169 ± 105	3.99 [1.99, 6.17]	1.96 ± 1.10

Mean ± SD
[a] Median [minimum, maximum]; [b] $t_{1/2}$ in terminal-phase

6.2.1.3 Japanese Phase II/III study (CTD 5.3.5.1-1, Study EFC14059 [November 2014 to [redacted] 20[redacted]]

Patients with RA received once every 2 weeks multiple subcutaneous doses of 150 or 200 mg of sarilumab in combination with MTX in the Japanese clinical study [see Section "7.2.1 Japanese study in patients with RA inadequately responding to MTX"]. Table 11 shows serum trough concentrations of sarilumab.

The serum trough concentrations of sarilumab reached a steady state after Weeks 20 to 24, and were approximately 4-fold higher at Week 24 than Week 2 after the first dose. Comparison between dose levels revealed a more than dose-proportional increase in the trough concentrations.

6.2.1.4 Japanese Phase III study (CTD 5.3.5.2-1, Study LTS13618 [February 2015 to [redacted] 20[redacted]])

Patients with RA received once every 2 weeks multiple subcutaneous doses of 150 or 200 mg of sarilumab with or without concomitant use of a cDMARD in the Japanese clinical study [see Section "7.3.3 Japanese study in patients with RA"]. Table 11 shows serum trough concentrations of sarilumab.

Table 11. Serum trough concentrations (μg/mL) of sarilumab in Japanese patients with RA receiving multiple subcutaneous doses of sarilumab

Study	Dose	Week 2	Week 20	Week 24
EFC14059	150 mg q2w with MTX	3.62 ± 3.40 (80)	15.0 ± 10.7 (66)	16.1 ± 10.6 (67)
	200 mg q2w with MTX	7.87 ± 4.83 (80)	28.7 ± 16.7 (60)	30.5 ± 16.9 (57)
LTS13618	150 mg q2w with a cDMARD	5.79 ± 2.85 (15)	26.1 ± 11.2 (13)	25.4 ± 12.6 (13)
	200 mg q2w with a cDMARD	13.9 ± 6.77 (14)	53.1 ± 34.8 (11)	63.2 ± 39.3 (10)
	150 mg q2w without a cDMARD	4.43 ± 4.72 (29)	19.5 ± 22.4 (25)	20.9 ± 22.0 (27)
	200 mg q2w without a cDMARD	11.9 ± 6.09 (30)	41.1 ± 23.3 (25)	39.7 ± 25.3 (28)

Mean ± SD (number of subjects)

6.2.1.5 Foreign Phase II study (CTD 5.3.5.1-2, Study EFC11072 Part A [March 2010 to May 2011])

Patients with RA received multiple subcutaneous doses of 100, 150, or 200 mg of sarilumab once every 2 weeks or 100 or 150 mg of sarilumab once every week, in combination with MTX in the foreign clinical study [see Section "7.1.1 Foreign study in patients with RA inadequately responding to MTX"]. Table 12 shows serum trough concentrations of sarilumab.

6.2.1.6 Foreign Phase III study (CTD 5.3.5.1-3, Study EFC11072 Part B [March 2011 to October 2013])

In the foreign clinical study in patients with RA, sarilumab was subcutaneously administered once every 2 weeks at a dose of 150 or 200 mg in combination with MTX [see Section "7.3.1 Foreign study in patients with RA inadequately responding to MTX"]. Table 12 shows serum trough concentrations of sarilumab.

The serum trough concentrations of sarilumab reached a steady state after 12 to 24 weeks of treatment, and approximately 4-fold higher at Week 24 than Week 2 of treatment. Comparison between dose levels revealed a more than dose-proportional increase in the concentrations.

6.2.1.7 Foreign Phase III study (CTD 5.3.5.1-4, Study EFC10832 [October 2012 to March 2015])

In the foreign clinical study in patients with RA, sarilumab was subcutaneously administered once every 2 weeks at a dose of 150 or 200 mg in combination with cDMARD [see Section "7.3.2 Foreign study in patients with RA inadequately responding to TNF inhibitors"]. Table 12 shows serum trough concentrations of sarilumab.

Table 12. Serum trough concentrations (μg/mL) of sarilumab in non-Japanese patients with RA receiving multiple subcutaneous doses of sarilumab

Study	Dose	Week 2	Week 12	Week 24	Week 52
EFC11072 Part A	100 mg q2w	0.176 ± 1.00 (49)	0.250 ± 0.949 (41)		
	150 mg q2w	1.49 ± 3.58 (47)	4.52 ± 5.29 (44)		
	200 mg q2w	3.67 ± 4.00 (44)	14.1 ± 12.2 (39)		
	100 mg qw	6.44 ± 5.71 (46)	17.0 ± 11.3 (35)		
	150 mg qw	12.5 ± 9.32 (46)	38.3 ± 20.3 (38)		
EFC11072 Part B	150 mg q2w	1.98 ± 3.12 (369)	5.28 ± 6.72 (341)	7.63 ± 9.73 (274)	8.21 ± 10.2 (230)
	200 mg q2w	5.40 ± 6.41 (366)	16.5 ± 13.9 (331)	18.8 ± 16.3 (266)	18.9 ± 16.5 (213)
EFC10832	150 mg q2w	1.70 ± 2.73 (167)	7.07 ± 8.18 (144)	6.97 ± 8.98 (115)	
	200 mg q2w	5.15 ± 5.21 (172)	14.9 ± 12.5 (154)	19.3 ± 16.7 (114)	

Mean ± SD (number of subjects)

6.2.2 Population pharmacokinetic analysis (CTD 5.3.3.5-2)

A population pharmacokinetic analysis (NONMEM ver. 7.3.0) was conducted using the data of serum sarilumab concentrations (12,088 sampling points in 2453 patients) obtained from Japanese and foreign clinical studies conducted in patients with RA.

The basic model consists of 2 compartments model incorporating 2 types of elimination kinetics (linear kinetics and non-linear Michaelis-Menten kinetics) and first-order absorption. The final model incorporated the following covariates identified.

- Apparent linear clearance: Body weight, formulation, presence of ADAs, and sex
- Maximum elimination rate in the equation of non-linear clearance: Body weight, albumin level, creatinine clearance, and baseline CRP
- Absorption rate constant: Formulation

Table 13 shows estimated steady-state pharmacokinetic parameters of patients with RA following subcutaneous doses of 150 or 200 mg of sarilumab once every 2 weeks.

Table 13. Steady-state pharmacokinetic parameters of patients with RA estimated based on the final model

Dose	Study population	C_{max} (μg/mL)	C_{trough} (μg/mL)	$AUC_{0\text{-}14\ day}$ (μg·day/mL)
150 mg	All[a)]	22.5 ± 10	8.8 ± 9.38	240 ± 141
	Japanese[b)]	30.3 ± 11.6	15.6 ± 11.7	348 ± 167
200 mg	All[a)]	37.9 ± 16.1	19 ± 15.6	432 ± 225
	Japanese[b)]	48.8 ± 19	28.8 ± 19.4	585 ± 269

Mean ± SD

[a)] Japanese patients with RA receiving sarilumab in combination with cDMARD in Study EFC14059 or LTS13118 and non-Japanese patients with RA receiving sarilumab in combination with cDMARD in Study EFC11072 Part B or Study EFC10832.

[b)] Japanese patients with RA who participated in Study EFC14059 or LTS13118.

6.2.3 Exposure-response analysis (CTD 5.3.3.5-5)

An exposure-response analysis was conducted using measurements of efficacy endpoints (American College of Rheumatology [ACR] 20 response rate, ACR50 response rate, ACR70 response rate, Health Assessment Questionnaire Disability Index [HAQ-DI], modified Total Sharp Score [mTSS], Clinical Disease Activity Index [CDAI], and Disease Activity Score 28 joints C-reactive protein [DAS28-CRP])

and safety endpoints (neutrophil count, low-density lipoprotein, alanine aminotransferase [ALT, ratio to the upper limit of normal (ULN)]) and serum trough concentrations of sarilumab obtained in foreign clinical studies in patients with RA (Study EFC11072 Parts A and B and Study EFC10832). A log-linear model was used for ACR20 response rate, ACR50 response rate, ACR70 response rate, mTSS, CDAI, and DAS28-CRP and an E_{max} model was used for HAQ-DI, neutrophil count, low-density lipoprotein, and ALT (ratio to the ULN). In all studies, measurements of the efficacy endpoints except HAQ-DI tended to be increased with increasing exposure to sarilumab, and measurements of the safety endpoints showed a trend towards a stronger effect with increasing exposure to sarilumab.

6.2.4 Drug interactions (CTD 5.3.3.4-1, Study INT12684 [February 2014 to February 2015])

In the foreign clinical study in patients with RA, subjects received a single oral dose of 40 mg of simvastatin (a substrate of CYP3A4), and after a washout period, received a single subcutaneous dose of 200 mg of sarilumab, followed by a single oral dose of 40 mg of simvastatin a week later. The pharmacokinetic parameters of simvastatin and simvastatin acid in the presence and absence of sarilumab are shown in Table 14. Exposures to simvastatin and simvastatin acid decreased in the presence of sarilumab.

The applicant's explanation:
IL-6 is known to reduce the expression of mRNAs of CYP isoforms (*Drug Metab. Dispos.* 2011;39:1415-22). The blood concentrations of drugs metabolized by CYP enzymes decreased probably due to enhanced CYP activity resulting from IL-6Rα inhibition by sarilumab. Therefore, cautionary advice will be given on the concomitant use of sarilumab with a CYP3A4 substrate such as simvastatin.

Table 14. Effect of sarilumab on pharmacokinetic parameters following a single oral dose of simvastatin

	Sarilumab	Number of subjects	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	Geometric mean ratio [90% CI]	
					C_{max}	AUC_{inf}
Simvastatin	Without concomitant use	17	21.3 ± 12.8	84.3 ± 53.6	0.541 [0.422, 0.694]	0.547 [0.472, 0.633]
	With concomitant use[a)]	17	11.0 ± 5.83	47.9 ± 33.4		
Simvastatin acid	Without concomitant use	17	4.18 ± 3.43	31.5 ± 23.3	0.641 [0.555, 0.741]	0.641 [0.541, 0.758]
	With concomitant use[a)]	17	2.95 ± 2.83	22.2 ± 19.0		

Mean ± SD
[a)] A single subcutaneous dose of 200 mg of sarilumab was administered 7 days before treatment with simvastatin.

6.R Outline of the review conducted by PMDA

6.R.1 Ethnic difference in the pharmacokinetics of sarilumab

The applicant's explanation about the effects of ethnic factors on the pharmacokinetics of sarilumab:
As shown in Tables 11 and 12, the Japanese and foreign clinical study data showed that the serum trough concentrations of sarilumab in patients with RA receiving multiple doses of sarilumab tended to be higher in Japanese subjects than in non-Japanese subjects. The mean maximum serum concentrations (C_{max}) (coefficient of variation [CV] in %) following 200 mg of subcutaneous sarilumab in Studies TDU13402 (Japanese patients) and PKM12058 (non-Japanese patients), after adjustment for body

weight (70 kg), were 21.5 (36.6) and 19.6 (46.6) μg/mL/70 kg, respectively, and the mean values of AUC_{last} (CV%) 260 (48.9) and 186 (60.6) μg·day/mL/70 kg, respectively, indicating no ethnic differences. In addition, in the population pharmacokinetic analysis [see Section "6.2.2 Population pharmacokinetic analysis"], body weight was selected as a covariate but race was not. The evaluation of the estimated mean exposure to sarilumab in Japanese and non-Japanese patients with RA by body weight subgroup revealed an increase in exposure to sarilumab with decreasing body weight and a comparable mean exposure levels between Japanese and non-Japanese patients among most of the body weight subgroups (Table 15). The body weight difference (the mean body weight was 56.6 kg in Japanese subjects and 73.7 kg in non-Japanese subjects) is thus a major contributory factor to the higher exposure to sarilumab among Japanese patients than among non-Japanese patients.

The exposure in patients with RA receiving a single subcutaneous dose of 50 to 200 mg of sarilumab was not substantially different between Japanese and non-Japanese subjects, as shown in Figure 1, suggesting no clear ethnic difference in the pharmacokinetics of sarilumab.

Table 15. Estimated pharmacokinetic parameters of Japanese and non-Japanese subjects in clinical studies conducted in patients with RA

150 mg q2w								
Body weight	Japanese (EFC14059 and LTS13618)				Non-Japanese (EFC11072 Part B and EFC10832)			
	Number of subjects	C_{max} (μg/mL)	C_{trough} (μg/mL)	$AUC_{0\text{-}14\ day}$ (μg·day/mL)	Number of subjects	C_{max} (μg/mL)	C_{trough} (μg/mL)	$AUC_{0\text{-}14\ day}$ (μg·day/mL)
Total	126	30.3 ± 11.6	15.6 ± 11.7	348 ± 167	490	20.5 ± 8.5	7.04 ± 7.78	212 ± 118
<50 kg	44	37.2 ± 12.2	22 ± 13	446 ± 175	16	36.6 ± 10.4	19.9 ± 11	427 ± 151
50-60 kg	48	30.9 ± 8.8	16.3 ± 9.5	359 ± 126	77	27.8 ± 9.1	12.8 ± 9.9	311 ± 129
60-70 kg	19	23.4 ± 6.1	9.22 ± 6.64	253 ± 88	130	22.6 ± 6.9	8.53 ± 6.88	240 ± 97
70-80 kg	10	17.3 ± 4.7	3.52 ± 4.62	156 ± 75	124	18.8 ± 5.5	5.19 ± 5.31	186 ± 77
80-90 kg	3	13.0 ± 2.0	1.04 ± 1.27	110 ± 19	66	15.5 ± 5.1	3.71 ± 4.61	146 ± 71
90-100 kg	2	16.8 ± 5.8	3.00 ± 3.68	149 ± 85	40	15.1 ± 4.8	2.47 ± 4.18	132 ± 67
≥100 kg					37	11.7 ± 3.3	1.44 ± 1.42	97.9 ± 37.7
200 mg q2w								
Body weight	Japanese (EFC14059 and LTS13618)				Non-Japanese (EFC11072 Part B and EFC10832)			
	Number of subjects	C_{max} (μg/mL)	C_{trough} (μg/mL)	$AUC_{0\text{-}14\ day}$ (μg·day/mL)	Number of subjects	C_{max} (μg/mL)	C_{trough} (μg/mL)	$AUC_{0\text{-}14\ day}$ (μg·day/mL)
Total	126	48.8 ± 19	28.8 ± 19.4	585 ± 269	596	35.6 ± 14.3	16.9 ± 13.9	399 ± 200
<50 kg	38	64.6 ± 18.5	44.2 ± 19.3	809 ± 260	26	56.8 ± 22	37.3 ± 22	697 ± 308
50-60 kg	52	46.4 ± 14.7	26.2 ± 15.6	550 ± 207	90	48.1 ± 12.5	28.1 ± 13.4	573 ± 180
60-70 kg	23	38.7 ± 13.3	19.8 ± 13.8	449 ± 187	136	40.9 ± 10.6	21.5 ± 11.6	473 ± 153
70-80 kg	7	29.9 ± 9.4	9.98 ± 10.2	307 ± 135	133	33.4 ± 10.4	14.7 ± 9.7	367 ± 137
80-90 kg	5	32.2 ± 9.7	13.3 ± 11.2	345 ± 152	90	28.8 ± 9.3	10.6 ± 9.4	307 ± 129
90-100 kg	1	20.7	0.65	158	51	26 ± 9	7.81 ± 6.4	261 ± 107
≥100 kg					70	21.5 ± 5.9	4.75 ± 5.07	204 ± 80

Mean ± SD

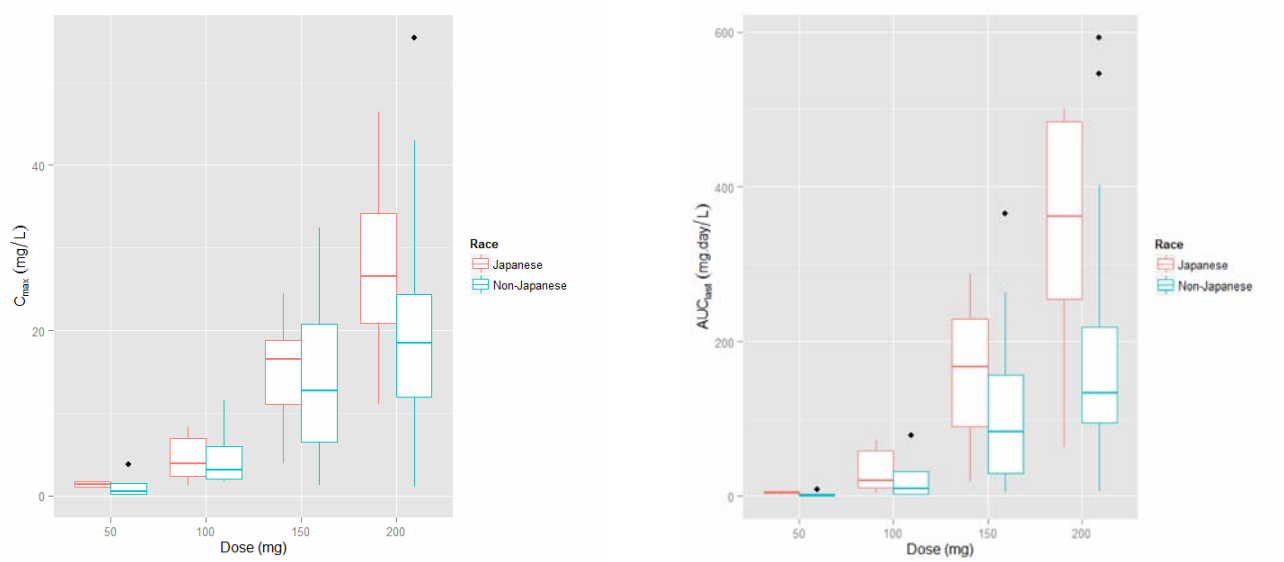

Figure 1. Pharmacokinetic parameters in patients with RA after a single subcutaneous dose of sarilumab

(Japanese patients, Studies TDU13402 and PDY14191; non-Japanese patients, Studies TDU10809/6R88-RA-0801, 6R88-RA-1309, and PKM12058)

PMDA accepted the above explanation.

6.R.2 ADA

The applicant's explanation about the incidence of ADA and the impact of ADA formation on the pharmacokinetics, efficacy, and safety of sarilumab:

Data of a clinical study in non-Japanese patients with RA showed decreased serum sarilumab concentrations (trough concentration [C_{trough}]) in ADA-positive subjects as compared with ADA-negative subjects, but no clear impact of the decreased concentration on its efficacy was observed (Table 16). In Study EFC14059 in Japanese patients with RA, ADAs were detected in 3 subjects in the 150 mg once every 2 weeks (q2w) group, 3 subjects in the 200 mg q2w group, and 2 subjects in the placebo group, and the impact on serum sarilumab concentrations or on the efficacy was not substantially different from those in non-Japanese patients with RA.

Table 16. Impact of ADA formation in a clinical study in non-Japanese patients with RA (Study EFC11072 Part B)

Group	Safety analysis set			ITT population		
	ADA-positive subjects	C_{trough} (μg/mL) at Week 24		ADA-positive subjects	ACR20 response rate (%) at Week 24	
Placebo	16/397			16/398	Positive	50.0 (8/16)
					Negative	32.7 (125/382)
150 mg q2w	75/400	Positive	1.01 ± 1.66 (14)	74/400	Positive	54.1 (40/74)
		Negative	8.02 ± 9.86 (259)		Negative	58.9 (192/326)
200 mg q2w	56/396	Positive	12.2 ± 12.9 (8)	57/399	Positive	63.2 (36/57)
		Negative	18.8 ± 16.3 (257)		Negative	67.0 (229/342)

In addition, no clear impact of ADA formation was observed on the safety in the pooled Japanese population or in the foreign long-term safety population [for the definition of these populations, see Section "7.R.3 Safety"] (Table 17).

Based on the results, there is no clear impact of ADA formation on the efficacy or safety of sarilumab.

Table 17. Adverse events in ADA-positive and -negative patients with RA in the pooled Japanese population and foreign long-term safety population

	Pooled Japanese population				Foreign long-term safety population					
Group	150 mg q2w		200 mg q2w		150 mg q2w		200 mg q2w		All dose groups combined	
ADA	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
Number of subjects	8	118	6	164	237	862	148	1096	417	2138
Total exposure time (subject-year)	3.7	52.3	2.2	59.5	140.8	546.8	197.1	1539.0	571.5	3113.6
Adverse event	17 458.9	329 629.6	14 648.1	382 642.1	432 306.8	1905 348.4	526 266.8	4419 287.1	1451 253.9	8735 280.5

Upper row, number of events; bottom row, number of events per 100 subject-years after adjustment for total exposure time.

PMDA's view:

Although currently available data do not suggest any clinical issues associated with ADA formation, patients with a substantially diminished response or hypersensitive reaction during treatment should be closely monitored for the impact of ADA.

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

The applicant submitted the results of clinical studies listed in Table 18 as the primary efficacy and safety evaluation data.

Table 18. List of clinical studies on efficacy and safety

Data category	Region	Study	Phase	Subjects	Number of subjects[a),b)]	Dosage regimen[b)] (all subcutaneous)	Main objectives
Evaluation	Japan	EFC14059 (bridging study)	II/III	Patients with RA who have not responded adequately to MTX	(a) 81 (b) 80 (c) 81	(a) Sarilumab 150 mg q2w (b) Sarilumab 200 mg q2w (c) Placebo	Efficacy Safety
	Japan	LTS13618	III	(A) Patients with RA who have not responded adequately to cDMARDs other than MTX (B) Patients with RA who are intolerant of, inappropriate for, or have not responded adequately to MTX	(A-a) 15 (A-b) 15 (B-a) 30 (B-b) 31	(A-a) Sarilumab 150 mg q2w (A-b) Sarilumab 200 mg q2w (B-a) Sarilumab 150 mg q2w (B-b) Sarilumab 200 mg q2w	Efficacy Safety
	Foreign	EFC11072 Part A	II	Patients with RA who have not responded adequately to MTX	(a) 51 (b) 52 (c) 51 (d) 50 (e) 50 (f) 51	(a) Sarilumab 100 mg q2w (b) Sarilumab 150 mg q2w (c) Sarilumab 200 mg q2w (d) Sarilumab 100 mg qw (e) Sarilumab 150 mg qw (f) Placebo	Efficacy Safety
	Foreign	EFC11072 Part B (study to be bridged)	III	Patients with RA who have not responded adequately to MTX	(a) 400 (b) 399 (c) 398	(a) Sarilumab 150 mg q2w (b) Sarilumab 200 mg q2w (c) Placebo	Efficacy Safety
	Foreign	EFC10832	III	Patients with RA who have not responded adequately to or are intolerant of TNF inhibitors	(a) 181 (b) 184 (c) 181	(a) Sarilumab 150 mg q2w (b) Sarilumab 200 mg q2w (c) Placebo	Efficacy Safety

a) Safety analysis set
b) Dosage regimen for Cohort 2 is presented for Study EFC11072 Part B.

7.1 Phase II study

7.1.1 Foreign study in patients with RA inadequately responding to MTX (CTD 5.3.5.1-2, Study EFC11072 Part A [March 2010 to May 2011])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients with RA showing inadequate response to MTX[5)] (target sample size, 300 subjects [50 per group]) to evaluate the efficacy and safety of sarilumab in 19 foreign countries.

Subjects received 100, 150, or 200 mg of sarilumab subcutaneously once every 2 weeks, or 100 or 150 mg of sarilumab or placebo once every week, in combination with a fixed dose of MTX[6)] for 12 weeks.

All of the 306 randomized subjects (51 in the 100 mg q2w group, 51 in the 150 mg q2w group, 52 in the 200 mg q2w group, 50 in the 100 mg once every week [qw] group, 50 in the 150 mg qw group, and 52 in the placebo group) were included in the intent-to-treat (ITT) population, which was used for the efficacy analysis. Of the randomized subjects, subjects who received ≥1 dose of the study drug (51 in the 100 mg q2w group, 52 in the 150 mg q2w group, 51 in the 200 mg q2w group, 50 in the 100 mg qw

5) Patients with RA who meet the following criteria: (a) disease duration ≥3 months; (b) tender joint count ≥8; (c) swollen joint count ≥6; (d) CRP >10 mg/L; and (e) treatment with MTX for ≥12 weeks, which includes ≥6-week fixed-dose (10-25 mg/week) treatment.
6) Dose adjustment for safety reasons was permitted.

group, 50 in the 150 mg qw group, and 51 in the placebo group) were included in the safety analysis set.[7)] Study discontinuation was observed in 6 of 51 subjects (11.8%) in the 100 mg q2w group, 3 of 51 subjects (5.9%) in the 150 mg q2w group, 6 of 52 subjects (11.5%) in the 200 mg q2w group, 13 of 50 subjects (26.0%) in the 100 mg qw group, 4 of 50 subjects (8.0%) in the 150 mg qw group, and 3 of 52 subjects (5.8%) in the placebo group. Main reasons for discontinuation included adverse events (3 of 51 [5.9%] in the 100 mg q2w group, 2 of 51 [3.9%] in the 150 mg q2w group, 4 of 52 [7.7%] in the 200 mg q2w group, 13 of 50 [26.0%] in the 100 mg qw group, 1 of 50 [2.0%] in the 150 mg qw group, and 1 of 52 [1.9%] in the placebo group).

ACR20 response rates at Week 12, the primary efficacy endpoint, are shown in Table 19. A pairwise comparison between the 150 mg qw and placebo groups revealed a statistically significant difference.

Table 19. ACR20 response rates at Week 12 (ITT population, last observation carried forward [LOCF])

	100 mg q2w	150 mg q2w	200 mg q2w	100 mg qw	150 mg qw	Placebo
ACR20 response rate	49.0 (25/51)	66.7 (34/51)	65.4 (34/52)	62.0 (31/50)	72.0 (36/50)	46.2 (24/52)
Odds ratio relative to placebo [95% CI][a)]	1.17 [0.52, 2.61]	2.38 [1.06, 5.35]	2.34 [1.03, 5.29]	1.99 [0.85, 4.64]	3.84 [1.53, 9.63]	
Adjusted *P*-value[b)]	*P* = 0.7119	*P* = 0.1090	*P* = 0.1277	*P* = 0.2311	*P* = 0.0203	

% (number of subjects)
[a)] Mantel-Haenszel estimate
[b)] Comparison was performed between each sarilumab dose group and placebo group by two-sided Cochran-Mantel-Haenszel test including a history of biologic use and geographical region as strata. Multiplicity was adjusted by the Hommel procedure at a two-sided significance level of 5%.

Adverse events were reported by 22 of 51 subjects (43.1%) in the 100 mg q2w group, 28 of 52 subjects (53.8%) in the 150 mg q2w group, 33 of 51 subjects (64.7%) in the 200 mg q2w group, 36 of 50 subjects (72.0%) in the 100 mg qw group, 27 of 50 subjects (54.0%) in the 150 mg qw group, and 24 of 51 subjects (47.1%) in the placebo group. Major events are listed in Table 20.

One subject in the 100 mg q2w group died due to cerebrovascular accident/acute respiratory distress syndrome. A causal relationship to the study drug could not be ruled out for acute respiratory distress syndrome. Serious adverse events occurred in 3 of 51 subjects (5.9%) in the 100 mg q2w group, 3 of 50 subjects (6.0%) in the 100 mg qw group, and 2 of 51 subjects (3.9%) in the placebo group. A causal relationship to the study drug could not be ruled out for the events that occurred in 2 subjects in the 100 mg q2w group (acute respiratory distress syndrome and rheumatoid arthritis in 1 subject each) and 2 subjects in the 100 mg qw group (neutropenia and hypersensitivity in 1 subject each). Adverse events led to treatment discontinuation in 4 of 51 subjects (7.8%) in the 100 mg q2w group, 2 of 52 subjects (3.8%) in the 150 mg q2w group, 4 of 51 subjects (7.8%) in the 200 mg q2w group, 13 of 50 subjects (26.0%) in the 100 mg qw group, 3 of 50 subjects (6.0%) in the 150 mg qw group, and 2 of 51 subjects (3.9%) in the placebo group.

Adverse drug reactions occurred in 8 of 51 subjects (15.7%) in the 100 mg q2w group, 12 of 52 subjects (23.1%) in the 150 mg q2w group, 19 of 51 subjects (37.3%) in the 200 mg q2w group, 21 of 50 subjects

[7)] One subject in the 200 mg q2w group who did not receive the study drug was excluded. One subject in the placebo group who temporarily received 150 mg of sarilumab once every 2 weeks was included in the 150 mg q2w group for the purpose of safety analysis.

(42.0%) in the 100 mg qw group, 16 of 50 subjects (32.0%) in the 150 mg qw group, and 8 of 51 subjects (15.7%) in the placebo group.

Table 20. Adverse events occurring in ≥2 subjects in any group (safety analysis set)

Event term	100 mg q2w (n = 51)	150 mg q2w (n = 52)	200 mg q2w (n = 51)	100 mg qw (n = 50)	150 mg qw (n = 50)	Placebo (n = 51)
Neutropenia	0	1 (1.9)	10 (19.6)	7 (14.0)	5 (10.0)	0
Rheumatoid arthritis	2 (3.9)	0	0	0	3 (6.0)	1 (2.0)
Accidental overdose	1 (2.0)	3 (5.8)	2 (3.9)	2 (4.0)	3 (6.0)	5 (9.8)
Bronchitis	0	1 (1.9)	0	1 (2.0)	2 (4.0)	0
Upper respiratory tract infection	0	2 (3.8)	3 (5.9)	1 (2.0)	2 (4.0)	2 (3.9)
Leukopenia	0	0	1 (2.0)	0	2 (4.0)	0
Injection site reaction	0	1 (1.9)	1 (2.0)	0	2 (4.0)	1 (2.0)
Fatigue	1 (2.0)	1 (1.9)	0	1 (2.0)	2 (4.0)	1 (2.0)
ALT increased	0	3 (5.8)	2 (3.9)	2 (4.0)	2 (4.0)	0
Nasopharyngitis	2 (3.9)	2 (3.8)	2 (3.9)	2 (4.0)	1 (2.0)	3 (5.9)
Headache	1 (2.0)	2 (3.8)	1 (2.0)	0	1 (2.0)	0
Diarrhoea	1 (2.0)	1 (1.9)	2 (3.9)	0	1 (2.0)	0
Arthralgia	1 (2.0)	0	1 (2.0)	0	1 (2.0)	2 (3.9)
Urinary tract infection	1 (2.0)	1 (1.9)	1 (2.0)	3 (6.0)	0	1 (2.0)
Hypertension	2 (3.9)	0	0	0	0	1 (2.0)
Aphthous stomatitis	0	2 (3.8)	0	0	0	0
Dermatitis allergic	0	2 (3.8)	0	0	0	0
Haemoglobin decreased	0	0	0	0	0	2 (3.9)

Number of subjects (%)

7.2 Phase II/III study

7.2.1 Japanese study in patients with RA inadequately responding to MTX (CTD 5.3.5.1-1, Study EFC14059 [November 2014 to October 2016]) (bridging study)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients with RA inadequately responding to MTX[8)] (target sample size, 240 subjects [80 in each sarilumab group, 40 in the placebo group]) to evaluate the efficacy and safety of sarilumab.

Subjects received sarilumab 150 or 200 mg or placebo subcutaneously in combination with a fixed dose of MTX once every 2 weeks for 24 weeks. After that, subjects in the sarilumab group subcutaneously received sarilumab at the same dose as before, and subjects in the placebo group received subcutaneously sarilumab 150 or 200 mg, once every 2 weeks for 28 weeks (for a total duration of treatment of 52 weeks). Subjects who met the definition of inadequate response[9)] at Week 16 or later were allowed to receive subcutaneously sarilumab 200 mg once every 2 weeks in an unblinded manner.

Of 243 randomized subjects (81 in the 150 mg q2w group, 80 in the 200 mg q2w group, 42 in the placebo/150 mg q2w group, and 40 in the placebo/200 mg q2w group), subjects who received ≥1 dose of the study drug and were evaluable for the primary endpoint (81 in the 150 mg q2w group, 80 in the 200 mg q2w group, and 81 in the placebo group) were included in the modified intent-to-treat (mITT) population,[10)] which was used for the efficacy analysis. Of the randomized subjects, those who received ≥1 dose of the study drug were included in the safety analysis set[10)] (81 in the 150 mg q2w group, 80 in

8) Patients with RA who meet the following criteria: (a) disease duration ≥3 months; (b) tender joint count ≥8; (c) swollen joint count ≥6; (d) CRP ≥6 mg/L; and (e) prior treatment with MTX for ≥12 weeks, which includes ≥6-week fixed-dose (6-16 mg/week) treatment.

9) Patients who experienced <20% improvement in the swollen or tender joint count from baseline at 2 consecutive time points (for 4 consecutive weeks).

10) One subject in the placebo/150 mg q2w group who did not receive the study drug was excluded.

the 200 mg q2w group, and 81 in the placebo group). Study discontinuation was observed in 7 of 81 subjects (8.6%) in the 150 mg q2w group, 10 of 80 subjects (12.5%) in the 200 mg q2w group, and 10 of 82 subjects (12.2%) in the placebo group by 24 weeks of treatment; the reasons for discontinuation included adverse events (6 of 81 [7.4%] in the 150 mg q2w group, 8 of 80 [10.0%] in the 200 mg q2w group, and 5 of 82 [6.1%] in the placebo group) and insufficient response (1 of 81 [1.2%] in the 150 mg q2w group, 2 of 80 [2.5%] in the 200 mg q2w group, and 5 of 82 [6.1%] in the placebo group).

ACR20 response rate at Week 24, the primary efficacy endpoint, are shown in Table 21. Pairwise comparisons between the 150 mg q2w and placebo groups and between the 200 mg q2w and placebo groups revealed a statistically significant difference, demonstrating superiority of treatment with sarilumab 150 or 200 mg once every 2 weeks over placebo.

Table 21. ACR20 response rates at Week 24 (mITT population, non-responder imputation [NRI])

	150 mg q2w	200 mg q2w	Placebo
ACR20 response rate	67.9 (55/81)	57.5 (46/80)	14.8 (12/81)
Odds ratio relative to placebo [95% CI],[a] *P*-value[b]	12.19 [5.58, 26.59] *P* <0.0001	7.23 [3.45, 15.16] *P* <0.0001	

% (number of subjects)
[a] Mantel-Haenszel estimate
[b] Comparison was performed between each sarilumab dose group and placebo group by two-sided Cochran-Mantel-Haenszel test including a history of biologic use and body weight as strata, and multiplicity was adjusted by the Hochberg procedure at a two-sided significance level of 5%.

Adverse events by 24 weeks of treatment were reported by 65 of 81 subjects (80.2%) in the 150 mg q2w group, 60 of 80 subjects (75.0%) in the 200 mg q2w group, and 49 of 81 subjects (60.5%) in the placebo group. Major events are listed in Table 22.

No deaths occurred. Serious adverse events occurred in 4 of 81 subjects (4.9%) in the 150 mg q2w group, 4 of 80 subjects (5.0%) in the 200 mg q2w group, and 6 of 81 subjects (7.4%) in the placebo group. Of the serious adverse events that occurred in 18 subjects including the above 14 subjects (3 subjects who experienced a serious adverse event after the regimen change from placebo to open-label treatment with sarilumab, and 1 subject in the placebo group who experienced a serious adverse event after the completion of the study), a causal relationship to the study drug could not be ruled out for the events that occurred in 4 subjects in the 150 mg q2w group (chronic gastritis, *Pneumocystis jirovecii* pneumonia, herpes zoster, and sepsis in 1 subject each), 2 subjects in the 200 mg q2w group (organising pneumonia and pulmonary fibrosis in 1 subject each), and 5 subjects in the placebo group (spinal column stenosis, leukopenia,[11)] gastroenteritis bacterial,[11)] pneumonia pneumococcal,[11)] and tendon rupture in 1 subject each). Adverse events leading to discontinuation occurred in 6 of 81 subjects (7.4%) in the 150 mg q2w group, 7 of 80 subjects (8.8%) in the 200 mg q2w group, and 3 of 81 subjects (3.7%) in the placebo group.

Adverse drug reactions occurred in 42 of 81 subjects (51.9%) in the 150 mg q2w group, 39 of 80 subjects (48.8%) in the 200 mg q2w group, and 22 of 81 subjects (27.2%) in the placebo group.

11) Occurred during open-label treatment with 200 mg of sarilumab.

Table 22. Adverse events occurring in ≥3% of subjects in any group (placebo-controlled period, safety analysis set)

Event term	150 mg q2w (n = 81)	200 mg q2w (n = 80)	Placebo (n = 81)
Nasopharyngitis	16 (19.8)	12 (15.0)	12 (14.8)
Neutropenia	7 (8.6)	9 (11.3)	0
Stomatitis	5 (6.2)	8 (10.0)	3 (3.7)
Hepatic function abnormal	6 (7.4)	8 (10.0)	4 (4.9)
Injection site erythema	7 (8.6)	7 (8.8)	0
Upper respiratory tract infection	6 (7.4)	4 (5.0)	4 (4.9)
Hypertension	2 (2.5)	4 (5.0)	0
Abdominal pain upper	1 (1.2)	4 (5.0)	1 (1.2)
Injection site pruritus	4 (4.9)	4 (5.0)	0
Gastroenteritis	1 (1.2)	3 (3.8)	1 (1.2)
Thrombocytopenia	3 (3.7)	3 (3.8)	0
Headache	1 (1.2)	3 (3.8)	3 (3.7)
Eczema	4 (4.9)	3 (3.8)	1 (1.2)
ALT increased	5 (6.2)	3 (3.8)	4 (4.9)
Dizziness	0	2 (2.5)	3 (3.7)
Rash	3 (3.7)	2 (2.5)	0
Rheumatoid arthritis	1 (1.2)	2 (2.5)	3 (3.7)
Cystitis	3 (3.7)	1 (1.3)	1 (1.2)
Pharyngitis	3 (3.7)	1 (1.3)	1 (1.2)
Contact dermatitis	1 (1.2)	1 (1.3)	3 (3.7)
White blood cell count decreased	3 (3.7)	1 (1.3)	0
AST increased	3 (3.7)	0	1 (1.2)
Conjunctivitis	3 (3.7)	0	0

Number of subjects (%)

Adverse events were reported by 76 of 81 subjects (93.8%) in the 150 mg q2w group and 71 of 80 subjects (88.8%) in the 200 mg q2w group during the entire study period. Major events are listed in Table 23.

No deaths were reported. Serious adverse events occurred in 8 of 81 subjects (9.9%) in the 150 mg q2w group and 5 of 80 subjects (6.3%) in the 200 mg q2w group. A causal relationship to the study drug could not be ruled out for the events occurred by Week 24 and those occurred in 2 subjects in the 150 mg q2w group (pharyngeal abscess and infective myositis in 1 subject each), 2 subjects in the placebo/200 mg q2w group (*Pneumocystis jirovecii* pneumonia and lumbar spinal stenosis in 1 subject each), and 1 subject in the 200 mg q2w group (lymphoma, after the completion of the study). Adverse events led to discontinuation in 11 of 81 subjects (13.6%) in the 150 mg q2w group and 8 of 80 subjects (10.0%) in the 200 mg q2w group.

Adverse drug reactions occurred in 57 of 81 subjects (70.4%) in the 150 mg q2w group and 47 of 80 subjects (58.8%) in the 200 mg q2w group.

Table 23. Adverse events occurring in ≥3% of subjects in either group (entire study period, safety analysis set)

Event term	150 mg q2w (n = 81)	200 mg q2w (n = 80)
Nasopharyngitis	27 (33.3)	23 (28.8)
Neutropenia	10 (12.3)	9 (11.3)
Stomatitis	6 (7.4)	8 (10.0)
Upper respiratory tract infection	8 (9.9)	7 (8.8)
Hepatic function abnormal	8 (9.9)	7 (8.8)
Injection site erythema	8 (9.9)	7 (8.8)
Gastroenteritis	2 (2.5)	6 (7.5)
Hypertension	4 (4.9)	5 (6.3)
Abdominal pain upper	1 (1.2)	4 (5.0)
Nausea	0	4 (5.0)
Eczema	7 (8.6)	4 (5.0)
Rash	4 (4.9)	4 (5.0)
Rheumatoid arthritis	2 (2.5)	4 (5.0)
Injection site pruritus	5 (6.2)	4 (5.0)
ALT increased	7 (8.6)	4 (5.0)
Thrombocytopenia	3 (3.7)	3 (3.8)
Insomnia	2 (2.5)	3 (3.8)
Headache	1 (1.2)	3 (3.8)
Dizziness	0	3 (3.8)
Dental caries	2 (2.5)	3 (3.8)
Gastrooesophageal reflux disease	0	3 (3.8)
Contact dermatitis	1 (1.2)	3 (3.8)
Pharyngitis	4 (4.9)	2 (2.5)
White blood cell count decreased	4 (4.9)	2 (2.5)
Cystitis	5 (6.2)	1 (1.3)
Herpes zoster	3 (3.7)	1 (1.3)
Bronchitis	4 (4.9)	1 (1.3)
Cellulitis	3 (3.7)	1 (1.3)
Injection site rash	3 (3.7)	0
AST increased	4 (4.9)	0
Fall	3 (3.7)	0
Skin abrasion	4 (4.9)	0
Periodontitis	4 (4.9)	0
Conjunctivitis	3 (3.7)	0

Number of subjects (%)

7.3 Phase III studies

7.3.1 Foreign study in patients with RA inadequately responding to MTX (CTD 5.3.5.1-3, Study EFC11072 Part B [March 2011 to October 2013]) (study to be bridged)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients with RA inadequately responding to MTX[12)] (target sample size, 1288 subjects [172 in Cohort 1, 1116 (372/group) in Cohort 2]) to evaluate the efficacy and safety of sarilumab in 30 foreign countries and regions.

This study began before the completion of Study EFC11072 Part A [see Section "7.1.1 Foreign study in patients with RA inadequately responding to MTX"]. Therefore, subjects in Cohort 1 received subcutaneously sarilumab 100, 150, or 200 mg once every 2 weeks, or sarilumab 100 or 150 mg or placebo once every week, in combination with a fixed dose of MTX for 52 weeks. Subjects who did not receive the 2 sarilumab regimens that were selected based on the results of Study EFC11072 Part A were

12) Patients with RA who meet the following criteria: (a) disease duration ≥3 months; (b) tender joint count ≥8; (c) swollen joint count ≥6; (d) CRP >10 mg/L (changed to >6 mg/L due to a protocol amendment); and (e) treatment with MTX for ≥12 weeks, which includes ≥6-week fixed-dose (10-25 mg/week) (6-25 mg/week in Taiwan, Korea, Malaysia, Philippines, Thailand, and India) treatment.

withdrawn from the study.[13] Subjects in Cohort 2 were to receive subcutaneously at a dose of sarilumab according to either of the above selected 2 regimens or placebo in combination with a fixed dose of MTX for 52 weeks. Subjects who met the definition of insufficient response[14] at Week 16 or later were allowed to receive sarilumab at the currently allowed maximum dose[15] in an unblinded manner. Based on the results of Study EFC11072 Part A, 150 or 200 mg of subcutaneous sarilumab once every 2 weeks was selected as the dosing regimens for this study.

All of the 1369 randomized subjects (28 in the 100 mg q2w group, 30 in the 150 mg q2w group, 28 in the 200 mg q2w group, 29 in the 100 mg qw group, 27 in the 150 mg qw group, and 30 in the placebo group in Cohort 1; 400 in the 150 mg q2w group, 399 in the 200 mg q2w group, and 398 in the placebo group in Cohort 2) were included in the ITT population. The Cohort 2 ITT population was used for the efficacy analysis. Of all of the randomized subjects in Cohort 2 and the 150 mg q2w, 200 mg q2w, or placebo group in Cohort 1, subjects who received ≥1 dose of the study drug (431 in the 150 mg q2w group, 424 in the 200 mg q2w group, 427 in the placebo group) were included in the safety analysis set.[16] In Cohort 2, 73 of 400 subjects (18.3%) in the 150 mg q2w group, 82 of 399 subjects (20.6%) in the 200 mg q2w group, and 46 of 398 subjects (11.6%) in the placebo group discontinued the double-blind treatment. The main reason for discontinuation was adverse event (50 of 400 [12.5%] in the 150 mg q2w group, 57 of 399 [14.3%] in the 200 mg q2w group, and 21 of 398 [5.3%] in the placebo group).

The ACR20 response rate at Week 24, change in HAQ-DI from baseline to Week 16, and change in mTSS from baseline to Week 52 were defined as the co-primary efficacy endpoints of the study. As shown in Table 24 and Figure 2, pairwise comparisons between the 150 mg q2w and placebo groups and between the 200 mg q2w and placebo groups revealed a statistically significant difference for all these endpoints in both sarilumab groups, demonstrating superiority of treatment with sarilumab 150 or 200 mg once every 2 weeks over placebo.

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13) Participation in the extension study (Study LTS11210) was permitted.
14) Patients who experienced <20% improvement in the swollen or tender joint count from baseline at 2 consecutive time points.
15) Sarilumab 150 mg was subcutaneously administered once every week until the start of Cohort 2, and sarilumab 200 mg was subcutaneously administered once every 2 weeks thereafter.
16) Two subjects in the 150 mg q2w group and 1 subject in the 200 mg q2w group in Cohort 2 who did not receive the study drug were excluded. In Cohort 2, 2 subjects in the 150 mg q2w group received 200 mg, 3 subjects in the 200 mg q2w group received 150 mg, and 1 subject in the placebo group received 200 mg of the study drug by mistake. The each wrong dose was given only once. For the purpose of safety analysis, these subjects were included in dose groups corresponding to the lowest dose that they actually received.

Table 24. Efficacy endpoint data in Cohort 2 (ITT population)

	150 mg q2w	200 mg q2w	Placebo
ACR20 response rate at Week 24[a)]	58.0 (232/400)	66.4 (265/399)	33.4 (133/398)
Odds ratio relative to placebo [95% CI][b)] *P* value[c), g)]	2.77 [2.08, 3.70] *P* < 0.0001	3.98 [2.96, 5.34] *P* < 0.0001	
Change in HAQ-DI from baseline to Week 16	−0.54 ± 0.55 (362)	−0.58 ± 0.63 (365)	−0.30 ± 0.58 (378)
Difference from placebo in least squares mean [95% CI][d)] *P* value[d), g)]	−0.24 [−0.31, −0.16] *P* < 0.0001	−0.26 [−0.34, −0.18] *P* < 0.0001	
Change in mTSS from baseline to Week 52[e)]	0.90 ± 4.66 (352)	0.25 ± 4.61 (359)	2.78 ± 7.73 (352)
Median (first quartile, third quartile) *P* value[f), g)]	0.00 (−1.00, 2.00) *P* < 0.0001	0.00 (−0.50, 1.00) *P* < 0.0001	1.00 (0.00, 4.31) -

% (number of subjects) or mean ± SD (number of subjects)
[a)] NRI
[b)] Mantel-Haenszel estimate
[c)] Two-sided Cochran-Mantel-Haenszel test stratified by history of biologic use and geographical region
[d)] Mixed model for repeated measures (MMRM) with the baseline value as a covariate, and treatment group, geographical region, past history of biologic use, time point (all time points from 2-16 weeks), and treatment-time interaction as fixed effects.
[e)] Linear extrapolation
[f)] Baseline-adjusted rank analysis of covariance (ANCOVA) (two-sided) including treatment group, past history of biologic use, and geographical region as factors.
[g)] To adjust multiplicity, hierarchical test with a two-sided significance level of 2.5% was planned for each sarilumab dose group in the following order: 1) ACR20 response rate at Week 24, 2) change in HAQ-DI from baseline to 16 Week, and 3) change in mTSS from baseline to Week 52.

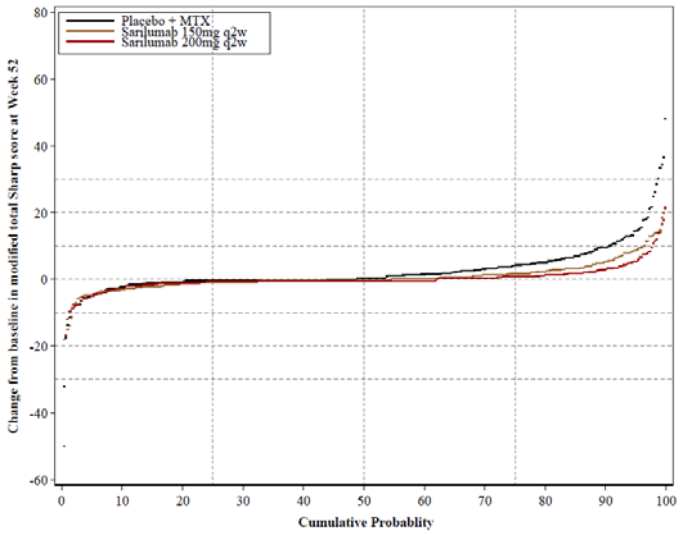

Figure 2. Cumulative probability distribution of change in mTSS from baseline to Week 52 (ITT population, linear extrapolation)

Adverse events occurred in 321 of 431 subjects (74.5%) in the 150 mg q2w group, 331 of 424 subjects (78.1%) in the 200 mg q2w group, and 263 of 427 subjects (61.6%) in the placebo group. Major events are listed in Table 25.

Deaths occurred in 2 subjects in the 150 mg q2w group (pulmonary oedema and respiratory distress in 1 subject each), 3 subjects in the 200 mg q2w group (cerebrovascular accident, metastatic bronchial carcinoma,[17)] and pneumonitis[18)] in 1 subject each), and 3 subjects in the placebo group (completed suicide, acute respiratory failure/cardiovascular insufficiency/brain oedema, and ductal adenocarcinoma of pancreas[17)] in 1 subject each). A causal relationship to the study drug was ruled out for all of these

[17)] Occurred during open-label treatment with sarilumab.
[18)] Occurred 15 days after the last visit (56 days after the last dose of the study drug).

deaths. Serious adverse events were reported by 38 of 431 subjects (8.8%) in the 150 mg q2w group, 48 of 424 subjects (11.3%) in the 200 mg q2w group, and 23 of 427 subjects (5.4%) in the placebo group. A causal relationship to the study drug could not be ruled out for the events that occurred in 16 subjects in the 150 mg q2w group (neutropenia [2 subjects]: decreased neutrophil count/thrombocytopenia, arthritis bacterial, ALT increased, cutaneous lupus erythematosus, transaminases increased, drug-induced liver injury, interstitial lung disease, gastroenteritis, abscess limb, invasive lobular breast carcinoma, embolic cerebral infarction/aortic thrombosis/embolism arterial, upper respiratory tract infection, pericarditis, and duodenal ulcer haemorrhage [1 subject each]), 21 subjects in the 200 mg q2w group (neutropenia [4 subjects]; chronic obstructive pulmonary disease/malignant melanoma, bronchitis fungal, pelvic abscess, erysipelas/cellulitis, herpes zoster, erysipelas, thrombocytopenia, ALT increased, pneumonia, bronchitis, immediate post-injection reaction, leukopenia, blood alkaline phosphatase increased, pyelonephritis, abdominal wall haematoma, osteomyelitis, and dyspnoea [1 subject each]), and 8 subjects in the placebo group (bronchitis and cellulitis [2 subjects each]; meningioma, syncope, urinary tract infection, and pyrexia/subacute endocarditis/duodenal ulcer/myocardial ischaemia/ischaemic stroke/duodenitis/haemorrhoids [1 subject each]). During the open-label treatment with sarilumab, serious adverse events with a suspected causal relationship to the study drug occurred in 3 subjects in the 150 mg q2w group (syncope, wound infection, and *Escherichia* urinary tract infection [1 subject each]), 1 subject in the 200 mg q2w group (myelitis transverse), and 5 subjects in the placebo group (VIIth nerve paralysis, cellulitis, neutropenia, paronychia, and subcutaneous abscess [1 subject each]). Adverse events led to discontinuation in 54 of 431 subjects (12.5%) in the 150 mg q2w group, 59 of 424 subjects (13.9%) in the 200 mg q2w group, and 20 of 427 subjects (4.7%) in the placebo group.

Adverse drug reactions occurred in 164 of 431 subjects (38.1%) in the 150 mg q2w group, 197 of 424 subjects (46.5%) in the 200 mg q2w group, and 102 of 427 subjects (23.9%) in the placebo group.

Table 25. Adverse events occurring in ≥3% of subjects in any group (safety analysis set)

Event term	150 mg q2w (n = 431)	200 mg q2w (n = 424)	Placebo (n = 427)
Neutropenia	40 (9.3)	61 (14.4)	1 (0.2)
Upper respiratory tract infection	36 (8.4)	37 (8.7)	24 (5.6)
ALT increased	37 (8.6)	32 (7.5)	14 (3.3)
Injection site erythema	25 (5.8)	28 (6.6)	5 (1.2)
Accidental overdose	28 (6.5)	28 (6.6)	25 (5.9)
Bronchitis	14 (3.2)	24 (5.7)	17 (4.0)
Urinary tract infection	22 (5.1)	23 (5.4)	16 (3.7)
Nasopharyngitis	25 (5.8)	22 (5.2)	18 (4.2)
Leukopenia	9 (2.1)	18 (4.2)	0
Diarrhoea	12 (2.8)	17 (4.0)	9 (2.1)
Headache	15 (3.5)	15 (3.5)	18 (4.2)
Rheumatoid arthritis	4 (0.9)	15 (3.5)	18 (4.2)
Transaminases increased	10 (2.3)	15 (3.5)	3 (0.7)
Hypertension	18 (4.2)	14 (3.3)	14 (3.3)
Nausea	9 (2.1)	13 (3.1)	9 (2.1)
Influenza	15 (3.5)	11 (2.6)	17 (4.0)
Injection site pruritus	13 (3.0)	11 (2.6)	1 (0.2)
Pharyngitis	13 (3.0)	10 (2.4)	11 (2.6)

Number of subjects (%)

7.3.2 Foreign study in patients with RA inadequately responding to TNF inhibitors (CTD 5.3.5.1-4, Study EFC10832 [October 2012 to March 2015])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients with RA inadequately responding to TNF inhibitors[19] (target sample size, 522 subjects [174 per group]) to evaluate the efficacy and safety of sarilumab in 27 foreign countries and regions.

Subjects received sarilumab 150 or 200 mg or placebo subcutaneously in combination with a fixed dose of a cDMARD once every 2 weeks for 24 weeks. Subjects who met the definition of insufficient response[20] at Week 12 or later were allowed to participate in the extension study (Study LTS11210).

All of the 546 randomized subjects (181 in the 150 mg q2w group, 184 in the 200 mg q2w group, and 181 in the placebo group) were included in the ITT population, which was used for the efficacy analysis. The randomized subjects who received ≥1 dose of the study drug (181 in the 150 mg q2w group, 184 in the 200 mg q2w group, and 181 in the placebo group) were included in the safety analysis set. Study discontinuation occurred in 31 of 181 subjects (17.1%) in the 150 mg q2w group, 25 of 184 subjects (13.6%) in the 200 mg q2w group, and 17 of 181 subjects (9.4%) in the placebo group. The main reasons for discontinuation included adverse events (18 of 181 [9.9%] in the 150 mg q2w group, 17 of 184 [9.2%] in the 200 mg q2w group, and 9 of 181 [5.0%] in the placebo group).

ACR20 response rate at Week 24 and change in HAQ-DI from baseline to Week 12 were the co-primary efficacy endpoints of the study. As shown in Table 26, pairwise comparisons between the 150 mg q2w and placebo groups and between the 200 mg q2w and placebo groups revealed a statistically significant difference in both endpoints in sarilumab groups, demonstrating superiority of treatment with sarilumab 150 or 200 mg once every 2 weeks over placebo.

Table 26. Efficacy endpoint data (ITT population)

	150 mg q2w	200 mg q2w	Placebo
ACR20 response rate at Week 24[a)]	55.8 (101/181)	60.9 (112/184)	33.7 (61/181)
Odds ratio relative to placebo [95% CI][b)] *P* value[c), e)]	2.71 [1.73, 4.25] *P* < 0.0001	3.28 [2.11, 5.12] *P* < 0.0001	
Change in HAQ-DI from baseline to Week 12	−0.50 ± 0.64 (165)	−0.49 ± 0.56 (171)	−0.29 ± 0.54 (170)
Difference from placebo in least squares mean [95% CI][d)] *P* value[d), e)]	−0.20 [−0.32, −0.09] *P* = 0.0007	−0.21 [−0.33, −0.10] *P* = 0.0004	

% (number of subjects) or mean ± SD (number of subjects)
[a)] NRI
[b)] Mantel-Haenszel estimate
[c)] Two-sided Cochran-Mantel-Haenszel test stratified by geographical region and number of prior TNF inhibitors
[d)] MMRM with baseline value as a covariate, and treatment group, geographical region, number of prior TNF inhibitors, time point (all time points from 2-12 weeks), and treatment-time interaction as fixed effects.
[e)] To adjust multiplicity, hierarchical test with a two-sided significance level of 2.5% was planned for each sarilumab dose group in the following order: 1) ACR20 response rate at Week 24, and 2) change in HAQ-DI from baseline to Week 12.

Adverse events occurred in 119 of 181 subjects (65.7%) in the 150 mg q2w group, 120 of 184 subjects (65.2%) in the 200 mg q2w group, and 90 of 181 subjects (49.7%) in the placebo group. Major events are listed in Table 27.

[19)] Patients with RA who meet the following criteria: (a) disease duration ≥6 months; (b) tender joint count ≥8; (c) swollen joint count ≥6; (d) CRP ≥8 mg/L; (e) insufficient response to or intolerance to ≥1 TNF inhibitor administered at the locally approved dose for ≥3 months; (f) treatment with ≥1 non-biologic cDMARD for ≥12 weeks, which includes ≥6-week fixed-dose treatment.
[20)] Patients who experienced <20% improvement in the swollen or tender joint count from baseline at 2 consecutive time points (at ≥4-week intervals).

One subject in the placebo group died due to road traffic accident, and a causal relationship to the study drug was ruled out for the event. Serious adverse events occurred in 6 of 181 subjects (3.3%) in the 150 mg q2w group, 10 of 184 subjects (5.4%) in the 200 mg q2w group, and 6 of 181 subjects (3.3%) in the placebo group. A causal relationship to the study drug could not be ruled out for the events that occurred in 3 subjects in the 150 mg q2w group (neutropenia, cellulitis/osteomyelitis, and gastric ulcer haemorrhage [1 subject each]), 4 subjects in the 200 mg q2w group (neutropenia, neutrophil count decreased, cellulitis, and atrioventricular block second degree [1 subject each]), and 3 subjects in the placebo group (bronchitis/bacteraemia, cellulitis, and mixed liver injury [1 subject each]). Adverse events led to discontinuation in 14 of 181 subjects (7.7%) in the 150 mg q2w group, 17 of 184 subjects (9.2%) in the 200 mg q2w group, and 8 of 181 subjects (4.4%) in the placebo group.

Adverse drug reactions occurred in 61 of 181 subjects (33.7%) in the 150 mg q2w group, 72 of 184 subjects (39.1%) in the 200 mg q2w group, and 30 of 181 subjects (16.6%) in the placebo group.

Table 27. Adverse events occurring in ≥3% of subjects in any group (safety analysis set)

Event term	150 mg q2w (n = 181)	200 mg q2w (n = 184)	Placebo (n = 181)
Neutropenia	23 (12.7)	23 (12.5)	2 (1.1)
Urinary tract infection	6 (3.3)	13 (7.1)	12 (6.6)
ALT increased	5 (2.8)	10 (5.4)	2 (1.1)
Accidental overdose	7 (3.9)	9 (4.9)	5 (2.8)
Hypertension	3 (1.7)	8 (4.3)	4 (2.2)
Nasopharyngitis	11 (6.1)	7 (3.8)	9 (5.0)
Injection site erythema	11 (6.1)	7 (3.8)	0
Pharyngitis	2 (1.1)	6 (3.3)	3 (1.7)
Upper respiratory tract infection	4 (2.2)	6 (3.3)	6 (3.3)
Headache	5 (2.8)	6 (3.3)	7 (3.9)
Diarrhoea	2 (1.1)	6 (3.3)	7 (3.9)
AST increased	2 (1.1)	6 (3.3)	0
Hypertriglyceridaemia	11 (6.1)	5 (2.7)	3 (1.7)
Hypercholesterolaemia	6 (3.3)	4 (2.2)	0
Rheumatoid arthritis	3 (1.7)	4 (2.2)	8 (4.4)

Number of subjects (%)

7.3.3 Japanese study in patients with RA (CTD 5.3.5.2-1, Study LTS13618 [February 2015 to November 2016])

A randomized, double-blind, uncontrolled study was conducted in patients with RA[21)] (target sample size, 90 subjects [30 in the sarilumab + cDMARD group (15 per group), 60 in the sarilumab alone group (30 per group)]) to evaluate the safety and efficacy of sarilumab.

Subjects received sarilumab 150 or 200 mg subcutaneously once every 2 weeks for 52 weeks. Subjects in the sarilumab + cDMARD group concomitantly received a fixed dose of a cDMARD (excluding MTX).

21) Patients with RA who meet the following criteria: (a) disease duration ≥3 months; (b) tender joint count ≥4 and swollen joint count ≥4; (c) CRP ≥4 mg/L or erythrocyte sedimentation rate ≥28 mm/h; (d) treatment with ≥1 non-biologic cDMARD (excluding MTX) for ≥12 weeks, which includes ≥6-week fixed-dose treatment (sarilumab + cDMARD group only); (e) inappropriate for or intolerant to MTX treatment according to the investigator's opinion, or insufficient response to treatment with MTX for ≥12 weeks, which includes ≥6-week fixed-dose treatment (≤12 patients may be enrolled) (sarilumab alone group only).

Of 91 randomized subjects (30 in the 150 mg q2w group, 31 in the 200 mg q2w group, 15 in the cDMARD/150 mg q2w group, and 15 in the cDMARD/200 mg q2w group), 91 subjects who received at ≥1 dose of the study drug (30 in the 150 mg q2w group, 31 in the 200 mg q2w group, 15 in the cDMARD/150 mg q2w group, and 15 in the cDMARD/200 mg q2w group) were included in the safety analysis set. Of the randomized subjects, subjects who received ≥1 dose of the study drug and were evaluable for the efficacy endpoints (30 in the 150 mg q2w group, 31 in the 200 mg q2w group, 15 in the cDMARD/150 mg q2w group, and 15 in the cDMARD/200 mg q2w group) were included in the mITT population, which was used for the efficacy analysis. Study discontinuation occurred in 3 of 30 subjects (10.0%) in the 150 mg q2w group, 1 of 31 subjects (3.2%) in the 200 mg q2w group, 2 of 15 subjects (13.3%) in the cDMARD/150 mg q2w group, and 6 of 15 subjects (40.0%) in the cDMARD/200 mg q2w group. The main reason for discontinuation was adverse event (2 of 30 [6.7%] in the 150 mg q2w group, 1 of 31 [3.2%] in the 200 mg q2w group, 2 of 15 [13.3%] in the cDMARD/150 mg q2w group, and 5 of 15 [33.3%] in the cDMARD/200 mg q2w group).

The time course of the ACR20 response rates, the efficacy endpoint, are shown in Table 28.

Table 28. Time course of ACR20 response rates (mITT population)

	150 mg q2w (n = 30)	200 mg q2w (n = 31)	cDMARDs/150 mg q2w (n = 15)	cDMARDs/200 mg q2w (n = 15)
Week 2	20.0 (6)	25.8 (8)	33.3 (5)	0
Week 4	40.0 (12)	29.0 (9)	46.7 (7)	46.7 (7)
Week 8	50.0 (15)	54.8 (17)	73.3 (11)	53.3 (8)
Week 12	60.0 (18)	58.1 (18)	73.3 (11)	66.7 (10)
Week 24	73.3 (22)	64.5 (20)	80.0 (12)	73.3 (11)
Week 52	76.7 (23)	74.2 (23)	73.3 (11)	40.0 (6)

% (number of subjects)

Adverse events occurred in 25 of 30 subjects (83.3%) in the 150 mg q2w group, 28 of 31 subjects (90.3%) in the 200 mg q2w group, 14 of 15 subjects (93.3%) in the cDMARD/150 mg q2w group, and 13 of 15 subjects (86.7%) in the cDMARD/200 mg q2w group. Major adverse events are listed in Table 29.

No deaths were reported. Serious adverse events occurred in 1 of 30 subjects (3.3%) in the 150 mg q2w group, 2 of 31 subjects (6.5%) in the 200 mg q2w group, and 3 of 15 subjects (20.0%) in the cDMARD/200 mg q2w group. A causal relationship to the study drug could not be ruled out for the events that occurred in 1 subject in the 150 mg q2w group (herpes zoster oticus), 1 subject in the 200 mg q2w group (pneumonia bacterial), and 1 subject in the cDMARDs/200 mg q2w group (chronic sinusitis/periorbital abscess). In addition, 1 subject in the 200 mg q2w group experienced incisional hernia after the completion of the study (139 days after the last dose of the study drug).A causal relationship to the study drug could not be ruled out for incisional hernia. Adverse events led to treatment discontinuation in 1 of 30 subjects (3.3%) in the 150 mg q2w group, 2 of 15 subjects (13.3%) in the cDMARD/150 mg q2w group, and 5 of 15 subjects (33.3%) in the cDMARD/200 mg q2w group.

Adverse drug reactions occurred in 18 of 30 subjects (60.0%) in the 150 mg q2w group, 23 of 31 subjects (74.2%) in the 200 mg q2w group, 9 of 15 subjects (60.0%) in the cDMARD/150 mg q2w group, and 9 of 15 subjects (60.0%) in the cDMARD/200 mg q2w group.

Table 29. Adverse events occurring in ≥2 subjects in any group (safety analysis set)

Event term	150 mg q2w (n = 30)	200 mg q2w (n = 31)	cDMARDs/150 mg q2w (n = 15)	cDMARDs/200 mg q2w (n = 15)
Nasopharyngitis	13 (43.3)	14 (45.2)	4 (26.7)	5 (33.3)
Injection site erythema	1 (3.3)	6 (19.4)	0	1 (6.7)
Stomatitis	3 (10.0)	4 (12.9)	3 (20.0)	4 (26.7)
Hepatic function abnormal	1 (3.3)	4 (12.9)	1 (6.7)	0
Neutropenia	1 (3.3)	3 (9.7)	5 (33.3)	3 (20.0)
Hypercholesterolaemia	1 (3.3)	2 (6.5)	0	0
Conjunctivitis allergic	0	2 (6.5)	0	0
Oropharyngeal pain	3 (10.0)	2 (6.5)	0	0
Rhinitis allergic	0	2 (6.5)	0	0
Abdominal pain upper	0	2 (6.5)	0	0
Rheumatoid arthritis	4 (13.3)	2 (6.5)	1 (6.7)	0
Injection site swelling	0	2 (6.5)	0	1 (6.7)
Eczema	1 (3.3)	2 (6.5)	0	1 (6.7)
Dizziness	2 (6.7)	1 (3.2)	0	2 (13.3)
Contact dermatitis	2 (6.7)	1 (3.2)	0	0
Neutrophil count decreased	2 (6.7)	1 (3.2)	1 (6.7)	1 (6.7)
Gastroenteritis	1 (3.3)	1 (3.2)	2 (13.3)	0
Epistaxis	2 (6.7)	0	0	0
Gastritis	2 (6.7)	0	0	0
Periodontitis	2 (6.7)	0	0	1 (6.7)
Contusion	2 (6.7)	0	3 (20.0)	0

Number of subjects (%)

7.R Outline of the review conducted by PMDA

7.R.1 Applicability of foreign clinical study data

The applicant's explanation about the applicability of foreign clinical study data to the current application for marketing approval:

There was no substantial difference between Japan and overseas in the definition or diagnosis of or treatment system for RA or no intrinsic ethnic differences in the pharmacokinetics of sarilumab observed between Japanese and non-Japanese patients [see Section "6.R.1 Ethnic difference in the pharmacokinetics of sarilumab"]. The development of sarilumab is thus feasible in Japan in light of the International Council for Harmonisation E5 guideline ("Ethnic Factors in the Acceptability of Foreign Clinical Data," PMSB/ELD Notification No. 672 dated August 11, 1998). A Japanese Phase II/III study (Study EFC14059) was conducted as the bridging study, and a foreign Phase III study (Study EFC11072 Part B) as the study to be bridged. A clinical data package for the current application was planned to be developed by extrapolating foreign clinical study data after bridging was successfully achieved.

The ACR20 response rates at Week 24 in the bridging study and the study to be bridged are shown in Table 30.

Table 30. ACR20 response rates at Week 24 in the bridging study and the study to be bridged (efficacy analysis population, NRI)

	150 mg q2w	200 mg q2w	Placebo
Study EFC14059 (bridging study)	67.9 (55/81)	57.5 (46/80)	14.8 (12/81)
Odds ratio relative to placebo [95% CI]	12.19 [5.58, 26.59]	7.23 [3.45, 15.16]	
Study EFC11072 Part B (study to be bridged)	58.0 (232/400)	66.4 (265/399)	33.4 (133/398)
Odds ratio relative to placebo [95% CI]	2.77 [2.08, 3.70]	3.98 [2.96, 5.34]	

% (number of subjects)

Patient characteristics of the 2 studies were compared. Study EFC14059 showed trends toward higher age (54.9 ± 10.7 years in Japanese patients and 50.8 ± 11.7 years in non-Japanese patients), smaller proportion of female subjects (77.8% and 81.7%), lower body weight (56.62 ± 11.81 kg and 74.39 ± 18.52 kg), lower BMI (22.52 ± 4.10 and 28.26 ± 6.34), shorter duration of RA (7.84 ± 7.86 years and 9.03 ± 7.85 years), and lower rheumatoid factor positivity (73.6% and 84.9%) than Study EFC11072 Part B. The ACR20 response rates at Week 24 in individual subgroups are shown in Table 31. There was no substantial between-study difference in the subgroup analysis data. However, the data of small subgroups need to be interpreted carefully.

Table 31. Subgroup analysis of ACR20 response rates at Week 24 in the bridging study and the study to be bridged (efficacy analysis population, NRI)

		EFC14059			EFC11072 Part B		
Patient characteristics		150 mg q2w	200 mg q2w	Placebo	150 mg q2w	200 mg q2w	Placebo
Age	<65 years	68.2 (45/66)	58.6 (34/58)	10.8 (7/65)	58.2 (209/359)	68.4 (238/348)	33.9 (121/357)
	≥65 years	66.7 (10/15)	54.5 (12/22)	31.3 (5/16)	56.1 (23/41)	52.9 (27/51)	29.3 (12/41)
Sex	Male	77.8 (14/18)	52.6 (10/19)	35.3 (6/17)	59.3 (48/81)	62.9 (39/62)	33.8 (26/77)
	Female	65.1 (41/63)	59.0 (36/61)	9.4 (6/64)	57.7 (184/319)	67.1 (226/337)	33.3 (107/321)
Body weight	<60 kg	67.9 (38/56)	60.0 (33/55)	12.3 (7/57)	70.2 (59/84)	80.7 (67/83)	26.7 (23/86)
	≥60 kg	68.0 (17/25)	52.0 (13/25)	20.8 (5/24)	55.1 (173/314)	62.9 (198/315)	35.3 (110/312)
BMI	<25 kg/m^2	73.0 (46/63)	57.8 (37/64)	13.1 (8/61)	66.4 (97/146)	73.6 (95/129)	29.8 (37/124)
	≥25 kg/m^2	50.0 (9/18)	56.3 (9/16)	20.0 (4/20)	54.0 (135/250)	63.2 (170/269)	35.2 (96/273)
Duration of RA	≤3 years	59.3 (16/27)	72.4 (21/29)	18.8 (6/32)	56.1 (60/107)	71.4 (70/98)	37.9 (39/103)
	>3 years	72.2 (39/54)	49.0 (25/51)	12.2 (6/49)	58.7 (172/293)	64.8 (195/301)	31.9 (94/295)
Rheumatoid factor	Positive	72.6 (45/62)	56.7 (34/60)	16.4 (9/55)	59.4 (205/345)	69.8 (229/328)	33.0 (111/336)
	Negative	52.6 (10/19)	60.0 (12/20)	12.0 (3/25)	49.0 (25/51)	50.7 (35/69)	35.5 (22/62)

% (number of subjects)

The safety analysis revealed adverse events common to both studies, namely, neutropenia, thrombocytopenia, hepatic function disorder, lipids increased, and injection site reaction. There was no tendency that the incidences of adverse events substantially differ between the 2 studies, as shown in Tables 23 and 25.

Based on these observation, the data from the Japanese Phase II/III study, Japanese Phase III study, and foreign Phase III studies can be utilized to develop a clinical data package for the current application.

PMDA's view:

No substantial differences were found between Japan and overseas in the pathological conditions or symptoms of RA, or no clinically significant differences in diagnosis, therapeutic goal, or system for RA treatment. The difference in patient characteristics between Study EFC14059 and Study EFC11072 Part B did not affect ACR20 response rate or other endpoints. Based on these observations, the data from the Japanese Phase II/III study, Japanese Phase III study, and foreign Phase III study (Study EFC11072 Part B) can be included in the clinical data package for the evaluation of the efficacy and safety of sarilumab in patients with RA.

7.R.2 Efficacy

The applicant's explanation about the efficacy of sarilumab against clinical symptoms of RA:

In Japanese Phase II/III study (Study EFC14059) and foreign Phase III study (Study EFC11072 Part B) in patients with RA inadequately responding to MTX, pairwise comparisons between the 150 mg q2w and placebo groups and between the 200 mg q2w and placebo groups revealed a statistically significant difference for the endpoints including ACR20 response rate (primary endpoint), demonstrating superiority of sarilumab 150 or 200 mg once every 2 weeks over placebo [see Sections "7.2.1 Japanese study in patients with RA inadequately responding to MTX" and "7.3.1 Foreign study in patients with RA inadequately responding to MTX"]. Data of secondary endpoints of these studies are shown in Table 32. For all endpoints, sarilumab 150 mg q2w and 200 mg q2w were superior to placebo. The efficacy of sarilumab against clinical symptoms of RA was thus demonstrated.

The inhibitory effect on structural joint damage in Japanese patients is planned to be evaluated through clinical studies in the future.

Table 32. Efficacy endpoints at Week 24 in Japanese Phase II/III study and foreign Phase III study (efficacy analysis population)

	EFC14059 (in Japan)			EFC11072 Part B (overseas)		
	150 mg q2w	200 mg q2w	Placebo	150 mg q2w	200 mg q2w	Placebo
ACR20 response rate	67.9 (55/81)	57.5 (46/80)	14.8 (12/81)	58.0 (232/400)	66.4 (265/399)	33.4 (133/398)
ACR50 response rate	43.2 (35/81)	38.8 (31/80)	9.9 (8/81)	37.0 (148/400)	45.6 (182/399)	16.6 (66/398)
ACR70 response rate	18.5 (15/81)	15.0 (12/80)	3.7 (3/81)	19.8 (79/400)	24.8 (99/399)	7.3 (29/398)
Change in HAQ-DI	−0.53 ± 0.53	−0.56 ± 0.52	−0.30 ± 0.35	−0.62 ± 0.58	−0.64 ± 0.64	−0.43 ± 0.61
Change in DAS28-CRP	−2.83 ± 1.04	−2.79 ± 1.05	−1.53 ± 1.22	−2.68 ± 1.40	−3.02 ± 1.26	−1.62 ± 1.44
Change in SDAI	−25.19 ± 11.61	−23.82 ± 11.25	−16.03 ± 11.60	−28.01 ± 14.83	−29.70 ± 13.85	−20.37 ± 16.54
SDAI remission rate	6.2 (5/81)	12.5 (10/80)	1.2 (1/81)	10.3 (41/400)	13.0 (52/399)	4.8 (19/398)

PMDA's view:

The efficacy of sarilumab against clinical symptoms of RA in Japanese patients was demonstrated by Study EFC14059 and Study EFC11072 Part B. Sarilumab 150 or 200 mg once every 2 weeks was superior over placebo in terms of the ACR20 response rate at Week 24, and the secondary endpoint values tended to improve in the sarilumab groups as compared with the placebo group.

However, the inhibitory effect of sarilumab on structural joint damage demonstrated in foreign clinical studies has not been studied in Japanese patients with RA. The inhibition of structural joint damage is another ultimate goal of RA treatment besides improvement of clinical symptoms. Therefore, sarilumab's inhibitory effect on structural joint damage and clinical positioning in relation to other anti-rheumatic drugs should be clarified in Japanese clinical studies in the future (Japan College of Rheumatology guideline 2014).

7.R.3 Safety

The applicant's explanation about the safety of sarilumab:

The safety of sarilumab was analyzed based on the pooled data from Phase II/III study (Study EFC14059) and Phase III study (Study LTS13618) in Japanese patients with RA (pooled Japanese population); pooled data from Phase II study (Study EFC11072 Part A), Phase III study (Study EFC11072 Part B and Study EFC10832) in non-Japanese patients with RA (foreign placebo-controlled population); and pooled data from Phase II study (Study EFC11072 Part A) and Phase III study (Study EFC11072 Part B, and Studies EFC10832, SFY13370, EFC11574, MSC12665, and LTS11210) in non-Japanese patients with RA (foreign long-term safety population).

Table 33 is a summary of the safety of sarilumab in the foreign placebo-controlled population, foreign long-term safety population, and pooled Japanese population.

Table 33. Summary of the safety of sarilumab in clinical studies in patients with RA

	Foreign placebo-controlled population			Foreign long-term safety population		Pooled Japanese population	
	150 mg q2w	200 mg q2w	Placebo	150 mg q2w	200 mg q2w	150 mg q2w	200 mg q2w
Number of subjects	660	661	661	1155	1351	140	185
Total exposure time (subject-year)	440.7	441.4	382.3	701.9	1758.6	135.0	169.4
Deaths	2	1	3	2	7	0	0
Adverse event	465 (70.5) 338.1	488 (73.8) 385.8	378 (57.2) 260.0	764 (66.1) 339.9	1101 (81.5) 289.5	127 (90.7) 512.7	166 (89.7) 515.4
Serious adverse events	42 (6.4) 15.2	59 (8.9) 18.4	31 (4.7) 12.8	62 (5.4) 13.7	187 (13.8) 15.6	9 (6.4) 8.9	16 (8.6) 10.6
Adverse events leading to treatment discontinuation	72 (10.9) 20.4	83 (12.6) 20.6	31 (4.7) 8.6	116 (10.0) 20.5	211 (15.6) 13.6	15 (10.7) 13.3	21 (11.4) 14.2
Adverse drug reactions	234 (35.5) 133.4	289 (43.7) 167.0	139 (21.0) 59.9	402 (34.8) 136.9	695 (51.4) 118.7	91 (65.0) 280.0	126 (68.1) 294.0

Upper row, number of subjects (%)
Lower row, number of events per 100 subject-years adjusted for total exposure time

Major adverse events observed in the foreign placebo-controlled population are shown in Table 34. Major adverse events observed during the placebo-controlled period (after 24 weeks of treatment) in Study EFC14059, which constitutes a part of the pooled Japanese population, are shown in Table 22. No substantial difference was observed in the incidences of major adverse events. There were no clear differences in the types or incidences of major adverse events between the foreign long-term safety population and pooled Japanese population, as shown in Table 35.

Table 34. Adverse events occurring in ≥2% of subjects in any group (foreign placebo-controlled population)

Event term	150 mg q2w (n = 660)	200 mg q2w (n = 661)	Placebo (n = 661)
Neutropenia	65 (9.8)	94 (14.2)	3 (0.5)
Upper respiratory tract infection	42 (6.4)	47 (7.1)	32 (4.8)
ALT increased	44 (6.7)	45 (6.8)	17 (2.6)
Accidental overdose	36 (5.5)	40 (6.1)	34 (5.1)
Urinary tract infection	29 (4.4)	38 (5.7)	28 (4.2)
Injection site erythema	35 (5.3)	35 (5.3)	6 (0.9)
Nasopharyngitis	37 (5.6)	28 (4.2)	31 (4.7)
Bronchitis	17 (2.6)	25 (3.8)	19 (2.9)
Diarrhoea	15 (2.3)	25 (3.8)	16 (2.4)
Leukopenia	11 (1.7)	23 (3.5)	0
Headache	22 (3.3)	22 (3.3)	24 (3.6)
Hypertension	19 (2.9)	21 (3.2)	20 (3.0)
Transaminases increased	12 (1.8)	18 (2.7)	3 (0.5)
Rheumatoid arthritis	7 (1.1)	18 (2.7)	27 (4.1)
Influenza	17 (2.6)	16 (2.4)	19 (2.9)
Injection site pruritus	17 (2.6)	16 (2.4)	1 (0.2)
Pharyngitis	15 (2.3)	16 (2.4)	14 (2.1)
Sinusitis	14 (2.1)	16 (2.4)	11 (1.7)
Nausea	10 (1.5)	15 (2.3)	12 (1.8)
Back pain	10 (1.5)	15 (2.3)	9 (1.4)
Hypertriglyceridaemia	19 (2.9)	12 (1.8)	5 (0.8)

Number of subjects (%)

Table 35. Major adverse events occurring in the foreign long-term safety population and pooled Japanese population

Foreign long-term safety population (occurring in ≥2% of subjects in either group)			Pooled Japanese population (occurring in ≥3% of subjects in either group)		
Event term	150 mg q2w (n = 1155)	200 mg q2w (n = 1351)	Event term	150 mg q2w (n = 140)	200 mg q2w (n = 185)
Neutropenia	130 (11.3)	228 (16.9)	Nasopharyngitis	49 (35.0)	64 (34.6)
ALT increased	61 (5.3)	128 (9.5)	Stomatitis	14 (10.0)	23 (12.4)
Upper respiratory tract infection	72 (6.2)	121 (9.0)	Neutropenia	18 (12.9)	22 (11.9)
Urinary tract infection	43 (3.7)	103 (7.6)	Injection site erythema	10 (7.1)	19 (10.3)
Accidental overdose	56 (4.8)	97 (7.2)	Hepatic function abnormal	10 (7.1)	14 (7.6)
Nasopharyngitis	63 (5.5)	88 (6.5)	Upper respiratory tract infection	9 (6.4)	13 (7.0)
Injection site erythema	60 (5.2)	87 (6.4)	Hypertension	5 (3.6)	11 (5.9)
Hypertension	23 (2.0)	83 (6.1)	Eczema	9 (6.4)	10 (5.4)
Bronchitis	33 (2.9)	73 (5.4)	Gastroenteritis	5 (3.6)	10 (5.4)
Rheumatoid arthritis	19 (1.6)	65 (4.8)	Diarrhoea	2 (1.4)	9 (4.9)
Diarrhoea	25 (2.2)	58 (4.3)	Rheumatoid arthritis	7 (5.0)	9 (4.9)
Pharyngitis	23 (2.0)	48 (3.6)	Nausea	0	8 (4.3)
Leukopenia	23 (2.0)	47 (3.5)	White blood cell count decreased	5 (3.6)	8 (4.3)
Headache	35 (3.0)	44 (3.3)	Abdominal pain upper	1 (0.7)	7 (3.8)
Sinusitis	25 (2.2)	44 (3.3)	ALT increased	12 (8.6)	7 (3.8)
Back pain	18 (1.6)	44 (3.3)	Injection site pruritus	7 (5.0)	7 (3.8)
Injection site pruritus	32 (2.8)	40 (3.0)	Pharyngitis	5 (3.6)	6 (3.2)
Influenza	22 (1.9)	40 (3.0)	Rash	6 (4.3)	6 (3.2)
Fall	20 (1.7)	36 (2.7)	Insomnia	3 (2.1)	6 (3.2)
Nausea	15 (1.3)	34 (2.5)	Dizziness	2 (1.4)	6 (3.2)
Hypertriglyceridaemia	23 (2.0)	32 (2.4)	Neutrophil count decreased	6 (4.3)	5 (2.7)
Transaminases increased	13 (1.1)	33 (2.4)	Bronchitis	5 (3.6)	3 (1.6)
Gastroenteritis	13 (1.1)	31 (2.3)	Contusion	8 (5.7)	3 (1.6)
Hypercholesterolaemia	20 (1.7)	29 (2.1)	Periodontitis	6 (4.3)	2 (1.1)
Thrombocytopenia	13 (1.1)	29 (2.1)	Cystitis	5 (3.6)	2 (1.1)
AST increased	10 (0.9)	29 (2.1)	Conjunctivitis	5 (3.6)	0
Dyslipidaemia	11 (1.0)	28 (2.1)			
Arthralgia	12 (1.0)	27 (2.0)			

Number of subjects (%)

In Japanese studies, no deaths occurred in subjects receiving sarilumab. In foreign studies, 22 subjects died (pneumonia in 3 subjects; cardiac failure, cerebrovascular accident, pneumonia viral, sepsis, septic shock, cervix cancer metastatic, cardiac failure acute/coronary artery dissection/papillary muscle rupture, lung squamous cell carcinoma metastatic, metastatic bronchial carcinoma, *Clostridium difficile* infection/left ventricular failure, cerebrovascular accident/acute respiratory distress syndrome, cardiac failure/acute respiratory failure, pulmonary oedema, respiratory distress, death, sudden death, multi-organ failure, pulmonary embolism, and alcohol poisoning/toxicity to various agents in 1 subject each). A causal relationship to the study drug could not be ruled out for acute respiratory distress syndrome, septic shock, lung squamous cell carcinoma metastatic, sepsis, pneumonia viral, and cervix cancer metastatic.

In the pooled Japanese population, serious adverse events were observed in 9 of 140 subjects (6.4%) in the 150 mg q2w group and 16 of 185 subjects (8.6%) in the 200 mg q2w group, and there were no serious adverse events observed in ≥2 subjects in either group. In the foreign long-term safety population, serious adverse events were observed in 439 of 2887 subjects (15.2%), and major events included pneumonia (27 subjects, 0.9%), rheumatoid arthritis (21 subjects, 0.7%), osteoarthritis (20 subjects, 0.7%), and neutropenia (16 subjects, 0.6%).

The following subsections describe PMDA's discussion on adverse events from the aspects of the pharmacological activity of sarilumab and incidences of the events in the clinical studies.

7.R.3.1 Infections

The applicant's explanation about the incidence of infections associated with sarilumab:

The incidences of infections in the clinical studies are shown in Table 36. The majority events were mild or moderate in severity. Infections commonly reported in the Japanese and foreign studies included upper respiratory tract infection and nasopharyngitis.

Table 36. Incidences of infection-related adverse events

	Foreign placebo-controlled population			Foreign long-term safety population			Pooled Japanese population	
	150 mg q2w (n = 660)	200 mg q2w (n = 661)	Placebo (n = 661)	150 mg q2w (n = 1155)	200 mg q2w (n = 1351)	All dose groups combined (n = 2887)	150 mg q2w (n = 140)	200 mg q2w (n = 185)
Infection	227 (34.4) 81.0	233 (35.2) 84.5	189 (28.6) 75.1	365 (31.6) 80.5	572 (42.3) 66.5	1313 (45.5) 64.0	90 (64.3) 132.6	101 (54.6) 104.5
Serious infection	12 (1.8) 3.6	19 (2.9) 5.2	12 (1.8) 3.9	17 (1.5) 3.1	64 (4.7) 4.3	158 (5.5) 4.2	6 (4.3) 4.4	5 (2.7) 3.5
Upper respiratory tract infection	42 (6.4) 12.3	47 (7.1) 12.5	32 (4.8) 10.2	72 (6.2) 12.5	121 (9.0) 9.3	298 (10.3) 9.5	9 (6.4) 8.1	13 (7.0) 10.6
Nasopharyngitis	37 (5.6) 9.5	28 (4.2) 6.8	31 (4.7) 9.2	63 (5.5) 10.1	88 (6.5) 5.7	216 (7.5) 6.0	49 (35.0) 57.0	64 (34.6) 50.2
Opportunistic infection	4 (0.6) 0.9	6 (0.9) 1.4	3 (0.5) 0.8	4 (0.3) 0.6	18 (1.3) 1.1	44 (1.5) 1.0	2 (1.4) 1.5	2 (1.1) 1.2
Herpes zoster[a)]	4 (0.6) 0.9	5 (0.8) 1.1	3 (0.5) 0.8	4 (0.3) 0.6	16 (1.2) 1.0	36 (1.2) 0.8	0	0
Tuberculosis[b)]	0	0	0	0	0	2 (<0.1) 0.04	0	0

Upper row, number of subjects (%)
Bottom row, number of events per 100 subject-years adjusted for total exposure time
[a)] Herpes zoster-related events diagnosed as an opportunistic infection by investigator
[b)] Tuberculosis-related events diagnosed as an opportunistic infection by investigator

The incidence of serious infections was similar between the foreign long-term safety population and the foreign placebo-controlled population. It showed no trend toward increased incidence of serious infections associated with long-term use of sarilumab or no substantial difference from that in the pooled Japanese population. The risk of serious infections associated with sarilumab in patients with RA is comparable to that associated with TNF inhibitors or tocilizumab based on the following facts: (1) A foreign study (Study EFC14092) showed a comparable incidence of serious infections between sarilumab and adalimumab (a TNF inhibitor) groups (1.1% [2.5 events per 100 subject-years] in both groups); and (2) according to a literature article, the exposure-adjusted incidence rates of serious infections in patients treated with TNF inhibitors or tocilizumab range from 3.03 to 10.68 events per 100 subject-years *(Arthritis Res Ther*. 2015;17:74) while the incidence rate of serious infections in the foreign long-term safety population was 3.5 events per 100 subject-years.

Opportunistic infection in the pooled Japanese population included *Pneumocystis jirovecii* pneumonia in 2 subjects, furuncle in 1 subject, and herpes zoster oticus in 1 subject. All events resolved. In the foreign long-term safety population, opportunistic infections were observed in 44 subjects (herpes zoster in 36 subjects, candida infection in 6 subjects, and tuberculosis in 2 subjects). Herpes zoster in 7 subjects out of 36 were serious. The events was assessed as unresolved in 1 subject while resolved in the rest.

Candida infection in 1 patient was serious and resolved. Although herpes zoster was the most common opportunistic infection in the foreign clinical studies, the risk of herpes zoster is comparable between sarilumab and the approved biological products, based on the exposure-adjusted incidence rates of herpes zoster in patients treated with approved biological products in the published post-marketing data in Japan (1.3-2.2 events per 100 subject-years).

Tuberculosis was not reported in the pooled Japanese population, while 2 subjects in the foreign long-term safety population were affected. The 2 subjects were infected in epidemic areas of tuberculosis (Brazil and South Africa) and the subjects tested negative for latent tuberculosis infection at screening. These events are thus considered newly acquired infection.

In a Japanese study (Study EFC14059), hepatitis B DNA assay positive was observed in 1 subject, but no hepatitis was reported. Because tocilizumab caused an increase in transaminase without accompanying a hepatic disorder, the clinical studies excluded patients with ALT or aspartate aminotransferase (AST) of >1.5-fold the ULN, patients with total bilirubin exceeding ULN, and those with hepatitis B or are at a risk of hepatitis B reactivation. This precludes the determination of a relationship between sarilumab and hepatitis B virus reactivation.

These clinical study data suggest comparable risks of serious infection, opportunistic infection (including tuberculosis), and reactivation of hepatitis B and C viruses between sarilumab and the approved biological products for RA treatment. Healthcare professionals will be advised through the package insert to carefully examine patients before treatment for serious infections, opportunistic infections, tuberculosis, and hepatitis B virus infection and instruct patients to contact a physician immediately when any sign or symptom of infection manifests during treatment with sarilumab.

PMDA's view:
The sarilumab groups tended to have higher incidences of infections than in the placebo group with dose dependency, and were found to have had a certain number of serious infections including opportunistic infections. Foreign clinical study data and published literature indicated comparable infection risk levels between sarilumab and the approved biological products. Therefore, healthcare professionals must take strict safety measures against serious infection as practiced for tocilizumab and other biological products, and this should be advised in the package insert. Because of the limited clinical experience with sarilumab, the impact of its prolonged use, i.e., whether it will increase the infection risk or will make difference in the risk levels between sarilumab and its analogues, is unknown. Post-marketing data should be collected from infected patients via surveillance, etc. for careful assessment and discussion on whether to take any further safety measures.

7.R.3.2 Gastrointestinal perforation

The applicant's explanation about the incidence of gastrointestinal perforation associated with sarilumab:
Based on the post-marketing data in Japan on the use of infliximab, etanercept, adalimumab, and tocilizumab, gastrointestinal perforation has been reported only from patients treated with tocilizumab (0.2%, 0.3 events per 100 subject-years) (*J Rheumatol*. 2014;41:15-23). Therefore, a risk of gastrointestinal perforation associated with sarilumab was investigated.

Gastrointestinal perforation was not observed in the Japanese clinical studies. In all dose groups combined in the foreign long-term safety population, gastrointestinal perforation was observed in 7 of 2887 subjects (0.2%), at an incidence rate per 100 subject-years being 0.16 events. An estimation based on a large medical database (*Clin Rheumatol*. 2011;30:1471-4) showed that the incidence rates per 100 subject-years of gastrointestinal perforation in patients with RA receiving corticosteroids and those receiving TNF inhibitors were 0.39 and 0.13 events, respectively, which were comparable to that in patients receiving sarilumab. Risk factors for gastrointestinal perforation in patients with RA include age, a history of diverticulitis, and use of corticosteroids or NSAIDs (*Clin Rheumatol*. 2011;30:1471-4).

Based on the above, sarilumab should be administered carefully to patients with a high risk of gastrointestinal perforation, and a cautionary statement about gastrointestinal perforation will be included in the package insert.

PMDA's view:
Because gastrointestinal perforation is a serious event with a possible fatal outcome. Gastrointestinal perforation occurred in subjects treated with sarilumab in the clinical studies, and an increase in the incidence of gastrointestinal perforation was suggested in patients with RA receiving tocilizumab, a sarilumab analogue drug (*Arthritis Rheumatol*. 2016;68:2612-7). Cautionary advice should be, therefore, given as practiced for tocilizumab. In addition to further investigation on the incidence of gastrointestinal perforation, affected patients should be characterized based on post-marketing surveillance data, etc. Findings should be communicated to healthcare professionals accordingly.

7.R.3.3 Hypersensitivity and anaphylaxis

The applicant's explanation about the incidences of hypersensitivity and anaphylaxis associated with sarilumab:
Table 37 shows the incidences of hypersensitivity-related adverse events in the foreign placebo-controlled population, foreign long-term safety population, and pooled Japanese population. The incidences tended to be higher in the sarilumab group than in the placebo group.

Table 37. Incidences of hypersensitivity-related adverse events

	Foreign placebo-controlled population			Foreign long-term safety population			Pooled Japanese population	
	150 mg q2w (n = 660)	200 mg q2w (n = 661)	Placebo (n = 661)	150 mg q2w (n = 1155)	200 mg q2w (n = 1351)	All dose groups combined (n = 2887)	150 mg q2w (n = 140)	200 mg q2w (n = 185)
Hypersensitivity[a)]	45 (6.8)	48 (7.3)	26 (3.9)	78 (6.8)	99 (7.3)	243 (8.4)	30 (21.4)	32 (17.3)
Serious hypersensitivity[a)]	0	1 (0.2)	0	1 (<0.1)	1 (<0.1)	4 (0.1)	0	0
Hypersensitivity leading to treatment discontinuation[a)]	3 (0.5)	6 (0.9)	1 (0.2)	7 (0.6)	11 (0.8)	27 (0.9)	0	0

Number of subjects (%)
a) Events classified under Standardized MedDRA Query "Hypersensitivity"

Major events observed in the pooled Japanese population included eczema, rash, and contact dermatitis. Major events reported in the foreign long-term safety population included injection site rash, rash, urticaria, contact dermatitis, and dermatitis allergic. Serious hypersensitivity occurred in 4 subjects in the foreign long-term safety population (immediate post-injection reaction, angioedema, hypersensitivity, and skin necrosis). Skin necrosis remained unresolved because the subject died due to

another adverse event, while all other events resolved. Anaphylaxis was not reported in any of these populations. Hypersensitivity led to treatment discontinuation in 27 subjects in the foreign long-term safety population; major events included rash generalised, rash erythematous, and injection site rash. Neither serious hypersensitivity nor hypersensitivity leading to treatment discontinuation was observed in the pooled Japanese population.

In the pooled Japanese population, hypersensitivity-related events occurred in 34.8% (8 of 23) of ADA-positive subjects and 17.9% (54 of 302) of ADA-negative subjects. In the foreign long-term safety population, relevant events occurred in 5.3% (22 of 417) of ADA-positive subjects and 8.5% (181 of 2138) of ADA-negative subjects. The results showed no trend toward a consistently higher incidence in ADA-positive subjects.

In light of the higher incidence of hypersensitivity-related events in the sarilumab group as compared with the placebo group and serious hypersensitivity associated with sarilumab shown by the above clinical study data, serious hypersensitivity reaction will be listed in the "Clinically Significant Adverse Reactions" section. Patients should be closely monitored during treatment with sarilumab and appropriate measures should be taken for hypersensitivity-related events. This will be reminded in the package insert.

PMDA's view:
No anaphylactic events were reported in the clinical studies. Nevertheless, hypersensitivity-related adverse events tended to occur more frequently in the sarilumab group than in the placebo group, and the possibility of treatment-related serious hypersensitivity (including shock and anaphylaxis) still remains. Therefore, the package insert should call attention to relevant events, and data on the incidences of shock and anaphylaxis should be continuously collected via post-marketing surveillance, etc. Findings should be communicated to healthcare professionals accordingly.

7.R.3.4 Injection site reaction

The applicant's explanation about the incidence of injection site reaction associated with sarilumab:
Table 38 shows the incidences of injection site reaction-related adverse events in the foreign placebo-controlled population, foreign long-term safety population, and pooled Japanese population. The incidences tended to be higher in the sarilumab group than in the placebo group, but most of these events were mild or moderate in severity. No serious injection site reaction were reported in any study population. Severe injection site reactions led to treatment discontinuation in 1 subject in the 200 mg q2w group and 4 subjects in all dose groups combined in the foreign long-term safety population.

Based on the above clinical study data, injection site reaction associated with sarilumab is comparable to that commonly observed following subcutaneous injection.

Table 38. Incidences of injection site reaction-related adverse events

	Foreign placebo-controlled population			Foreign long-term safety population			Pooled Japanese population	
	150 mg q2w (n = 660)	200 mg q2w (n = 661)	Placebo (n = 661)	150 mg q2w (n = 1155)	200 mg q2w (n = 1351)	All dose groups combined (n = 2887)	150 mg q2w (n = 140)	200 mg q2w (n = 185)
Injection site reaction[a)]	53 (8.0)	63 (9.5)	9 (1.4)	92 (8.0)	134 (9.9)	311 (10.8)	15 (10.7)	22 (11.9)
Serious injection site reaction[a)]	0	0	0	0	0	0	0	0
Injection site reaction leading to treatment discontinuation[a)]	1 (0.2)	2 (0.3)	0	3 (0.3)	9 (0.7)	18 (0.6)	0	0

Number of subjects (%)
[a)] Events classified under High Level Term "Injection site reactions"

PMDA's view:
Because injection site reaction occurred more frequently in the sarilumab group than in the placebo group in the clinical studies, a risk of injection site reaction should be highlighted, and relevant data should be further collected via post-marketing surveillance, etc. Findings should be communicated to healthcare professionals accordingly.

7.R.3.5 Malignant tumors

The applicant's explanation about the incidence of malignant tumors associated with sarilumab:
Approved biological products have a potential risk for malignant tumors due to their immunosuppressive activity. Therefore, the risk of malignant tumors associated with sarilumab was investigated.

In the pooled Japanese population, malignant tumors occurred in 2 subjects in the 200 mg q2w group (breast cancer female and gastric cancer). A causal relationship to the study drug was ruled out for both events. Gastric cancer was assessed as resolving, and breast cancer female resolved. The incidences of malignant tumors in the foreign placebo-controlled population and foreign long-term safety population are shown in Table 39. The incidences of malignant tumors were comparable between the placebo and sarilumab groups.

Table 39. Incidences of malignant tumor-related adverse events

	Foreign placebo-controlled population			Foreign long-term safety population			Pooled Japanese population	
	150 mg q2w (n = 660)	200 mg q2w (n = 661)	Placebo (n = 661)	150 mg q2w (n = 1155)	200 mg q2w (n = 1351)	All dose groups combined (n = 2887)	150 mg q2w (n = 140)	200 mg q2w (n = 185)
Malignant tumor[a)]	5 (0.8) 1.1	4 (0.6) 0.9	3 (0.5) 1.0	9 (0.8) 1.3	14 (1.0) 0.9	33 (1.1) 0.8	0 0	3 (1.6) 1.8
Non-melanoma skin cancers [NMSC][b)]	0 0	2 (0.3) 0.5	2 (0.3) 0.8	1 (<0.1) 0.1	7 (0.5) 0.4	11 (0.4) 0.2	0 0	1 (0.5) 0.6
Malignant tumor (excluding NMSC)	5 (0.8) 1.1	2 (0.3) 0.5	1 (0.2) 0.3	8 (0.7) 1.1	8 (0.6) 0.5	23 (0.8) 0.5	0 0	2 (1.1) 1.2
Solid cancer (excluding NMSC)	5 (0.8) 1.1	2 (0.3) 0.5	1 (0.2) 0.3	8 (0.7) 1.1	8 (0.6) 0.5	22 (0.8) 0.5	0 0	2 (1.1) 1.2
Haematological cancer	0 0	0 0	0 0	0 0	0 0	1 (<0.1) 0.0	0 0	0 0

Upper row, number of subjects (%); bottom row, number of events per 100 subject-years adjusted for total exposure time
[a)] Events classified under Standardized MedDRA Query "Malignant or unspecified tumours"
[b)] Events classified under High Level Term "Skin neoplasms malignant and unspecified (excl melanoma)"

The following observations indicate that sarilumab is unlikely to increase the risk of malignant tumors: (1) The number of malignant tumors occurring in the sarilumab group in the foreign long-term safety population was compared to that in general population or patients with RA based on databases. The standardized incidence ratio of malignant tumors in the population receiving sarilumab was 1.09 based on SEER and 0.60 based on Clinformatics Data Mart; (2) post-marketing data in Japan showed that the incidence rates of malignant tumors in the use of infliximab, etanercept, adalimumab, or tocilizumab ranged from 0.3 to 1.0 events per 100 patient-years; (3) a database-based evaluation of malignant tumor risks in Japanese patients with RA (*Mod Rheumatol*. 2016;26:642-50) showed that the non-adjusted incidence rate (per 100 patient-years) of non-haematological malignant tumors associated with biological products, namely, infliximab, etanercept, adalimumab, and tocilizumab was 0.401, 0.578, 0.597, and 0.451 events, respectively.

PMDA's view:
It is difficult to draw a conclusion on the malignant tumor risk associated with sarilumab from currently available data. Malignant tumors occurred in the clinical studies, and the potential for sarilumab to increase the risk of malignant tumors cannot be ruled out in light of its pharmacological activity. While data on the occurrence of malignant tumors are presented to healthcare professionals, the incidence of malignant tumors including that in prolonged treatment with sarilumab should be further investigated via post-marketing surveillance, etc. Findings should be communicated to healthcare professionals accordingly.

7.R.3.6 Interstitial lung disease

The applicant's explanation about the incidence of interstitial lung disease associated with sarilumab:
Because interstitial lung disease is a common complication in patients with RA that may lead to a fatal outcome, the risk of interstitial lung disease associated with sarilumab was investigated.

In the Japanese clinical studies, 1 subject suffered an interstitial lung disease-related event[22)] (pulmonary fibrosis). It was a serious event leading to treatment discontinuation but was eventually assessed as resolving. In the foreign long-term safety population, the incidence of interstitial lung disease-related events was 0.2% (2 of 1155, 0.3 events per 100 subject-years) in the 150 mg q2w group, 0.3% (4 of 1351, 0.2 events per 100 subject-years) in the 200 mg q2w group, and 0.4% (12 of 2887, 0.3 events per 100 subject-years) in all dose groups combined. Events observed in the 12 subjects were idiopathic pulmonary fibrosis, interstitial lung disease, pneumonitis, and pulmonary fibrosis (3 subjects each). Of these, 7 subjects suffering serious interstitial lung disease had a smoking history, an abnormal finding (atelectasis or emphysema) on screening chest X-ray, baseline chronic obstructive pulmonary disease (COPD)/pneumosclerosis or COPD/pneumonia, or a treatment history with a biological product, etc. Based on the post-marketing data of Japanese patients treated with infliximab, etanercept, adalimumab, or tocilizumab, the incidences of interstitial lung disease during a 6-month to 28-week observation ranged from 0.5% to 0.7% (*Ann Rheum Dis*. 2008;67:189-94, *Mod Rheumatol*. 2011;21:343-51, *Mod Rheumatol.* 2014;24:390-8, *J Rheumatol.* 2014;41:15-23), which was comparable to those associated with sarilumab.

Based on the above, sarilumab is unlikely to increase the risk of interstitial lung disease.

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22) Events classified under Standardized MedDRA Query "Interstitial lung disease"

PMDA's view:

Interstitial lung disease occurred in the clinical studies, a Japanese patient with RA suffered a serious event. Thus, the possibility remains that the combination of sarilumab with another anti-rheumatic drug enhance the risk of interstitial lung disease. The possible interstitial lung disease caused by sarilumab should be communicated to healthcare professionals. In addition, the incidence of interstitial lung disease during treatment with sarilumab including that in its prolonged use should be continuously investigated via post-marketing surveillance, etc., and findings should be communicated to healthcare professionals accordingly.

7.R.3.7 Neutropenia

The applicant's explanation about the incidence of neutropenia associated with sarilumab and a relationship between sarilumab and infections:

Because the toxicity studies of sarilumab [see Section "5.2 Repeated-dose toxicity"] and the Phase I studies of sarilumab and clinical studies of tocilizumab (*Arthritis Res Ther*. 2011;13:1-13, *Arthritis Care Res [Hoboken]*. 2014;66:344-54) revealed transient decreases in neutrophil count related to IL-6 inhibition, the risk of neutropenia associated with sarilumab was investigated.

Table 40 shows the incidences of neutropenia and neutrophil count decreased in the foreign placebo-controlled population, foreign long-term safety population, and pooled Japanese population. The incidences tended to be higher in the sarilumab groups than in the placebo group and increased in a dose-dependent manner. Many events were classified as Grade 1 or 2. Grade ≥3 neutrophil count decreased was transient and tended to resolve during the treatment or after the discontinuation of sarilumab.

Table 40. Incidences of neutropenia-related adverse events

	Foreign placebo-controlled population			Foreign long-term safety population			Pooled Japanese population	
	150 mg q2w (n = 660)	200 mg q2w (n = 661)	Placebo (n = 661)	150 mg q2w (n = 1155)	200 mg q2w (n = 1351)	All dose groups combined (n = 2887)	150 mg q2w (n = 140)	200 mg q2w (n = 185)
Neutropenia	65 (9.8)	94 (14.2)	3 (0.5)	130 (11.3)	228 (16.9)	486 (16.8)	18 (12.9)	22 (11.9)
Neutrophil count decreased (Grade 1)	89 (13.5)	107 (16.3)	24 (3.6)	179 (15.5)	267 (19.8)	548 (19.0)	25 (17.9)	36 (19.5)
Neutrophil count decreased (Grade 2)	82 (12.4)	99 (15.0)	7 (1.1)	152 (13.2)	246 (18.3)	522 (18.1)	31 (22.1)	51 (27.6)
Neutrophil count decreased (Grade 3)	32 (4.8)	55 (8.4)	1 (0.2)	68 (5.9)	131 (9.7)	282 (9.8)	19 (13.6)	19 (10.3)
Neutrophil count decreased (Grade 4)	8 (1.2)	6 (0.9)	0	11 (1.0)	15 (1.1)	40 (1.4)	2 (1.4)	1 (0.5)

Number of subjects (%) (The incidences of neutropenia were calculated based on the number of subjects measured.)

Clinical concern in decreased neutrophil count is enhanced risk of infection. Grade 4 neutrophil count decreased persisting for ≥10 consecutive days is known to be related to the frequency and seriousness of infection (*Am Soc Hematol Educ Program*. 2001:113-39). Therefore, the occurrence of neutrophil count decreased and infections was investigated. The incidences of infections are shown in Table 41 by grade of neutrophil count decreased; no relationship was found between the occurrence of neutrophil count decreased and infections in the foreign long-term safety population or pooled Japanese population.

Based on these the clinical study results, healthcare professionals are to be advised through the package insert to determine the patient's eligibility for sarilumab based on neutrophil count before starting treatment and to monitor neutrophil count during treatment.

Table 41. Incidences of infections by grade of neutrophil count decreased

		Foreign long-term safety population			Pooled Japanese population	
		150 mg q2w (n = 1153)	200 mg q2w (n = 1346)	All dose groups combined (n = 2879)	150 mg q2w (n = 140)	200 mg q2w (n = 185)
Neutrophil count ≥ lower limit of normal (LLN)	n	743	687	1487	66	83
	Infection	240 (32.3)	295 (42.9)	642 (43.2)	39 (59.1)	40 (48.2)
	Serious infection	11 (1.5)	29 (4.2)	76 (5.1)	4 (6.1)	4 (4.8)
Neutrophil count < LLN	n	410	659	1392	74	102
	Infection	125 (30.5)	277 (42.0)	671 (48.2)	51 (68.9)	61 (59.8)
	Serious infection	6 (1.5)	35 (5.3)	82 (5.9)	2 (2.7)	1 (1.0)
Neutrophil count decreased (Grade 1)	n	179	267	548	23	35
	Infection	55 (30.7)	114 (42.7)	267 (48.7)	16 (69.6)	18 (51.4)
	Serious infection	4 (2.2)	20 (7.5)	44 (8.0)	0	0
Neutrophil count decreased (Grade 2)	n	152	246	522	30	48
	Infection	46 (30.3)	117 (47.6)	257 (49.2)	22 (73.3)	27 (56.3)
	Serious infection	1 (0.7)	13 (5.3)	28 (5.4)	0	1 (2.1)
Neutrophil count decreased (Grade 3)	n	68	131	282	19	18
	Infection	24 (35.3)	40 (30.5)	138 (48.9)	12 (63.2)	15 (83.3)
	Serious infection	1 (1.5)	2 (1.5)	10 (3.5)	2 (10.5)	0
Neutrophil count decreased (Grade 4)	n	11	15	40	2	1
	Infection	0	6 (40.0)	9 (22.5)	1 (50.0)	1 (100)
	Serious infection	0	0	0	0	0

Number of subjects (%)

PMDA's view:

A decrease in neutrophil count is expected in the use of sarilumab because of its pharmacological activity. The incidence of neutropenia in the clinical studies tended to be higher in the sarilumab groups than in the placebo group, and the possibility remains that reduced neutrophil count due to sarilumab's activity may enhance the risk for infection. The applicant should call attention to neutrophil count decreased associated with sarilumab and further investigate its relationship with the incidence of infections via post-marketing surveillance, etc. Findings should be communicated to healthcare professionals accordingly.

7.R.3.8 Thrombocytopenia

The applicant's explanation about the incidence of thrombocytopenia associated with sarilumab:

Because the clinical studies of tocilizumab [see Section "7.R.3.7 Neutropenia"] revealed transient decreases in platelet count, the risk of thrombocytopenia associated with sarilumab was investigated.

Table 42 shows the incidences of thrombocytopenia-related adverse events in the foreign placebo-controlled population, foreign long-term safety population, and pooled Japanese population. Relevant events were observed in the sarilumab group only. The incidence was comparable between the 150 mg q2w and 200 mg q2w groups in the pooled Japanese population. In contrast, in the foreign placebo-controlled population and foreign long-term safety population, incidence was higher in the 200 mg q2w group, with a tendency toward greater reduction in platelet count, than in the 150 mg q2w group. Serious thrombocytopenia was observed in 4 subjects in foreign clinical studies. The event in 1 subject was assessed as unresolved due to their death from cardiogenic pulmonary oedema, while the event in

another subject had an unknown outcome. The events in the rest of subjects resolved. Thrombocytopenia leading to treatment discontinuation remained unresolved in 3 subjects in the foreign clinical studies but resolved in all subjects affected in the pooled Japanese population.

Platelet count decreased was a transient event in most subjects. In the pooled Japanese population, none of the subjects presenting with thrombocytopenia were reported to have bleeding events. A total of 57 subjects had a platelet count of $<100 \times 10^9$/L in the foreign long-term safety population. Of these, 5 subjects experienced an event classified under Standardized Medical dictionary for regulatory activities (MedDRA) Query "Haemorrhages." However, the time of onset of the event and that of decreased platelet count was inconsistent in 4 of these subjects, and the remaining 1 subject was found to have injection site ecchymosis.[23)]

These clinical study results indicate a relationship between sarilumab and platelet count decreased, despite no clear influence on bleeding identified. Healthcare professionals are to be advised through the package insert to determine the patient's eligibility for sarilumab based on platelet count measured before starting treatment and to monitor platelet count during treatment.

Table 42. Incidences of thrombocytopenia-related adverse events

	Foreign placebo-controlled population			Foreign long-term safety population			Pooled Japanese population	
	150 mg q2w (n = 660)	200 mg q2w (n = 661)	Placebo (n = 661)	150 mg q2w (n = 1155)	200 mg q2w (n = 1351)	All dose groups combined (n = 2887)	150 mg q2w (n = 140)	200 mg q2w (n = 185)
Thrombocytopenia[a)]	6 (0.9)	11 (1.7)	0	15 (1.3)	35 (2.6)	70 (2.4)	6 (4.3)	7 (3.8)
Serious thrombocytopenia[a)]	1 (0.2)	1 (0.2)	0	1 (<0.1)	1 (<0.1)	4 (0.1)	0	0
Thrombocytopenia leading to treatment discontinuation[a)]	1 (0.2)	3 (0.5)	0	1 (<0.1)	5 (0.4)	12 (0.4)	0	3 (1.6)
Platelet count decreased ($\geq$75 and $<100 \times 10^9$/L)	3 (0.5)	5 (0.8)	0	6 (0.5)	21 (1.6)	33 (1.1)	2 (1.4)	3 (1.6)
Platelet count decreased ($\geq$50 and $<75 \times 10^9$/L)	1 (0.2)	3 (0.5)	0	2 (0.2)	4 (0.3)	14 (0.5)	2 (1.4)	3 (1.6)
Platelet count decreased ($\geq$25 and $<50 \times 10^9$/L)	0	1 (0.2)	0	0	2 (0.1)	3 (0.1)	1 (0.7)	0
Platelet count decreased ($<25 \times 10^9$/L)	0	2 (0.3)	0	0	3 (0.2)	7 (0.2)	0	0

Number of subjects (%) (the incidence of thrombocytopenia was calculated based on subjects with measurements)
[a)] Events classified under Standardized MedDRA Query "Haematopoietic thrombocytopenia"

PMDA's view:

Platelet count decreased were reported only in the sarilumab groups in the clinical studies, and the possibility remains that reduced platelet count due to sarilumab's activity may enhance the risk of bleeding. The applicant should call attention to thrombocytopenia associated with sarilumab, and further investigate its relationship with the incidence of bleeding-related events via post-marketing surveillance, etc. Findings should be communicated to healthcare professionals accordingly.

7.R.3.9 Hepatic function disorder

The applicant's explanation about the incidence of hepatic disorder associated with sarilumab:

[23)] Platelet count at the onset of this event was 58 to 91 $\times 10^9$/L.

Because increased transaminases was observed during treatment with cDMARDs such as MTX and in the clinical studies on tocilizumab [see Section "7.R.3.7 Neutropenia"], the risk of hepatic function disorder associated with sarilumab was investigated.

Table 43 shows the incidences of hepatic function disorder-related adverse events in the foreign placebo-controlled population, foreign long-term safety population, and pooled Japanese population. The incidences tended to be higher in the sarilumab groups than in the placebo group. In the pooled Japanese population, the incidences were comparable between the 150 mg q2w and 200 mg q2w groups. In contrast, in the foreign long-term safety population, events occurred more frequently in the 200 mg q2w group with a trend toward higher grade than in the 150 mg q2w group.

Table 43. Incidences of hepatic function disorder-related adverse events

	Foreign placebo-controlled population			Foreign long-term safety population			Pooled Japanese population	
	150 mg q2w (n = 660)	200 mg q2w (n = 661)	Placebo (n = 661)	150 mg q2w (n = 1155)	200 mg q2w (n = 1351)	All dose groups combined (n = 2887)	150 mg q2w (n = 140)	200 mg q2w (n = 185)
Hepatic disorder[a)]	63 (9.5)	72 (10.9)	25 (3.8)	87 (7.5)	178 (13.2)	378 (13.1)	27 (19.3)	32 (17.3)
Serious hepatic disorder[a)]	5 (0.8)	2 (0.3)	1 (0.2)	5 (0.4)	7 (0.5)	12 (0.4)	0	0
Hepatic disorder leading to treatment discontinuation[a)]	15 (2.3)	14 (2.1)	3 (0.5)	22 (1.9)	34 (2.5)	80 (2.8)	5 (3.6)	6 (3.2)
ALT								
1-1.5[b)] × ULN	163 (24.7)	178 (27.1)	127 (19.2)	269 (23.4)	373 (27.7)	752 (26.1)	30 (21.4)	52 (28.1)
1.5-3[b)] × ULN	124 (18.8)	162 (24.7)	70 (10.6)	203 (17.6)	353 (26.2)	725 (25.2)	33 (23.6)	32 (17.3)
3-5[b)] × ULN	36 (5.5)	31 (4.7)	10 (1.5)	48 (4.2)	85 (6.3)	191 (6.6)	15 (10.7)	11 (5.9)
5-10[b)] × ULN	9 (1.4)	10 (1.5)	1 (0.2)	11 (1.0)	27 (2.0)	53 (1.8)	2 (1.4)	5 (2.7)
10-20[b)] × ULN	4 (0.6)	1 (0.2)	0	4 (0.3)	2 (0.1)	6 (0.2)	0	0
20 × ULN <	0	1 (0.2)	0	0	3 (0.2)	4 (0.1)	0	0
Total bilirubin								
1.5 × ULN <	17 (2.6)	18 (2.7)	1 (0.2)	34 (3.0)	51 (3.8)	117 (4.1)	3 (2.1)	6 (3.2)
2 × ULN <	5 (0.8)	5 (0.8)	1 (0.2)	8 (0.7)	17 (1.3)	37 (1.3)	0	2 (1.1)

Number of subjects (%) (the values of ALT and bilirubin were calculated based on subjects with measurements)
[a)] Events classified under Standardized MedDRA Query "Drug related hepatic disorders - comprehensive search"
[b)] Inclusive of the higher value and exclusive of the lower value

Serious hepatic function disorder occurred in 12 subjects in the foreign clinical studies, but none of them had an event suggestive of drug-induced hepatic dysfunction. The ALT level of all these subjects returned to normal or fell below 1.5-fold the ULN at the last measurement. No subjects presented with a clinically significant increase in bilirubin. ALT increased to ≤3-fold the ULN in many subjects. In the majority of subjects with ALT increased to >3-fold the ULN, it returned to normal or achieved a level of ≤1.5-fold the ULN after the completion or discontinuation of treatment with sarilumab (50 of 63 subjects in the 150 mg q2w group, 72 of 117 subjects in the 200 mg q2w group, and 202 of 254 subjects in all dose groups combined in the foreign long-term safety population; 13 of 17 subjects in the 150 mg q2w group and 11 of 16 subjects in the 200 mg q2w group in the pooled Japanese population). No subjects met the criteria of Hy's law[24)] in any study populations.

These clinical study results indicate a relationship between sarilumab and elevated transaminase but do not suggest hepatitis or hepatic dysfunction. Healthcare professionals are to be advised through the

[24)] Consisting of the following 3 criteria: (a) ALT >3-fold the ULN, (b) total bilirubin >2-fold the ULN, and (c) suspected drug-induced liver injury.

package insert to determine the patient's eligibility for sarilumab based on liver function test before starting treatment and to monitor liver function through test results during treatment.

PMDA's view:
The clinical studies showed a higher incidence of adverse events related to abnormal hepatic function in the sarilumab groups than in the placebo group. The applicant should call attention to abnormal hepatic function during treatment with sarilumab, and the occurrence of relevant adverse events should be further monitored via post-marketing surveillance, etc. Findings should be communicated to healthcare professionals accordingly.

7.R.3.10 Lipid abnormalities and cardiovascular events

The applicant's explanation about the incidences of lipid abnormalities and cardiovascular events associated with sarilumab:
Because the clinical studies on tocilizumab [see Section "7.R.3.7 Neutropenia"] revealed the elevation of lipid parameters, the risk of lipid abnormalities associated with sarilumab was investigated. Table 44 shows the incidences of lipid increased-related adverse events in the foreign placebo-controlled population, foreign long-term safety population, and pooled Japanese population. The incidences tended to be higher in the sarilumab group than in the placebo group and higher in the 200 mg q2w group than in the 150 mg q2w group. A serious lipid increased was observed in 1 subject in the foreign long-term safety population (hypertriglyceridaemia), who was receiving a lipid-lowering medication at a 3-fold lower dose than recommended. Pancreatitis acute associated with mild exacerbation of hyperlipidaemia occurred in 1 subject in the 200 mg q2w group in the pooled Japanese population, and it resolved.

Table 44. Incidences of lipid increased-related adverse events

	Foreign placebo-controlled population			Foreign long-term safety population			Pooled Japanese population	
	150 mg q2w (n = 660)	200 mg q2w (n = 661)	Placebo (n = 661)	150 mg q2w (n = 1155)	200 mg q2w (n = 1351)	All dose groups combined (n = 2887)	150 mg q2w (n = 140)	200 mg q2w (n = 185)
Lipid increased[a)]	39 (5.9)	33 (5.0)	13 (2.0)	60 (5.2)	118 (8.7)	263 (9.1)	3 (2.1)	12 (6.5)
Serious lipid increased[a)]	0	0	0	0	0	1 (<0.1)	0	0
Lipid increased leading to treatment discontinuation[a)]	0	0	0	0	0	0	0	0

Number of subjects (%)
[a)] Events classified under Standardized MedDRA Query "Dyslipidaemia"

Sarilumab increased the incidence of lipid increased. Patients with RA are known to have a high morbidity and mortality due to cardiovascular diseases associated with chronic inflammatory conditions (*Curr Rheumatol Rep*. 2012;14:428-37). Therefore, the risk of cardiovascular events associated with sarilumab was investigated. Table 45 shows the incidences of cardiovascular events determined by the independent cardiovascular event committee established by the sponsor. The incidence rates did not exceed those of cardiovascular events (cardiovascular death, non-fatal myocardial infarction, and stroke) in patients with RA receiving cDMARDs (1.11 events per 100 subject-years; *Ann Rheum Dis*. 2015;74:326-32).

Table 45. Incidences of cardiovascular events

	Foreign placebo-controlled population			Foreign long-term safety population			Pooled Japanese population	
	150 mg q2w (n = 660)	200 mg q2w (n = 661)	Placebo (n = 661)	150 mg q2w (n = 1155)	200 mg q2w (n = 1351)	All dose groups combined (n = 2887)	150 mg q2w (n = 140)	200 mg q2w (n = 185)
Cardiovascular event[a)]	2 (0.3) 0.5	2 (0.3) 0.5	0 0	2 (0.2) 0.3	12 (0.9) 0.7	26 (0.9) 0.6	0 0	0 0
Cardiovascular event (narrow)[b)]	2 (0.3) 0.5	2 (0.3) 0.5	0 0	2 (0.2) 0.3	11 (0.8) 0.6	23 (0.8) 0.5	0 0	0 0

Upper row, number of subjects (%); bottom row, incidence rate (number of events) per 100 subject-years after adjustment for total exposure time

[a)] Cardiovascular death (including those from unknown cause), myocardial infarction, stroke, unstable angina requiring hospitalization, and transient ischaemic attack requiring hospitalization

[b)] Cardiovascular death (including those from unknown cause), myocardial infarction, and stroke

Based on these clinical study data, healthcare professionals will be reminded of possible sarilumab-induced abnormal lipid levels and the importance of regular lipid tests during treatment through the package insert.

PMDA's view:

RA itself is suggested to be a risk factor for arteriosclerosis, and patients with RA are known to have a high risk of cardiovascular events. Given that an abnormal lipid level is also a risk factor for cardiovascular events, the applicant should call attention to the occurrence of abnormal lipid levels in patients receiving sarilumab. Lack of data precludes a conclusion that increased lipid caused by sarilumab has no effect on pancreatitis and cardiovascular events. Data on abnormal lipid level and its relationship with pancreatitis and cardiovascular events should be continuously collected via post-marketing surveillance, etc. Findings should be communicated to healthcare professionals accordingly.

7.R.3.11 Use in elderly patients

The applicant's explanation about the incidences of adverse events in elderly subjects:

Table 46 shows the incidences of adverse events in elderly (≥65 years) and non-elderly (<65 years) patients in the foreign placebo-controlled population, foreign long-term safety population, and pooled Japanese population. The incidences of serious adverse events tended to be higher in the elderly patients than in non-elderly patients in any of the populations. The incidences of serious infections, neutrophil count decreased, and ALT increased were compared by age group. Serious infections and neutrophil count decreased tended occur more frequently in elderly patients in the foreign placebo-controlled population and foreign long-term safety population.

Although these clinical study data indicate no clear difference in the safety profile of sarilumab between elderly and non-elderly patients overall, elderly patients have a high infection risk generally due to reduced physiological function. Careful administration of sarilumab in elderly patients will be reminded in the package insert.

Table 46. Incidences of adverse events by age group

		Foreign placebo-controlled population			Foreign long-term safety population			Pooled Japanese population	
		150 mg q2w (n = 660)	200 mg q2w (n = 661)	Placebo (n = 661)	150 mg q2w (n = 1155)	200 mg q2w (n = 1351)	All dose groups combined (n = 2887)	150 mg q2w (n = 140)	200 mg q2w (n = 185)
<65 years	Number of subjects	574	569	573	983	1165	2464	109	139
	Adverse event	406 (70.7)	418 (73.5)	326 (56.9)	643 (65.4)	949 (81.5)	1965 (79.7)	98 (89.9)	125 (89.9)
	Serious adverse event	35 (6.1)	42 (7.4)	24 (4.2)	47 (4.8)	139 (11.9)	332 (13.5)	5 (4.6)	9 (6.5)
	Adverse event leading to death	1 (0.2)	1 (0.2)	3 (0.5)	1 (0.1)	5 (0.4)	11 (0.4)	0	0
	Adverse event leading to treatment discontinuation	60 (10.5)	66 (11.6)	24 (4.2)	92 (9.4)	168 (14.4)	429 (17.4)	13 (11.9)	13 (9.4)
	Serious infection	8 (1.4)	15 (2.6)	10 (1.7)	10 (1.0)	51 (4.4)	121 (4.9)	4 (3.7)	4 (2.9)
	Neutrophil count decreased[a)]	34 (5.9)	50 (8.8)	0	63 (6.4)	119 (10.2)	269 (10.9)	15 (13.8)	17 (12.2)
	ALT increased[b)]	46 (8.0)	41 (7.2)	10 (1.7)	59 (6.0)	109 (9.4)	235 (9.5)	16 (14.7)	14 (10.1)
≥65 years	Number of subjects	86	92	88	172	186	423	31	46
	Adverse event	59 (68.6)	70 (76.1)	52 (59.1)	121 (70.3)	152 (81.7)	349 (82.5)	29 (93.5)	41 (89.1)
	Serious adverse event	7 (8.1)	17 (18.5)	7 (8.0)	15 (8.7)	48 (25.8)	107 (25.3)	4 (12.9)	7 (15.2)
	Adverse event leading to death	1 (1.2)	0	0	1 (0.6)	2 (1.1)	8 (1.9)	0	0
	Adverse event leading to treatment discontinuation	12 (14.0)	17 (18.5)	7 (8.0)	24 (14.0)	43 (23.1)	109 (25.8)	2 (6.5)	8 (17.4)
	Serious infection	4 (4.7)	4 (4.3)	2 (2.3)	7 (4.1)	13 (7.0)	37 (8.7)	2 (6.5)	1 (2.2)
	Neutrophil count decreased[a)]	6 (7.0)	11 (12.0)	1 (1.1)	16 (9.3)	27 (14.5)	53 (12.5)	6 (19.4)	4 (8.7)
	ALT increased[b)]	3 (3.5)	2 (2.2)	1 (1.1)	4 (2.3)	8 (4.3)	19 (4.5)	1 (3.2)	2 (4.3)

Number of subjects (%)
[a)] $<1.0 \times 10^9$/L; [b)] >3 × ULN

PMDA's view:

At present, it is difficult to make a conclusion about the impact of aging on the safety of sarilumab. However, the trend toward higher incidences of serious adverse events and adverse events leading to treatment discontinuation in elderly patients indicates that healthcare professionals should be advised of careful monitoring of elderly patients receiving sarilumab. Given the limited use of on sarilumab in elderly patients in the clinical studies, data should be continuously collected from this population via post-marketing surveillance, etc., and findings should be communicated to healthcare professionals accordingly.

Based on the discussions in Section 7.R.3, the use of sarilumab requires attention to the onset of infections, gastrointestinal perforation, hypersensitivity, injection site reaction, neutropenia, thrombocytopenia, hepatic function disorder, and lipid abnormalities. Nevertheless, safety signals of sarilumab detected in the clinical studies were fewer than those of the approved biological products for RA. Therefore, these adverse events are controllable by similar safety measures as taken for the approved biological products for RA, as long as sarilumab is prescribed by physicians with adequate knowledge on sarilumab and expertise and experience in pharmacotherapy of RA. However, the dosing regimen of sarilumab should be carefully selected because the incidences of adverse events related to neutropenia, thrombopenia, and hepatic function disorders tended to be higher in the 200 mg q2w group than in the 150 mg q2w group [see Section "7.R.4 Dosage and administration"].

7.R.4 Dosage and administration

7.R.4.1 Usual dosage and administration

The applicant explained that, based on the following findings from Study EFC14059 and Study EFC11072 Parts A and B in Japanese and non-Japanese patients with RA, treatment with sarilumab 200 mg once every 2 weeks is appropriate as usual dosing regimen.

- In Study EFC11072 Part B, efficacy endpoints including the ACR20 response rate at Week 24 (primary endpoint) tended to be higher in the 200 mg q2w group than in the 150 mg q2w group [see Section "7.R.2"].
- The guidelines for the management of RA recommends that the treatment goal be clinical remission or low disease activity, which should be rapidly achieved to suppress irreversible progression of joint destruction (*Ann Rheum Dis*. 2016;75:3-15, *Arthritis Care & Res*. 2016;68:1-25, *Ann Rheum Dis*. 2014;73:492-509). The data at Week 12 obtained in Study EFC14059 (Table 47) showed superior results in the 200 mg q2w group.
- A study on tocilizumab, a sarilumab analogue drug, revealed that Japanese patients with RA who achieved a normal CRP level within 12 weeks of treatment had a higher DAS28-ESR remission rate and a higher improvement rate of swollen and tender joint counts at Weeks 24 and 52 than those who did not achieve a normal CRP (*Mod Rheumatol*. 2013;23:977-85). In Study EFC14059, the proportion of subjects who achieved a CRP level of <0.1 mg/dL was consistently higher in the 200 mg q2w group than in the 150 mg q2w group at Week 2 or later as shown in Figure 3.
- The Japanese and foreign clinical studies showed no clinically significant difference in the safety profile between the 150 mg q2w and 200 mg q2w groups, indicating no substantial tolerability problems with 200 mg q2w regimen [see Section "7.R.3 Safety"].

Table 47. Efficacy endpoint data at Week 12 in Study EFC14059 (mITT population, NRI)

	150 mg q2w	200 mg q2w	Placebo
ACR20 response rate	66.7 (54/81)	65.0 (52/80)	18.5 (15/81)
ACR50 response rate	27.2 (22/81)	31.3 (25/80)	6.2 (5/81)
ACR70 response rate	6.2 (5/81)	18.8 (15/80)	1.2 (1/81)
DAS28-CRP remission rate	25.9 (21/81)	33.8 (27/80)	3.7 (3/81)
SDAI remission rate	2.5 (2/81)	8.8 (7/80)	0 (0/81)
CDAI remission rate	1.2 (1/81)	6.3 (5/80)	0 (0/81)

% (number of subjects)

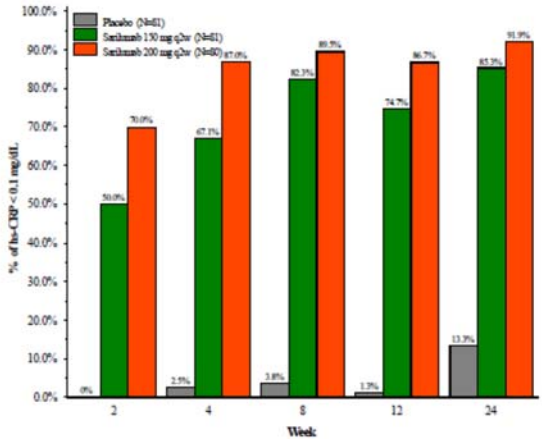

Figure 3. Proportion of subjects who achieved a CRP level of <0.1 mg/dL in Study EFC14059

PMDA's view:

In light of the submitted clinical study data and sarilumab's therapeutic goal of early achievement of clinical remission recommended by the recent guidelines for the management of RA, the appropriate usual dosage and administration should be 200 mg of sarilumab administered once every 2 weeks.

7.R.4.2 Dose adjustment

PMDA asked the applicant to explain the rationale for dose adjustment to 150 mg based on the clinical study data.

The applicant's rationale for the proposed Dosage and Administration:
The proposed Dosage and Administration notes that "The dose may be adjusted to 150 mg according to the patient's body weight" with Precautions for Dosage and Administration noting that "Dose adjustment to 150 mg should also be considered for patients with a body weight of <60 kg."

In Study EFC11072 Part B in non-Japanese patients with RA, results were consistently superior in the 200 mg q2w group over the 150 mg q2w group [see Section "7.R.2 Efficacy"]. In Study EFC14059 in Japanese patients with RA, many of the efficacy endpoints were comparable between the 150 mg q2w and 200 mg q2w groups. The difference between the results of 2 studies are partly attributed to the difference in the average body weight between Japanese (56.6 kg) and non-Japanese (74.3 kg) subjects resulting in a comparable exposure between Japanese subjects receiving treatment with sarilumab 150 mg once every 2 weeks and non-Japanese subjects receiving treatment with sarilumab 200 mg once every 2 weeks. Therefore, body weight-based dose adjustment was included in the "proposed Dosage and Administration" section and "Precautions for Dosage and Administration" section although there was no safety concern related to the subjects' body weight.

However, an evaluation by body weight group was performed after the submission of the application using the data from the bridging study and the study to be bridged. The results showed neither trend suggesting comparability in the ACR20 response rate between the 150 mg q2w and 200 mg q2w groups among subjects weighing <60 kg (Table 48) nor body weight group with comparable efficacy between the 150 mg q2w and 200 mg q2w groups. Therefore, the statement on body weight-based dose adjustment should be deleted.

Table 48. ACR20 response rate at Week 24 by body weight group (efficacy analysis population, NRI)

	EFC14059			EFC11072 Part B		
Body weight group[a)]	150 mg q2w (n = 81)	200 mg q2w (n = 80)	Placebo (n = 81)	150 mg q2w (n = 400)	200 mg q2w (n = 399)	Placebo (n = 398)
<50 kg	77.8 (21/27)	70.0 (14/20)	16.0 (4/25)	70.6 (12/17)	75.9 (22/29)	26.7 (4/15)
50-60 kg	58.6 (17/29)	54.3 (19/35)	9.4 (3/32)	69.1 (47/68)	83.3 (45/54)	26.8 (19/71)
60-70 kg	69.2 (9/13)	44.4 (8/18)	17.6 (3/17)	57.0 (61/107)	68.9 (62/90)	34.4 (32/93)
70-80 kg	85.7 (6/7)	50.0 (2/4)	0 (0/3)	57.8 (52/90)	66.7 (68/102)	37.5 (36/96)
80-90 kg	33.3 (1/3)	100.0 (2/2)	50.0 (1/2)	58.3 (28/48)	62.0 (31/50)	36.5 (19/52)
90-100 kg	50.0 (1/2)	100.0 (1/1)	0 (0/1)	46.7 (14/30)	45.9 (17/37)	30.0 (12/40)
≥100 kg	0 (0/0)	0 (0/0)	100.0 (1/1)	45.0 (18/40)	54.1 (20/37)	35.5 (11/31)

% (number of subjects)
[a)] Inclusive of the lower value and exclusive of the higher value

On the other hand, the pharmacological activity of sarilumab is expected to affect neutrophil count, platelet count, and liver function parameters, and such effects were actually observed dose-dependently in the clinical studies [see Sections "7.R.3.7 Neutropenia" to "7.R.3.9 Hepatic function disorder"]. In light of these observations, a foreign extension study (Study LTS11210) began with a starting dose[25)] of

[25)] The 150 mg once every week regimen was used until the dosage regimen for the phase III study was determined.

sarilumab 200 mg once every 2 weeks allowing dose reduction to 150 mg once every 2 weeks in patients who met the dose reduction criteria[26] based on a laboratory abnormality. As a result, 248 of 1630 subjects (15.2%) underwent dose reduction. The main reasons for dose reduction included neutrophil count decreased (163 subjects) and ALT increased (51 subjects). After dose reduction, the causative changes in the test values (Table 49) tended to improve. No apparent decrease in the efficacy was observed after dose reduction (Table 50).

Based on the above, patients experiencing neutrophil count decreased may continue to receive treatment if the dose is reduced to 150 mg once every 2 weeks. Therefore, the deletion of the text "according to the patient's body weight" from the statement of the "Dosage and Administration" section and replacement with "according to the patient's condition or clinical response" are appropriate.

Table 49. Changes in test values that led to dose reduction in Study LTS11210

Neutrophil count	Before dose reduction (n = 175)[b]	1 month after dose reduction (n = 121)[b]	3 months after dose reduction (n = 146)[b]	6 months after dose reduction (n = 131)[b]
≥ LLN	6 (3.4)	42 (34.7)	68 (46.6)	63 (48.1)
1.5 × 10^9/L to LLN[a]	23 (13.1)	26 (21.5)	21 (14.4)	21 (16.0)
1.0-1.5 × 10^9/L[a]	51 (29.1)	33 (27.3)	39 (26.7)	39 (29.8)
0.5-1.0 × 10^9/L[a]	95 (54.3)	17 (14.0)	17 (11.6)	8 (6.1)
<0.5 × 10^9/L	0	3 (2.5)	1 (0.7)	0
ALT	Before dose reduction (n = 61)[c]	1 month after dose reduction (n = 34)[c]	3 months after dose reduction (n = 46)[c]	6 months after dose reduction (n = 46)[c]
≤ULN	1 (1.6)	6 (17.6)	13 (28.3)	16 (34.8)
1-1.5[d] × ULN	1 (1.6)	8 (23.5)	12 (26.1)	11 (23.9)
1.5-3[d] × ULN	7 (11.5)	12 (35.3)	20 (43.5)	17 (37.0)
3-5[d] × ULN	50 (82.0)	7 (20.6)	1 (2.2)	2 (4.3)
5-10[d] × ULN	2 (3.3)	1 (2.9)	0	0
10-20[d] × ULN	0	0	0	0
20 × ULN<	0	0	0	0

Number of subjects (%)
[a] Inclusive of the lower value and exclusive of the higher value
[b] Including subjects who had their starting dose changed from sarilumab 150 mg once every week to sarilumab 200 mg once every 2 weeks and those who did not meet the dose reduction criteria but underwent dose reduction to prevent neutrophil count drop to <1.0 × 10^9/L at the discretion of the investigator
[c] Including subjects who had their starting dose changed from sarilumab 150 mg once every week to sarilumab 200 mg once every 2 weeks and those who did not meet the dose reduction criteria but underwent dose reduction to prevent ALT increase to >3 × ULN at the discretion of the investigator
[d] Inclusive of the higher value and exclusive of the lower value

Table 50. ACR20 response rate after dose reduction of sarilumab in Study LTS11210

	Randomized study	
	EFC11072 Part B (n = 1197)	EFC10832 (n = 546)
Immediately before dose reduction	79.1 (125/158)	88.1 (37/42)
Week 12 after dose reduction	80.0 (124/155)	81.0 (34/42)
Week 24 after dose reduction	83.3 (115/138)	77.4 (24/31)

% (number of subjects)

PMDA's view:

Based on the above investigation, many patients with laboratory abnormalities such as neutrophil count decrease tended to improve after dose reduction to 150 mg once every 2 weeks and were expected to exhibit a certain level of response. Therefore, the dose may be adjusted to 150 mg once every 2 weeks

[26] Patients with (a) a neutrophil count of 0.5 to <1.0 × 10^9/L and no infections; (b) a platelet count of ≥50 and <100 × 10^9/L and no bleeding events; or (c) an ALT level of ≥3- and <5-fold the ULN

according to the patient's condition. The criteria for dose reduction or discontinuation of sarilumab based on a laboratory abnormality that were used in the clinical studies should be communicated to healthcare professionals as reference information.

PMDA's conclusion on the dosage and administration described above will be finalized, taking account of comments from the Expert Discussion.

7.R.5 Clinical positioning

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

The applicant's explanation about the clinical positioning of sarilumab relative to the approved biological products for RA treatment:

In Japan, MTX is used for basic treatment of RA. Patients who have not responded adequately to 3-month treatment with MTX or are intolerant or have contraindication to MTX are treated with other cDMARDs such as bucillamine, sulfasalazine, and leflunomide. Patients with inadequate response or are intolerant to these therapies are treated with a biological product such as TNF inhibitors (the Guidelines for the management of rheumatoid arthritis 2014). Outside Japan, 30% to 40% of patients did not respond adequately or showed intolerance to TNF inhibitors, 26% to 36% discontinued treatment within the first year, and 38% to 55% discontinued after 5 years of treatment. The same situation is seen in Japan (e.g., *Nature Rev Rheumatol*. 2015;11:276-89, *Mod Rheumatol*. 2015;25:350-7). A literature article suggested that patients who have had an inadequate response or intolerance to TNF inhibitors may receive greater clinical benefit by a biological product with a different mechanism of action (*Arthritis Rheum*. 2007;56:13-20), and thus such drugs are in demand.

Table 51 shows the efficacy data in Japanese patients with RA obtained from main clinical studies of sarilumab and the approved biological products, namely, tocilizumab, infliximab, etanercept, and adalimumab. The efficacy in Japanese patients with RA is comparable between sarilumab and the approved biological products. However, the data should be interpreted carefully for inter-study comparisons.

Table 51. Comparison of efficacy in Japanese patients with RA based on clinical studies of sarilumab and other biological products (with concomitant use of MTX)

	Sarilumab[a)] (n = 242)	Tocilizumab[b)] (n = 164)	Infliximab[c)] (n = 147)	Etanercept[d)] (n = 147)	Adalimumab[e)] (n = 334)
Study population of patients with RA	Inadequate response to MTX	Inadequate response to cDMARDs	Inadequate response to MTX	Inadequate response to cDMARDs	Inadequate response to cDMARDs
Evaluation time point	Week 12	Week 12	Week 14	Week 12	Week 12
ACR20 response rate	150 mg: 66.7% 200 mg: 65.0%	4 mg/kg: 57.4% 8 mg/kg: 78.2%	3 mg/kg: 61.2% 10 mg/kg: 59.2%	10 mg: 64.0% 25 mg: 65%	76.6%
ACR50 response rate	150 mg: 27.2% 200 mg: 31.3%	4 mg/kg: 25.9% 8 mg/kg: 40.0%	3 mg/kg: 30.6% 10 mg/kg: 35.3%	-	53.2%
ACR70 response rate	150 mg: 6.2% 200 mg: 18.8%	4 mg/kg: 20.4% 8 mg/kg: 16.4%	3 mg/kg: 10.2% 10 mg/kg: 15.7%	-	25.7%

[a)] Study EFC14059; [b)] *Arthritis Rheum*. 2004;50:1761-9; [c)] *J Rheumatol*. 2006;33:37-44; [d)] *Mod Rheumatol*. 2015;25:173-86; e) *Ann Rheum Dis*. 2014;73:536-43

The safety data showed no trend toward higher incidences of major adverse events in patients receiving sarilumab than in patients receiving an approved biological product, as shown in Table 52.

Table 52. Comparison of safety based on clinical study data on sarilumab and Japanese post-marketing data on other biological products

	Sarilumab		Tocilizumab[a)]	Infliximab[b)]	Etanercept[c)]	Adalimumab[d)]
	Foreign long-term safety population	Pooled Japanese population				
Number of subjects	2887	296	7901	5000	13,894	7740
Total exposure time (subject-years)	4481.8	118.5	3831.8	2359.3	6942.2 (estimation)	4153.4 (estimation)
Serious infection	158 (3.5)	6 (5.1)	298 (7.8)	202 (8.6)	330 (4.8)	182 (4.4)
Tuberculosis	2 (<0.1)	0	5 (0.1)	14 (0.6)	12 (0.2)	9 (0.2)
Herpes zoster	36 (0.8)	4 (3.4)	86 (2.2)	-	115 (1.7)	56 (1.3)
Pneumocystis pneumonia	0	1 (0.8)	14 (0.4)	22 (0.9)	25 (0.4)	26 (0.6)
Malignant tumor	33 (0.7)	2 (1.7)	39 (1.0)	9 (0.4)	30 (0.4)	13 (0.3)
Demyelinating disorder	0	0	-	-	0	2 (<0.1)
Injection site reaction	311 (6.9)	30 (25.3)	-	-	610 (8.8)	317 (7.6)
Lupus-like syndrome	4 (0.1)	0	-	-	5 (0.1)	-
Gastrointestinal perforation	7 (0.2)	0	13 (0.3)	-	-	-

Number of subjects (number of events per 100 subject-years after adjustment for total exposure time)
[a)] *J Rheumatol*. 2014;41:15-23; [b)] *Ann Rheum Dis*. 2008;67:189-94; [c)] *Mod Rheumatol*.2011;21:343-51; d) *Mod Rheumatol*. 2014;24:390-8

Based on the above, sarilumab is expected to have efficacy and safety comparable to those of the approved biological products. Sarilumab is expected to be a new treatment option for RA.

PMDA's view:
Given the available efficacy and safety profiles, the clinical positioning of sarilumab is the same as that of the approved biological products for RA treatment.

7.R.5.2 Concomitant use of sarilumab with conventional treatments and sarilumab monotherapy

The applicant's explanation about concomitant use of sarilumab with conventional treatments and sarilumab monotherapy:
As shown in Table 53, the data of the ACR20 response rate at Week 24 in Japanese and foreign clinical studies of sarilumab showed a certain level of efficacy of sarilumab monotherapy and the combination of sarilumab with a cDMARD in patients with RA who have responded inadequately to conventional treatments, despite difficulty in direct comparison of the data from each study.

Table 53. Comparison of ACR20 response rate at Week 24

Study population of patients with RA	Inadequate response to MTX		Inadequate response to cDMARDs[a)]	Inadequate response or intolerance to TNF inhibitors	Inadequate response or intolerance to MTX	Inadequate response to cDMARDs
Concomitant cDMARD	MTX		cDMARD[a)]	cDMARD	None	None
Region	Japan	Foreign	Japan	Foreign	Japan	Foreign
Study	EFC14059	EFC11072 Part B	LTS13618	EFC10832	LTS13618	EFC13752
150 mg q2w	67.9 (55/81)	58.0 (232/400)	80.0 (12/15)	55.8 (101/181)	73.3 (22/30)	73.8 (48/65)
200 mg q2w	57.5 (46/80)	66.4 (265/399)	73.3 (11/15)	60.9 (112/184)	64.5 (20/31)	71.6 (48/67)
Placebo	14.8 (12/81)	33.4 (133/398)	-	33.7 (61/181)	-	-

% (number of subjects)
a) Excluding MTX

Based on the above, sarilumab is expected to be used in the following patients:

- Sarilumab with a cDMARD: patients who have had an inadequate response to cDMARDs
- Sarilumab with a cDMARD: patients who have had an inadequate response or are intolerant to TNF inhibitors
- Sarilumab monotherapy: patients who are intolerant to or have had an inadequate response to MTX

PMDA's view:
Sarilumab is expected to be used as monotherapy or in combination with a cDMARD based on the clinical study data. Because of limited number of subjects in the studies, data should be further collected via post-marketing surveillance, etc. to investigate the impact of the concomitant use on sarilumab's safety, and findings should be communicated to healthcare professionals. Sarilumab is thought to have similar risks to those of the approved biological products for RA treatment, and it has never been used in combination with a biological product. Thus, sarilumab should not be used with a biological product.

7.R.6 Indication

PMDA's view:
Based on the data submitted and the discussions in "Sections 7.R.2 Efficacy," "7.R.3 Safety," and "7.R.5 Clinical positioning," sarilumab is recommended for patients with RA having an inadequate response to conventional treatments, and the proposed indication "Rheumatoid arthritis in patients who have had an inadequate response to conventional treatments" is appropriate. Sarilumab should be used for patients who have not responded adequately to appropriate treatment with at least 1 anti-rheumatic drug, and this should be reminded in the "Precautions for Indications" section of the package insert.

7.R.7 Self-administration

The applicant's explanation about the efficacy and safety of self-administered sarilumab:
Data on self-administration in Study EFC14059 show that sarilumab was self-administered by 22 of 81 subjects in the 150 mg q2w group, 19 of 80 subjects in the 200 mg q2w group, and 17 of 81 subjects in the placebo group. Of these, 4 of 22 subjects (18.2%) in the 150 mg q2w group, 6 of 19 subjects (31.6%) in the 200 mg q2w group, and 2 of 17 subjects (11.8%) in the placebo group performed self-

administration throughout the 24-week treatment period (a total of 11 doses). Table 54 shows the efficacy endpoint (ACR20, ACR50, and ACR70) data from subjects who performed self-administration and those who did not, indicating no impact of self-administration on efficacy.

Table 54. Comparison of efficacy between self-administration and non- self-administration (Study EFC14059)

	Self-administered			Not self-administered		
	150 mg q2w (n = 22)	200 mg q2w (n = 19)	Placebo (n = 17)	150 mg q2w (n = 59)	200 mg q2w (n = 61)	Placebo (n = 64)
ACR20 response rate	72.7 (16/22)	52.6 (10/19)	0 (0/17)	66.1 (39/59)	59.0 (36/61)	18.8 (12/64)
ACR50 response rate	45.5 (10/22)	42.1 (8/19)	0 (0/17)	42.4 (25/59)	37.7 (23/61)	12.5 (8/64)
ACR70 response rate	13.6 (3/22)	15.8 (3/19)	0 (0/17)	20.3 (12/59)	14.8 (9/61)	4.7 (3/64)

% (number of subjects)

Although there are limitations to safety evaluation due to the limited number of subjects who performed self-administration, no substantial difference was observed in the occurrence of adverse events within the first 24 weeks of treatment. The incidence of adverse events in subjects who performed self-administration was 81.8% (18 of 22) in the 150 mg q2w group, 57.9% (11 of 19) in the 200 mg q2w group, and 41.2% (7 of 17) in the placebo group; and that in subjects who did not perform self-administration was 79.7% (47 of 59) in the 150 mg q2w group, 80.3% (49 of 61) in the 200 mg q2w group, and 65.6% (42 of 64) of subjects in the placebo group in the population. The incidence of injection site reaction in subjects who performed self-administration was 13.6% (3 of 22) in the 150 mg q2w group, 5.3% (1 of 19) in the 200 mg q2w group, and 0% in the placebo group, and that in subjects who did not perform self-administration was 8.5% (5 of 59) in the 150 mg q2w group, 11.5% (7 of 61) in the 200 mg q2w group, and 0% in the placebo group, indicating no clear difference between self-administration and non-self-administration.

Based on the above, there is no particular problem with the efficacy and safety of self-administered sarilumab in Japanese patients with RA.

PMDA's view:

The clinical studies have suggested no particular problems with the safety and efficacy of self-administered sarilumab at present. However, the treating physician should allow patients to perform self-administration only after due consideration of its appropriateness. The patients must receive adequate training and acquire a good understanding of its risks and ways to manage those risks, as well as the solid skill for self-administration. If any adverse drug reaction of sarilumab such as infection is suspected in a patient on self-administration, or when the patient has difficulty in continuing self-administration, the physician should advise the patient to withdraw from self-administration immediately, closely monitor, and appropriately treat the patient. The applicant should communicate the importance of these actions to healthcare professionals. Further, the applicant should prepare written materials using examples from the approved biological products and take other necessary safety measures. Because of limited safety and efficacy data on self-administered sarilumab in Japanese patients with RA, further investigation via post-marketing surveillance, etc. is needed.

7.R.8 Post-marketing safety measures

The applicant's explanation about post-marketing safety measures:

The applicant plans to collect data on the occurrences of serious infections and gastrointestinal perforation through post-marketing surveillance to confirm the safety (including long-term safety) of sarilumab in post-marketing routine clinical settings. When information on new or known safety concerns became available, the applicant will revise the package insert and materials for healthcare professionals and patients.

PMDA's view:
The safety profile of sarilumab is not largely different from that of tocilizumab or other approved biological products. So far it does not suggest safety concerns greater than those with the approved biological products. However, experience with sarilumab particularly in its prolonged use is limited. Serious infections and malignant tumors are common concerns with immunosuppressive drugs like the approved biological products, and further data collection on the occurrences of these events is necessary. Thus, the post-marketing surveillance for sarilumab should be designed to accommodate such needs.

Safety measures for sarilumab should be similar to those taken for the approved biological products. To facilitate the proper use of sarilumab, both healthcare professionals and patients should have appropriate and prompt access to information. Written materials should be distributed to physicians and other healthcare professionals, and easy-to-understand materials about the risks of sarilumab should also be prepared for patients.

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 Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.1-1 and CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection and assessment revealed no noteworthy issues. PMDA thus 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 sarilumab has efficacy in the treatment of patients with RA who have had an inadequate response to conventional treatments and acceptable safety in view of its benefits. Sarilumab offers a new therapeutic option for patients with RA and is of a clinical significance. Sarilumab should be used with similar safety measures as taken for the approved biological

products for RA treatment. The incidence of serious infections, etc. associated with sarilumab in its prolonged use should be further investigated via post-marketing surveillance.

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

10. Others

The Definitions of efficacy endpoints used in the clinical studies of Kevzara are shown below.

Endpoint	Definition
ACR20, ACR50, or ACR70 response rate	The proportion of subjects achieving ≥20%, ≥50%, or ≥70% reduction from baseline in tender joint count out of 68 joints and swollen joint count out of 66 joints and ≥20%, ≥50%, or ≥70% improvement from baseline in ≥3 of the following: patient assessment pain by VAS, patient global assessment by VAS, physician global assessment by VAS, daily activity assessment (HAQ-DI, an RA-specific health assessment questionnaire), and CRP
CDAI	Disease activity assessment score calculated by the following formula based on tender joint count (TJC) and swollen joint count (SJC) out of 28 joints, physician global assessment by VAS (EGA), and patient global assessment by VAS (PGA) CDAI = TJC + SJC + EGA + PGA
CDAI remission	CDAI of ≤2.8 at assessment
DAS28-CRP	Disease activity assessment score calculated by the following formula based on tender joint count (TJC) and swollen joint count (SJC) out of 28 joints, CRP, and patient global assessment by VAS (GH). $DAS28-CRP = 0.56\sqrt{TJC} + 0.28\sqrt{SJC} + 0.36\{\ln(CRP + 1)\} + 0.014 \times GH + 0.96$
DAS28-CRP remission	DAS28-CRP of <2.6 at assessment
HAQ-DI	Physical function assessment score of RA patients calculated based on subjective difficulty in daily activities of 8 categories (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities [errands and chores]) assessed on a scale of 0 to 3 (the mean score of each category)
mTSS	Structural joint damage score based on the sum of quantified degrees of bone erosion (44 joints) and joint space narrowing (42 joints) in X-ray images of both hands/wrists and feet
SDAI	Disease activity assessment score calculated by the following formula based on tender joint count (TJC) and swollen joint count (SJC) out of 28 joints, CRP, physician global assessment by VAS (EGA), and patient global assessment by VAS (PGA). SDAI = TJC + SJC + CRP + EGA + PGA
SDAI remission	SDAI of ≤3.3 at assessment

VAS: Visual analog scale

Review Report (2)

July 18, 2017

Product Submitted for Approval

Brand Name	Kevzara 150 mg Syringe for SC Injection
	Kevzara 200 mg Syringe for SC Injection
	Kevzara 150 mg Auto-injector for SC Injection
	Kevzara 200 mg Auto-injector for SC Injection
Non-proprietary Name	Sarilumab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	October 7, 2016

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 in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy and indication

At the Expert Discussion, PMDA's conclusions regarding the efficacy and indication of Kevzara 150 mg Syringe for SC Injection, Kevzara 200 mg Syringe for SC Injection, Kevzara 150 mg Auto-injector for SC Injection, and Kevzara 200 mg Auto-injector for SC Injection (hereinafter referred to as Kevzara) described in the Review Report (1) were supported by the expert advisors.

1.2 Dosage and administration

At the Expert Discussion, PMDA's conclusions about the dosage and administration of Kevzara described in the Review Report (1) were supported by the expert advisors. Besides, the following comments were raised from the expert advisors:

- The usual dosage of sarilumab 200 mg once every 2 weeks (q2w) determined based on the Japanese and foreign clinical study data is acceptable. However, the rationale for the dose selection should be further clarified because of the primary endpoint results in the Japanese clinical studies that were comparable between the 150 mg q2w and 200 mg q2w groups.

PMDA has concluded that, in light of the discussion in "Section 7.R.4 Dosage and administration" and due to the following reasons, the appropriate usual dosage of sarilumab should be 200 mg once every 2 weeks, and the dosage of 150 mg once every 2 weeks should be considered according to the patient's condition including laboratory test values.

- Current Japanese and foreign guidelines for the management of rheumatoid arthritis (RA) recommend that treatment should aim to achieve early clinical remission or low disease activity to suppress irreversible progression of joint destruction, in accordance with the Treat to Target (T2T) recommendation (*Ann Rheum Dis*. 2010;69:631-7) published in 2010. While the American College of Rheumatology/European League Against Rheumatism recommend remission criteria based on SDAI and CDAI as measures of clinical remission to be used in clinical studies of RA (*Ann Rheum Dis*. 2011;70:404-413), Japanese Phase II/III study (Study EFC14059) and foreign Phase III study (Study EFC11072 Part B) showed a trend toward higher SDAI and CDAI remission rates in the 200 mg q2w group than in the 150 mg q2w group (Table 55).

- Although the Japanese and foreign clinical studies revealed no substantial problems with the tolerability of the sarilumab 200 mg q2w regimen, the dose-dependent changes and the trend in reversibility in laboratory test values at the reduced dose of 150 mg [see Section "7.R.4.2 Dose adjustment"] indicate the need of dose adjustment to 150 mg according to individual patients' condition including laboratory test values.

Table 55. SDAI and CDAI remission rates in Study EFC14059 and Study EFC11072 Part B (efficacy analysis population)

	Week 12			Week 24		
Japanese Phase II/III study	150 mg q2w	200 mg q2w	Placebo	150 mg q2w	200 mg q2w	Placebo
SDAI remission rate	2.5 (2/81)	8.8 (7/80)	0 (0/81)	6.2 (5/81)	12.5 (10/80)	1.2 (1/81)
CDAI remission rate	1.2 (1/81)	6.3 (5/80)	0 (0/81)	6.2 (5/81)	10.0 (8/80)	1.2 (1/81)
Foreign Phase III study	150 mg q2w	200 mg q2w	Placebo	150 mg q2w	200 mg q2w	Placebo
SDAI remission rate	3.5 (14/400)	7.5 (30/399)	2.0 (8/398)	10.3 (41/400)	13.0 (52/399)	4.8 (19/398)
CDAI remission rate	3.8 (15/400)	7.0 (28/399)	3.0 (12/398)	10.3 (41/400)	13.8 (55/399)	5.0 (20/398)

% (number of subjects)

On the basis of the results of the Expert Discussion, PMDA concluded that the appropriate dosage and administration statement be defined as shown below. PMDA instructed the applicant to provide healthcare professionals with the criteria for dose reduction or discontinuation of Kevzara based on laboratory abnormality that were used in the clinical studies for reference. The applicant agreed to follow the instruction.

Dosage and Administration
The usual adult dosage is 200 mg of sarilumab (genetical recombination) subcutaneously injected once every 2 weeks. The dose should be reduced to 150 mg according to the patient's condition.

1.3 Safety and draft risk management plan

At the Expert Discussion, PMDA's conclusions about the safety of sarilumab and post-marketing safety measures described in the Review Report (1) were supported by the expert advisors.

Based on the discussion in "Section 7.R.8 Post-marketing safety measures" of the Review Report (1) and the comments from the expert advisors at the Expert Discussion, PMDA concluded that the risk management plan (draft) for Kevzara should include the safety and efficacy specifications presented in Table 56, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 57. Thus, PMDA instructed the applicant to design post-marketing surveillance to accommodate these requirements.

Table 56. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Serious infection • Intestinal perforation • Serious hypersensitivity reactions including anaphylaxis • Interstitial pneumonia • Reactivation of hepatitis B virus • Neutropenia, leukopenia, agranulocytosis • Thrombocytopenia • Hepatic function disorder	• Malignant tumor • Immunogenicity	• None
Efficacy specification		
• Efficacy in routine clinical settings		

Table 57. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-result survey (in long-term)	• Early post-marketing phase vigilance • Preparation and distribution of materials for healthcare professionals • Preparation and distribution of materials for patients • Provision of information on the proper use prior to product delivery

The applicant's explanation:

As shown in Table 58, a specified drug use-results survey will be conducted in patients with RA who has had an inadequate response to conventional treatments with an observation period of 1 year (52 weeks) and a target sample size of 1000. The survey objective is to evaluate the safety and efficacy of Kevzara in routine clinical settings focusing on the key survey items, namely, serious infection (including tuberculosis), intestinal perforation, serious hypersensitivity reactions, interstitial pneumonia, reactivation of hepatitis B virus, serious haematologic disorders, hepatic function disorders, malignant tumors, and cardiovascular events. After the completion of the observation, the patients will be followed for serious infections and malignant tumors until 3 years from the start of treatment to further investigate the long-term safety.

Table 58. Outline of specified use-results survey plan (draft)

Objective	To confirm the long-term safety and efficacy of Kevzara in routine clinical settings
Survey method	Central registration system
Population	Patients with RA who have had an inadequate response to conventional treatments
Observation period	1 year (52 weeks) (followed by a 2-year follow-up)
Planned sample size	1000 (as population for safety analysis)
Main survey item(s)	• Key survey items: serious infections (including tuberculosis), intestinal perforation, serious hypersensitivity reactions, interstitial pneumonia, reactivation of hepatitis B virus, serious haematologic disorders, hepatic function disorders, malignant tumors, and cardiovascular events • Patient characteristics (body weight, age, severity, disease duration, prior treatment, complications, etc.) • Status of treatment with Kevzara • Concomitant drugs/therapies • Laboratory tests • Adverse events • Efficacy

2. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved for the modified indication and dosage and administration as shown below, with the following condition. Kevzara is a drug with a new active ingredient, and the re-examination period is 8 years. The product is classified as a biological product, and the drug product and its drug substance are both classified as powerful drugs.

Indication

Rheumatoid arthritis in patients who have had an inadequate response to conventional treatments

Dosage and Administration

The usual adult dosage is 200 mg of sarilumab (genetical recombination) subcutaneously injected once every 2 weeks. The dose should be reduced ~~may be adjusted~~ to 150 mg according to the patient's condition ~~body weight~~.

(Strike-through denotes deleted text, and underline denotes addition.)

Condition of Approval

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