Report on the Deliberation Results

June 4, 2020
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Enspryng Syringes for Subcutaneous Injection 120 mg
Non-proprietary Name	Satralizumab (Genetical Recombination) (JAN*)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	November 8, 2019

Results of Deliberation

In its meeting held on May 29, 2020, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product. The re-examination period is 10 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

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

2. Because data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey involving all patients treated with the product until data from a specified number of patients have been gathered in order to identify the characteristics of patients using the product, and to promptly collect safety and efficacy data, so that necessary measures are taken to ensure the proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

May 11, 2020
Pharmaceuticals and Medical Devices Agency

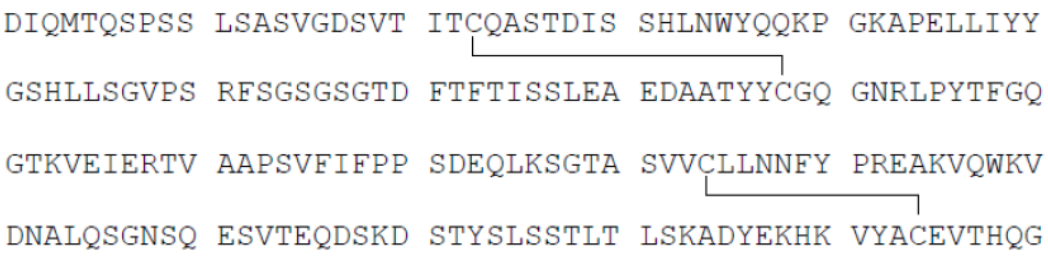
The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Enspryng Syringes for Subcutaneous Injection 120 mg
Non-proprietary Name	Satralizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	November 8, 2019
Dosage Form/Strength	Injection: Each syringe (1 mL) contains 120 mg of Satralizumab (Genetical Recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Satralizumab is a recombinant humanized monoclonal antibody composed of complementarity-determining regions derived from a mouse anti-human interleukin-6 receptor monoclonal antibody, human framework regions and human IgG2 constant regions. In the H-chain, the amino acid residues at position 133, 135, 139, 140, 221, 266, 353, 417 and 432 are substituted by Ser, Lys, Gly, Gly, Ser, Gln, Gln, Glu and Ala respectively, and Gly and Lys at the C-terminus are deleted. Satralizumab is produced in Chinese hamster ovary cells. Satralizumab is a glycoprotein (molecular weight: ca. 146,000) composed of 2 H-chains (γ2-chains) consisting of 443 amino acid residues each and 2 L-chains (κ-chains) consisting of 214 amino acid residues each.

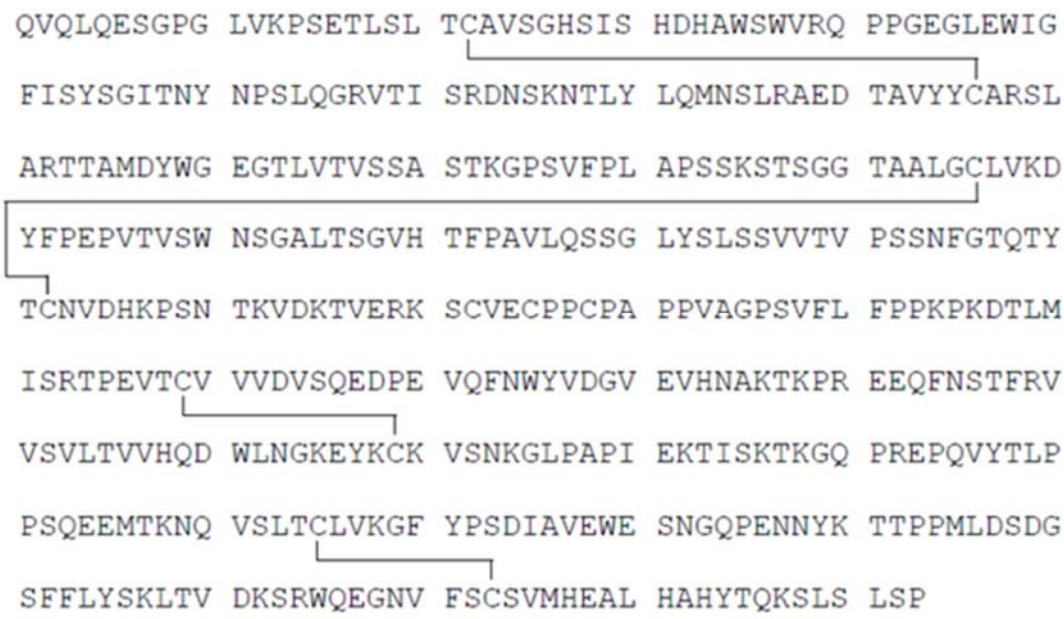
Structure

Amino acid sequences and disulfide bonds:

L-chain:



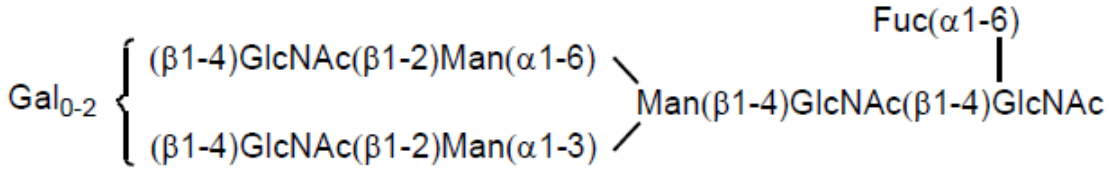
H-chain:



Pyroglutamate formation (partial) at Q1 in H-chain, glycosylation at N295 in H-chain

Disulfide bonds between C214 in L-chain and C222 in H-chain, C225 in H-chain and C225 in H-chain, and C228 in H-chain and C228 in H-chain

Estimated structure of main carbohydrate chain



$C_{6340}H_{9776}N_{1684}O_{2022}S_{46}$ (protein portion, 4 chains)

H chain: $C_{2155}H_{3328}N_{572}O_{671}S_{17}$

L chain: $C_{1015}H_{1564}N_{270}O_{340}S_{6}$

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 443 of 2019 [*31 yaku*]; PSEHB/PED Notification No. 0912-1 dated September 12, 2019, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug III

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the prevention of the relapse of neuromyelitis optica spectrum disorder (including neuromyelitis optica), and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions.

Indication Prevention of relapse of neuromyelitis optica spectrum disorder (including neuromyelitis optica)

Dosage and Administration The usual dosage of satralizumab (genetical recombination) for adults and children is 120 mg administered by subcutaneous injection at Weeks 0, 2, and 4, and every 4 weeks thereafter.

Approval Conditions

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

2. Because data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing drug use-results survey involving all patients treated with the product until data from a specified number of patients have been gathered in order to identify the characteristics of patients using the product, and to promptly collect safety and efficacy data, so that necessary measures are taken to ensure the proper use of the product.

Attachment

Review Report (1)

March 25, 2020

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

Product Submitted for Approval

Brand Name	Enspryng Syringes for Subcutaneous Injection 120 mg
Non-proprietary Name	Satralizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	November 8, 2019
Dosage Form/Strength	Injection: Each syringe (1 mL) contains 120 mg of Satralizumab (Genetical Recombination).
Proposed Indication	Neuromyelitis optica spectrum

Proposed Dosage and Administration

The usual dosage of satralizumab (genetical recombination) for adults and children aged ≥12 years is 120 mg administered by subcutaneous injection at Weeks 0, 2, and 4, and every 4 weeks thereafter.

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List of Abbreviations

See Appendix.

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

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory demyelinating disease in the central nervous system, and characterized by severe optic neuritis and transverse myelitis. Anti-aquaporin-4 (AQP4) antibody, an autoantibody against the water channel AQP4 expressed in the central nervous system, is considered to be involved in the pathology of NMOSD. In contrast, some patients with NMOSD are anti-AQP4 antibody-negative, suggesting that autoantibodies other than anti-AQP4 antibody may also contribute to the pathogenesis of the disease(*J Neurol Neurosurg Psychiatry*. 2013;84:922-30, *Eur J Neurol.* 2015;22:1511-18). Untreated patients with NMOSD experienced 1 to 1.5 relapses within 1 year on average (*Brain.* 2012;135:1834-49). Recurrent NMOSD attacks result in the accumulation of disability. Most of patients with NMOSD experience severe relapses, with a single attack potentially leading to blindness and wheelchair-dependence. Approximately 35% of patients with NMOSD are eventually inflicted with irreversible spinal cord disorder, and approximately 25% of the patients become wheelchair-dependent (*2017 Japanese guidelines for multiple sclerosis and neuromyelitis optica* [in Japanese]. Igaku Shoin; 2017). Patients with higher anti-AQP4 antibody titers tend to have serious relapses (*2017 Japanese guidelines for multiple sclerosis and neuromyelitis optica* [in Japanese]. Igaku Shoin; 2017).

The estimated prevalence of NMOSD is 0.52 to 4.4 per 100,000 people globally (*Mult Scler*. 2015;21:845-53) and 3.65 per 100,000 people in Japan (the total number of patients in Japan is approximately 4370) (*Japanese Journal of Clinical Medicine*. 2014;11:1903-7). Satralizumab has been designated as an orphan drug with the intended indication of "neuromyelitis optica and neuromyelitis optica-related diseases" (Orphan Drug Designation No. 443 of 2019 [*31 yaku*]).

Satralizumab, a humanized anti-interleukin-6 receptor (IL-6R) immunoglobulin G (IgG)2 monoclonal antibody, was discovered by Chugai Pharmaceutical Co., Ltd.

In Japan, a clinical study was initiated in November 11, 2010. The applicant has submitted a marketing application for satralizumab with the claim that the efficacy and safety of satralizumab in patients with neuromyelitis optica spectrum has been demonstrated by the global phase III study and other data.

Outside of Japan, marketing applications for satralizumab were submitted in the US and Europe in August 2019 and are currently under review. As of February 2020, satralizumab has not been approved in any country or region.

In Japan, Eculizumab (Genetical Recombination) ("eculizumab") was approved in November 2019 for "prevention of relapses of neuromyelitis optica spectrum disorder (including neuromyelitis optica)."

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

2.1 Drug substance

2.1.1 Generation and control of cell substrate

The gene fragments encoding the variable regions of the heavy and light chains isolated from mouse hybridoma cells producing mouse anti-human IL-6R monoclonal antibody ([redacted]) (*J Immunol.* 1989;143:2900-6) were humanized, subjected to amino acid substitution for [redacted]

[redacted], and then fused with the gene fragments encoding the constant region of modified human IgG2 heavy chain and human κ light chain to obtain the gene fragments of interest. Thus-obtained gene expression constructs were introduced into Chinese hamster ovary (CHO) cells, and a master cell bank (MCB) and a working cell bank (WCB) were prepared from the clone best suited for the manufacture of satralizumab drug substance.

Characterization and purity test of the MCB, WCB, and post process cells (PPC) were performed according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q5A (R1), Q5B, and Q5D guidelines. Results confirmed genetic stability during the manufacturing of satralizumab drug substance. Except for endogenous retrovirus-like particles commonly observed in rodent-derived cell lines, no viral or non-viral adventitious agents were detected within the range of the tests performed.

The MCB and WCB are stored in the vapor phase of liquid nitrogen. [redacted] and a new WCB will be generated as necessary.

2.1.2 Manufacturing process

The manufacturing process for the drug substance comprises thawing of WCB, seed culture, inoculation culture, production culture, harvesting, [redacted] chromatography, [redacted] virus inactivation, [redacted] chromatography, viral [redacted], [redacted] chromatography, [redacted] chromatography, [redacted] filtration, dilution and adjustment, filtration, filling, testing, and storage.

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

The manufacturing process for the drug substance was validated on a commercial scale and at a down-scaled model.

2.1.3 Safety evaluation of adventitious agents

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

Purity tests were performed on the MCB, WCB, and PPC [see Section 2.1.1]. An unprocessed bulk manufactured on a commercial scale was subjected before harvest to bioburden testing, mycoplasma testing, *in vitro* adventitious virus testing, transmission electron microscopy, and mouse minute virus testing. No contamination with either viral or non-viral adventitious agents was detected within the range of the tests performed. These tests for unprocessed bulk, except for transmission electron microscopy, are included in the in-process controls.

A virus clearance study was performed using model viruses for the purification process. Results showed that the purification process has sufficient virus clearance capacity (Table 1).

Table 1. Results of virus clearance tests

Manufacturing process	Viral reduction factor (log_{10})		
	Xenotropic murine leukemia virus	Minute virus of mice	SV-40
[redacted] virus inactivation	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]
Virus [redacted]	[redacted]	[redacted]	[redacted]
Total reduction factor	≥15.92	≥8.16	≥10.44

2.1.4 Manufacturing process development

Main changes made to the manufacturing process during the development of the drug substance (process for toxicity studies, G1 process, and proposed process) are described below. The phase I studies and the double-blind period of the phase III study used the formulations produced from the drug substance manufactured by the G1 process. The open-label extension period of the phase III study used the formulation produced from the drug substance manufactured by the proposed process.

- From the process for toxicity studies to the G1 process: Changes in [redacted], [redacted], [redacted], etc.
- From the G1 process to the proposed process: [redacted], changes in [redacted], and change in [redacted]

After the process change from the G1 process to the proposed process, the comparability of quality attributes of the pre-change and post-change drug substance was demonstrated by comparability studies.

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

2.1.5 Characterization

2.1.5.1 Structure and characteristics

Characterization studies were conducted as shown in Table 2.

Table 2. Test parameters and methods for characterization

Primary structure/higher order structure	Amino acid sequence, posttranslational modification ([redacted], [redacted], [redacted]), secondary structure, disulfide bond, free thiol group
Physicochemical properties	Molecular weight, isoelectric point, molecular weight species (high molecular weight species, low molecular weight species), charge variants
Carbohydrate chain structure	[redacted]
Biological properties	IL-6R-binding activity (pH dependency), inhibition of IL-6-induded proliferation of cells
	FcγR-binding activity ([redacted], [redacted], [redacted], [redacted]), FcRn-binding activity, C1q-binding activity, ADCC activity, CDC activity

As for main biological characteristics, the competitive inhibitory activity of satralizumab against IL-6-induced-proliferation was demonstrated by the test system using IL-6-dependent [redacted]. A test for antigen-binding activity by [redacted] showed pH-dependent association/dissociation reaction [redacted] pH [redacted] pH [redacted].

Studies on effector functions demonstrated that the profile of satralizumab for Fcγ receptor (FcγR)-binding activity was characteristic of IgG2, that the FcγR-binding activity and C1q-binding activity were similar to, or lower than, those of the control IgG2 antibody, and that satralizumab has little or no antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity.

2.1.5.2 Product-related substances/Product-related impurities

No product-related substances were identified. Based on the results of the characterization in Section 2.1.5.1, the following were identified as product-related impurities: Variant A [redacted], [redacted], Variant B [redacted], [redacted], Variant C [redacted], [redacted], Variant D [redacted], [redacted], Variant E, and Variant F. Among the product-related impurities, Variant A, [redacted], and [redacted] are controlled adequately by the specifications for the drug substance and the drug product, and Variant E by the in-process controls. No routine controls are required for other product-related impurities because of the negligible or unchanged content or because of no increase in the amount observed in the stability study.

2.1.5.3 Process-related impurities

Host cell protein (HCP), host cell-derived deoxyribonucleic acid (DNA), and Process-related Impurity A were identified as process-related impurities. All of them have been confirmed to be removed completely during the manufacture process.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (peptide mapping), osmolality, pH, purity (capillary gel electrophoresis with sodium dodecyl sulfate [CE-SDS (non-reduced)], size exclusion chromatography [SEC], and anion exchange chromatography [AEX]), bacterial endotoxins, microbial limit, [redacted], potency (inhibition of IL-6-induced proliferation of cells), and assay (ultraviolet-visible spectrophotometry).

2.1.7 Stability of drug substance

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

Table 3. Summary of main stability studies of drug substance

	Manufacturing process	Number of batches	Storage condition	Study period	Storage container
Long-term testing	Proposed process	3[a)]	[redacted] ± [redacted]°C	[redacted] months	[redacted]
Accelerated testing	Proposed process	3	[redacted] ± [redacted]°C	[redacted] months	[redacted]
Stress testing	Proposed process	1	[redacted] ± [redacted]°C/[redacted]% RH	[redacted] weeks	[redacted] container

a) Conducted up to [redacted] months for 1 batch. The stability study is ongoing up to [redacted] months in all batches.

The long-term testing and the accelerated testing did not show any clear change in the quality attributes throughout the study period.

The stress testing showed [redacted], [redacted], and [redacted] in [redacted], [redacted] and [redacted] in [redacted], and [redacted] and [redacted] in [redacted].

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

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a solution for injection containing 120 mg of satralizumab per syringe (1 mL). The excipients contained in the drug product are L-histidine, L-aspartic acid, L-arginine, poloxamer 188, and water for injection. The drug product is a combination product comprised of a pre-filled plastic syringe with a needle, equipped with a device to prevent needle-stick injury. The plastic syringe with a needle is [redacted] ([redacted]).

2.2.2 Manufacturing process

The manufacturing process for the drug product comprises drug solution preparation, sterile filtration, filling/sealing, inspection, assembly, packaging/labeling, and storage/testing.

[redacted] and [redacted] have been defined as critical steps.

The manufacturing process for the drug product was validated on a commercial scale.

2.2.3 Manufacturing process development

Major changes made to the manufacturing process during the development of the drug product (Process A, Process B, and the proposed process) are described below. The phase III study used the formulation manufactured by Process B and by the proposed process.

- From Process A to Process B: Changes in [redacted], etc.
- From Process B to the proposed process: Changes in [redacted], [redacted], etc.

After the changes in the manufacturing process, the comparability of quality attributes of the pre-change and post-change drug product was demonstrated by comparability studies.

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

2.2.4 Control of drug product

The proposed specifications for the drug product consist of strength, description, identification (peptide mapping), osmolality, pH, purity (CE-SDS [non-reduced], SEC, and AEX), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, potency (inhibition of IL-6-induced proliferation of cells), and assay (ultraviolet-visible spectrophotometry).

2.2.5 Stability of drug product

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

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

	Number of batches [a)]	Storage conditions	Study period	Storage container[c)]
Long-term testing	4	5 ± 3°C	[redacted] months[b)]	[redacted] syringe and [redacted] cap and plunger stopper
Accelerated testing	8	[redacted]°C/[redacted]% RH	[redacted] months	
Stress testing (light)	1	Overall illumination of ≥1.2 million lux·h, integrated near ultraviolet energy of ≥200 W·h/m^2		

a) Both the drug substance and the drug product were manufactured by the proposed process.
b) Up to [redacted] months for 1 batch.
c) Separately, 3 batches each of [redacted] was shown not to affect the stability.

The long-term testing showed [redacted] and [redacted] in [redacted]. Some batches were found to contain visible particles detected by the foreign insoluble matter test after [redacted], and the visible particles were identified as complex of protein and [redacted] by [redacted]. There were no clear changes over time in other attributes tested throughout the study period.

The accelerated testing showed [redacted] and [redacted] in [redacted].

The stress testing (light) showed that the drug product is sensitive to light.

Based on the above, a shelf-life of 24 months has been proposed for the drug product when stored at 2°C to 8°C in a primary container ([redacted] syringe, [redacted] cap, and plunger stopper) protected from light in a paper box.

2.3 QbD

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

- Identification of critical quality attributes (CQAs)

  The following CQAs were identified from among the quality attributes related to product-related impurities, process-related impurities, and drug product formulation, based on the information obtained during the development of the drug substance and the drug product and related findings.

  CQAs: [redacted], adventitious agents, [redacted], sterility, and [redacted]

- Characterization of process:

  The acceptable control range for each process parameter was determined, based on the analysis of the impact of each process on CQAs.

- Establishment of control strategy

  Based on the knowledge on the process including the above characterization of process and on risk assessment related to quality attributes, etc., the control strategy for the quality attributes of the drug substance and the drug product was established by the combination of the process parameters, in-process controls, and specifications [see Sections 2.1.5.2 and 2.1.5.3 for the control of product-related impurities and process-related impurities].

2.R Outline of the review conducted by PMDA

PMDA conducted the following review on the submitted data and concluded that the submitted data indicate that the quality of the drug substance and the drug product is controlled adequately, though further investigations are needed to improve the stability of the drug product.

2.R.1 Insoluble visible particles detected in the drug product

Taking account of the presence of batches showing visible particles under the long-term storage conditions after [redacted], PMDA asked the applicant to explain (a) the remedial measures attempted so far and future actions, and (b) the quality control of the proposed drug product and the shelf-life of the drug product.

The applicant's explanation:

(a) In order to prevent the formation of visible particles during the storage of the drug product, [redacted] was attempted but failed to solve the problem. [redacted] is suspected to contribute to the formation of visible particles. The drug product in which visible particles were observed during the storage was used in clinical studies without any significant safety problem [see Section 7.R.2.7]. This suggests that the quality is within the acceptable range and that no changes are necessary for the formulation or dosage form of the drug product.

(b) Visible particles in the drug product are controlled at [redacted] according to the Foreign Insoluble Matter Test for Injections stipulated in the General Tests of Japanese Pharmacopoeia. If visible particles are detected [redacted], [redacted] will be performed to ensure that [redacted] visible particles are present as a complex of protein and [redacted]. As a [redacted], the stability of the drug product is confirmed by ensuring the absence of easily detectable foreign insoluble matter other than visible particles [redacted]. On the basis of these controls and results of other tests, the proposed shelf-life (24 months) for the drug product is considered appropriate.

PMDA's view:

- Visible particles in the drug product is a risk factor for immunogenicity and other aspects. The formation of visible particles was also observed in the study drug used in clinical studies, with some clinical experience of the drug product. However, the presence of visible particles vary from batch to batch. To assess this risk factor, the applicant should investigate several issues, including but not limited to [redacted]

[redacted], and continue to elucidate the cause of the visible particles and to device a preventive measure, thereby to take appropriate actions.

- Taking account of the facts that the drug product is a solution for subcutaneous injection and that no safety problem related to the visible particles is reported currently in clinical studies in which the drug product containing visible particles was used, the proposed specification for insoluble foreign matter in the drug product and the proposed shelf-life of the drug product are acceptable on the premise that further investigation is performed and appropriate measures are taken.

The applicant agreed to take actions for the above, and PMDA accepted the applicant's response.

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

The applicant submitted the results of primary pharmacodynamic studies as those of the nonclinical pharmacology study of satralizumab. No independent safety pharmacology study was conducted. Instead, the effect on the central nervous system, cardiovascular system, and respiratory system was investigated in 4- and 26-week repeated-dose toxicity studies in cynomolgus monkeys. Data are expressed in geometric mean (geometric standard deviation) unless specified otherwise. In *in vivo* studies, 150 mmol/L arginine-aspartate buffer (containing 20 mmol/L histidine and 0.5 mg/mL poloxamer 188) was used as vehicle. Results of main studies are described below.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Binding affinity to IL-6R

Using CHO cells expressing human or cynomolgus monkey membrane-bound IL-6R, binding affinity of satralizumab and Tocilizumab (Genetical Recombination) ("tocilizumab"), another anti-IL6R antibody, to IL-6R was investigated by flow cytometry. Both satralizumab and tocilizumab bound to the receptor in a concentration-dependent manner, with effective concentration, 50% (EC_{50}) of 0.019 μg/mL (1.0) and 0.017 μg/mL (1.1), respectively, to human membrane-bound IL-6R and EC_{50} of 0.019 μg/mL (1.1) and 0.018 μg/mL (1.1), respectively, to cynomolgus monkey membrane-bound IL-6R (CTD 4.2.1.1-1).

Table 5 shows the binding affinity of satralizumab and tocilizumab for human and cynomolgus monkey soluble IL-6R at pH 7.4 investigated by Surface Plasmon Resonance (SPR). Satralizumab showed a higher binding affinity for human soluble IL-6R than did tocilizumab (Common Technical Document [CTD] 4.2.1.1-2).

Table 5. Binding affinity for human and cynomolgus monkey soluble IL-6R

	Soluble IL-6R	k_a		k_d		K_D	
		Geometric mean ($\times 10^4$ $[mol/L]^{-1}s^{-1}$)	Geometric standard deviation	Geometric mean ($\times 10^{-4}$ s^{-1})	Geometric standard deviation	Geometric mean (nmol/L)	Geometric standard deviation
Satralizumab	Human	61.4	1.0	9.4	1.0	1.5	1.0
	Cynomolgus monkey	57.9	1.0	11.8	1.0	2.0	1.0
Tocilizumab	Human	20.1	1.0	11.6	1.0	5.8	1.1
	Cynomolgus monkey	17.2	1.0	14.7	1.0	8.5	1.0

Table 6 shows the binding affinity of satralizumab for human soluble IL-6R at pH 6.0, 6.5, 7.0, and 7.4 investigated by SPR. As shown in Table 6, dissociation rate constant ($k_{d)}$) and dissociation constant (K_D) increased with the decrease in pH, indicating that satralizumab is rapidly dissociated from human soluble IL-6R with the decrease in pH, demonstrating pH-dependent binding affinity (CTD 4.2.1.1-3).

Table 6. Binding affinity of satralizumab for human soluble IL-6R under different pH conditions

pH	k_a ($\times 10^4$ $[mol/L]^{-1}s^{-1}$)	k_d ($\times 10^{-4}$ s^{-1})	K_D (nmol/L)
6.0	32.7 ± 1.0	110 ± 1.0	33.6 ± 1.4
6.5	43.8 ± 3.9	29.9 ± 0.70	6.87 ± 0.80
7.0	47.0 ± 1.5	12.4 ± 0.96	2.64 ± 0.25
7.4	46.8 ± 1.7	8.85 ± 0.32	1.89 ± 0.026

Mean ± standard deviation (SD)

3.1.1.2 IL-6R-mediated inhibition of IL-6 activity (CTD 4.2.1.1-6)

Using the combination of BaF/hIL-6R cell line[1)] and human IL-6 or BaF/CyIL-6R cell line[2)] and cynomolgus monkey IL-6, the inhibitory effect of satralizumab and tocilizumab against cell growth through signaling mediated by membrane-bound IL-6R was investigated. Both satralizumab and tocilizumab inhibited membrane-bound IL-6R-mediated cell growth in a concentration-dependent manner, with 50% inhibitory concentration (IC_{50}) of 11 μg/mL (1.3) and 5.1 μg/mL (1.8), respectively, against cell growth mediated by human membrane-bound IL-6R and IC_{50} of 3.9 μg/mL (2.3) and 2.1 μg/mL (1.8), respectively, against cell growth mediated by cynomolgus monkey membrane-bound IL-6R.

Using a combination of (1) BaF/hgp130 cell line,[3)] human soluble IL-6R, and human IL-6, or (2) BaF/hgp130 cell line, cynomolgus monkey soluble IL-6R, and cynomolgus monkey IL-6, the inhibitory effect of satralizumab and tocilizumab against cell growth through signaling mediated by soluble IL-6R was investigated. Both satralizumab and tocilizumab inhibited soluble IL-6R-mediated cell growth in a concentration-dependent manner, with IC_{50} of 0.038 μg/mL (1.4) and 0.078 μg/mL (1.3), respectively, against cell growth mediated by human soluble IL-6R and IC_{50} of 0.046 μg/mL (1.5) and 0.067 μg/mL (1.6), respectively, against cell growth mediated by cynomolgus monkey soluble IL-6R.

1) Mouse pro-B cell-derived Ba/F3 cell line transduced with human membrane-bound IL-6R and human gp130
2) Mouse pro-B cell-derived Ba/F3 cell line transduced with cynomolgus monkey membrane-bound IL-6R and human gp130
3) Mouse pro-B cell-derived Ba/F3 cell line transduced with human gp130

3.1.1.3 Binding affinity for FcRn and FcγR (CTD 4.2.1.1-4)

Binding affinity of satralizumab and Panitumumab (Genetical Recombination) ("panitumumab"), natural type human IgG2 antibody, for human and cynomolgus monkey neonatal Fc receptor (FcRn) was investigated by SPR. K_D at pH 6.0 was 0.68 μmol/L (1.0) and 2.1 μmol/L (1.0), respectively, for human FcRn and 0.64 μmol/L (1.0) and 1.9 μmol/L (1.0), respectively, for cynomolgus monkey FcRn, showing that satralizumab has a higher binding affinity for FcRn than does panitumumab.

The binding affinity of satralizumab, tocilizumab, natural type human IgG1 antibody, and panitumumab, natural type human IgG2 antibody, for human FcγR (Ia, IIa, IIb, IIIa, IIIb) and cynomolgus monkey FcγR (Ia, IIa, IIb, IIIa) was investigated by SPR. The binding affinity of satralizumab for either human or cynomolgus monkey FcγR did not tend to be higher than that of tocilizumab or panitumumab.

3.1.1.4 ADCC and CDC activities (CTD 4.2.1.1-5)

Using human B lymphoma-derived U266 cell line expressing human IL-6R, ADCC and CDC activities of satralizumab were investigated. Satralizumab did not show ADCC activity (satralizumab concentration 0.0064-100 μg/mL) or CDC activity (satralizumab concentration 0.0064-10 μg/mL) against U266 cell line.

3.1.1.5 Inhibitory effect against IL-6-induced IgG1 production by human plasmablasts (CTD 4.2.1.1-8)

Using plasmablasts isolated from peripheral blood of healthy adults, the effect of satralizumab on IL-6-induced IgG1 production by plasmablasts was investigated by enzyme-linked immunosorbent assay (ELISA). Satralizumab (1 μg/mL) inhibited IL-6-induced IgG1 production by plasmablasts.

3.1.2 *In vivo* studies

3.1.2.1 Inhibition of IL-6 activity in cynomolgus monkeys (CTD 4.2.1.1-11)

A single dose of satralizumab (0.5 mg/kg) or tocilizumab (1.0 mg/kg) was administered subcutaneously to cynomolgus monkeys, followed by once-daily subcutaneous administration of cynomolgus monkey IL-6 (5 μg/kg) from Days 3 to 10, and the effect on IL-6-induced C-reactive protein (CRP) production was investigated. Satralizumab inhibited cynomolgus monkey IL-6-induced CRP production continuously for 11 days. Plasma tocilizumab concentration decreased below the lower limit of quantitation at Day 7, whereas plasma satralizumab concentration was maintained at 0.984 ± 0.091 μg/mL (mean ± standard error [SE]) even at Day 10.

A single dose of satralizumab (1.0 or 2.0 mg/kg) or tocilizumab (2.0 mg/kg) was administered subcutaneously to cynomolgus monkeys, followed by repeated subcutaneous administration of cynomolgus monkey IL-6 (5 μg/kg) every other day from Days 5 to 27, and the effect on IL-6-induced CRP production was investigated. Satralizumab (2.0 mg/kg) inhibited cynomolgus monkey IL-6-induced CRP production continuously for 28 days. Plasma tocilizumab concentration and plasma satralizumab concentration (following administration of 1.0 mg/kg) decreased below the lower limit of quantitation at Day 14 and at Day 26, respectively, whereas, following administration of 2.0 mg of

satralizumab, plasma satralizumab concentration was maintained at 1.14 ± 0.60 μg/mL (mean ± SE) even at Day 28.

3.2 Safety pharmacology

Safety pharmacology parameters were investigated in the 4- and 26-week repeated-dose toxicity studies in cynomolgus monkeys. Table 7 summarizes the results.

Table 7. Outline of the results of safety pharmacology studies

Organ system	Test system	Endpoints and methods	Dose	Route of administration	Findings	CTD
Central nervous system Cardiovascular system Respiratory system	Cynomolgus monkeys (4/sex/group)	Clinical signs, respiratory rate, electrocardiogram, blood pressure, and pathological examinations (necropsy, histology of organs and tissues related to central nervous, respiratory, and cardiovascular systems)	2, 10, and 50 mg/kg once weekly for 4 weeks	s.c.	No effect	4.2.3.2-2
	Cynomolgus monkeys (5/sex/group)		2, 10, and 50 mg/kg once weekly for 26 weeks	s.c.	No effect	4.2.3.2-3

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of satralizumab

PMDA asked the applicant to explain the pathogenesis of NMOSD and the mechanism of action of satralizumab against NMOSD.

The applicant's explanation:

- NMOSD is considered to develop mainly as a result of anti-AQP4 antibody-mediated injury of astrocytes in the central nervous system. Thus, anti-AQP4 antibody that has infiltrated in the central nervous system induces astrocyte dysfunction and local inflammation, leading eventually to demyelination and axonal injury, precipitating in the development of neurological symptoms characteristic of NMOSD (*Lancet Neurol.* 2007;6:805-15). The pathogenesis of NMOSD in anti-AQP4 antibody-negative patients remains to be elucidated, but involvement of anti-myelin oligodendrocyte glycoprotein (MOG) and anti-glucose-regulated protein (GRP)78 autoantibodies is suggested (*Neurology*. 2014;82:474-81, *Sci Transl Med.* 2017;9). Also, possible involvement of Th17 cells in the etiology of NMOSD is suggested by the report of increase in Th17 cell count in blood in patients with NMOSD (*J Clin Neurosci.* 2011;18:1313-7).

- IL-6 is an inflammatory cytokine with a variety of functions including inflammatory reaction, induction of differentiation and growth of various cells, regulation of immune response, and platelet production. IL-6 concentration in serum and cerebrospinal fluid (CSF) increases in patients with NMOSD when the disease relapses (*Int J Neurosci.* 2010;120:71-5, *Mult Scler.* 2010;16:1443-52). IL-6 is considered to be involved in the pathogenesis of NMOSD which consists of the following mechanisms: (1) Enhanced production of antibodies such as anti-AQP4 and other antibodies by B cells, (2) enhancement of maturation of B cells to autoantibody-producing cells, (3) differentiation of cluster of differentiation (CD)4-positive T cells into Th17 cells, and (4) increase in the permeability of the blood-brain barrier leading to enhanced infiltration of white blood cells (such as neutrophils) and autoantibodies into the central nervous system. (*Clin Exp Neuroimmunology.* 2013;4:167-72, *Neurol Neuroimmunol Neuroinflamm*. 2016;4:e311).

- Satralizumab is a humanized monoclonal antibody against human IL-6R. Satralizumab is considered to exhibit a therapeutic effect on NMOSD by inhibiting IL-6 signaling through inhibition of the binding of IL-6 to membrane-bound and soluble IL-6R.

PMDA asked the applicant to explain the difference between satralizumab and existing anti-IL-6R antibody preparations (e.g., tocilizumab) in the mechanism of action of inhibiting IL-6 signaling, also taking account of the characteristic property of satralizumab, i.e., pH-dependent binding to IL-6R, and to explain adverse events that may occur associated with satralizumab.

The applicant's explanation:

- Satralizumab binds to IL-6R in a pH-dependent manner, and is rapidly dissociated from IL-6R under acidic conditions [see Section 3.1.1.1]. This characteristic property of satralizumab is considered to contribute to suppression of degradation of antibody-antigen complex within endosomes and thereby to release of intact satralizumab for retention in plasma.

- In human blood and CSF with physiological pH, in contrast, the dissociation characteristics of satralizumab from IL-6R is similar to those for tocilizumab [see Section 3.1.1.1]. Also, the binding affinity of satralizumab for IL-6R and the inhibition of cell growth mediated by IL-6 signaling were similar to those observed with tocilizumab [see Section 3.1.1.2]. These results suggest that, under physiological pH conditions, the mechanism of action of satralizumab to inhibit IL-6 signaling is similar to that of tocilizumab.

- Based on the above, blood satralizumab is considered to be maintained over a long-time period thanks to its pH-dependent binding to IL-6R, but that the mechanism of action to inhibit IL-6 signaling under physiological pH condition does not differ between satralizumab and existing anti-IL-6R antibody preparations.

- IL-6 is involved in actions in the immune system (B cell survival and differentiation, antibody production, regulation of CD4 T cell differentiation, inhibition of differentiation to regulatory T cells, differentiation to Th17 cells, protection from infection), in liver (acute phase protein production, liver regeneration, antibody presentation to CD8 T cells by sinusoidal cells), in the hematopoietic system (neutrophil mobilization, thrombocytosis, iron metabolism regulation), and in the lipid system (lipid metabolism regulation) (*Int J Mol Sci.* 2018;19:3528, *Immunity.* 2019;50:1007-23).

- It is reported that existing anti-IL-6R antibody preparations cause the following adverse events associated with these actions of IL-6: Infection, intestinal perforation, hepatic dysfunction, neutropenia/leukopenia/agranulocytosis, thrombocytopenia, and dyslipidemia. Satralizumab also is expected to cause similar adverse events by inhibiting IL-6 signaling.

PMDA's view:

Explanation of the mechanism of action of satralizumab is provided based on the currently available information. Efficacy of satralizumab in patients negative for anti-AQP4 antibody is discussed in Section 7.R.1.1, and safety of satralizumab in Section 7.R.2.

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

The applicant submitted the data on absorption, distribution, and excretion of satralizumab in cynomolgus monkeys as non-clinical pharmacokinetic studies. Since satralizumab is a monoclonal antibody which is considered to be degraded into peptides and amino acids as are the cases with endogenous IgG, no data on metabolism were submitted. Plasma satralizumab concentration was determined by ELISA (lower limit of quantitation 0.05 μg/mL), and plasma anti-satralizumab antibody by electrochemiluminescence immunoassay and by ELISA (lower limit of quantitation 0.50 μg/mL). Unless specified otherwise, t_{max} was expressed in median and other pharmacokinetic parameters in mean or mean ± standard deviation (SD). In the following are described the results of main non-clinical pharmacokinetic studies.

4.1 Absorption

4.1.1 Single-dose study

A single dose of satralizumab (0.4, 2.0, 10, or 50 mg/kg) was administered intravenously or subcutaneously to male cynomolgus monkeys (n = 3/group). Table 8 shows pharmacokinetic parameters of satralizumab in plasma. C_{max} and AUC were nonlinear in the low-dose range. The bioavailability following the single subcutaneous administration was 62.3% to 78.2% (CTD 4.2.2.2-1 and CTD 4.2.2.2-2).

Anti-satralizumab antibody was positive in 4 of 12 animals receiving intravenous administration, and neutralizing activity was observed in all of the 4 animals. Anti-satralizumab antibody was positive in 5 of 12 animals receiving subcutaneous administration, and neutralizing activity was observed in 4 of them.

Table 8. Pharmacokinetic parameters of satralizumab in plasma following a single intravenous or subcutaneous administration to male cynomolgus monkeys

Route of administration	Dose (mg/kg)	C_{max} (μg/mL)	t_{max} (day)[a)]	$t_{1/2}$ (day)	$AUC_{0\text{-}7d}$ (μg•day/mL)	AUC_{inf} (μg•day/mL)	CTD
i.v.	0.4	10.3 ± 0.3[b)]		1.9 ± 0.7	28.1 ± 3.9	33.1 ± 5.4	4.2.2.2-1
	2.0	51.5 ± 4.9[b)]		6.4 ± 6.5	163 ± 15	-	
	10	258 ± 36[b)]		25.8 ± 18.7	1040 ± 40	4460 ± 1420	
	50	1320 ± 150[b)]		22.6 ± 2.2	5290 ± 1210	24400 ± 9600	
s.c.	0.4	3.33 ± 0.35	4.0 [2.0, 4.0]	2.2 ± 0.8	18.3 ± 2.2	25.9 ± 5.6	4.2.2.2-2
	2.0	23.2 ± 2.6	4.0 [2.0, 4.0]	4.0[c)]	131 ± 10	406[c)]	
	10	108 ± 7	4.0 [2.0, 4.0]	22.7 ± 11.3	575 ± 46	2780[c)]	
	50	616 ± 152	4.0 [4.0, 4.0]	18.4 ± 7.2	3190 ± 600	17400 ± 4500	

Mean ± SD; Number of animals evaluated, 3/group; -, Not calculated

a) Median [min, max]

b) Plasma concentration at 0 hour after intravenous administration, calculated by extrapolation

c) Calculated from the data of 2 anti-satralizumab antibody-negative animals, excluding an anti-satralizumab antibody-positive animal, because of extremely low plasma satralizumab concentration observed in an animal with anti-satralizumab antibody with neutralizing activity.

4.1.2 Repeated-dose study

Toxicokinetics was investigated in a 26-week repeated subcutaneous toxicity study in male and female cynomolgus monkeys (n = 5/sex/group). Table 9 shows pharmacokinetic parameters of satralizumab in plasma. The exposure to satralizumab increased with the increase in the frequency of administration, with the ratio of AUC at the last to the first dose being 2.7 to 11.6. Anti-satralizumab antibody turned positive in 9 of 30 animals, and neutralizing antibody was detected in 4 animals in the 2 mg/kg group. In 2 of 4 animals positive for neutralizing antibody, C_{max} following the last dose (Week 26) could be determined to be 0.139 and 24.7 μg/mL, respectively, showing that plasma satralizumab concentration in the anti-satralizumab antibody-positive animals was lower than that in the negative animals (CTD 4.2.3.2-3).

Table 9. Pharmacokinetic parameters of satralizumab in plasma following 26-week repeated subcutaneous administration of satralizumab in male and female cynomolgus monkeys

Measuring time point	Dose (mg/kg/week)	Sex	No. of animals evaluated[a)]	C_{max} (μg/mL)	t_{max} (h)[b)]	$AUC_{0\text{-}7d}$ (μg•day/mL)	CTD
Day 1	2	M	4	11.2 ± 1.9	132 [96, 168]	58.3 ± 11.3	4.2.3.2-3
		F	2	17.0	96 [96, 96]	89.6	
	10	M	5	114 ± 28	96 [48, 168]	608 ± 125	
		F	5	187 ± 88	96 [48, 168]	942 ± 458	
	50	M	5	367 ± 70	96 [8, 168]	2150 ± 460	
		F	5	1130 ± 280	96 [48, 168]	5040 ± 1580	
Week 4	2	M	4	87.2 ± 37.9	72 [48, 96]	488 ± 183	
		F	2	51.9	72 [48, 96]	317	
	10	M	5	378 ± 27	24 [8, 168]	2060 ± 300	
		F	5	231 ± 64	8 [0, 168]	1280 ± 470	
	50	M	5	1650 ± 190	48 [48, 96]	10400 ± 1000	
		F	5	1360 ± 200	48 [0, 96]	7880 ± 1210	
Week 13	2	M	4	128 ± 36	16 [0, 24]	733 ± 204	
		F	2	82.5	72 [48, 96]	513	
	10	M	5	525 ± 83	96 [24, 96]	3310 ± 460	
		F	5	399 ± 127	96 [24, 96]	2530 ± 830	
	50	M	5	2460 ± 680	48 [24, 168]	15800 ± 4100	
		F	5	2110 ± 360	24 [8, 48]	13400 ± 2100	
Week 26	2	M	4	107 ± 37	8 [8, 96]	679 ± 242	
		F	2	95.2	8 [8, 8]	513	
	10	M	5	541 ± 104	48 [24, 168]	3020 ± 640	
		F	5	530 ± 142	24 [8, 48]	2580 ± 640	
	50	M	5	3810 ± 950	48 [8, 168]	23000 ± 6700	
		F	5	3300 ± 340	24 [0, 48]	20000 ± 1600	

Mean ± SD
a) Excluding animals positive for neutralizing anti-satralizumab antibody
b) Median [min, max]

4.2 Distribution

4.2.1 Placental transfer

In an expanded pre- and postnatal development study in pregnant cynomolgus monkeys (n = 16-17/group), satralizumab (2 or 50 mg/kg) was administered subcutaneously once weekly from Gestation Day 20 until delivery. Table 10 shows plasma satralizumab concentration in maternal animals and offspring on Postnatal Day 14, which suggested that satralizumab, after administration to maternal animals, crossed the blood-placental barrier and was distributed in fetuses (CTD 4.2.3.5-1). Taking account of the observation suggesting the crossing of satralizumab through the blood-placental barrier in cynomolgus monkeys, the applicant explained that it would be cautioned that satralizumab should be used in pregnant women only if the expected therapeutic benefits outweigh the possible risks associated with treatment, as is the case with other anti-IL-6 antibody preparations.

Table 10. Plasma satralizumab concentration on Postnatal Day 14 in pregnant cynomolgus monkeys receiving repeated administration of satralizumab

Dose (mg/kg/week)	Maternal animals		Offspring	
	No. of animals evaluated	Plasma satralizumab concentration (μg/mL)	No. of animals evaluated	Plasma satralizumab concentration (μg/mL)
2[a)]	9	44.4 ± 13.8	14	46.2 ± 14.6
50[b)]	11	1300 ± 480	13	1860 ± 460

Mean ± SD
a) n = 17, b) n = 16

4.3 Excretion

4.3.1 Excretion in milk

In the expanded pre- and postnatal development study in pregnant cynomolgus monkeys (n = 16-17/group), satralizumab (2 or 50 mg/kg) was administered subcutaneously once weekly from Gestation Day 20 until delivery, and excretion of satralizumab in milk was investigated. Table 11 shows satralizumab concentration in milk of maternal animals on Postpartum Day 14. Excretion of satralizumab in milk was observed (CTD 4.2.3.5-1). Taking account of the observation of satralizumab excretion in milk of cynomolgus monkeys, the applicant explained that it would be cautioned during lactation that whether to continue breastfeeding should be considered by taking into account the benefit of the expected therapeutic treatment and the usefulness of breast feeding, as is the case with other anti-IL6R antibody preparations.

Table 11. Satralizumab concentration in milk of maternal animals on Postpartum Day 14 in repeated satralizumab administration to pregnant cynomolgus monkeys

Dose (mg/kg/week)	No. of animals evaluated	Satralizumab concentration in milk (μg/mL)
2[a)]	8	0.0320 ± 0.0712
50[b)]	11	1.03 ± 0.48

Mean ± SD
a) n = 17, b) n = 16

4.R Outline of the review conducted by PMDA

On the basis of the results of the non-clinical pharmacokinetic studies submitted, PMDA concluded that there were no particular problems.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the data of repeated-dose toxicity studies, reproductive and developmental toxicity studies, and other studies as toxicology studies of satralizumab.

5.1 Single-dose toxicity

Acute toxicity of satralizumab was evaluated in 4- and 26-week repeated-dose toxicity studies in cynomolgus monkeys (Table 12). The approximate lethal dose of satralizumab in monkeys was determined to be >200 mg/kg in intravenous administration and >50 mg/kg in subcutaneous administration.

Table 12. Outline of the results of single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	CTD
Male and female cynomolgus monkeys	i.v.	0,[a] 8, 40, 200	Acute toxicity was evaluated in the 4-week repeated intravenous toxicity study. No noteworthy findings	>200	Reference 4.2.3.2.-1
Male and female cynomolgus monkeys	s.c.	0,[b] 2, 10, 50	Acute toxicity was evaluated in the 4- and 26-week repeated subcutaneous toxicity study. No noteworthy findings	>50	4.2.3.2.-2 4.2.3.2.-3

a) Vehicle: 50 mmol/L Arginine-glutamate buffer (containing 20 mmol/L histidine)
b) Vehicle: 150 mmol/L Arginine-aspartate buffer (containing 20 mmol/L histidine and 0.5 mg/mL poloxamer 188)

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies (4 and 26 weeks) were conducted using cynomolgus monkeys (Table 13). Satralizumab caused increase in IL-6 concentration in blood supposedly due to IL-6R inhibition, the pharmacological action of satralizumab, but no noteworthy toxic findings were observed. The exposure to satralizumab ($AUC_{0\text{-}7d}$, 20,000-23,000 μg•day/mL) at the no observed adverse effect level (NOAEL) (50 mg/kg) in the 26-week repeated subcutaneous toxicity study was approximately 30 times the exposure ($AUC_{0\text{-}28d}$, 705 μg•day/mL[4)]) in humans treated with satralizumab at the clinical dose (120 mg at Weeks 0, 2, 4, and every 4 weeks thereafter).

Table 13. Outline of repeated-dose toxicity studies

Test system	Route of administration	Administration period	Dose (mg/kg/week)	Main findings	NOAEL (mg/kg/week)	CTD
Male and female cynomolgus monkeys	i.v.	4 weeks (once weekly)	0,[a] 8, 40, 200	≥8: Anti-satralizumab antibody positive (only in males)[b]	200	Reference 4.2.3.2-1
Male and female cynomolgus monkeys	s.c.	4 weeks (once weekly)	0,[c] 2, 10, 50	≥2: Blood IL-6 concentration increased, anti-satralizumab antibody positive[b]	50	4.2.3.2-2
Male and female cynomolgus monkeys [d]	s.c.	26 weeks (once weekly) + 13-week withdrawal	0,[c] 2, 10, 50	≥2: Blood IL-6 concentration increased, anti-satralizumab antibody positive,[b] atrophy of bilateral testicular seminiferous tubules Reversible	50	4.2.3.2-3

a) Vehicle: 50 mmol/L Arginine-glutamate buffer (containing 20 mmol/L histidine)
b) With neutralizing activity. Satralizumab concentration decreased in antibody-positive animals.
c) Vehicle: 150 mmol/L Arginine-aspartate buffer (containing 20 mmol/L histidine and 0.5 mg/mL poloxamer 188)
d) Includes evaluation of fertility based on estrous cycle, sperm analysis, testis size measurement, and histopathological examination of male and female reproductive organs.

5.3 Genotoxicity

Since satralizumab is an antibody drug, no genotoxicity study was conducted according to "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (PFSB/ELD Notification No. 0323-1 dated March 23, 2012).

4) The median of values at steady state (at Week 52) in the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) and the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG), estimated by population pharmacokinetic analysis (CTD 5.3.3.5-2).

5.4 Carcinogenicity

Satralizumab does not cross-react with IL-6R of mice or rats. Although alloantibody for mice (rat anti-mouse IL-6R antibody) was prepared, it induced production of anti-drug antibodies by its immunogenicity, which in turn reduced blood drug concentration to an extremely low level, precluding the interpretation of the effect of the antibody. For these reasons, no standard carcinogenicity study in rodents was conducted. Since IL-6 pathway may possibly be involved in antitumor reaction by regulating the immune cell surveillance within tumor environment, as is the case with other immunoregulatory pathways such as those of tumor necrosis factor (TNF)-α, the possible risk of malignant tumor development by inhibition of IL-6R-mediated IL-6 signaling cannot be completely excluded. However, no events related to tumorigenic transformation, including hypertrophy and hyperplasia, were observed or reported for satralizumab or tocilizumab, the drug in the same class, in a repeat-dose toxicity study of up to 26 weeks in cynomolgus monkeys, the animal species in which these antibodies cross-react with their IL-6R. Based on these findings, the applicant explained that satralizumab is unlikely to be tumorigenic.

5.5 Reproductive and developmental toxicity

An expanded pre- and postnatal development study was conducted in pregnant cynomolgus monkeys (Table 14). No teratogenicity was observed. The exposure ($AUC_{0\text{-}7d}$, 18,000 μg•day/mL) at the NOAEL for the offspring (50 mg/kg) was 26 times the exposure ($AUC_{0\text{-}28d}$, 705 μg•day/mL[4)]) in humans treated with satralizumab at the clinical dose (120 mg at Weeks 0, 2, and 4, and every 4 weeks thereafter).

Table 14. Outline of reproductive and developmental toxicity study

Study	Test system	Route of administration	Administration period	Dose (mg/kg/week)	Main findings	NOAEL (mg/kg/week)	CTD
Expanded pre- and postnatal development study	Female cynomolgus monkeys	s.c.	Gestation day 20 to delivery (once weekly)	0,[a)] 2, 50	Parental animals ≥2: Blood IL-6 increased, anti-satralizumab antibody positive[b)] Offspring [c)]: ≥2: Blood IL-6 increased, TDAR suppressed, anti-satralizumab antibody positive[b)]	Parental animals (general toxicity): 50 Offspring: 50	4.2.3.5-1

a) Vehicle: 150 mmol/L Arginine-aspartate buffer (containing 20 mmol/L histidine and 0.5 mg/mL poloxamer 188)
b) With neutralizing activity. Satralizumab concentration decreased in antibody-positive animals.
c) Satralizumab was detected in plasma of the offspring up to 63 days after birth in the 2 mg/kg group, and up to 203 days after birth in the 50 mg/kg group.

5.6 Local tolerance

Local tolerance of satralizumab was evaluated in the 4- and 26-week repeated subcutaneous toxicity studies in cynomolgus monkeys. No skin irritation was observed at the site of administration.

5.7 Other toxicity studies

5.7.1 Cross-reactivity

In a tissue cross-reactivity study using the tissues of humans and cynomolgus monkeys (Table 15), satralizumab showed characteristic reactions at the sites reported to express IL-6R (*Regul Toxicol Pharmacol.* 2009;53:46-51), showing similar staining patterns in humans and cynomolgus monkeys.

Table 15. Summary of cross-reactivity study

Study		Main findings	CTD
In vitro	*In vitro* tissue cross reactivity was evaluated using frozen tissue sections of humans and cynomolgus monkeys.	Specific reaction was observed in the following human tissues: Mononuclear cells in lymphatic tissues (lymph nodes/spleen/thymus/tonsil/esophagus mesentery lymph tissues, peripheral blood), bone-marrow hematopoietic cells, adherent or migratory mononuclear cells in salivary gland/stomach/bladder, glomerular cells in kidney, Hofbauer cells in placenta, spermatogenic cells in testis, hepatic sinusoidal cells, epithelial cells in breast/fallopian tube/uterus/rete testis/small intestine/pancreas/pituitary gland/salivary gland/skin/urinary duct/bladder/urethra, etc. A similar staining pattern was observed in tissues of cynomolgus monkeys as well.	4.2.3.7.7-1

5.7.2 Human blood compatibility

Neither hemolysis nor agglutination reaction was observed in a hemocompatibility study using human blood (Table 16).

Table 16. Summary of hemocompatibility study using human blood

Study		Results	CTD
In vitro	Evaluation of hemolysis and agglutination reaction in human blood or plasma (5 healthy adults)	Satralizumab (1.182 mg/mL) did not cause hemolysis nor agglutination.	4.2.3.7.7-2

5.7.3 Evaluation of risk for cytokine release syndrome

The risk of cytokine release was evaluated using human blood (Table 17). Satralizumab induced the release of IL-6 and IL-8. Comparison of the frequency of increase in IL-6, IL-8, and TNF showed that satralizumab's risk of causing cytokine release syndrome was lower than that of Alemtuzumab (Genetical Recombination) ("alemtuzumab") and TGN1412,[5)] drugs known to cause cytokine release syndromes clinically, and comparable to that of tocilizumab. In clinical studies, alemtuzumab frequently caused infusion reactions with the main symptoms such as pyrexia, chills, nausea, hypotension, urticaria, dyspnoea, rash, diarrhoea, bronchospasm, etc. (Review Report of MabCampath 30 mg I.V. Infusion, dated August 20 2014). In contrast, no cytokine release syndrome has been reported either with satralizumab or with tocilizumab, based on which the applicant explained that the risk of cytokine release syndrome is low at the clinical dose of satralizumab.

Table 17. Outline of the risk for cytokine release

Study		Results	CTD
In vitro	IL-6, IL-8, and TNF concentrations in blood (collected from 12 healthy adults) were measured at 24 hours after addition of satralizumab.	Satralizumab (1-100 μg/mL) increased IL-6 or IL-8 concentration in 4 of 12 subjects. Tocilizumab increased IL-6 or IL-8 concentration in 5 of 12 subjects, TGN1412 increased IL-6 or IL-8 concentration in 9 of 12 subjects, and alemtuzumab increased IL-6, IL-8, or TNF concentration in 12 of 12 subjects.	Reference 4.2.3.7.7-3

5.R Outline of the review conducted by PMDA

Based on the documents submitted, PMDA concluded that use of satralizumab does not pose any toxicological concern. However, since IL-6 signaling pathway is possibly related to the risk of malignant tumor [see Section 5.4], the carcinogenic risk of satralizumab is reviewed further in Section 7.R.2.11 below.

5) Antibody prepared by the applicant that has the identical sequence as that of TGN1412.

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 applicant did not submit "Data on biopharmaceutical studies." Serum satralizumab concentration was measured by [redacted] (lower limit of quantitation [redacted] ng/mL), binding antibody to satralizumab by [redacted] (relative sensitivity [redacted] ng/mL), and neutralizing antibody against satralizumab by [redacted] (relative sensitivity [redacted] ng/mL). Both vial preparation and prefilled syringe preparation were used in the clinical studies of satralizumab.

6.2 Clinical pharmacology

The applicant submitted results of the following clinical pharmacology studies: A Japanese phase I study in Japanese and non-Japanese healthy adults (CTD 5.3.3.1-1, Study SA-001JP), a Japanese phase I study in Japanese patients with rheumatoid arthritis (CTD 5.3.3.2-1, Study SA-105JP), a global phase III study in Japanese and non-Japanese patients with NMOSD (CTD 5.3.5.1-1, Study SA-307JG), a foreign phase III study in non-Japanese patients with NMOSD (CTD 5.3.5.1-2, Study SA-309JG), and a population pharmacokinetic analysis (CTD 5.3.3.5-1 and CTD 5.3.3.5-2). Unless specified otherwise, t_{max} was expressed in median, and other pharmacokinetic parameters in mean ± SD. In the following are described only the results of main pharmacokinetic studies.

6.2.1 Single-dose study

A single dose of placebo or satralizumab 30, 60, 120, or 240 mg was administered subcutaneously or a single dose of satralizumab 60 or 120 mg was administered intravenously to healthy Japanese and non-Japanese adults (70 subjects evaluable for PK analysis). Table 18 shows pharmacokinetic parameter values. After single subcutaneous administration, serum satralizumab concentration increased more than in proportion to dose (CTD 5.3.3.1-1, Study SA-001JP). The absolute bioavailability (mean [90% confidence interval (CI)]) after a single subcutaneous administration of satralizumab (60 or 120 mg) was 0.636 [0.425, 0.953] and 0.694 [0.564, 0.854], respectively.

Table 18. Pharmacokinetic data following single-dose subcutaneous or intravenous administration of satralizumab in healthy Japanese and non-Japanese adults

Dose (mg)	Route of administration	Japanese/ non-Japanese	N	C_{max} (μg/mL)	t_{max} (days)[a)]	$t_{1/2}$ (days)	AUC_{inf} (μg•days/mL)
30	s.c.	Japanese	6	1.94 ± 0.432	5.50 [3.33, 7.02]	3.81[b)]	20.2[b)]
60		Japanese	6	6.33 ± 2.80	4.00 [3.33, 7.02]	5.26 ± 1.69[c)]	105 ± 48.4[c)]
120		Japanese	12	15.3 ± 2.72	6.99 [3.33, 7.03]	4.56 ± 1.49	311 ± 74.4
		Non-Japanese	10	13.7 ± 2.67	4.00 [2.33, 7.05]	4.40 ± 1.24	255 ± 67.0
240		Japanese	12	33.7 ± 7.45	5.50 [3.00, 14.0]	6.58 ± 2.78	987 ± 244
		Non-Japanese	12	25.9 ± 5.40	7.02 [4.00, 14.0]	5.92 ± 2.80	731 ± 179
60	i.v.	Japanese	6	19.8 ± 1.71		6.25 ± 0.862	150 ± 19.1
120		Japanese	6	38.7 ± 5.97		4.80 ± 1.06	442 ± 73.7

Mean ± SD
a) Median [min, max]; b) n = 1; c) n = 4

6.2.2 Multiple-dose study

Satralizumab 120 mg was administered to Japanese patients with rheumatoid arthritis (11 PK-evaluable subjects per group) at Weeks 0, 2, and 4, followed by satralizumab 30, 60, or 120 mg every 4 weeks up to Week 16. Table 19 shows trough serum satralizumab concentration, which reached the steady state between Week 4 and Week 8 in the 120 mg group, and decreased almost to

zero in all patients at or before Week 32 (16 weeks after the end of treatment) (CTD 5.3.3.2-1, Study SA-105JP).

Table 19. Trough serum satralizumab concentration following multiple administration of satralizumab in Japanese patients with rheumatoid arthritis

Measuring time point (Week)	Dose from Week 8					
	30 mg		60 mg		120 mg	
	N	Serum satralizumab concentration (μg/mL)	N	Serum satralizumab concentration (μg/mL)	N	Serum satralizumab concentration (μg/mL)
1	11	6.98 ± 3.68	11	7.94 ± 2.02	11	10.9 ± 3.27
2	11	5.27± 3.88	11	7.54 ± 2.93	11	9.78 ± 2.71
4	10	12.3 ±7.27	10	16.1 ± 4.98	10	19.3 ± 4.13
8	10	10.1 ± 8.82	10	17.0 ± 8.10	9	19.7 ± 4.76
12	10	3.83 ± 5.29	9	10.4 ± 8.05	9	18.6 ± 4.90
16	9	1.55 ± 2.40	9	6.24 ± 5.88	9	18.3 ± 5.41
20	9	0.713 ± 1.22	9	4.64 ± 5.38	9	20.3 ± 6.13
24	9	0.100 ± 0.00	7	1.09 ± 2.04	9	8.37 ± 4.95
28	-	-	8	0.113 ± 0.0375	9	1.85 ± 2.22
32	-	-	-	-	9	0.244 ± 0.265

Mean ± SD; -, Not evaluated.

6.2.3 Studies in patients with NMOSD

Japanese and non-Japanese patients with NMOSD aged ≥12 years (83 subjects evaluable for PK analysis) received the basal treatment,[6)] followed by satralizumab 120 mg at Weeks 0, 2, and 4, and every 4 weeks thereafter, and trough serum satralizumab concentration was measured (CTD 5.3.5.1-1, Study SA-307JG). In a separate study, non-Japanese patients with NMOSD aged ≥18 years (95 subjects evaluable for PK analysis) received satralizumab 120 mg alone at Weeks 0, 2, and 4, and every 4 weeks thereafter, and trough serum satralizumab concentration was measured (CTD 5.3.5.1-2, Study SA-309JG). Table 20 shows the results.

Table 20. Trough serum satralizumab concentration following multiple administration of satralizumab to patients with NMOSD

Measuring time point (Week)	Study SA-307JG (CTD 5.3.5.1-1)		Study SA-309JG (CTD 5.3.5.1-2)	
	N	Serum satralizumab concentration (μg/mL)	N	Serum satralizumab concentration (μg/mL)
2	41	11.3 ± 5.13	61	8.10 ± 4.54
4	38	22.2 ± 8.00	56	14.6 ± 8.93
8	39	21.2 ± 9.05	60	14.9 ± 9.96
12	38	20.9 ± 9.54	55	14.8 ± 10.7
16	35	20.3 ± 10.7	53	14.6 ± 11.3
20	33	20.1 ± 10.7	55	14.1 ± 12.5
24	30	20.2 ± 10.1	55	15.6 ± 13.3
36	26	21.1 ± 11.2	50	16.1 ± 14.6
48	25	23.3 ± 14.0	44	16.7 ± 16.8
60	24	23.1 ± 15.8	43	16.1 ± 14.8
72	23	26.6 ± 15.0	42	12.9 ± 13.8
84	21	27.0 ± 15.5	40	11.7 ± 13.7
96	21	26.8 ± 15.1	31	14.0 ± 12.6
108	21	26.1 ± 12.5	22	16.0 ± 13.5
120	20	24.9 ± 13.2	14	16.6 ± 16.8
144	15	28.0 ± 11.5	11	16.1 ± 13.8
168	9	23.7 ± 11.6	10	14.2 ± 9.91
192	2	32.7 ± 7.85	2	28.8 ± 22.4
216	1	28.6	-	-

Mean ± SD; -, Not evaluated.

6) Azathioprine, mycophenolate mofetil, and/or oral corticosteroid

6.2.4 Population pharmacokinetics (CTD 5.3.3.5-1 and CTD 5.3.3.5-2)

Population pharmacokinetic analysis was conducted using serum satralizumab concentration data (4715 measuring points in 226 subjects) obtained from a single-dose study in healthy adults (CTD 5.3.3.1-1, Study SA-001JP), a global phase III study in patients with NMOSD (CTD 5.3.5.1-1, Study SA-307JG), and a foreign phase III study in patients with NMOSD (CTD 5.3.5.1-2, Study SA-309JG). The results showed that the pharmacokinetics of satralizumab in patients with NMOSD were described by a 2-comparment model with the first-order absorption process. In the final model, the following parameters were included as covariates: Effect of disease conditions for linear clearance (CL); effect of body weight for CL, inter-compartmental clearance (Q), central volume of distribution (Vc), and peripheral volume of distribution (Vp); effect of drug formulation for CL, effect of anti-satralizumab antibody expression for CL and for bioavailability.

6.R Outline of the review conducted by PMDA

6.R.1 Effect of ethnicity on pharmacokinetics

PMDA asked the applicant to explain the effect of ethnicity on the pharmacokinetics of satralizumab.

The applicant's explanation about the pharmacokinetics of satralizumab in Japanese and non-Japanese subjects:

- In the Japanese phase I study (CTD 5.3.3.1-1, Study SA-001JP) administering satralizumab (120 or 240 mg) subcutaneously as a single dose, serum satralizumab concentration tended to be slightly higher in Japanese than in non-Japanese subjects [see Section 6.2.1]. Investigation of covariates in the population pharmacokinetic analysis suggested that body weight, type of drug formulation, and anti-satralizumab antibody expression affected the pharmacokinetics of satralizumab, and difference was observed in body weight (60.22 ± 9.190 kg in Japanese in the 120 mg group, 61.48 ± 5.784 kg in Japanese in the 240 mg group; 70.95 ± 7.872 kg in non-Japanese in the 120 mg group, 74.49 ± 6.582 kg in non-Japanese in the 240 mg group) and percentage of subjects positive for anti-satralizumab antibody (66.7% [8 of 12] of Japanese subjects in the 120 mg group, 16.7% [2 of 12] of Japanese subjects] in the 240 mg group; 66.7% [8 of 12] of non-Japanese subjects in the 120 mg group, 66.7% [8 of 12] of non-Japanese subjects in the 240 mg group) between Japanese and non-Japanese subjects. These differences (body weight was lighter by approximately 10 kg, and the percentage of anti-satralizumab antibody lower, in Japanese subjects) were considered to have contributed to the observed differences in the exposure between Japanese and non-Japanese subjects. In single subcutaneous administration in Study SA-001JP, the mean ratio of AUC_{inf} in Japanese subjects to that in non-Japanese subjects, adjusted by dose per body weight, was 0.973 [0.853, 1.11] at 120 mg and 0.895 [0.779, 1.03] at 240 mg, suggesting that ethnic factors other than body weight are unlikely to affect the pharmacokinetics of satralizumab.

- In the global phase III study (CTD 5.3.5.1-1, Study SA-307JG), the incidences of adverse events were similar between the Japanese population and the non-Japanese population, showing no tendency of incidence of adverse events unique to the Japanese patient population [see Section 7.R.1.2.2].

- Thus, although the exposure to satralizumab tends to be higher in Japanese subjects than in non-Japanese subjects, ethnic factors are unlikely to have a significant impact clinically.

PMDA accepted the explanation of the applicant.

6.R.2 Effect of age on pharmacokinetics

PMDA asked the applicant to explain the effect of age on the pharmacokinetics of satralizumab.

The applicant's explanation:

- In the global phase III study (CTD 5.3.5.1-1, Study SA-307JG), serum satralizumab concentration 8 weeks after the first dose was 16.7 ± 7.30 μg/mL in children (≥12 to <18 years old) and 21.8 ± 9.17 μg/mL in adults (≥18 to ≤74 years old).

- Although serum satralizumab concentration 8 weeks after the first dose tended to be lower in children than in adults, the concentration range in children overlapped with that in adults, showing no significant difference in serum satralizumab concentration between the two age groups.

- In the population pharmacokinetic analysis [see Section 6.2.4], age was not identified as a covariate for the pharmacokinetics of satralizumab. Median [fifth percentile, 95th percentile] of C_{max} and trough serum satralizumab concentration at steady state (Week 52) in Studies SA-307JG and SA-309JG, predicted from the population pharmacokinetic analysis, were 23.4 [9.49, 62.5] μg/mL and 13.7 [3.29, 44.5] μg/mL, respectively, in subjects aged <18 years and 29.5 [10.4, 56.9] μg/mL and 18.8 [2.88, 40.2] μg/mL, respectively, in subjects aged ≥18 years, showing no tendency of difference between children and adults.

- These results suggest that age is unlikely to affect the pharmacokinetics of satralizumab.

PMDA accepted the explanation of the applicant.

6.R.3 Anti-satralizumab antibody

PMDA asked the applicant to explain the incidence of anti-satralizumab antibody after administration of satralizumab and the effect of anti-satralizumab antibody on the pharmacokinetics, efficacy, and safety of satralizumab.

The applicant's explanation:

The incidence of anti-satralizumab antibody after administration of satralizumab was 54.2% (39 of 72) of subjects in the Japanese phase I study in healthy adults (CTD 5.3.3.1-1, Study SA-001JP) and 6.1% (2 of 33) of subjects in the Japanese phase I study in patients with rheumatoid arthritis (CTD 5.3.3.2-1, Study SA-105JP). In the global phase III study in patients with NMOSD (CTD 5.3.5.1-1, Study SA-307JG), the incidence was 41.5% (17 of 41) of subjects in the double-blind period and 52.3% (34 of 65 subjects) in the entire treatment period. In the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG), the incidence was 71.4% (45 of 63) of subjects in the double-blind period and 72.5% (58 of 80) of subjects in the entire treatment period. Neutralizing antibody was not measured in Study

SA-001JP, detected in 2 subjects in Study SA-105JP, in 3 subjects in the double-blind period and 11 subjects in the entire treatment period of Study SA-307JG, and in 17 subjects in the double-blind period and 29 subjects in the entire treatment period of Study SA-309JG.[7)]

The applicant's explanation about the effect of anti-satralizumab antibody on the pharmacokinetics, efficacy, and safety of satralizumab, based on the above:

- The effect of anti-satralizumab antibody on the pharmacokinetics of satralizumab was investigated based on the population pharmacodynamic analysis [see Section 6.2.4]. Table 21 shows the pharmacokinetic parameter values in anti-satralizumab antibody-positive and negative patients, estimated by the population pharmacokinetic analysis. The exposure in anti-satralizumab antibody-positive patients tended to be lower than in negative patients, as revealed by the analysis of the effect of anti-satralizumab antibody on bioavailability and on CL. On the other hand, there was a positive correlation between body weight and antibody-positive rate, with the median [fifth percentile, 95th percentile] body weight of 76.6 [49.8, 132] kg in anti-satralizumab antibody-positive patients and 60.0 [47.9, 90.3] kg in negative patients, suggesting the possibility that, in addition to anti-satralizumab antibody, body weight also affected the decrease in serum satralizumab concentration. Thus, both anti-satralizumab antibody and body weight contributed to the lower exposure in anti-satralizumab antibody-positive patients than in negative patients.

Table 21. Pharmacokinetic parameters after administration of satralizumab (120 mg) in anti-satralizumab antibody-positive and negative patients, estimated from the population pharmacokinetic analysis

Anti-satralizumab antibody		C_{max} (μg/mL)	C_{min} (μg/mL)	AUC (μg/mL•day)
Negative		42.9 [21, 61.7]	28.7 [11.2, 45.2]	1010 [468, 1600]
Positive	Analysis 1[a)]	30.1 [9.65, 57.2]	17.2 [1.88, 43.5]	671 [172, 1460]
	Analysis 2[b)]	22.7 [6.99, 45.9]	11.9 [0.485, 34.2]	517 [109, 1160]
	Analysis 3[c)]	17.4 [5.98, 39.2]	6.75 [0.17, 29.7]	304 [82.5, 988]

Median [95% CI]

a) Analysis conducted without taking account of the effect of anti-satralizumab antibody
b) Analysis conducted by taking account of the effect of anti-satralizumab antibody on bioavailability
c) Analysis conducted by taking account of the effect of anti-satralizumab antibody on bioavailability and CL

- As for efficacy, Table 22 shows the incidence of the initial protocol-defined relapse (PDR) during the double-blind period in anti-satralizumab antibody-positive and negative patients in Studies SA-307JG and SA-309JG, suggesting efficacy both in anti-satralizumab antibody-positive and negative patients with no significant difference in the efficacy between the two patient groups. In neutralizing antibody-positive patients, the incidence of the initial PDR during the double-blind period was 33.3% (1 of 3) of subjects in Study SA-307JG and 17.6% (3 of 17) of subjects in Study SA-309JG, which was not different in tendency from the incidence in anti-satralizumab antibody-positive or negative patients.

7) Neutralizing antibody test was considered to give a false-positive or false-negative result if serum satralizumab concentration exceeded 1 μg/mL. Therefore, neutralizing antibody was evaluated only when anti-satralizumab was positive after the initial dose of satralizumab and serum satralizumab concentration was ≤1 μg/mL.

Table 22. Incidence of the initial PDR in anti-satralizumab antibody-positive and negative patients (double-blind period)

	Study SA-307JG			Study SA-309JG		
	Placebo	Satralizumab		Placebo	Satralizumab	
		Anti-satralizumab antibody positive	Anti-satralizumab antibody negative		Anti-satralizumab antibody positive	Anti-satralizumab antibody negative
No. of patients evaluated	42	17	24	32	45	18
No. of patients with PDR (%)	18 (42.9)	5 (29.4)	3 (12.5)	16 (50.0)	14 (31.1)	5 (27.8)
Hazard ratio[a)] [95% CI]		0.68 [0.25, 1.83]	0.20 [0.06, 0.68]		0.43 [0.20, 0.91]	0.50 [0.18, 1.40]

a) Based on Cox-proportional hazard model stratified by allocation factor

- As for safety, Table 23 shows the incidence of adverse events in anti-satralizumab antibody-positive and negative patients during the entire treatment period of Studies SA-307JG and SA-309JG. In Study SA-307JG, the incidence of adverse events leading to treatment discontinuation tended to be higher in anti-satralizumab antibody-positive patients than in negative patients, whereas there were no infusion-related adverse events leading to treatment discontinuation. The incidence of serious adverse events was higher in anti-satralizumab antibody-positive patients than in negative patients, whereas there were no events related to immunogenicity.[8)] Among neutralizing antibody-positive patients, infusion-related reaction was observed in 18.2% (2 of 11) of patients in Study SA-307JG and in 10.3% (3 of 29) of patients in Study SA-309JG, but the incidence in neutralizing antibody-positive patients did not tend to be higher than that in anti-satralizumab antibody-positive patients or in negative patients.

Table 23. Incidence of adverse events in anti-satralizumab antibody-positive and negative patients (entire treatment period)

	Study SA-307JG		Study SA-309JG	
	Anti- satralizumab antibody positive	Anti- satralizumab antibody negative	Anti- satralizumab antibody positive	Anti- satralizumab antibody negative
No. of patients evaluated	34	31	58	22
All adverse events	31 (91.2)	30 (96.8)	55 (94.8)	21 (95.5)
Events resulting in death	0	0	0	0
Serious adverse events other than death	9 (26.5)	5 (16.1)	10 (17.2)	3 (13.6)
Adverse events leading to treatment discontinuation	5 (14.7)	1 (3.2)	0	1 (4.5)
Infusion related reaction[a)]	5 (14.7)	4 (12.9)	7 (12.1)	4 (18.2)

n (%)

a) Adverse events observed within 24 hours after administration of study drug (excluding events that were considered non-allergic reactions)

Based on the above, the applicant explained that although anti-satralizumab antibody may possibly decrease serum satralizumab concentration, there is no clear effect of anti-satralizumab antibody, and that the efficacy of satralizumab is expected in anti-satralizumab antibody-positive patients as well, with no significant safety problem.

PMDA's view:

- The exposure tended to be lower in anti-satralizumab antibody-positive patients than in negative patients, suggesting that anti-satralizumab antibody may affect pharmacokinetics of satralizumab. Also, in Study SA-307JG, the incidence of initial PDR tended to be higher in anti-satralizumab

8) Anaphylaxis, haemolytic anaemia, serum sickness, and glomerulonephritis

antibody-positive patients than in negative patients and, in Studies SA-307JG and SA-309JG, the incidence of serious adverse events tended to be higher in anti-satralizumab antibody-positive patients than in negative patients.

- Only a limited number of patients were investigated in clinical studies.

- Given the above situations, the effect of immunogenicity should be further investigated after the market launch.

6.R.4 Dosage regimen from the point of view of clinical pharmacology

PMDA asked the applicant to explain the appropriateness of the dosage regimen from the point of view of clinical pharmacology, based on the rationale for dosage regimen used in the phase III study.

The applicant's explanation about the rationale for the dosage regimen in the phase III study from the point of view of clinical pharmacology:

- From the changes in serum IL-6 concentration and soluble interleukin 6 receptor (sIL-6R) concentration in the phase I study (Study CTD 5.3.3.1-1, SA-001JP), a dose of ≥120 mg was considered necessary to inhibit IL-6 signaling continuously for 28 days. Table 24 shows satralizumab, sIL-6R, CRP, and IL-6 concentrations in serum over time in the phase I study in patients with rheumatoid arthritis (CTD 5.3.3.2-1, Study SA-105JP). At all doses tested, sIL-6R and IL-6 increased, and CRP decreased, with the increase in serum satralizumab concentration, and sIL-6R and IL-6 decreased, and CRP tended to return to baseline, with the decrease in serum satralizumab concentration. Table 25 shows the percentage of patients[9)] in whom CRP normalized in Study SA-105JP. Results showed that the decreased serum CRP concentration, caused by inhibition of IL-6 signaling, was maintained in the group receiving satralizumab 120 mg once every 4 weeks.

9) Percentage of subjects in whom serum CRP concentration decreased to ≤0.3 mg/dL

Table 24. Changes in trough satralizumab concentration, serum IL-6 concentration, serum sIL-6R concentration, and serum CRP concentration following multiple administration of satralizumab in Japanese patients with rheumatoid arthritis

Dose from Week 8	Measuring time point (Week)	No. of patients evaluated	Trough satralizumab concentration (μg/mL)	Serum IL-6 concentration (pg/mL)	Serum sIL-6R concentration (ng/mL)	Serum CRP concentration (mg/dL)
30 mg	Baseline	11	-	57.9 ± 55.5	36.7 ± 11.1	1.78 ± 1.54
	2	11	5.27 ± 3.88	208 ± 175	455 ± 126	0.192 ± 0.241
	4	10	12.3 ± 7.27	158 ± 133	560 ± 152	0.0827 ± 0.136
	8	10	10.1 ± 8.82	88.5 ± 111	584 ± 251	0.382 ± 1.09
	12	10	3.83 ± 5.29	54.6 ± 63.3	365 ± 296	1.09 ± 1.43
	16	9	1.55 ± 2.40	26.4 ± 22.3	293 ± 326	1.40 ± 1.95
	20	9	0.713 ± 1.22	46.6 ± 52.1	216 ± 295	2.02 ± 2.54
	24	9	0.100 ± 0.00	33.5 ± 50.6	97.7 ± 131	2.32 ± 2.67
60 mg	Baseline	11	-	49.6 ± 41.3	40.6 ± 11.9	2.23 ± 2.39
	2	11	7.54 ± 2.93	241 ± 277	491 ± 69.2	0.662 ± 1.78
	4	10	16.1 ± 4.98	211 ± 312	636 ± 60.1	0.0698 ± 0.154
	8	10	17.0 ± 8.10	107 ± 122	685 ± 103	0.0520 ± 0.108
	12	9	10.4 ± 8.05	91.9 ± 167	626 ± 131	0.0281 ± 0.0360
	16	9	6.24 ± 5.88	87.5 ± 147	560 ± 236	0.115 ± 0.159
	20	9	4.64 ± 5.38	74.4 ± 123	466 ± 256	0.250 ± 0.454
	24	7	1.09 ± 2.04	-	369 ± 258	0.848 ± 1.55
	28	8	0.113 ± 0.0375	34.4 ± 75.1	72.9 ± 49.5	1.80 ± 2.98
120 mg	Baseline	11	-	32.2 ± 26.4	45.8 ± 16.8	0.942 ± 0.569
	2	11	9.78 ± 2.71	134 ± 112	537 ± 89.2	0.0284 ± 0.0459
	4	10	19.3 ± 4.13	112 ± 130	658 ± 72.0	0.0109 ± 0.0112
	8	9	19.7 ± 4.76	74.0 ± 83.5	783 ± 124	0.00742 ± 0.00663
	12	9	18.6 ± 4.90	58.5 ± 46.7	760 ± 126	0.0106 ± 0.0101
	16	9	18.3 ± 5.41	41.4 ± 40.3	802 ± 145	0.00837 ± 0.00876
	20	9	20.3 ± 6.13	53.8 ± 67.1	797 ± 129	0.00857 ± 0.00960
	24	9	8.37 ± 4.95	-	726 ± 178	0.0253 ± 0.0351
	28	9	1.85 ± 2.22	-	527 ± 207	0.197 ± 0.359
	32	9	0.244 ± 0.265	29.1 ± 47.6	227 ± 207	0.505 ± 0.593

Mean ± SD; -, Not evaluated.

Table 25. Percentage of patients with rheumatoid arthritis showing normalized CRP level

Measuring time point	30 mg	60 mg	120 mg
Week 8	10/11 (90.9)	9/11 (81.8)	10/10 (100)
Week 20	3/9 (33.3)	8/10 (80.0)	10/10 (100)

No. of patients with normalized CRP level/No. of patients evaluated (%)

- Based on the above, satralizumab 120 mg was to be administered at Weeks 0, 2, 4, and every 4 weeks thereafter in the phase III study.

PMDA's view:

- There are no major problems in the explanation of the applicant. However, since increases in sIL-6R and IL-6, and decrease in CRP, were observed up to 16 weeks after the end of administration of satralizumab in Study SA-105JP, it should be included in the package insert that inhibition of IL-6 signaling continues even after the end of administration of satralizumab.

- The above conclusion will be finalized, taking account of comments raised in the Expert Discussion. The appropriateness of the dosage regimen of satralizumab is further discussed in Section 7.R.5.1.

6.R.5 Pharmacokinetic drug interactions

PMDA asked the applicant to explain the pharmacokinetic drug interactions of satralizumab.

The applicant's explanation about the possible effect of satralizumab on the pharmacokinetics of concomitant drugs:

- The cytokine IL-6 is known to suppress the expression level of cytochrome P450 (CYP) and, in patients with inflammatory reaction, CYP expression is suppressed by excess production of IL-6 (*J Interferon Cytokine Res.* 2001;21:821-6, *Br J Cancer.* 2002;87:277-80). In addition, when an IL-6R inhibitor is administered to patients with rheumatoid arthritis, expression of the suppressed CYP3A4 and CYP2C19 was recovered (*Japanese journal of clinical pharmacology and Therapeutics*. 2007;38 Suppl:S236). These results suggest the possibility that administration of satralizumab induces the recovery of CYP expression suppressed by IL-6 and thereby stimulates the metabolism of drugs that serve as substrates for CYP.

- In patients with NMOSD, mean [minimum, maximum] serum IL-6 concentration before the start of administration of study drug was 1.92 [1.6, 9.6] pg/mL in the satralizumab group and 1.63 [1.6, 4.1] pg/mL in the placebo group of the global phase III study (CTD 5.3.5.1-1, Study SA-307JG), and 3.49 [1.6, 37.2] pg/mL in the satralizumab group and 3.66 [1.6, 34.2] pg/mL in the placebo group of the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG). These values tended to be lower than those observed in each dose group (57.9 [1.57, 178] pg/mL in the 30 mg group, 49.6 [3.33, 116] pg/mL in the 60 mg group, 32.2 [1.57, 93.6] pg/mL in the 120 mg group) of the phase I study in patients with rheumatoid arthritis (CTD 5.3.3.2-1, Study SA-105JP). These results suggest that the effect of CYP-mediated pharmacokinetic interactions caused by satralizumab-induced inhibition of IL-6 signaling is relatively smaller in patients in NMOSD patients than in patients with rheumatoid arthritis.

- In a study using the physiologically based pharmacokinetics (PBPK) model[10)] (CTD 5.3.2.2-1, AAPS J 2019;21:42), the effect of change in serum IL-6 concentration (from 10 pg/mL to 0 pg/mL[11)]) on C_{max} and AUC of the concomitant drug in the Japanese population was simulated[12)] by referring to serum IL-6 concentration in Studies SA-307JG and SA-309JG. Table 26 shows the estimated ratios of C_{max} and AUC of drugs that serve as substrates of each CYP, which suggested that satralizumab-induced decrease in serum IL-6 concentration is unlikely to have a clinically significant effect on the pharmacokinetics of concomitant drugs.

10) Simcyp version 16 R1 was used for PBPK model analysis. A minimal PBPK model was used to estimate IL-6 concentration at steady state. The relationship between expression level of CYP and IL-6 was described by a semimechanistic direct reaction model, using published data of minimum amount of active enzyme observed in the *in vitro* system (E_{min}) and concentration of inducer that supports the half maximal induction/suppression ($IndC_{50}$) of each CYP (*Drug Metab Dispos.* 2011;39:1415-22). The default value of Simcyp was used for drugs that serve as substrates.

11) IL-6 concentration was assumed to be 0 pg/mL in order to express satralizumab-induced inhibition of IL-6 signaling.

12) A hypothetical population of 100 subjects was generated using Simcyp. Default values of Simcyp were used for demographics, physiological parameters, and CYP isoforms. Height, body weight, and kidney weight were adjusted by data published by the Ministry of Health, Labour and Welfare (http://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/kenkou/kenkounippon21/eiyouchousa/keinen_henka_shintai.html. http://www.mhlw.go.jp/toukei/kouhyo/data-kou18/data12/junkan-h12-4.pdf). Conditions for simulation: Simvastatin, 40 mg single oral administration; dextromethorphan, 30 mg single oral administration; caffeine, 150 mg single oral administration; omeprazole, 20 mg single oral administration; midazolam, 5 mg single oral administration; *S*-warfarin, 10 mg single oral administration

Table 26. Estimated ratios of C_{max} and AUC of each substrate when serum IL-6 concentration was changed from 0 to 10 pg/mL in Japanese patients

Substrate	Geometric mean ratio[a)] [95% CI]	
	C_{max}	AUC
Simvastatin (CYP3A4)	1.14 [1.13, 1.15]	1.17 [1.16, 1.17]
Dextromethorphan (CYP2D6)	1.04 [1.03, 1.04]	1.05 [1.05, 1.05]
Caffeine (CYP1A2)	1.00 [1.00, 1.00]	1.01 [1.01, 1.01]
Omeprazole (CYP2C19)	1.07 [1.06, 1.08]	1.12 [1.11, 1.13]
Midazolam (CYP3A4)	1.10 [1.09, 1.11]	1.15 [1.14, 1.16]
S-warfarin (CYP2C9)	1.00 [1.00, 1.00]	1.04 [1.04, 1.05]

a) Without satralizumab/with satralizumab

- On the other hand, the maximum serum IL-6 concentration was 37.2 pg/mL before the start of administration of study drug in Studies SA-307JG and SA-309JG, and 80 pg/mL in patients with NMOSD (*Mult Scler.* 2010:16;1443-52). Therefore, as a worst-case scenario, the effect of change in serum IL-6 concentration from 100 to 0 pg/mL on C_{max} and AUC was estimated by a simulation using the PBPK model. Table 27 shows the estimated ratios of C_{max} and AUC of drugs that serve as substrates of each CYP, which predicted that AUC of simvastatin, the drug that showed the maximum change in the simulation, would decrease by approximately 56%. In Studies SA-307JG and SA-309JG, however, serum IL-6 concentration was <5 pg/mL in 157 of 173 patients and >10 pg/mL in only 5 patients (10.1, 14.3, 17.3, 34.2, and 37.2 pg/mL, respectively), suggesting that, in patients with NMOSD, satralizumab-induced drug interactions are unlikely.

Table 27. Estimated ratios of C_{max} and AUC of each substrate when serum IL-6 concentration changed from 0 to 100 pg/mL in Japanese patients

Substrate	Geometric mean ratio[a)] [95% CI]	
	C_{max}	AUC
Simvastatin (CYP3A4)	1.96 [1.91, 2.02]	2.25 [2.18, 2.32]
Dextromethorphan (CYP2D6)	1.28 [1.25, 1.30]	1.39 [1.36, 1.42]
Caffeine (CYP1A2)	1.01 [1.01, 1.01]	1.06 [1.06, 1.06]
Omeprazole (CYP2C19)	1.41 [1.38, 1.45]	1.88 [1.83, 1.94]
Midazolam (CYP3A4)	1.59 [1.54, 1.64]	2.06 [1.99, 2.13]
S-warfarin (CYP2C9)	1.02 [1.02, 1.03]	1.29 [1.26, 1.33]

a) Without satralizumab/with satralizumab

- The above results suggest that satralizumab is unlikely to significantly affect the pharmacokinetics of concomitant drugs. Nevertheless, it should be included in the package insert that satralizumab may restore suppressed CYP expression, thereby attenuating the efficacy of concomitant drugs that are metabolized by CYP.

PMDA accepted the above explanation of the applicant.

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

The applicant submitted the results of the studies listed in Table 28 as the efficacy and safety data.

Table 28. List of clinical studies on efficacy and safety

Data category	Region	Study identifier, CTD	Phase	Study population	No. of patients treated	Outline of dosage regimen	Main endpoints
Evaluation	Japan	SA-001JP 5.3.3.1-1	I	Japanese and non-Japanese healthy adult men	84	Part A: Single dose of placebo or satralizumab 30, 60, 120, or 240 mg as subcutaneous administration (SC) (Japanese subjects) Part B: Single dose of placebo or satralizumab 120 or 240 mg SC (non-Japanese subjects) Part C: Single dose of satralizumab 60 or 120 mg as intravenous administration (IV) (Japanese subjects)	Safety Pharmacokinetics
	Japan	SA-105JP 5.3.3.2-1	I	Japanese patients with rheumatoid arthritis	33	Primary evaluation period Group A: Satralizumab 120 mg SC at Weeks 0, 2, and 4, followed by satralizumab 120 mg SC every 4 weeks until Week 16. Group B: Satralizumab 120 mg SC at Weeks 0, 2, and 4, followed by satralizumab 60 mg SC every 4 weeks until Week 16. Group C: Satralizumab 120 mg SC at Weeks 0, 2, and 4, followed by satralizumab 30 mg SC every 4 weeks until Week 16.	Safety Pharmacokinetics
					28	Extension period: Satralizumab 120 mg SC at Weeks 0, 2, and 4, followed by satralizumab 120 mg SC every 4 weeks.	
	Global	SA-307JG 5.3.5.1-1	III	Japanese and non-Japanese patients with NMO or NMOSD	83	Double-blind period: In addition to basal treatment, placebo or satralizumab 120 mg SC at Weeks 0, 2, and 4, and every 4 weeks thereafter.	Efficacy Safety Pharmacokinetics
					42	Open-label extension period: With or without add-on basal treatment, satralizumab 120 mg SC at Weeks 0, 2, and 4, and every 4 weeks thereafter.	
	Foreign	SA-309JG 5.3.5.1-2	III	Non-Japanese patients with NMO or NMOSD	95	Double-blind period: Placebo or satralizumab 120 mg SC at Weeks 0, 2, and 4, and every 4 weeks thereafter.	Efficacy Safety Pharmacokinetics
					35	Open-label extension period: Satralizumab 120 mg SC at Weeks 0, 2, and 4, and every 4 weeks thereafter.	

7.1 Phase I studies

7.1.1 Japanese phase I study (CTD 5.3.3.1-1, Study SA-001JP [November 2010 to June 2011])

A clinical study in Japanese and non-Japanese healthy adult men (target sample size, 84 subjects) was conducted to investigate the safety and pharmacokinetics of satralizumab following single subcutaneous administration of satralizumab [see Section 6.2.1 for pharmacokinetics]. The study consisted of Part A (Japanese subjects), Part B (non-Japanese subjects), and Part C (Japanese subjects).

(a) Part A

A placebo-controlled, randomized, double-blind, ascending dose study was conducted in healthy Japanese adult men (target sample size, 44 subjects [8 in the placebo group, 6 in the satralizumab 30 mg group, 6 in the satralizumab 60 mg group, 12 in the satralizumab 120 mg group, 12 in the satralizumab 240 mg group]) to investigate the safety and pharmacokinetics of satralizumab following single subcutaneous administration of satralizumab.

A single dose of placebo or satralizumab (30, 60, 120, or 240 mg) was administered subcutaneously in the abdomen.

All of the 44 subjects receiving the study drug (8 in the placebo group, 6 in the satralizumab 30 mg group, 6 in the 60 mg group, 12 in the 120 mg group, and 12 in the 240 mg group) were included in the safety analysis population. None of them discontinued the study.

Adverse events (including laboratory abnormalities) were observed in none of the subjects in the placebo group, 33.3% (2 of 6) of subjects in the satralizumab 30 mg group, 83.3% (5 of 6) of subjects in the 60 mg group, 83.3% (10 of 12) of subjects in the 120 mg group, and 83.3% (10 of 12) of subjects in the 240 mg group. No death or serious adverse events were observed. Adverse events for which a causal relationship to the study drug (including laboratory abnormalities) could not be ruled out were observed in none of the subjects in the placebo group, in 16.7% (1 of 6) of subjects in the satralizumab 30 mg group, 83.3% (5 of 6) of subjects in the 60 mg group, 83.3% (10 of 12) of subjects in the 120 mg group, and 75.0% (9 of 12) of subjects in the 240 mg group. The most common adverse events were blood fibrinogen decreased (0 subject in the placebo group, 0 subject in the satralizumab 30 mg group, 3 subjects in the 60 mg group, 8 subjects in the 120 mg group, 9 subjects in the 240 mg group) and oropharyngeal pain (0 subject, 0 subject, 3 subjects, 3 subjects, 0 subject).

Vital signs (blood pressure, pulse rate, and body temperature) and electrocardiogram did not show any clinically significant changes.

(b) Part B

A placebo-controlled, randomized, double-blind, ascending dose study was conducted to investigate the safety and pharmacokinetics of satralizumab in non-Japanese healthy adult men (target sample size, 28 subjects [4 in the placebo group, 12 in the satralizumab 120 mg group, 12 in the satralizumab 240 mg]).

A single dose of placebo or satralizumab (120 or 240 mg) was administered subcutaneously in the abdomen.

All of the 28 subjects receiving the study drug (4 in the placebo group, 12 in the satralizumab 120 mg group, and 12 in the 240 mg group) were included in the safety analysis population. None of them discontinued the study.

Adverse events (including laboratory abnormalities) were observed in 50.0% (2 of 4) of subjects in the placebo group, 58.3% (7 of 12) of subjects in the satralizumab 120 mg group, and 58.3% (7 of 12) of subjects in the 240 mg group. No death or serious adverse events were observed. Adverse events for which a causal relationship to the study drug could not be ruled out (including laboratory abnormalities) were observed in 50.0% (2 of 4) of subjects in the placebo group, 41.7% (5 of 12) of subjects in the satralizumab 120 mg group, and 25.0% (3 of 12) of subjects in the 240 mg group. The most common adverse event was blood fibrinogen decreased (0 subject in the placebo group, 5 subjects in the satralizumab 120 mg group, 3 subjects in the 240 mg group).

Vital signs (blood pressure, pulse rate, and body temperature) and electrocardiogram did not show any clinically significant changes.

(c) Part C

An open-label, uncontrolled study was conducted to investigate the safety and pharmacokinetics of satralizumab in healthy Japanese adult men (target sample size, 12 subjects [6 in the satralizumab 60 mg group, 6 in the satralizumab 120 mg group]) .

A single dose of satralizumab (60 or 120 mg) was administered as an intravenous infusion.

All of the 12 subjects receiving the study drug (6 in the satralizumab 60 mg group, 6 in the 120 mg group) were included in the safety analysis population. None of them discontinued the study.

Adverse events (including laboratory abnormalities) were observed in 83.3% (5 of 6) of subjects in the satralizumab 60 mg group and in 100.0% (6 of 6) of subjects in the 120 mg group. No death or serious adverse events were observed. Adverse events for which a causal relationship to the study drug could not be ruled out (including laboratory abnormalities) were observed in 83.3% (5 of 6) of subjects in the satralizumab 60 mg group and in 100% (6 of 6) of subjects in the 120 mg group. The most common adverse event was blood fibrinogen decreased (4 subjects in the satralizumab 60 mg group, 4 subjects in the 120 mg group).

Vital signs (blood pressure, pulse rate, and body temperature) and electrocardiogram did not show any clinically significant changes.

7.1.2 Japanese phase I study (CTD 5.3.3.2-1, Study SA-105JP [March 2012 to September 2013])

An open-label, parallel-group study was conducted in Japanese patients with rheumatoid arthritis[13)] (target sample size; 30 subjects, 10 per group) to investigate the safety and pharmacokinetics of satralizumab following multiple subcutaneous administration of satralizumab [see Section 6.2.2 for pharmacokinetics]. The study consisted of a primary evaluation period (satralizumab 120 mg group [Group A], 32 weeks; satralizumab 60 mg group [Group B], 28 weeks; satralizumab 30 mg group [Group C], 24 weeks) and an extension period.

During the primary evaluation period, satralizumab 120 mg was administered subcutaneously (SC) in the abdomen every 2 weeks for the first 3 doses (Weeks 0, 2, and 4), followed by satralizumab 30, 60, or 120 mg SC in the abdomen every 4 weeks for the subsequent 3 doses (Weeks 8, 12, and 16). As a general rule, after Week 16, subjects were followed up for 16 weeks (satralizumab 120 mg group [Group A]), 12 weeks (satralizumab 60 mg group [Group B]), and 8 weeks (satralizumab 30 mg group

13) Patients who met both of the following criteria were enrolled in the study:
- Patients who were diagnosed with rheumatoid arthritis according to the American Rheumatism Association 1987 revised criteria and had been suffering from the disease for ≥6 months.
- In the test conducted within 2 weeks before the start of study treatment, CRP exceeded the upper limit of normal.

[Group C]).[14] During the extension period, satralizumab 120 mg was administered subcutaneously in the abdomen every 2 weeks for the first 3 doses (Weeks 0, 2, and 4 of the extension period) to subjects in all groups, followed by satralizumab 120 mg SC in the abdomen every 4 weeks for the subsequent 4 doses (Weeks 8, 12, 16, and 20 of the extension period), and by follow-up until Week 32 of the extension period.

All of the randomized 33 subjects (11 in Group A, 11 in Group B, 11 in Group C) were included in the safety analysis population. Treatment discontinuation occurred in 9 subjects (1 subject, 4 subjects, 4 subjects) during the entire treatment period. The reasons for treatment discontinuation were inadequate response (0 subject, 2 subjects, 3 subjects), adverse events (1 subject, 0 subject, 1 subject), treatment refusal or non-cooperation (0 subject, 2 subjects, 0 subject).

During the entire treatment period, adverse events (including laboratory abnormalities) were observed in 90.9% (10 of 11) of subjects in Group A, 81.8% (9 of 11) of subjects in Group B, and 72.7% (8 of 11) of subjects in Group C. No death occurred. Serious adverse events other than death were observed in 1 subject in Group A (interstitial lung disease) and in 1 subject in Group B (bronchopneumonia), and a causal relationship to the study drug could not be ruled out for either of these events. Adverse events for which a causal relationship to the study drug could not be ruled out (including laboratory abnormalities) were observed in 54.5% (6 of 11) of subjects in Group A, 45.5% (5 of 11) of subjects in Group B, and 63.6% (7 of 11) of subjects in Group C. The most common adverse events were injection related reaction (2 subjects, 0 subject, 0 subject), pharyngitis (1 subject, 0 subject, 1 subject), hyperlipidaemia (0 subject, 1 subject, 1 subject), and diabetes mellitus (0 subject, 1 subject, 1 subject).

Vital signs (blood pressure, pulse rate, and body temperature) and electrocardiogram did not show any clinically significant changes.

7.2 Phase III studies

7.2.1 Global phase III study (CTD 5.3.5.1-1, Study SA-307JG [ongoing since February 2014 {data cut-off, June 2018}])

A placebo controlled, randomized, double-blind, parallel-group study was conducted in 11 countries or regions[15] to evaluate the efficacy, safety, and pharmacokinetics of satralizumab. The subjects enrolled[16] were Japanese and non-Japanese patients with neuromyelitis optica (NMO) or NMOSD aged 12 to 74 years who were (1) diagnosed with NMO according to the 2006 criteria (*Neurology.* 2006;66:1485-9) or (2) positive for anti-AQP4 antibodies and diagnosed with NMOSD according to the 2007 criteria (*Lancet Neurol*. 2007;6:805-15) (target sample size, 70 subjects; 35 in the placebo group and 35 in the satralizumab group) [see Section 6.2.3 for pharmacokinetics].

[14] Patients with serum satralizumab concentrations below the detection limit at or after Week 20 were allowed to enter the extension period.
[15] Spain, Germany, UK, France, Hungary, Italy, Japan, Poland, Taiwan, Ukraine, and US
[16] The patients enrolled in the study were patients who had at least 2 documented relapses (including the newly diagnosed rheumatoid arthritis) within 2 years before the screening and had at least one relapse within 12 months before the screening. The maximum proportion of 18- to 74-year-old patients negative for anti-AQP4 antibodies was specified at approximately 30% of all patients. At least 8 patients aged 12 to 17 years were to be enrolled, and at least 4 patients positive for anti-AQP4 antibody were to be enrolled.

During the double-blind period, placebo or satralizumab 120 mg was administered subcutaneously every 2 weeks for the first 3 doses (Weeks 0, 2, and 4), and every 4 weeks thereafter.[17] During the open-label extension period, satralizumab 120 mg was administered subcutaneously every 2 weeks for the first 3 doses (Weeks 0, 2, and 4), followed by satralizumab 120 mg SC every 4 weeks.[18] Oral corticosteroid or an immunosuppressant was administered as the basal treatment.[19]

The double-blind period was terminated at the time point when the total number of PDRs,[20] adjudicated by the Clinical Endpoint Committee (CEC), reached 26. Patients who experienced a relapse during the double-blind period[21] were allowed to enter the open-label extension period within 31 to 60 days after the relapse if the disease condition was stabilized. Patients who had no relapse during the double-blind period were allowed to enter the open-label extension period 4 weeks after the last dose. During the open-label extension period, patients self-injected satralizumab.[22]

All of the 83 randomized subjects (42 in the placebo group, 41 in the satralizumab group) were included in the primary efficacy analysis population (intention-to-treat [ITT] population) and the safety analysis population. During the double-blind period, treatment discontinuation occurred in 13 subjects (10 subjects, 3 subjects). The reasons for treatment discontinuation were adverse events (5 subjects, 3 subjects), treatment refusal or non-cooperation (2 subjects, 0 subject), consent withdrawal (2 subjects, 0 subject), and violation of exclusion criteria (1 subject, 0 subject). During the open-label extension period, treatment discontinuation occurred in 9 subjects (5 subjects, 4 subjects) as of the date of data cut-off. The causes of treatment discontinuation were adverse events (2 subjects, 1 subject), inadequate response (clinical relapse) (3 subjects, 0 subject), consent withdrawal (0 subject, 2 subjects), and treatment refusal or non-cooperation (0 subject, 1 subject).

Table 29 and Figure 1 show the time to the first PDR during the double-blind period,[23] the primary endpoint. A statistically significant difference was observed between the satralizumab group and the placebo group.

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17) During the double-blind period, placebo and satralizumab in vials were used.

18) During the open-label extension period, satralizumab was switched from vial formulation to prefilled syringe. Patients who had entered the open-label extension period before the introduction of the prefilled syringe received the vial formulation until the introduction of the prefilled syringe.

19) From ≥8 weeks before baseline, azathioprine (≤3 mg/kg/day), mycophenolate mofetil (≤3000 mg/day), or oral corticosteroid (prednisolone equivalent ≤15 mg/day) was administered as the monotherapy at a stable dose. During the study period, dose reduction was allowed for safety reason, but the treatment was to be continued without dose increase (combination of azathioprine and oral corticosteroid, or combination of mycophenolate mofetil and oral corticosteroid was allowed in pediatric patients).

20) New or worsening neurological symptoms caused by NMO or NMOSD that met any of the following:
- An increase of ≥1 point on the Expanded Disability Status Scale (EDSS) score if the baseline score was ≥1 point, or an increase of ≥2 points if the baseline score was 0.
- An increase of ≥2 point on 1 of appropriate Functional System Score (FSS) scores
- If the baseline score on an appropriate FSS was ≥1, an increase of ≥1 point on ≥2 appropriate FSS scores.
- If the baseline FSS in single eye was ≥1 point, an increase of ≥1 point on FSS in the eye.

EDSS/FSS assessment score immediately before the relapse was used as the control for increase in score. An appropriate FSS referred to the score of factors affecting at least one of the functions of pyramidal tract, cerebellum, brainstem, sensation, rectum/bladder, or visual function (single eye)

21) Patients who experienced a clinical relapse and/or PDR requiring acute phase treatment

22) At the study sites in Japan, each patient assessed as capable of self-injection by the investigator (or subinvestigator) received injection of pre-filled syringe formulation from a healthcare professional for 24 weeks (healthcare professional administration period), and was then trained for self-injection. After that, the patient self-injected, or a caregiver injected, under the supervision of the investigator or the subinvestigator (self-injection period).

23) Time from randomization to the first attack of relapse during the double-blind period. The relapse had to be adjudicated as a PDR by the CEC, among the relapses evaluated for EDSS/FSS by the evaluator of the study site within 7 days after the patient reported the symptom to the study site.

Table 29. Time to the first PDR during the double-blind period (Study SA-307JG, ITT population)

	Treatment group	No. of patients evaluated	No. of patients with PDR (%)	Time to the first PDR (weeks)[a)]	Hazard ratio[b)] [95% CI]	*P* value[c)]	Percentage of patients relapse-free up to Week 96 (%)
Overall population	Placebo	42	18 (42.9)	120.6 (29.4, 178.1)	0.38 [0.16, 0.88]	0.0184	58.68%
	Satralizumab	41	8 (19.5)	- (110.0, -)			77.58%
Japanese population	Placebo	10	3 (30.0)	- (68.7, -)	-	-	51.85%
	Satralizumab	11	0	-			100%

-, Noncalculable
a) Median (first quartile, third quartile)
b) Based on Cox-proportional hazard model stratified by allocation factor.
c) Stratified log-rank test stratified by allocation factor
Allocation factor, baseline annualized relapse rate (1 or >1); geographic region (Asia or Europe/other)

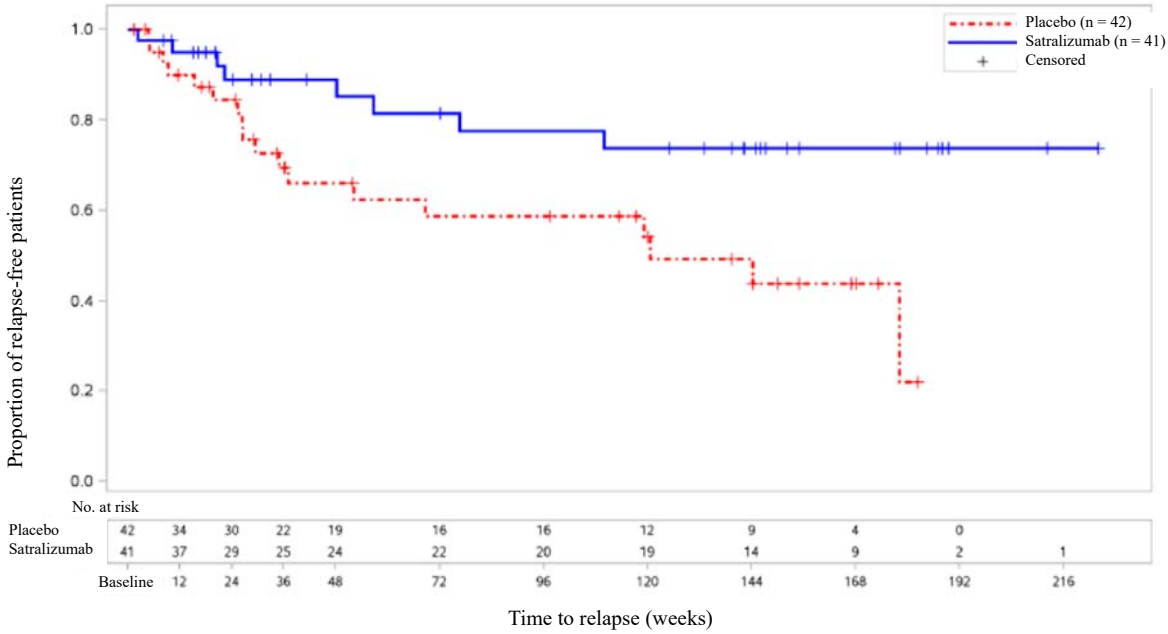

Figure 1. Kaplan-Meier curve during the period until the first PDR in the double-blind period (Study SA-307JG, ITT population)

During the double-blind period, adverse events (including laboratory abnormalities) were observed in 95.2% (40 of 42) of subjects in the placebo group and in 90.2% (37 of 41) of subjects in the satralizumab group. No death occurred. Table 30 shows the incidence of serious adverse events other than death.

Table 30. Incidence of serious adverse events other than death (Study SA-307JG, safety analysis population, double-blind period)

Treatment group	Incidence	Serious adverse events
Placebo	21.4% (9/42)	Hepatic cancer, leukopenia*/uterine polyp,* lymphopenia*/escherichia sepsis,* autoimmune thrombocytopenia,* retinal vein thrombosis, abdominal pain/urinary tract infection, breast cancer, appendicitis,* and dysuria in 1 patient each
Satralizumab	17.1% (7/41)	Anaemia macrocytic, femur fracture, tension headache, cervical dysplasia, spinal compression fracture, pneumonia,* and suicide attempt/urinary tract infection in 1 patient each

* Events for which a causal relationship to the study drug could not be ruled out

In the Japanese population, adverse events (including laboratory abnormalities) were observed in 100% (10 of 10) of subjects in the placebo group and in 100% (11 of 11) of subjects in the satralizumab group. No death occurred. Serious adverse events other than death were observed in 1 subject in the placebo group (appendicitis) and in 5 subjects in the satralizumab group (pneumonia, cervical dysplasia, and spinal compression fracture in 1 subject each). A causal relationship to the study drug could not be ruled out for appendicitis in the placebo group and pneumonia in the satralizumab group.

Adverse events for which a causal relationship to the study drug could not be ruled out (including laboratory abnormalities) were observed in 47.6% (20 of 42) of subjects in the placebo group and in 41.5% (17 of 41) of subjects in the satralizumab group. The common adverse events observed were cystitis (3 subjects in the placebo group, 0 subject in the satralizumab group), urinary tract infection (2 subjects, 0 subject), leukopenia (3 subjects, 5 subjects), lymphopenia (3 subjects, 3 subjects), anaemia (3 subjects, 1 subject), blood triglycerides increased (2 subjects, 0 subject), neutrophil count decreased (0 subject, 2 subjects), hypercholesterolaemia (3 subjects, 2 subjects), injection related reaction (1 subject, 5 subjects), pyrexia (2 subjects, 0 subject), hypertransaminasaemia (2 subjects, 0 subject), and oropharyngeal pain (0 subject, 2 subjects).

During the entire treatment period including the open-label extension period, adverse events (including laboratory abnormalities) were observed in 93.8% (61 of 65) of subjects. No death occurred. Serious adverse events other than death were observed in 21.5% (14 of 65) of subjects. Serious adverse events newly observed during the open-label extension period were spinal compression fracture/glaucoma, enterocolitis infectious, endocarditis, cellulitis, upper limb fracture/hepatitis E/influenza, Parkinsonism/gait disturbance, convulsion/urosepsis, and systemic lupus erythematosus (1 subject each). Among them, spinal compression fracture/glaucoma, enterocolitis infectious, and upper limb fracture/hepatitis E/influenza were observed in Japanese subjects. A causal relationship to the study drug could not be ruled out for endocarditis, enterocolitis infectious, and glaucoma.

During the entire satralizumab treatment period, adverse events for which a causal relationship to the study drug could not be ruled out (including laboratory abnormalities) were observed in 53.8% (35 of 65) of subjects. The common adverse events observed were leukopenia (11 subjects), injection related reaction (8 subjects), and lymphopenia (5 subjects).

Throughout the satralizumab treatment period, vital signs (blood pressure, pulse rate, and body temperature) and electrocardiogram did not show any clinically significant changes.

7.2.2 Foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG [ongoing since August 2014 (data cut-off, October 2018)])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in 13 countries or regions[24)] to evaluate the efficacy, safety, and pharmacokinetics of satralizumab. The subjects

[24)] Bulgaria, Canada, Croatia, Italy, Georgia, South Korea, Malaysia, Poland, Romania, Turkey, Taiwan, Ukraine, and US.

enrolled[25] were non-Japanese patients with NMO or NMOSD aged 18 to 74 years who were (1) diagnosed with NMO according to the 2006 criteria or (2) positive for AQP4 antibody at screening and diagnosed with NMOSD according to the 2007 criteria (target sample size, 90 subjects; 30 in the placebo group and 60 in the satralizumab group [see Section 6.2.3 for pharmacokinetics].

During the double-blind period, placebo or satralizumab 120 mg was administered subcutaneously every 2 weeks for the first 3 doses (Weeks 0, 2, and 4), and every 4 weeks thereafter.[26] During the open-label extension period, satralizumab 120 mg was administered subcutaneously every 2 weeks for the first 3 doses (Weeks 0, 2, and 4), followed by satralizumab 120 mg SC every 4 weeks.[27] Concomitant use of medications to prevent the relapse of NMOSD was prohibited from baseline.[28] The double-blind period was terminated at the time point when the total number of PDRs[20] reached 44 or when 1.5 years passed after the assignment of the last patient to a treatment group, whichever was earlier. Patients who experienced a relapse during the double-blind period[29] were allowed to enter the open-label extension period after ≥31 days after the relapse if the disease condition was stabilized. Patients who had no relapse during the double-blind period were allowed to enter the open-label extension period 4 weeks after the last dose.

All of the randomized 95 subjects (32 in the placebo group, 63 in the satralizumab group) were included in the primary efficacy analysis population (ITT population) and the safety analysis population. During the double-blind period, treatment discontinuation occurred in 11 subjects (4 subjects, 7 subjects). The reasons for treatment discontinuation were consent withdrawal (2 subjects, 2 subjects), adverse events (1 subject, 1 subject), treatment refusal or non-cooperation (0 subject, 1 subject), other protocol deviation (0 subject, 1 subject), and others (1 subject, 2 subjects). During the open-label extension period, treatment discontinuation occurred in 6 subjects (3 subjects, 3 subjects) as of the date of data cut-off. The reasons for treatment discontinuation were consent withdrawal (1 subject, 1 subject), others (1 subject, 1 subject), inadequate response (clinical relapse) (1 subject, 0 subject), and treatment refusal or non-cooperation (0 subject, 1 subject).

Table 31 and Figure 2 show the time to the first PDR during the double-blind period,[23] the primary endpoint, demonstrating a statistically significant difference between the satralizumab group and the placebo group.

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[25] Patients enrolled in the study were patients who had experienced at least 1 clinical relapse (including the first attack) within 12 months before screening but none within 30 days before the first dose. The proportion of patients negative for anti-AQP4 antibodies had to be within approximately 30% of all patients.

[26] During the double-blind period, placebo and satralizumab in vials were used.

[27] During the open-label extension period, satralizumab was switched from vial formulation to prefilled syringe. Patients who had entered the open-label extension period before the introduction of the prefilled syringe received the vial formulation until the introduction of the prefilled syringe.

[28] Only patients who had discontinued, or had not received, medications for preventing the relapse of NMOSD before baseline were enrolled in the study. The use of medications for preventing the relapse of NMOSD was prohibited from baseline until the end of the study.

[29] Patients who experienced a PDR adjudicated by CEC.

Table 31. Time to the first PDR during the double-blind period (Study SA-309JG, ITT population)

Treatment group	No. of patients evaluated	No. of patients with PDR (%)	Time to the first PDR (Week) [a)]	Hazard ratio [b)] [95% CI]	*P* value [c)]	Percentage of patients relapse-free up to Week 96 (%)
Placebo	32	16 (50.0)	128.3 (11.7, -)	0.45 [0.23, 0.89]	0.0184	51.21%
Satralizumab	63	19 (30.2)	- (69.3, -)			72.14%

-, Noncalculable
a) Median (first quartile, third quartile)
b) Based on Cox-proportional hazard model stratified by allocation factor.
c) Stratified log-rank test stratified by allocation factor
Allocation factor, Prior treatments for preventing NMOSD relapse (B-cell depletion drug or immunosuppressant/other); Onset immediately before screening (first attack or relapse)

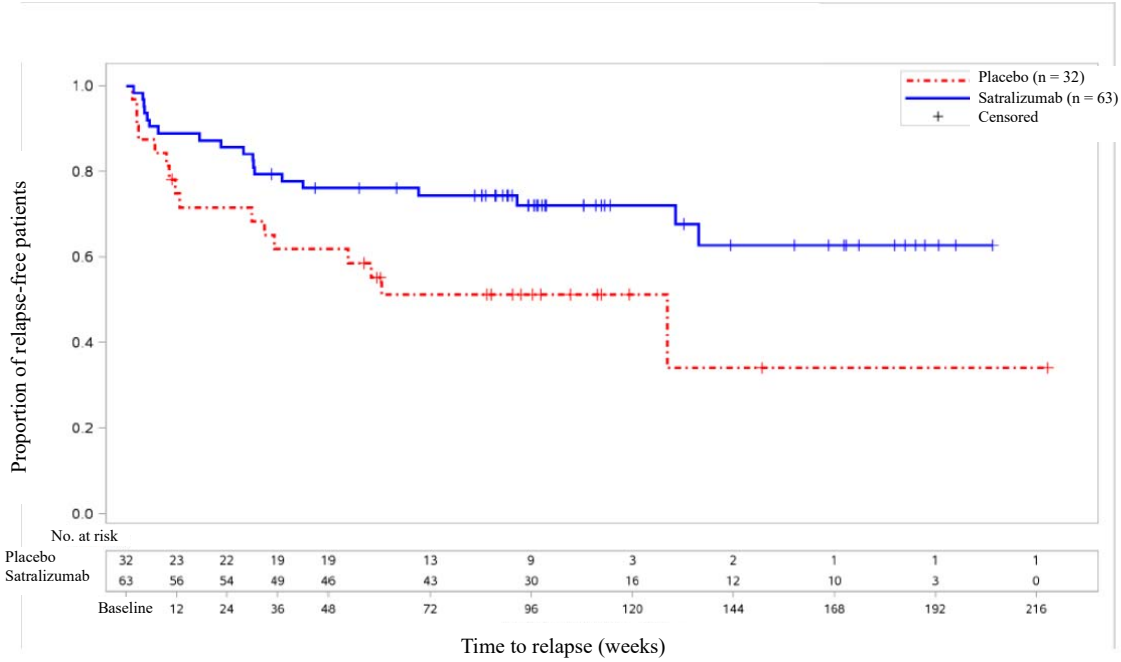

Figure 2. Kaplan-Meier curve during the period until the first PDR in the double-blind period (Study SA-309JG, ITT population)

During the double-blind period, adverse events (including laboratory abnormalities) were observed in 75.0% (24 of 32) of subjects in the placebo group and in 92.1% (58 of 63) of subjects in the satralizumab group. No death occurred. Table 32 shows the incidence of serious adverse events other than death.

Table 32. Incidence of serious adverse events other than death (Study SA-309JG, safety analysis population, double-blind period)

Treatment group	Incidence	Serious adverse events
Placebo	15.6% (5/32)	Cystitis, neuromyelitis optica, cervical radiculopathy, upper respiratory tract infection, and urinary tract infection* in 1 subject each
Satralizumab	19.0% (12/63)	Influenza in 2 subjects and nausea/acute myocardial infarction, radius fracture, non-cardiac chest pain, visual impairment/urosepsis/mental status changes, enterocolitis, pyelonephritis/bradycardia/apnoea/hypothermia/mental status changes, pulmonary oedema, pulmonary sepsis,* injury, and pneumonia* in 1 subject each

* Events for which a causal relationship to the study drug could not be ruled out.

During the double-blind period, adverse events for which a causal relationship to the study drug could not be ruled out (including laboratory abnormalities) were observed in 34.4% (11 of 32) of subjects in the placebo group and in 34.9% (22 of 63) of subjects in the satralizumab group. Main events were

neutropenia (1 subject in the placebo group, 2 subjects in the satralizumab group), lymphopenia (0 subject, 2 subjects), hypofibrinogenaemia (0 subject, 2 subjects), injection related reaction (5 subjects, 6 subjects), upper respiratory tract infection (1 subject, 2 subjects), urinary tract infection (2 subjects, 1 subject), sinusitis (0 subject, 2 subjects), lymphocyte count decreased (0 subject, 2 subjects), white blood cell count decreased (0 subject, 2 subjects), diarrhoea (0 subject, 4 subjects), nausea (1 subject, 2 subjects), influenza like illness (0 subject, 2 subjects), and pain in extremity (1 subject, 2 subjects).

During the entire treatment period including the open-label extension period, adverse events (including laboratory abnormalities) were observed in 95.0% (76 of 80) of subjects. No death occurred. Serious adverse events other than death were observed in 16.3% (13 of 80) of subjects. New adverse events reported during the open-label extension period were post procedural haematoma and intracranial aneurysm (1 subject each), and a causal relation to the study drug was ruled out for both of the events.

During the entire satralizumab treatment period, adverse events for which a causal relationship to the study drug could not be ruled out (including laboratory abnormalities) were observed in 37.5% (30 of 80) of subjects. The most common events observed were injection related reaction (9 subjects), upper respiratory tract infection (5 subjects), and diarrhoea (5 subjects).

Throughout the satralizumab treatment period, vital signs (blood pressure, pulse rate, and body temperature) and electrocardiogram did not show any clinically significant changes.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Efficacy in patients positive and negative for anti-AQP4 antibody

Taking account of the possible difference in the pathogenesis of NMOSD between patients positive and negative for anti-AQP4 antibodies [see Section 3.R.1], PMDA asked the applicant to explain the efficacy of satralizumab in anti-AQP4 antibody-positive patients and in negative patients.

The applicant's explanation:

- Satralizumab is expected to be effective even in anti-AQP4 antibody-negative patients because it inhibits IL-6 signaling. It is desirable to start the treatment of NMOSD immediately after diagnosis regardless of the status of anti-AQP4 antibodies. For the above reasons, the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) and the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG) included not only in anti-AQP4 antibody-positive patients but also in negative patients in order to provide the opportunity of treatment to as many patients with NMOSD as possible.

- Analyses were performed to evaluate the efficacy of satralizumab in anti-AQP4 antibody-positive and negative patients in Studies SA-307JG and SA-309JG. Table 33 shows the incidence of the first PDR in anti-AQP4 antibody-positive and negative patients. The efficacy of satralizumab in anti-AQP4 antibody-positive patients was demonstrated in Studies SA-307JG and SA-309JG, whereas a conclusion on the efficacy of satralizumab in anti-AQP4 antibody-negative patients

could not be reached due to the small number of negative patients and to the diverse clinical conditions of anti-AQP4 antibody-negative patients.

Table 33. Incidence of the first PDR in anti-AQP4 antibody-positive and negative patients (double-blind period)

Study	Treatment group	Anti-AQP4 antibody positive				Anti-AQP4 antibody negative			
		No. of patients evaluated	No. of patients with PDR (%)	Hazard ratio[a] [95% CI]	*P* value[b]	No. of patients evaluated	No. of patients with PDR (%)	Hazard ratio[a] [95% CI]	*P* value[b]
SA-307JG	Placebo	28	12 (42.9)	0.21 [0.06, 0.75]	0.0086	14	6 (42.9)	0.66 [0.20, 2.23]	0.50
	Satralizumab	27	3 (11.1)			14	5 (35.7)		
SA-309JG	Placebo	23	13 (56.5)	0.26 [0.11, 0.63]	0.0014	9	3 (33.3)	1.19 [0.30, 4.78]	0.80
	Satralizumab	41	9 (22.0)			22	10 (45.5)		

a) Based on Cox-proportional hazard model stratified by allocation factor in each study.
b) Stratified log-rank test stratified by allocation factor in each study. This analysis is positioned as an exploratory one and does not take into account the multiplicity of test.

- In order to investigate the factors that affected the evaluation of efficacy in anti-AQP4 antibody-negative patients in Studies SA-307JG and SA-309JG, a subpopulation analysis classified by patient characteristics[30] was conducted. Because of the limited number of anti-AQP4 antibody-negative patients investigated in both studies, it was difficult to clearly identify the factors affecting the efficacy evaluation in anti-AQP4 antibody-negative patients [see Section 7.R.1.3].

The applicant's explanation:
Satralizumab can, nevertheless, offer a new therapeutic option because it is expected to be effective in anti-AQP4 antibody-negative patients as well, based on the following evidence:

- IL-6 levels in blood and CSF increase in patients experiencing the relapse of NMOSD (*Int J Neurosci*. 2010; 120:71-5, *J Neurol*. 2009;256:2082-4, *Mult Scler*. 2010;16:1443-52), and is involved in the enhancement of the production of anti-AQP4 antibodies and other autoantibodies, in the pathogenesis of NMOSD, and in the induction of migration of white blood cells and autoantibodies to the central nervous system associated with the enhanced permeability of the blood-brain barrier (C*lin Exp Neuroimmunology*. 2013, *Neurol Neuroimmunol Neuroinflamm*. 2016;4:e311). Based on these reports, satralizumab, which blocks IL-6R, is expected to be effective for the treatment of both anti-AQP4 antibody-dependent and independent pathologic conditions of patients with NMOSD.

- Table 34 shows the percentage of patients with severe PDR by anti-AQP4 antibody status at the onset of relapse during the double-blind period of Studies SA-307JG and SA-309JG. Because of the limited number of anti-AQP4 antibody-negative patients, the studies could not clearly demonstrate the efficacy of satralizumab. Nevertheless, the results suggest that satralizumab possibly decreases the percentage of patients with severe PDR at relapse in not only anti-AQP4 antibody-positive patients but also negative patients.

[30] Age, race, region, baseline annualized relapse rate, NMO or NMOSD, type of basal therapeutic agent, sex, baseline EDSS, prior treatment to prevent NMOSD relapse, type of the attack (first or relapse) immediately before screening, and past annualized relapse rate

Table 34. Percentage of patients with severe PDR among anti-AQP4 antibody-positive and negative patients at the onset of relapse during the double-blind period

	Study SA-307JG				Study SA-309JG			
	Placebo		Satralizumab		Placebo		Satralizumab	
	No. of patients evaluated	No. of patients with severe PDR (%)	No. of patients evaluated	No. of patients with severe PDR[a)] (%)	No. of patients evaluated	No. of patients with severe PDR[a)] (%)	No. of patients evaluated	No. of patients with severe PDR[a)] (%)
Overall population	42	6 (14.3)	41	1 (2.4)	32	6 (18.8)	63	4 (6.3)
Anti-AQP4 antibody-positive	28	6 (21.4)	27	1 (3.7)	23	5 (21.7)	41	3 (7.3)
Anti-AQP4 antibody-negative	14	0	14	0	9	1 (11.1)	22	1 (4.5)

a) PDR was assessed as severe when Expanded Disability Status Scale (EDSS) score at the relapse decreased by ≥2 points compared with the score before the relapse.

Although the efficacy of satralizumab in anti-AQP4 antibody-negative patients remained unclear in Studies SA-307JG and SA-309JG, the applicant considers that satralizumab is effective in anti-AQP4 antibody-negative patients as well because IL-6 is involved in the pathology of NMOSD and because study results suggested the possibility that satralizumab decreases the percentage of patients with severe PDR at relapse.

PMDA's view:

- The subpopulation analyses of anti-AQP4 antibody-positive patients in Studies SA-307JG and SA-309JG showed that the risk of relapse decreased in the satralizumab group compared with the placebo group and that the percentage of patients with severe PDR at relapse in the satralizumab group were lower than that in the placebo group, demonstrating the efficacy of satralizumab in anti-AQP4 antibody-positive patients.

- In contrast, the subpopulation analyses of anti-AQP4 antibody-negative patients in Studies SA-307JG and SA-309JG did not show clear difference in the number of patients with the first PDR between the satralizumab group and the placebo group. Further, the incidence of severe PDR at relapse did not differ between the satralizumab group and the placebo group in Study SA-307JG, although a definite conclusion could not be drawn due to the limited number of patients with relapse. It is therefore difficult to definitely conclude that satralizumab decreased the percentage of severe PDR at relapse in anti-AQP4 antibody-negative patients. Thus, it is difficult to conclude that satralizumab is effective in anti-AQP4 antibody-negative patients.

- The above results show a tendency toward a difference in the efficacy of satralizumab between anti-AQP4 antibody-positive and negative patients, with the efficacy of satralizumab remaining inconclusive in anti-AQP4 antibody-negative patients.

- The above decision will be finalized, taking account of comments raised in the Expert Discussion. Whether satralizumab can be indicated for anti-AQP4 antibody-negative patients is further discussed in Section 7.R.4.2.

7.R.1.2 Evaluation based on the results of the global phase III study

7.R.1.2.1 Intrinsic and extrinsic ethnic factors

PMDA asked the applicant to explain how the consideration was given to the effect of ethnic factors on the efficacy and safety of satralizumab in Study SA-307JG (CTD 5.3.5.1-1) which was conducted as a global phase III study.

The applicant's explanation:

There are no significant differences in intrinsic or extrinsic ethnic factors between Japanese and non-Japanese patients, as suggested by the following findings:

- In the phase I study (CTD 5.3.3.1-1, Study SA-001JP) in Japanese and non-Japanese healthy adult men, a single dose of satralizumab up to 240 mg was safe and well-tolerated both in Japanese and non-Japanese subjects [see Section 7.1.1]. The pharmacokinetic study showed a tendency toward lower serum satralizumab concentrations in non-Japanese subjects than in Japanese subjects but, after data adjustment for body weight, no significant difference was observed between Japanese and non-Japanese subjects [see Section 6.R.1]. In the population pharmacokinetic analysis of data obtained from Studies SA-001JP and SA-307JG, and the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG), race was not identified as a covariate affecting pharmacokinetics [see Section 6.2.4].

- Study SA-307JG was conducted in patients who were diagnosed with NMO according to the 2006 criteria and patients who were anti-AQP4 antibody-positive and diagnosed with NMOSD according to the 2007 criteria. These criteria are widely used across the world, and there is no report suggesting a difference in the pathologies of NMO or NMOSD between Japanese and non-Japanese patients.

- When Study SA-307JG was ongoing, there were no therapeutic agents for NMSOD supported by evidence such as data from a head-to-head study or other methods, but conventional therapies, such as mainly corticosteroids in Japan and mainly immunosuppressants and Rituximab (Genetical Recombination) ("rituximab") in the US and Europe, were used to prevent the relapse of NMOSD (*2017 Japanese guidelines for multiple sclerosis and neuromyelitis optica* [in Japanese]. Igaku Shoin; 2017, *Mult Scler Relat Disord*. 2012;1:180-7). In Study SA-307JG, all patients used basal therapeutic agents, and the percentage of patients using each basal therapeutic agent is shown in Table 35. Table 36 shows the adverse events by basal therapeutic agent. There was no significant difference in the incidence of adverse events among patients on satralizumab who used different basal therapeutic agents.

Table 35. Basal therapeutic agents for NMOSD used in Japanese and non-Japanese populations (Study SA-307JG)

	Placebo		Satralizumab	
	Japanese population	Non-Japanese population	Japanese population	Non-Japanese population
No. of patients evaluated	10	32	11	30
Oral corticosteroid alone	10 (100.0)	10 (31.3)	11 (100.0)	6 (20.0)
Azathioprine alone	0	13 (40.6)	0	16 (53.3)
Mycophenolate mofetil alone	0	8 (25.0)	0	4 (13.3)
Azathioprine + oral corticosteroid	0	0	0	3 (10.0)
Mycophenolate mofetil + oral corticosteroid	0	1 (3.1)	0	1 (3.3)

n (%)

Table 36. Incidence of adverse events in patients receiving different basal treatments (Study SA-307JG, double-blind period)

	Placebo		Satralizumab	
	N	No. of patients with adverse events (%)	N	No. of patients with adverse events (%)
Oral corticosteroid alone	20	19 (95.0)	17	16 (94.1)
Azathioprine alone	13	13 (100.0)	16	14 (87.5)
Mycophenolate mofetil alone	8	7 (87.5)	4	4 (100.0)
Azathioprine + oral corticosteroid	0	0	3	2 (66.7)
Mycophenolate mofetil + oral corticosteroid	1	1 (100.0)	1	1 (100.0)

7.R.1.2.2 Differences in efficacy and safety between Japanese and non-Japanese populations in global phase III study

PMDA asked the applicant to explain differences in the efficacy and safety of satralizumab between Japanese and non-Japanese populations in the global phase III study (CTD 5.3.5.1-1, Study SA-307JG).

The applicant's explanation:

Table 37 shows the incidence of the first PDR in the Japanese and non-Japanese populations. In both populations, the incidence of PDR was lower in the satralizumab group than in the placebo group, showing a similar tendency.

Table 37. Incidence of the first PDR in Japanese and non-Japanese populations (Study SA-307JG, double-blind period)

	Overall population				Anti-AQP4 antibody positive				Anti-AQP4 antibody negative			
	Japanese population		Non-Japanese population		Japanese population		Non-Japanese population		Japanese population		Non-Japanese population	
	Placebo	Satralizumab	Placebo	Satralizumab	Placebo	Satralizumab	Placebo	Satralizumab	Placebo	Satralizumab	Placebo	Satralizumab
No. of patients evaluated	10	11	32	30	9	10	19	17	1	1	13	13
No. of patients with PDR (%)	3 (30.0)	0	15 (46.9)	8 (26.7)	3 (33.3)	0	9 (47.4)	3 (17.6)	0	0	6 (46.2)	5 (38.5)
Hazard ratio[a)] [95% CI]	-		0.51 [0.21, 1.24]		-		0.39 [0.10, 1.57]		-		0.66 [0.20, 2.23]	

-, Not estimable

a) Based on Cox proportional hazard model stratified by allocation factor

Table 38 shows the incidence of adverse events in the Japanese and the non-Japanese populations. The incidence of adverse events was similar between the Japanese and the non-Japanese populations, and there were no adverse events specific to the Japanese population.

Table 38. Incidence of adverse events in Japanese and non-Japanese populations (Study SA-307JG, double-blind period)

	Overall population		Japanese population		Non-Japanese population	
	Placebo	Satralizumab	Placebo	Satralizumab	Placebo	Satralizumab
No. of patients evaluated	42	41	10	11	32	30
Any adverse event	40 (95.2)	37 (90.2)	10 (100.0)	11 (100.0)	30 (93.8)	26 (86.7)
Death	0	0	0	0	0	0
Serious adverse events other than death	9 (21.4)	7 (17.1)	1 (10.0)	3 (27.3)	8 (25.0)	4 (13.3)
Most common adverse events						
Nasopharyngitis	7 (16.7)	10 (24.4)	2 (20.0)	5 (45.5)	5 (15.6)	5 (16.7)
Headache	4 (9.5)	10 (24.4)	3 (30.0)	2 (18.2)	1 (3.1)	8 (26.7)
Upper respiratory tract infection	6 (14.3)	10 (24.4)	1 (10.0)	0	5 (15.6)	10 (33.3)
Urinary tract infection	7 (16.7)	7 (17.1)	0	1 (9.1)	7 (21.9)	6 (20.0)
Leukopenia	4 (9.5)	6 (14.6)	0	1 (9.1)	4 (12.5)	5 (16.7)
Injection related reaction	2 (4.8)	5 (12.2)	0	0	2 (6.3)	5 (16.7)
Pharyngitis	3 (7.1)	4 (9.8)	2 (20.0)	2 (18.2)	1 (3.1)	2 (6.7)
Gastritis	0	4 (9.8)	0	2 (18.2)	0	2 (6.7)
Back pain	5 (11.9)	4 (9.8)	3 (30.0)	1 (9.1)	2 (6.3)	3 (10.0)
Hypercholesterolaemia	5 (11.9)	4 (9.8)	2 (20.0)	0	3 (9.4)	4 (13.3)
Cystitis	4 (9.5)	3 (7.3)	1 (10.0)	2 (18.2)	3 (9.4)	1 (3.3)
Oropharyngeal pain	1 (2.4)	3 (7.3)	1 (10.0)	2 (18.2)	0	1 (3.3)
Anaemia	5 (11.9)	3 (7.3)	1 (10.0)	0	4 (12.5)	3 (10.0)
Iron deficiency anaemia	1 (2.4)	2 (4.9)	1 (10.0)	2 (18.2)	0	0
Compression fracture	0	2 (4.9)	0	2 (18.2)	0	0
Hyperlipidaemia	0	2 (4.9)	0	2 (18.2)	0	0
Dental caries	2 (4.8)	2 (4.9)	2 (20.0)	1 (9.1)	0	1 (3.3)
Constipation	7 (16.7)	2 (4.9)	4 (40.0)	0	3 (9.4)	2 (6.7)
Blood CPK increased	2 (4.8)	1 (2.4)	2 (20.0)	0	0	1 (3.3)
Pyrexia	5 (11.9)	0	1 (10.0)	0	4 (12.5)	0

n (%)

PMDA's view on data presented in Sections 7.R.1.2.1 and 7.R.1.2.2:

Despite the difference in basal therapeutic agents used between Japanese and non-Japanese populations, no significant difference was observed between the populations in the incidence of adverse events in the satralizumab group, classified by basal therapeutic agents used. In Study SA-307JG, no significant difference was observed in the efficacy and safety of satralizumab between the Japanese and non-Japanese populations. PMDA concludes that there is no particular problem in the applicant's explanation, based on the above findings, that there is no significant difference in the ethnic factors affecting the efficacy and safety.

7.R.1.3 Factors affecting efficacy

PMDA asked the applicant to explain factors affecting the efficacy of satralizumab.

The applicant's explanation:

Table 39 shows the results of subgroup analyses for the incidence of the first PDR in anti-AQP4 antibody-positive patients in the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) and the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG), classified by patient characteristics. In all subgroup analyses, the incidence of PDR was lower in the satralizumab group than in the placebo group, with no factors affecting efficacy identified in anti-AQP4 antibody-positive patients. Subgroup analyses by patient characteristics were conducted also in anti-AQP4 antibody-negative patients. However, because of the limited number of anti-AQP4 antibody-negative patients in both studies, it seemed difficult to clearly identify factors affecting efficacy evaluation.

Table 39. Subgroup analyses by patient characteristics for the incidence of the first PDR in anti-AQP4 antibody-positive patients (double-blind period)

	Treatment group	Study SA-307JG				Study SA-309JG			
		Subgroup	N	No. of patients with PDR (%)	Hazard ratio[a] [95% CI]	Subgroup	N	No. of patients with PDR (%)	Hazard ratio[a] [95% CI]
Body weight (kg)[b]	Placebo	<58.4	11	3 (27.3)	0.56 [0.07, 4.18]	<70.5	14	6 (42.9)	0.19 [0.04, 0.95]
	Satralizumab		16	2 (12.5)			18	2 (11.1)	
	Placebo	≥58.4	17	9 (52.9)	0.14 [0.02, 1.15]	≥70.5	9	7 (77.8)	0.24 [0.07, 0.82]
	Satralizumab		11	1 (9.1)			23	7 (30.4)	
Oral corticosteroid at baseline	Placebo	Yes	14	6 (42.9)	<0.01 [0.00, -]				
	Satralizumab		15	0					
	Placebo	No	14	6 (42.9)	0.64 [0.14, 2.88]				
	Satralizumab		12	3 (25.0)					
Time to the first dose from the first attack of NMOSD (years)[b, c]	Placebo	<3.4	16	7 (43.8)	0.17 [0.02, 1.41]	<2.7	14	6 (42.9)	0.44 [0.14, 1.38]
	Satralizumab		11	1 (9.1)			18	6 (33.3)	
	Placebo	≥3.4	12	5 (41.7)	0.27 [0.05, 1.46]	≥2.7	9	7 (77.8)	0.07 [0.01, 0.36]
	Satralizumab		16	2 (12.5)			23	3 (13.0)	
Annualized relapse rate in the past[b]	Placebo	<1	0	0	-	<1	7	3 (42.9)	0.36 [0.07, 1.82]
	Satralizumab		0	0			19	4 (21.1)	
	Placebo	≥1	28	12 (42.9)	0.21 [0.06, 0.75]	≥1	16	10 (62.5)	0.16 [0.05, 0.49]
	Satralizumab		27	3 (11.1)			22	5 (22.7)	
Baseline EDSS score[b]	Placebo	<3.5	12	4 (33.3)	<0.01 [0.00, -]	<3.5	11	6 (54.5)	0.13 [0.02, 1.11]
	Satralizumab		5	0			12	1 (8.3)	
	Placebo	≥3.5	15	8 (53.3)	0.21 [0.05, 0.82]	≥3.5	12	7 (58.3)	0.30 [0.10, 0.88]
	Satralizumab		22	3 (13.6)			29	8 (27.6)	

-, Not estimable
a) Based on Cox proportional hazard model stratified by allocation factor
b) Classified by median value
c) The earliest date of the relapse of NMOSD that was collected in the study was handled as the date of first attack.

PMDA accepted the above explanation of the applicant.

7.R.2 Safety

7.R.2.1 Safety in anti-AQP4 antibody-positive and negative patients

PMDA asked the applicant to explain the safety of satralizumab in anti-AQP4 antibody-positive and negative patients with NMOSD.

The applicant's explanation:

Table 40 shows the incidence of the most common adverse events in anti-AQP4 antibody-positive and negative patients in the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) and in the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG). Results suggest that there is no significant difference in the safety profile of satralizumab between anti-AQP4 antibody-positive and negative patients.

Table 40. Incidence of adverse events in anti-AQP4 antibody-positive and negative patients (double-blind period)

	Study SA-307JG				Study SA-309JG			
	Anti-AQP4 antibody positive		Anti-AQP4 antibody negative		Anti-AQP4 antibody positive		Anti-AQP4 antibody negative	
	Placebo	Satralizumab	Placebo	Satralizumab	Placebo	Satralizumab	Placebo	Satralizumab
No. of patients evaluated	28	27	14	14	23	41	9	22
Any adverse event	27 (96.4)	25 (92.6)	13 (92.9)	12 (85.7)	16 (69.6)	36 (87.8)	8 (88.9)	22 (100)
Serious adverse events	7 (25.0)	7 (25.9)	2 (14.3)	0	3 (13.0)	7 (17.1)	2 (22.2)	5 (22.7)
Most common adverse events								
Upper respiratory tract infection	3 (10.7)	5 (18.5)	3 (21.4)	5 (35.7)	5 (21.7)	6 (14.6)	1 (11.1)	4 (18.2)
Urinary tract infection	5 (17.9)	4 (14.8)	2 (14.3)	3 (21.4)	5 (21.7)	8 (19.5)	3 (33.3)	3 (13.6)
Pharyngitis	2 (7.1)	3 (11.1)	1 (7.1)	1 (7.1)	0	1 (2.4)	0	0
Nasopharyngitis	5 (17.9)	8 (29.6)	2 (14.3)	2 (14.3)	1 (4.3)	5 (12.2)	0	4 (18.2)
Oral herpes	3 (10.7)	0	0	2 (14.3)	0	1 (2.4)	1 (11.1)	0
Back pain	4 (14.3)	3 (11.1)	1 (7.1)	1 (7.1)	3 (13.0)	3 (7.3)	0	1 (4.5)
Myalgia	2 (7.1)	0	0	1 (7.1)	0	3 (7.3)	0	1 (4.5)
Injection related reaction	1 (3.6)	2 (7.4)	1 (7.1)	3 (21.4)	3 (13.0)	4 (9.8)	2 (22.2)	4 (18.2)
Leukopenia	4 (14.3)	3 (11.1)	0	3 (21.4)	0	1 (2.4)	0	1 (4.5)
Neutropenia	1 (3.6)	1 (3.7)	1 (7.1)	1 (7.1)	1 (4.3)	4 (9.8)	0	0
Lymphopenia	3 (10.7)	2 (7.4)	1 (7.1)	1 (7.1)	0	0	0	0
Anaemia	3 (10.7)	3 (11.1)	2 (14.3)	0	0	1 (2.4)	0	1 (4.5)
Hyperfibrinogenaemia	2 (7.1)	0	0	0	1 (4.3)	0	0	0
Hypercholesterolaemia	5 (17.9)	3 (11.1)	0	1 (7.1)	0	1 (2.4)	0	1 (4.5)
Hyponatraemia	0	0	0	0	1 (4.3)	0	0	0
Headache	3 (10.7)	8 (29.6)	1 (7.1)	2 (14.3)	3 (13.0)	4 (9.8)	1 (11.1)	6 (27.3)
Diarrhoea	2 (7.1)	1 (3.7)	1 (7.1)	0	0	2 (4.9)	0	2 (9.1)
Nausea	2 (7.1)	2 (7.4)	1 (7.1)	1 (7.1)	2 (8.7)	6 (14.6)	0	5 (22.7)
Constipation	6 (21.4)	2 (7.4)	1 (7.1)	0	2 (8.7)	2 (4.9)	0	1 (4.5)
Pyrexia	5 (17.9)	0	0	0	0	0	0	1 (4.5)

n (%)

PMDA accepted the explanation of the applicant and, in the subsections below, further reviewed the following individual adverse events: Adverse events related to infection, hepatitis B virus reactivation, adverse events related to neutropenia/leukopenia/agranulocytosis, adverse events related to thrombocytopenia, adverse events related to hepatic dysfunction, adverse events related to hypersensitivity, adverse events related to lipids abnormal and cardiac disorder, adverse events related to intestinal perforation, adverse events related to interstitial pneumonia, and adverse events related to malignant tumor.

7.R.2.2 Adverse events related to infection

PMDA asked the applicant to explain the incidence of infection-related adverse events associated with satralizumab, taking account of the following: (1) Caution against infection is required in treatment with other anti-IL-6R antibody drugs, (2) satralizumab inhibits IL-6, a cytokine that regulates humoral immunity, and (3) a majority of patients with NMOSD use drugs with immunosuppressive activity [see Section 7.R.1.2.1].

The applicant's explanation:

Table 41 shows the incidence of infection-related adverse events[31)] in the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) and in the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG). In both studies, the incidence of adverse events was higher in the satralizumab group than in the placebo group, but the incidence of serious adverse events was similar between the placebo group and the satralizumab group.

[31)] Events coded to "Infections and infestations" in System Organ Class (SOC) in Medical Dictionary for Regulatory Activities (MedDRA).

Table 41. Incidence of infection-related adverse events (double-blind period)

	Study SA-307JG		Study SA-309JG	
	Placebo	Satralizumab	Placebo	Satralizumab
No. of patients evaluated	42	41	32	63
Any adverse event	26 (61.9)	28 (68.3)	14 (43.8)	34 (54.0)
Serious adverse events	3 (7.1)	2 (4.9)	3 (9.4)	6 (9.5)
Most common adverse events				
Upper respiratory tract infection	6 (14.3)	10 (24.4)	6 (18.8)	10 (15.9)
Nasopharyngitis	7 (16.7)	10 (24.4)	1 (3.1)	9 (14.3)
Urinary tract infection	7 (16.7)	7 (17.1)	8 (25.0)	11 (17.5)
Pharyngitis	3 (7.1)	4 (9.8)	0	0
Cystitis	4 (9.5)	3 (7.3)	0	0
Rhinitis	0	3 (7.3)	0	0
Sinusitis	0	3 (7.3)	0	0
Oral herpes	3 (7.1)	2 (4.9)	0	0
Influenza	4 (9.5)	0	2 (6.3)	5 (7.9)
Cellulitis	0	0	0	4 (6.3)
Bronchitis	0	0	2 (6.3)	2 (3.2)
Oral candidiasis	0	0	2 (6.3)	0
Tooth abscess	0	0	2 (6.3)	0

n (%)

PMDA asked the applicant to explain whether suppression of acute phase inflammatory reaction delays the detection of infection, resulting in serious conditions.

The applicant's explanation:
In Studies SA-307JG and SA-309JG, there were no cases of infection that became serious due to delay in the detection because of suppressed acute phase reaction. Therefore, the relationship between satralizumab and serious infection is unclear. However, since inhibition of IL-6 signaling suppresses the acute inflammatory reaction and the delay in the detection of infection may possibly occur, precipitating in serious conditions, a precaution similar to that given for other anti-IL-6R antibody drugs will be included in the package insert.

PMDA's view:
The above explanation of the applicant is acceptable. Given that infection-related events are risks expected from the pharmacological action of satralizumab and that only a limited number of patients were treated in the clinical studies of satralizumab, information on infection-related events should be collected continuously after the market launch.

7.R.2.3 Reactivation of hepatitis virus B

Cautions are raised against reactivation of hepatitis B in using other anti-IL-6 antibody drugs. PMDA asked the applicant to explain the incidence of adverse events related to hepatitis B reactivation.

The applicant's explanation:
Regarding the incidence of adverse events related to hepatitis B reactivation[32)] during the double-blind period of the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) and the foreign phase III study (CTD 5.3.5.1-2, SA-309JG), hepatitis B DNA assay positive was observed in 1 patient in the satralizumab group in Study SA-307JG, but a causal relationship to satralizumab was ruled out and administration of satralizumab was continued without any measures taken against the adverse event. The patient had a history of hepatitis B infection. At Week 12 of administration, the patient was reported to have turned positive for hepatitis B virus with DNA level of 1.76 IU/mL. Thereafter, the patient was monitored periodically for hepatitis B virus DNA at intervals of approximately 4 weeks during the study period, and the virus was negative in all measurements, with the viral DNA level below 20 IU/mL, showing no increase in the viral DNA level. Thus, the event did not fall under the definition of hepatitis B virus reactivation.

However, only the above patient in Study SA-307JG had a history of hepatitis B infection among patients enrolled in clinical studies, and no sufficient data have been collected for detailed evaluation. Therefore, a precaution similar to that given for other anti-IL-6R drugs will be included in the package insert.

PMDA's view:
- As is the case with other anti-IL-6 antibody drugs approved for the indication for rheumatoid arthritis, satralizumab may also cause immune suppression in patients with NMOSD when administered in combination with corticosteroid, etc. Therefore, serious hepatitis may occur due to reactivation of hepatitis B virus. However, it is possible to avoid aggravation of symptoms by appropriate precaution, screening before administration, and monitoring during administration.

- Therefore, the applicant's explanation to include a similar precaution as that for other anti-IL-6 antibody drugs in the package insert is acceptable.

- Given that hepatitis B virus reactivation is a risk expected from the pharmacological action of satralizumab and that there are only a limited number of patients treated with satralizumab in clinical studies, information on hepatitis B virus reactivation-related events should be collected continuously after the market launch.

7.R.2.4 Adverse events related to neutropenia/leukopenia/agranulocytosis

Taking account of the facts that caution is raised against neutropenia/leukopenia/agranulocytosis in administering other anti-IL-6 antibody drugs, and that IL-6 inhibition may cause decrease in neutrophil and white blood cell counts [see Section 3.R.1], PMDA asked the applicant to explain the incidence of adverse events related to neutropenia/leukopenia/agranulocytosis associated with satralizumab.

[32)] Events coded to any of the following in Preferred Term (PT) in MedDRA:
Acute hepatitis B, chronic hepatitis B, congenital hepatitis B infection, HBV-DNA polymerase increased, hepatitis B, hepatitis B antibody abnormal, hepatitis B antibody positive, hepatitis B core antibody positive, hepatitis B core antigen positive, hepatitis B DNA assay positive, hepatitis B DNA increased, hepatitis B e antibody positive, hepatitis B e antigen positive, hepatitis B surface antibody positive, hepatitis B surface antigen positive, hepatitis B virus test positive, hepatitis viral, hepatitis infectious, asymptomatic viral hepatitis, hepatic infection, viral hepatitis carrier, hepatitis virus test positive, and hepatobiliary infection.

The applicant's explanation:

Table 42 shows the incidence of adverse events related to neutropenia/leukopenia/agranulocytosis[33)] during the double-blind period of the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) and the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG). In both studies, the incidence of adverse events was higher in the satralizumab group than in the placebo group, but no serious adverse event was observed in the satralizumab group.

Table 42. Incidence of adverse events related to neutropenia/leukopenia/agranulocytosis (double-blind period)

	Study SA-307JG		Study SA-309JG	
	Placebo	Satralizumab	Placebo	Satralizumab
No. of patients evaluated	42	41	32	63
Any adverse event	5 (11.9)	11 (26.8)	3 (9.4)	11 (17.5)
Serious adverse events	2 (4.8)	0	0	0
Adverse events				
Leukopenia	4 (9.5)	6 (14.6)	0	2 (3.2)
Lymphopenia	4 (9.5)	3 (7.3)	0	2 (3.2)
Neutropenia	2 (4.8)	2 (4.9)	1 (3.1)	4 (6.3)
Neutrophil count decreased	0	2 (4.9)	2 (6.3)	1 (1.6)
White blood cell count decreased	0	1 (2.4)	0	5 (7.9)

n (%)

Table 43 shows the percentage of patients who had a post-baseline shift to higher (worse) National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade[34)] in neutropenia or leukopenia during the double-blind period in Studies SA-307JG and SA-309JG. The incidences of neutrophil count decreased and white blood cell count decreased were both higher in the satralizumab group than in the placebo group.

Table 43. Percentage of patients who had post-baseline shift to higher NCI-CTCAE grade in neutropenia or leukopenia (double-blind period)

	Study SA-307JG		Study SA-309JG	
	Placebo	Satralizumab	Placebo	Satralizumab
No. of patients evaluated	42	41	32	63
Neutrophil count decreased	8 (19.0)	12 (29.3)	8 (25.0)	21 (33.3)
White blood cell count decreased	20 (47.6)	26 (63.4)	5 (15.6)	19 (30.2)

n (%)

Decreased neutrophil or white blood cell count associated with satralizumab is unlikely to increase the risk of infection, judging from the following observations:

- Table 44 shows the incidence of infection, classified by the lowest neutrophil and white blood cell count (NCI-CTCAE grade). In Study SA-307JG, the higher the grade of the lowest neutrophil count, the higher the tendency of the incidence of infection, but the incidence was similar between the placebo group and the satralizumab group. In Study SA-309JG, the incidence of infection was similar among different grades of the lowest neutrophil count.

33) Events coded to "Neutropenias" or "Leukopenias NEC" in HLT, and events classified in "Neutrophil count decreased," "White blood cell count decreased," "Granulocyte count decreased," "Neutrophil count abnormal," "Band neutrophil count decreased," or "White blood cell count abnormal" in PT in MedDRA.

34) Neutrophils: Grade 1, ≥1500/mm^3 and <2000/mm^3; Grade 2, ≥1000/mm^3 and <1500/mm^3; Grade 3, ≥500/mm^3 and <1000/mm^3; Grade 4, <500/mm^3
White blood cells: Grade 1, ≥3000/mm^3 and <3300/mm^3; Grade 2, ≥2000/mm^3 and <3000/mm^3; Grade 3, ≥1000/mm^3 and <2000/mm^3, Grade 4, <1000/mm^3

Table 44. Incidence of infection, classified by the lowest neutrophil and white blood cell count (NCI-CTCAE grade) (double-blind period)

		Study SA-307JG				Study SA-309JG			
		Placebo		Satralizumab		Placebo		Satralizumab	
		No. of patients evaluated	No. of patients with infection[a)]	No. of patients evaluated	No. of patients with infection[a)]	No. of patients evaluated	No. of patients with infection[a)]	No. of patients evaluated	No. of patients with infection[a)]
All grades		42	26 (61.9)	41	28 (68.3)	32	14 (43.8)	63	34 (54.0)
Neutrophil count grade	Grade 0	33	17 (51.5)	29	18 (62.1)	24	10 (41.7)	42	22 (52.4)
	Grade ≥1	9	9 (100.0)	12	10 (83.3)	8	4 (50.0)	21	12 (57.1)
	Grade ≥3	2	2 (100.0)	5	5 (100.0)	2	2 (100.0)	5	3 (60.0)
Leucocyte count grade	Grade 0	28	14 (50.0)	15	9 (60.0)	21	7 (33.3)	25	14 (56.0)
	Grade ≥1	14	12 (85.7)	26	19 (73.1)	11	7 (63.6)	38	20 (52.6)
	Grade ≥3	4	4 (100.0)	4	4 (100.0)	0	0	2	0

a) n (%)

- Table 45 shows the number of infection, classified by neutrophil and white blood cell counts (NCI-CTCAE grade) immediately before infection. Among patients with Grade ≥3 neutrophil count, a condition with a high risk of infection (*Support Care Cancer.* 2016;24:4377-83), infection occurred in 2 patients in the satralizumab group of Study SA-307JG (2 events; nasopharyngitis and rhinitis in 1 patient each) and in 2 patients in the satralizumab group of Study SA-309JG (3 events; pyelonephritis/urinary tract infection and pneumonia in 1 patient each). Pyelonephritis in Study SA-309JG was the only severe event observed, and its causal relationship to satralizumab was ruled out. Among patients with Grade ≥3 white blood cell count immediately before infection, there was no clear difference in the tendency of incidence of infection between the placebo group and the satralizumab group.

Table 45. Number of infection, classified by neutrophil and white blood cell counts immediately before infection (NCI-CTCAE grade) (double-blind period)

		Study SA-307JG		Study SA-309JG	
		Placebo	Satralizumab	Placebo	Satralizumab
All Grades		89	104	66	115
Neutrophil count grade	Not low[a)]	85	89	62	107
	Grade 1	1	3	0	2
	Grade 2	3	10	4	3
	Grade 3	0	2	0	2
	Grade 4	0	0	0	1
Leucocyte count grade	Not low[a)]	56	63	54	86
	Grade 1	28	21	8	26
	Grade 2	4	19	4	3
	Grade 3	1	1	0	0
	Grade 4	0	0	0	0

a) Patients not classified in Grade ≥1 group

Thus, all of the adverse events related to neutropenia/leukopenia/agranulocytosis observed in the clinical studies of satralizumab were not serious, showing no tendency of increase in the risk of infection or occurrence of clinically significant events with the decrease in neutrophil or white blood cell count associated with satralizumab. Nevertheless, given that the incidence of adverse events related to neutropenia/leukopenia/agranulocytosis tends to be higher in the satralizumab group than in

the placebo group and that neutropenia and leukopenia may occur when IL-6 signaling is inhibited, a similar precaution to that for other anti-IL-6R antibody drugs will be included in the package insert.

PMDA's view:
The above explanation of the applicant is acceptable. However, events related to neutropenia/leukopenia/agranulocytosis are anticipated from the pharmacological action of satralizumab, and there are only a limited number of patients treated with satralizumab in clinical studies. Information on events related to neutropenia/leukopenia/agranulocytosis should be collected continuously after the market launch.

7.R.2.5 Adverse events related to thrombocytopenia

Taking account of the facts that caution is raised against thrombocytopenia in administering other anti-IL-6R antibody drugs, and that IL-6 inhibition may cause thrombocytopenia [see Section 3.R.1], PMDA asked the applicant to explain the incidence of adverse events related to thrombocytopenia associated with satralizumab.

The applicant's explanation:
Table 46 shows the incidence of adverse events related to thrombocytopenia[35)] during the double-blind period of the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) and the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG). In Study SA-309JG, the incidence of the adverse events was higher in the satralizumab group than in the placebo group, whereas no serious adverse events were observed in the satralizumab group in either of the studies.

Table 46. Incidence of adverse events related to thrombocytopenia (double-blind period)

	Study SA-307JG		Study SA-309JG	
	Placebo	Satralizumab	Placebo	Satralizumab
No. of patients evaluated	42	41	32	63
Any adverse event	2 (4.8)	1 (2.4)	1 (3.1)	3 (4.8)
Serious adverse events	1 (2.4)	0	0	0
Adverse events				
Thrombocytopenia	1 (2.4)	1 (2.4)	1 (3.1)	3 (4.8)
Autoimmune thrombocytopenia	1 (2.4)	0	0	0

n (%)

Table 47 shows the percentage of patients who had a post-baseline shift to a higher NCI-CTCAE grade in thrombocytopenia during the double-blind period in Studies SA-307JG and SA-309JG. The percentage was higher in the satralizumab group than in the placebo group.

Table 47. Percentage of patients who had post-baseline shift to higher NCI-CTCAE grade in thrombocytopenia (double-blind period)

	Study SA-307JG		Study SA-309JG	
	Placebo	Satralizumab	Placebo	Satralizumab
No. of patients evaluated	42	41	32	63
Platelet count decreased	6 (14.3)	11 (26.8)	1 (3.1)	14 (22.2)

n (%)

35) Events coded to "Thrombocytopenias" in HLT and events coded to "Platelet count decreased" or "Platelet count abnormal" in PT in MedDRA.

Thus, all of the adverse events related to thrombocytopenia observed in the clinical studies of satralizumab were non-serious and clinically insignificant. However, since thrombocytopenia may occur when IL-6 signaling is inhibited, a similar precaution to that for other anti-IL-6R antibody drugs will be included in the package insert.

PMDA's view:
The above explanation of the applicant is acceptable. Since events related to thrombocytopenia are anticipated from the pharmacological action of satralizumab, and there are only a limited number of patients treated with satralizumab in clinical studies, information on events related to thrombocytopenia should be collected continuously after the market launch.

7.R.2.6 Adverse events related to hepatic dysfunction

Taking account of the facts that caution is raised against hepatic dysfunction in administering other anti-IL-6R antibody drugs, and that IL-6 inhibition may cause hepatic dysfunction [see Section 3.R.1], PMDA asked the applicant to explain the incidence of hepatic dysfunction associated with satralizumab.

The applicant's explanation:
Table 48 shows the incidence of adverse events related to hepatic dysfunction[36)] during the double-blind period of the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) and the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG). No serious adverse events were observed in the satralizumab group in either of the studies.

Table 48. Incidence of adverse events related to hepatic dysfunction (double-blind period)

	Study SA-307JG		Study SA-309JG	
	Placebo	Satralizumab	Placebo	Satralizumab
No. of patients evaluated	42	41	32	63
Any adverse event	6 (14.3)	4 (9.8)	2 (6.3)	9 (14.3)
Serious adverse events	0	0	0	0
Most common adverse events				
AST increased	3 (7.1)	1 (2.4)	0	1 (1.6)
ALT increased	2 (4.8)	1 (2.4)	0	4 (6.3)
Hypertransaminasaemia	2 (4.8)	1 (2.4)	0	0
γ-GTP increased	1 (2.4)	0	0	1 (1.6)
Hypofibrinogenaemia	0	1 (2.4)	0	2 (3.2)

n (%)

During the double-blind period of Studies SA-307JG and SA-309JG, there were no patients who had liver function test abnormal suggestive of drug-induced liver disorder[37)] or patients who reported clinical symptoms of jaundice.

Thus, all of the adverse events related to hepatic dysfunction observed in the clinical studies of satralizumab were non-serious and clinically insignificant. However, since hepatic dysfunction may

36) Events coded to "Hepatic failure, hepatic fibrosis, hepatic cirrhosis, and other hepatocellular injuries (narrow)," "Liver-related laboratory tests, signs, and symptoms (narrow)," "Cholestasis and jaundice of hepatic cause (narrow)," "Liver-related coagulation and bleeding disturbances (narrow)," or "Hepatitis, non-infectious (narrow)," in Standardised MedDRA Queries (SMQ) and events coded to "Hepatocellular damage and hepatitis NEC" in HLT in MedDRA.

37) Increase in total bilirubin to >2 × ULN or increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) to >3 × ULN accompanied by clinical jaundice.

occur when IL-6 signaling is inhibited, a similar precaution to that for other anti-IL-6R antibody drugs will be included in the package insert.

PMDA's view:
The above explanation of the applicant is acceptable. However, since events related to hepatic dysfunction are anticipated from the pharmacological action of satralizumab, and since there are only a limited number of patients treated with satralizumab in clinical studies, information on events related to hepatic dysfunction should be collected continuously after the market launch.

7.R.2.7 Adverse events related to hypersensitivity

Taking account of the facts that caution is raised against hypersensitivity-related adverse events such as anaphylactic shock in administering other anti-IL-6R antibody drugs, PMDA asked the applicant to explain the incidence of hypersensitivity-related adverse events associated with satralizumab.

The applicant's explanation:
Table 49 shows the incidence of adverse events related to hypersensitivity[38)] during the double-blind period of the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) and the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG). Although neither anaphylaxis nor serious adverse events were observed in these studies, satralizumab is a protein drug and is expected to cause hypersensitivity-related events such as anaphylactic shock as are the cases with other protein drugs, an appropriate precaution will be included in the package insert.

Table 49. Incidence of adverse events related to hypersensitivity (double-blind period)

	Study SA-307JG		Study SA-309JG	
	Placebo	Satralizumab	Placebo	Satralizumab
No. of patients evaluated	42	41	32	63
Any adverse event	2 (4.8)	5 (12.2)	6 (18.8)	11 (17.5)
Serious adverse events	0	0	0	0
Main adverse events				
Injection related reaction	2 (4.8)	5 (12.2)	5 (15.6)	8 (12.7)
Hypersensitivity	0	0	1 (3.1)	2 (3.2)

n (%)

Taking account of the fact that visible particles were detected in Enspring under the long-term storage conditions [see Section 2.R.1], PMDA asked the applicant to explain the incidence of hypersensitivity-related adverse events caused by the drug product containing visible particles in clinical studies.

The applicant's explanation:

- Although visible particles may occur after [redacted] in the prefilled syringe preparation under the long-term storage, the timing of the formation of visible particles differs from batch to batch, precluding the identification of the timing of the occurrence of visible particles in clinical studies.

38) Events coded to "Anaphylactic/anaphylactoid shock conditions (narrow)" or "Anaphylactic reactions (narrow)" in SMQ, "Injection site reaction," "Infusion site reactions" "or "Administration site reactions NEC" in HLT, and events coded to "Hypersensitivity" or "Injection related reaction" in PT in MedDRA.

- Table 50 shows the detail of information on the use of the prefilled syringes that had been stored for <1 year or ≥1 year after manufacture, during the open-label extension period in Studies SA-307JG and SA-309JG.

Table 50. Administration of prefilled syringe preparation with different storage periods after manufacture (open-label extension period)

	Study SA-307JG		Study SA-309JG	
	<1 year	≥1 year	<1 year	≥1 year
Total No. of patients receiving satralizumab	11	34	23	29
Total No. of times of administration	11	266	112	147

- Hypersensitivity-related adverse events were not observed following the administration of the prefilled syringe preparation with a storage period of <1 year after manufacture in either study. With the prefilled syringe preparation with a storage period of ≥1 year, in contrast, adverse events were observed in 2 patients in Study SA-307JG (2 events; injection related reaction and injection site bruising in 1 patient each) and in 1 patient in Study SA-309JG (2 events; injection related reaction). Neither anaphylaxis nor a serious event was observed. There were no adverse events leading to treatment discontinuation.

- These results suggest that there is no significant difference in adverse events observed between prefilled syringes with <1 year of storage period after manufacture and those with ≥1 year of storage period, when adjusted for the total number of administrations of each preparation.

PMDA's view:
The above explanation of the applicant is acceptable. However, since hypersensitivity-related events is a risk anticipated for biological preparations, the drug category to which satralizumab belongs, and since there are only a limited number of patients treated with satralizumab in clinical studies, information on events related to hypersensitivity should be collected continuously after the market launch.

7.R.2.8 Adverse events related to lipid abnormality and cardiac disorder

Taking account of the facts that caution is raised against lipid abnormality in administering other anti-IL-6R antibody drugs, and that IL-6 is involved in the synthesis and secretion of apolipoprotein and satralizumab may possibly cause dyslipidemia-related events by its IL-6-inhibitory effect [see Section 3.R.1], PMDA asked the applicant to explain the incidence of adverse events related to lipid abnormality and cardiac disorder.

The applicant's explanation:
Table 51 shows the incidence of adverse events related to lipid abnormality[39)] during the double-blind period of the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) and the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG). No serious events were observed.

[39)] Events coded to "Dyslipidaemia (narrow)" in SMQ in MedDRA

Table 51. Incidence of lipid abnormality-related adverse events (double-blind period)

	Study SA-307JG		Study SA-309JG	
	Placebo	Satralizumab	Placebo	Satralizumab
No. of patients evaluated	42	41	32	63
Any adverse event	7 (16.7)	8 (19.5)	2 (6.3)	6 (9.5)
Serious adverse events	0	0	0	0
Most common adverse events				
Hypercholesterolaemia	5 (11.9)	4 (9.8)	0	2 (3.2)
Hyperlipidaemia	0	2 (4.9)	1 (3.1)	1 (1.6)
Blood cholesterol increased	0	2 (4.9)	0	1 (1.6)
Low density lipoprotein increased	0	2 (4.9)	0	1 (1.6)
Blood triglycerides increased	2 (4.8)	0	0	0

n (%)

Table 52 shows the percentage of patients who had a post-baseline shift to a higher NCI-CTCAE grade in total cholesterol concentration and triglyceride concentration during the double-blind period of Studies SA-307JG and SA-309JG. Although the percentage of patients tended to be higher in the satralizumab group than in the placebo group, there were no patients with severe conditions or adverse events leading to treatment discontinuation.

Table 52. Percentage of patients who had post-baseline shift to higher NCI-CTCAE grade in total cholesterol concentration and triglyceride concentration (double-blind period)

	Study SA-307JG		Study SA-309JG	
	Placebo	Satralizumab	Placebo	Satralizumab
No. of patients evaluated	42	41	32	63
Total cholesterol	15 (35.7)	15 (36.6)	10 (31.3)	29 (46.0)
Triglycerides	22 (52.4)	24 (58.5)	14 (43.8)	42 (66.7)

n (%)

Table 53 shows the incidence of cardiac disorder-related adverse events[40)] during the double-blind period of Studies SA-307JG and SA-309JG. In both studies, the incidence of adverse events was higher in the satralizumab group than in the placebo group. However, there were no serious adverse events in Study SA-307JG and, in Study SA-309JG, serious adverse events were observed in 3 patients in the satralizumab group (acute myocardial infarction, bradycardia, and pulmonary oedema in 1 patient each), but a causal relationship to satralizumab was ruled out for all of them.

Table 53. Incidence of cardiac disorder-related adverse events (double-blind period)

	Study SA-307JG		Study SA-309JG	
	Placebo	Satralizumab	Placebo	Satralizumab
No. of patients evaluated	42	41	32	63
Any adverse event	2 (4.8)	5 (12.2)	1 (3.1)	15 (23.8)
Serious adverse events	0	0	0	3 (4.8)
Most common adverse events				
Blood CPK increased	2 (4.8)	1 (2.4)	1 (3.1)	4 (6.3)
Oedema peripheral	0	1 (2.4)	0	4 (6.3)
Bradycardia	0	1 (2.4)	0	2 (3.2)
Tachycardia	0	0	0	2 (3.2)

n (%)

Table 54 shows the incidence of adverse events related to lipid abnormality and those related to cardiac disorder. In the satralizumab group of Study SA-309JG, cardiac disorder-related adverse events were observed in 3 patients among patients who had lipid abnormality-related adverse events.

40) Events coded to “Cardiac disorders” in SOC and events classified in “Cardiac failure (wide),” “Arrhythmia (wide),” or “Ischaemic heart disease (wide)” in SMQ in MedDRA.

The events were only mild blood creatine phosphokinase (CPK) increased in 2 patients. The remaining 1 patient experienced tachycardia, acute myocardial infarction, and coronary artery disease, but this patient was complicated by type 2 diabetes mellitus and a causal relationship of these adverse events to the study drug was ruled out, and the administration of the study drug was continued.

Table 54. Incidence of adverse events related to cardiac disorder or to lipid abnormality (double-blind period)

Adverse events related to cardiac disorder	Adverse events related to lipid abnormality							
	Study SA-307JG				Study SA-309JG			
	Placebo		Satralizumab		Placebo		Satralizumab	
	Occurred	Not occurred	Occurred	Not occurred	Occurred	Not occurred	Occurred	Not occurred
No. of patients evaluated	7	35	8	33	2	30	6	57
Occurred	1 (14.3)	1 (2.9)	0	5 (15.2)	1 (50.0)	0	3 (50.0)	12 (21.1)
Not occurred	6 (85.7)	34 (97.1)	8 (100.0)	28 (84.8)	1 (50.0)	30 (100.0)	3 (50.0)	45 (78.9)

n (%)

The applicant's explanation based on the above results:

The incidence of lipid abnormality-related adverse events in clinical studies on satralizumab did not significantly differ between the satralizumab group and the placebo group. All of the observed events were non-serious, and NCI-CTCAE grades of total cholesterol concentration and triglyceride concentration showed only mild to moderate increases.

The incidence of cardiac disorder-related adverse events in clinical studies on satralizumab was higher in the satralizumab group than in the placebo group, and serious adverse events were observed in 3 patients in the satralizumab group of Study SA-309JG. However, a causal relationship of the observed serious adverse events to satralizumab was ruled out, and no clear relationship was observed between adverse events related to lipid abnormality and those related to cardiac disorder.

These results suggest that there were no clinically significant safety problems. However, since the incidence of lipid abnormality-related events was higher in the satralizumab group than in the placebo group, and since lipid abnormality-related events may occur by inhibition of IL-6 signaling which is involved in lipid metabolism, precaution against lipid abnormality will be included in the package insert. On the other hand, there were no serious cardiac disorder-related adverse events causally related to satralizumab, with no clinically significant safety problems currently. It is therefore considered unnecessary to raise caution in the package insert, but information on the incidence of cardiac disorder-related adverse events will be collected continuously after the market launch.

PMDA's view:

The above explanation of the applicant is acceptable. However, since cardiac disorder-related adverse events are observed with other anti-IL-6R antibody drugs and caution is raised against such an adverse event, and since there are only a limited number of patients treated in clinical studies on satralizumab, information on cardiac disorder-related events should be collected continuously after the market launch.

7.R.2.9 Adverse events related to intestinal perforation

Taking account of the facts that caution is raised against intestinal perforation in administering other anti-IL-6R antibody drugs, PMDA asked the applicant to explain the incidence of adverse events related to intestinal perforation associated with satralizumab.

The applicant's explanation:

No adverse events related to intestinal perforation[41)] were observed either in the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) or in the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG). A high dose of non-steroidal anti-inflammatory drug (NSAID) is a risk factor of intestinal perforation (*Clinical Rheumatology and Related Research*. 2013;25:159-63). Frequency of using NSAIDs is high in patients with rheumatoid arthritis, the disease for which other anti-IL-6R antibody drugs are mainly indicated (*Clinical Rheumatology and Related Research*. 2007;19:11-16), whereas the frequency is considered to be lower in patients with NMOSD than in patients with rheumatoid arthritis, suggesting a lower risk of intestinal perforation in patients with NMOSD than in patients with rheumatoid arthritis. It is therefore considered unnecessary to include precaution against intestinal perforation in the package insert. However, since intestinal perforation is observed in patients treated with other anti-IL-6R antibody drugs, the possibility of intestinal perforation due to inhibition of IL-6 signaling cannot be ruled out. Therefore, information on the incidence of adverse events related to intestinal perforation will be collected continuously after the market launch.

PMDA's view:

The above explanation of the applicant is acceptable. However, since intestinal perforation-related adverse events are observed with other anti-IL-6R antibody drugs and caution is raised against such an adverse event, and since there are only a limited number of patients treated with satralizumab in clinical studies, information on events related to intestinal perforation should be collected continuously after the market launch.

7.R.2.10 Adverse events related to interstitial pneumonia

Taking account of the fact that caution is raised against interstitial pneumonia in administering other anti-IL-6R antibody drugs, PMDA asked the applicant to explain the incidence of adverse events related to interstitial pneumonia associated with satralizumab.

The applicant's explanation:

No adverse events related to interstitial pneumonia[42)] were observed either in the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) or in the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG). Interstitial pneumonia naturally occurs in patients with rheumatoid arthritis, the disease for which other anti-IL-6R antibody drugs are mainly indicated (Consensus statement for the diagnosis and treatment of drug-induced lung injuries, abbreviated version, Japanese Respiratory Society). Also, methotrexate, the first-line drug for the treatment of rheumatoid arthritis, has a risk of interstitial pneumonia. As a result, patients with rheumatoid arthritis have a high risk of developing interstitial pneumonia. In contrast, interstitial lung lesion was reported in none of the patients with NMOSD, the

41) Events coded to "Intestinal perforation (narrow)" in SMQ in MedDRA.
42) Events coded to "Interstitial lung disease (narrow)" in SMQ in MedDRA.

disease for which satralizumab is indicated, suggesting that the risk of interstitial pneumonia is low in this patient group. It is therefore considered unnecessary to include precaution against interstitial pneumonia in the package insert. However, since interstitial pneumonia is observed in patients treated with other anti-IL-6R antibody drugs, the possibility cannot be ruled out that satralizumab might cause interstitial pneumonia. Therefore, information on the incidence of interstitial pneumonia-related adverse events will be collected continuously after the market launch.

PMDA's view:
The above explanation of the applicant is acceptable. However, since interstitial pneumonia-related adverse events are observed with other anti-IL-6R antibody drugs and caution is raised against such adverse events, and since there are only a limited number of patients treated with satralizumab in clinical studies, information on events related to interstitial pneumonia should be collected continuously after the market launch.

7.R.2.11 Adverse events related to malignant tumor

Taking account of the possibility that IL-6 pathway is involved in anti-tumor reaction [see Section 5.4], PMDA asked the applicant to explain the incidence of malignant tumor in patients treated with anti-IL6R antibody drugs.

The applicant's explanation:

- According to the safety data obtained from past and ongoing clinical studies[43] on tocilizumab, an anti-IL-6R antibody drug, involving patients with moderate to severe rheumatoid arthritis, the incidence of malignant tumor (including non-melanoma skin cancer) in the entire subject population throughout the study period was 1.54 per 100 patient-years (95% CI; 1.35, 1.74). The incidence in long-term administration for ≥36 months was 1.60 per 100 patient-years (95% CI; 1.32, 1.93), which was not significantly higher than the incidence during a shorter treatment period.

- As for the risk of tocilizumab-induced malignant tumor, no statistically significant difference was observed in the incidence ratio[44] between the incidence of malignant tumor (excluding non-melanoma skin cancer) in the clinical studies[43] and the incidence[45] expected in the general population. However, the incidence ratio of malignant tumor in lung and bronchus was 2.19 (95% CI; 1.47, 3.15) and the incidence ratio of malignant tumor in uterine cervix was 3.51 (95% CI; 1.13, 8.19), showing that the incidence of malignant tumor in these organs was higher in the above clinical studies than the incidence expected in the general population. The following causes for the above results are considered: (1) In a meta-analysis of the incidence of malignant tumor in patients with rheumatoid arthritis, the incidence of lung cancer was higher in patients with rheumatoid arthritis than in the general population, with the incidence ratio of 1.63 (95% CI; 1.43, 1.87) (*Arthritis Res Ther*. 2008;10:R45), and (2) in clinical studies, cervix carcinoma was observed mainly in patients in South America and East Europe, the regions where the early screening

43) Studies WA17822, WA17823, WA18063, WA18062, WA17824, WP18663, WA18695, WA18696, and WA19924
44) The standardized incidence ratio (ratio of the number of observed malignant tumor to the number of malignant tumor predicted) adjusted for age and sex, calculated using the indirect standardization method.
45) The number of patients predicted based on the incidence of malignant tumor in the general population, calculated using Surveillance Epidemiology and End Results (SEER) Program of the National Cancer Institute. Non-melanoma skin cancer is not captured within the SEER database, and is therefore excluded.

program for cervical cancer is not yet fully established. As for non-melanoma skin cancer, the incidence of basal cell carcinoma and squamous cell carcinoma, which were the main non-melanoma skin cancer observed in clinical studies[46] was 0.20 (95% CI; 0.15, 0.27) and 0.09 (95% CI; 0.05, 0.14), respectively, per 100 patient-years, which did not tend to be higher than the incidence[47] in the general population in the US, the country where most of the patients were enrolled in these studies (*Adv Exp Med Biol.* 2014;810:120-40).

- Thus, there is no evidence suggesting that the risk of malignant tumor in patients with rheumatoid arthritis treated with tocilizumab far exceeds the risk in the general population. Therefore, the risk of carcinogenicity related to immune suppression is considered to be low.

PMDA asked the applicant to explain the incidence of malignant tumor-related adverse events associated with satralizumab.

The applicant's explanation:
Table 55 shows the incidence of adverse events related to malignant tumor[48] during the double-blind period of the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) and the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG). Squamous cell carcinoma was observed in 1 patient in the satralizumab group during the double-blind period of Study SA-309JG, but its causal relationship to satralizumab was ruled out, and the adverse event did not lead to discontinuation or interruption of administration of satralizumab. Since the incidence did not differ between the satralizumab group and placebo group and since there is no clear evidence of a relationship between the malignancy and satralizumab, precaution against malignant tumor will not be included in the package insert. However, given the mechanism of action of satralizumab, satralizumab may increase the risk of malignant tumor. Information on the incidence of adverse events related to malignant tumor will be collected continuously after the market launch.

Table 55. Incidence of adverse events related to malignant tumor (double-blind period)

	Study SA-307JG		Study SA-309JG	
	Placebo	Satralizumab	Placebo	Satralizumab
No. of patients evaluated	42	41	32	63
Any adverse event	2 (4.8)	0	0	1 (1.6)
Serious adverse events	2 (4.8)	0	0	0
Adverse events				
Squamous cell carcinoma	0	0	0	1 (1.6)
Hepatic cancer	1 (2.4)	0	0	0
Breast cancer	1 (2.4)	0	0	0

n (%)

PMDA's view:
The above explanation of the applicant is acceptable. However, given that satralizumab may increase the risk of malignant tumor, as is the case with other anti-IL6R antibody drugs, and that there are only a limited number of patients treated with satralizumab in clinical studies, information on events related to malignant tumor should be collected continuously after the market launch.

[46] Studies WA17823, WA18063, WA18062, WA17824, WA18695, WA18696, WA19926, WA22762, and NA25220
[47] Incidence of basal cell carcinoma, 0.92 (man) and 0.49 (woman) per 100 patient-years; incidence of squamous cell carcinoma, 0.36 (man) and 0.15 (woman) per 100 patient-years
[48] Events coded to "Malignant tumor (narrow)" in SMQ in MedDRA

7.R.3 Clinical positioning

PMDA asked the applicant to explain the clinical positioning of satralizumab.

The applicant's explanation:

- NMOSD is an immune-mediated disease of the central nervous system, characterized by severe optic neuritis and transverse myelitis. The definition of the disease has undergone changes over the years partially overlapping the timing of the development of satralizumab. The disease was previously called "Devic disease" as a monophasic disease accompanied by severe optic neuritis and transverse myelitis. Upon the discovery of anti-AQP4 antibody in 2004 (*Lancet.* 2004;364:2106-12), diagnostic criteria for NMO were proposed in 2006 (*Neurology.* 2006;66:1485-9). Subsequent analyses of anti-AQP4 antibody-positive patients revealed that there are also many cases with optic neuritis alone or myelitis alone which are considered to be partial symptoms of NMO, and that there are anti-AQP4 antibody-positive patients with brain lesion alone. In addition, based on the results of pathological studies and studies on animal models, it has become certain that anti-AQP4 antibody is not only a disease marker but also pathogenic to the central nervous system. Based on these findings, diseases characterized by anti-AQP4 antibody-positivity have come to be treated as a single disease entity and, in 2007, the spectrum of diseases associated with anti-AQP4 antibodies was defined and collectively named NMOSD (*Lancet Neurol.* 2007;6:805-15). In 2015, the diagnostic criteria were further refined by the International Panel for NMO Diagnosis and, as a result, NMOSD was defined as the unifying term (*Neurology*. 2015;85:177-89). The revised diagnostic criteria widely encompass a group of diseases that share the pathology associated with the production of a specific autoantibody called anti-AQP4 antibody. Currently in Japan, the 2015 diagnostic criteria are widely used (*2017 Japanese guidelines for multiple sclerosis and neuromyelitis optica* [in Japanese]. Igaku Shoin; 2017).

- Eculizumab was approved in Japan in November 2019 as a drug to prevent the relapse of NMOSD. Eculizumab is a humanized monoclonal antibody that targets human complement C5, and considered to inhibit the cleavage of complement C5, thereby suppressing astrocyte damage caused by anti-AQP4 antibody-mediated complement activation. In contrast, satralizumab is a humanized monoclonal antibody that targets IL-6R, and thought to block IL-6 signaling to inhibit antibody production by B cells and the permeability of the blood-brain barrier, thereby suppressing astrocyte damage [see Section 3.R.1].

- Both satralizumab and eculizumab have been shown to prevent the relapse of NMOSD although the relative clinical positioning of these drugs is unclear because of no head-to-head comparison in clinical studies. Of particular safety concerns with these drugs are infection caused by the IL-6-inhibitory activity of satralizumab and meningococcal infection caused by inhibition of complement complex formation by eculizumab. In patients with risk factors for meningococcal infection and patients in whom its risk is difficult to control, satralizumab will be the preferred treatment option. In addition, eculizumab is administered intravenously once every 2 weeks, whereas satralizumab is administered subcutaneously once every 4 weeks (once every 2 weeks up to Week 4).

- Although there is no clinical practice guideline that refers to the clinical positioning of satralizumab or eculizumab, they can be chosen depending on their safety, convenience, as well as patient characteristics and conditions, etc.

- The standard therapies other than eculizumab recommended for the prevention of relapse of NMOSD are oral corticosteroids and other immunosuppressive therapies (e.g., azathioprine and mycophenolate mofetil) (*2017 Japanese guidelines for multiple sclerosis and neuromyelitis optica* [in Japanese]. Igaku Shoin; 2017). However, these therapies fail to suppress the relapse in many patients and, even if the relapse is suppressed, adverse drug reactions associated with the prolonged use of corticosteroids may occur. A new treatment option is therefore needed.

- The efficacy and safety of satralizumab in patients with NMOSD have been demonstrated in the double-blind period of the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) and the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG). Therefore, satralizumab is expected to be a new treatment option for the prevention of the relapse of NMOSD.

PMDA accepted the explanation of the applicant.

7.R.4 Indication

7.R.4.1 Proposed indication "neuromyelitis optica spectrum"

In the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) and the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG), patients enrolled were those diagnosed with NMO according to the 2006 criteria or diagnosed with NMOSD according to the 2007 criteria; and Study SA-307JG included patients with documented relapse. Taking account of these facts, PMDA asked the applicant to explain the appropriateness of indicating satralizumab for "neuromyelitis optica spectrum."

The applicant's explanation about the appropriateness of indicating satralizumab for neuromyelitis optica spectrum:

- Results of Studies SA-307JG and SA-309JG demonstrated the efficacy and safety of satralizumab [see Sections 7.2.1 and 7.2.2].

- Most of the patients who meet the 2015 criteria for NMOSD, which are widely used currently in Japan, also meet the 2006 criteria for NMO or the 2007 criteria for NMOSD.

- Although there may be some patients who meet the 2015 criteria for NMOSD but do not meet the inclusion criteria for Studies SA-307JG and SA-309JG, all of them are considered to be anti-AQP4 antibody positive patients or anti-AQP4 antibody negative patients with optic neuritis or myelitis, who have pathological conditions similar to those observed in patients enrolled in the above 2 studies. Satralizumab is thus expected to be effective and safe in these patients, as in the case of patients enrolled in these studies.

The applicant's explanation about the appropriateness of including patients with first attack in the target patient population:

- Study SA-309JG included patients with clinical evidence of at least 1 documented relapse (including first attack) within 12 months before screening. Not only patients with documented relapse but also patients with the first attack were treated with the study drug. Table 56 shows the incidence of the first PDR in patients with the first attack and patients with relapse in Study SA-309JG, and Table 57 shows the incidence of adverse events. No clear difference was observed in the tendency of efficacy or safety profile between the patients with the first attack and the patients with relapse although there were limitations to the comparison because of the small number of the patients with the first attack.

- NMOSD repeats relapse, with the conditions often becoming more severe with each relapse. It is desirable to start treatment to prevent relapse promptly after the definitive diagnosis. Since the prevention of relapses serves as a therapy for the disease, patients diagnosed with the first attack of NMOSD should receive therapy for relapse prevention.

- Satralizumab should thus be indicated for patients with the first attack of NMOSD as well.

Table 56. Incidence of the first PDR in patients with first attack and patients with relapse (Study SA-309JG, double-blind period)

	Overall population				Anti-AQP4 antibody positive				Anti-AQP4 antibody negative			
	Patients with first attack		Patients with relapse		Patients with first attack		Patients with relapse		Patients with first attack		Patients with relapse	
	Placebo	Satralizumab	Placebo	Satralizumab	Placebo	Satralizumab	Placebo	Satralizumab	Placebo	Satralizumab	Placebo	Satralizumab
No. of patients evaluated	4	7	28	56	4	5	19	36	0	2	9	20
No. of patients with PDR (%)	1 (25.0)	3 (42.9)	15 (53.6)	16 (28.6)	1 (25.0)	1 (20.0)	12 (63.2)	8 (22.2)	0	2 (100)	3 (33.3)	8 (40.0)
Hazard ratio[a)] [95% CI]	0.995 [0.090, 11.018]		0.417 [0.205, 0.851]		0.693 [0.043, 11.156]		0.236 [0.094, 0.594]		-		1.192 [0.298, 4.775]	

-: Not estimable

a) Based on Cox proportional hazard model stratified by allocation factor

Table 57. Incidence of adverse events in patients with first attack and patients with relapse (Study SA-309JG, double-blind period)

	Patients with first attack		Patients with relapse	
	Placebo	Satralizumab	Placebo	Satralizumab
No. of patients evaluated	4	7	28	56
Any adverse event	2 (50.0)	5 (71.4)	22 (78.6)	53 (94.6)
Serious adverse events other than death	0	1 (14.3)	5 (17.9)	11 (19.6)
Adverse events leading to treatment discontinuation	0	0	1 (3.6)	1 (1.8)
Adverse events resulting in death	0	0	0	0
Most common adverse events				
Urinary tract infection	0	0	8 (28.6)	11 (19.6)
Upper respiratory tract infection	2 (50.0)	1 (14.3)	4 (14.3)	9 (16.1)
Pruritus	0	1 (14.3)	0	5 (8.9)
Headache	0	1 (14.3)	4 (14.3)	9 (16.1)
Sinus headache	0	1 (14.3)	0	0
Nausea	0	1 (14.3)	2 (7.1)	10 (17.9)
Diarrhoea	0	0	0	4 (7.1)
Pain in extremity	0	2 (28.6)	3 (10.7)	7 (12.5)
Glycosuria	0	1 (14.3)	0	0
Injection related reaction	0	0	5 (17.9)	8 (14.3)
Neutropenia	0	0	1 (3.6)	4 (7.1)
Hyponatraemia	0	0	1 (3.6)	0

n (%)

In Studies SA-307JG and SA-309JG, the primary endpoint was time to the first PDR, indicating that satralizumab is a therapeutic agent intended to be used for the prevention of relapses. Acute-phase treatment and relapse prevention are described separately in the Japanese clinical practice guideline (*2017 Japanese guidelines for multiple sclerosis and neuromyelitis optica* [in Japanese]. Igaku Shoin; 2017), suggesting that treatment options differ between acute-phase treatment and relapse prevention. Taking account of the above, PMDA asked the applicant to explain the necessity of specifying relapse prevention in the indication for satralizumab.

The applicant's explanation:

- The disability associated with NMOSD accumulates through relapses (first attack or relapse) and rarely progress secondarily. It is essential to minimize the progress of disability through the prevention of relapse of NMOSD. Because the prevention of relapses serves as a therapy, "neuromyelitis optica spectrum" is proposed as the indication of satralizumab.

- On the other hand, eculizumab was approved for "prevention of relapse of neuromyelitis optica spectrum disorder (including neuromyelitis optica)" after regulatory submission for satralizumab. The difference in the description of the indication between eculizumab and satralizumab may cause confusion in clinical practice.

- To avoid such confusion, it is considered preferable to include the term "prevention of relapse" in the indication of satralizumab. The indication is thus changed to "prevention of relapse of neuromyelitis optica spectrum disorder (including neuromyelitis optica)."

PMDA's view:

It is acceptable to indicate satralizumab for "prevention of relapse of neuromyelitis optica spectrum disorder (including neuromyelitis optica)," taking account of the following:

- The primary endpoint of Studies SA-307JG and SA-309JG was "time to relapse," indicating that satralizumab is intended to be used for the prevention of relapses.

- Acute-phase treatment and relapse prevention are described separately in the Japanese clinical practice guideline (*2017 Japanese guidelines for multiple sclerosis and neuromyelitis optica* [in Japanese]. Igaku Shoin; 2017), suggesting that treatment options differ between acute-phase treatment and relapse prevention. Inclusion of the term "prevention of relapse" in the indication will help healthcare professionals to recognize the intended use of satralizumab.

7.R.4.2 Use in anti-AQP4 antibody-negative patients

Taking into account that efficacy of satralizumab in anti-AQP4 antibody-negative patients was unclear in clinical studies [see Section 7.R.1.1], PMDA asked the applicant to explain the appropriateness of including anti-AQP4 antibody-negative NMOSD in the indication of satralizumab.

The applicant's explanation:
Satralizumab can be one of the treatment options for anti-AQP4 antibody-negative NMOSD, for the following reasons:

- Since relapses of NMOSD may result in severe disability, it is desirable to start treatment as soon as a definitive diagnosis of NMOSD is made, regardless of the results of test for anti-AQP4 antibodies. The anti-AQP4 antibody test may give false negative results depending on the test system or the timing of the test, but the basic treatment strategy for the prevention of relapses of NMOSD should be the same. Restricting the target patient population for satralizumab only to anti-AQP4 antibody-positive patients may deprive anti-AQP4 antibody-negative patients of the chance to receive treatment.

- In the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) and the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG), the efficacy of satralizumab was unclear in anti-AQP4 antibody-negative patients and in subgroups with specific characteristics among these patients, precluding the conclusion that benefits of satralizumab outweigh its risks. Nevertheless, satralizumab has been shown to potentially decrease the proportion of patients with severe PDR at relapse in anti-AQP4 antibody-negative patients, compared with placebo [see Section 7.R.1.1]. Also, no significant difference was observed in the safety between anti-AQP4 antibody-positive and negative patients [see Section 7.R.2.1].

- Given the involvement of IL-6 both in anti-AQP4 antibody-dependent and independent pathologic conditions, satralizumab is expected to be effective for both conditions, based on its mechanism of actions [see Section 3.R.1].

- Currently, there is no sufficient information to distinguish the concepts of the disease based on the anti-MOG or anti-AQP4 antibody status (positive or negative). If satralizumab were to be indicated only for anti-AQP4 antibody-positive patients, the treatment option would be lost in patients who could benefit from treatment with satralizumab, such as patients who are false-negative for anti-AQP4 antibodies and patients who are negative for anti-AQP4 antibodies but positive for anti-MOG antibodies and have a high serum IL-6 concentration.

The applicant added the following explanation:
In order to include not only anti-AQP4 antibody positive patients but also the negative patients in the target population of satralizumab, necessary information should be provided appropriately to healthcare professionals. To this end, the following precautions will be included in the package insert: (1) There is only little experience with the use of satralizumab in anti-AQP4 antibody-negative patients, with limited data available, and (2) before using satralizumab in anti-AQP4 antibody-negative patients, the eligibility of each patient should be identified by physicians with full understanding of the efficacy and safety of satralizumab.

PMDA's view:
- Given the seriousness of relapsed NMOSD, PMDA does not completely deny the applicant's assertion that there is a clinical need for satralizumab in anti-AQP4 antibody-negative patients. However, it is unclear whether the benefits of satralizumab overweigh its risks in anti-AQP4 antibody-negative patients, for the reasons mentioned below. As a rule, therefore, satralizumab should be indicated only for anti-AQP4 antibody positive NMOSD.
  (1) In Studies SA-307JG and SA-309JG, the efficacy of satralizumab tended to differ between anti-AQP4 antibody positive and negative patients, with the efficacy in anti-AQP4 antibody negative patients remaining unclear.
  (2) The mechanism of action of satralizumab in the treatment of anti-AQP4 antibody negative NMOSD is unknown.

- Decision on whether to include anti-AQP4 antibody negative patients in the target population will be finalized, taking account of comments raised in the Expert Discussion.

7.R.5 Dosage and administration

7.R.5.1 Appropriateness of dosage and administration

Since satralizumab was administered after the basal treatment in the global phase III study (CTD 5.3.5.1-1, Study SA-307JG), PMDA asked the applicant to explain the appropriateness of the dosage regimen with or without the basal treatment.

The applicant's explanation about the justification for the dosage and administration:
- The dosage regimen was determined based on the results of the phase I single dose study (CTD 5.3.3.1-1, Study SA-001JP) and the phase I multiple-dose study (CTD 5.3.3.2-1, Study SA-105JP), and satralizumab 120 mg was administered every 2 weeks for the first 3 doses, followed by satralizumab 120 mg every 4 weeks in the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) and the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG). As a result, serum satralizumab concentration was maintained at a constant level, resulting in continuous inhibition of IL-6 signaling. The dosage regimen employed in the global phase III study and the foreign phase III study was chosen based on the above results [see Section 6.R.4].

- Since NMOSD is an irreversible disease possibly leading to blindness or other disability, it is critical to achieve the steady-state serum satralizumab concentration as promptly as possible, thereby obtaining the treatment effect from the early stage of the treatment. The first 3 doses of

satralizumab were administered every 2 weeks to achieve the steady-state serum satralizumab concentration as promptly as possible.

- Studies SA-307JG and SA-309JG demonstrated the efficacy of satralizumab without significant safety problem [see Section 7.2], and did not identify any specific patient characteristics affecting the efficacy of satralizumab [see Section 7.R.1.3]. The proposed dosage regimen ("satralizumab 120 mg every 2 weeks for the first 3 doses, and every 4 weeks thereafter") is appropriate.

The applicant's explanation about the justification for satralizumab monotherapy:

- The basal treatment was given before administration of satralizumab in Study SA-307JG but not in Study SA-309JG. In Study SA-309JG, comparison between satralizumab monotherapy and placebo demonstrated the efficacy of satralizumab without any particular safety problems [see Section 7.2.2]. The global phase III study (CTD 5.3.5.1-1, SA-307JG) demonstrated the consistency between the results in the Japanese population and the non-Japanese population [see Section 7.R.1.2]. Thus, from the results of Study SA-309JG, satralizumab monotherapy in the Japanese population is expected to be effective with no safety problems. No Japanese patients were enrolled in Study SA-309JG because relapse of NMOSD may result in blindness and death, and because a comparative study with the placebo group without the basal treatment was considered ethically infeasible in Japan.

- Satralizumab monotherapy may be given in cases including the following: (1) Treatment with satralizumab is started in combination with the basal treatment (e.g., oral corticosteroid), but basal treatment is discontinued because of its adverse drug reaction, etc., and (2) satralizumab monotherapy is started after the discontinuation of the basal treatment because of no response to the basal treatment. Thus, there is a medical need for satralizumab monotherapy in Japan.

- Taking account of the above, the monotherapy should be included in the dosage regimen.

PMDA's view:

- Given that Studies SA-307JG and SA-309JG demonstrated the efficacy of satralizumab without significant safety problems, there is no problem in selecting the following dosage regimen of satralizumab: Satralizumab 120 mg is administered every 2 weeks for the first 3 doses, and every 4 weeks thereafter.

- Since treatment with satralizumab alone in Study SA-309JG demonstrated the efficacy of satralizumab without any particular safety problems, the inclusion of satralizumab monotherapy in the dosage regimen is acceptable. The decision on the appropriateness of the dosage regimen and satralizumab monotherapy will be finalized, also taking account of comments raised in the Expert Discussion.

7.R.5.2 Dosage and administration in pediatrics

PMDA asked the applicant to explain (1) the reason for specifying pediatric patients aged ≥12 years for enrollment in the global phase III study (CTD 5.3.5.1-1, Study SA-307JG), and (2) the appropriateness of the dosage regimen in pediatric patients aged ≥12 years.

The applicant's explanation for specifying pediatric patients aged ≥12 years for enrollment in Study SA-307JG:

- Although the peak age for the onset of NMOSD ranges from early 30s to early 40s, the disease occurs over a wide range of age groups, i.e., from children to the elderly (*Pediatrics.* 2008;122:e1039-47, *2017 Japanese guidelines for multiple sclerosis and neuromyelitis optica* [in Japanese]. Igaku Shoin; 2017). The childhood onset of NMO accounts for approximately 4% of cases (*Neurology.* 2016;86:245-52), with the median age of pediatric patients with NMOSD being 10 to 14 years (*Arch Neurol.* 2012;69:1039-43, *Neurology.* 2008;71:93-100).

- Since the clinical, neuroimaging, and laboratorial characteristics of pediatric patients with NMOSD are mostly similar to those of adult patients with NMOSD, it is considered appropriate to apply the diagnostic criteria for adults to children (*Neurology.* 2015;85:177-89). NMOSD is a serious disease, which once relapsed, may result in disabilities such as blindness, and the applicant therefore considered that the development of satralizumab should be undertaken to treat a wide range of patients including pediatric patients.

- Pediatric patients aged ≥12 years were enrolled in the study because (1) pediatrics aged ≥12 years are considered to have mature drug elimination process and (2) the mean body weight of boys and girls aged 12 years is 44.0 kg and 43.7 kg, respectively (School Health Survey 2018, Ministry of Education, Culture, Sports, Science and Technology). In the Japanese phase I study in adult patients with rheumatoid arthritis (CTD 5.3.3.2-1, Study SA-105JP), subjects weighing 42.3 to 72.5 kg were assigned to the satralizumab 120 mg group. No significant difference was observed in pharmacokinetics among the subjects treated.

- On the basis of the above findings, the applicant considered it possible to evaluate the efficacy and safety of satralizumab in pediatrics aged ≥12 years at the same dosage regimen as that in adults. Accordingly, pediatric patients aged ≥12 years was also included in Study SA-307JG. In Europe, the development of satralizumab for pediatrics aged <12 years is currently being planned, and for this purpose, a clinical study in pediatric patients with NMOSD aged 2 to <12 years will be conducted.

The applicant's explanation about the appropriateness of the dosage regimen in pediatrics aged ≥12 years:

- Pharmacokinetics:
  In Study SA-307JG, the mean serum satralizumab concentration tended to be lower in patients aged <18 years than in patients aged ≥18 years, but the difference was not significant [see Section 6.R.2]. The population pharmacokinetic analysis using the data obtained from Study SA-307JG and

the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG) showed that the pharmacokinetics in pediatric patients was similar to that in adult patients [see Section 6.R.2].

- Efficacy:

  Table 58 shows the incidence of the first PDR in different age groups in Study SA-307JG. In the population of patients aged <18 years, there was no clear trend toward worsening symptoms in the satralizumab group compared with the placebo group, though the evaluation of the results was difficult due to the small number of patients aged <18 years. The percentage [95% CI] of patients aged <18 years who had experienced no PDR until Week 48 was not estimable in the placebo group[49)] and 75.00% [12.79%, 96.05%] in the satralizumab group. The percentage [95% CI] of patients aged ≥18 years who had experienced no PDR until Week 48 was 68.14% [49.72%, 81.01%] in the placebo group and 90.59% [73.42%, 96.89%] in the satralizumab group. The lowest age of patients actually enrolled in Study SA-307JG was 13, and the median body weight [minimum, maximum] of patients enrolled in this study was 79.60 [47.5, 140.4] kg in patients aged <18 years and 58.00 [39.4, 103.0] kg in patients aged ≥18 years. The mean body weight of Japanese boys and girls aged 12 years in the body weight range. It is inferred that the difference in body weight between age groups with a difference of 1 year is within the inter-individual variability. Given these findings, the difference of 1 year of age in age is unlikely to cause a significant difference in efficacy, safety, or pharmacokinetic profile. Satralizumab is thus expected to be effective in pediatric patients aged ≥12 years as well.

Table 58. Incidence of first PDR by age group (Study SA-307JG, double-blind period)

	Overall population				Anti-AQP4 antibody positive				Anti-AQP4 antibody negative			
	<18 years		≥18 years		<18 years		≥18 years		<18 years		≥18 years	
	Placebo	Satralizumab	Placebo	Satralizumab	Placebo	Satralizumab	Placebo	Satralizumab	Placebo	Satralizumab	Placebo	Satralizumab
No. of patients evaluated	3	4	39	37	2	1	26	26	1	3	13	11
No. of patients with PDR (%)	1 (33.3)	1 (25.0)	17 (43.6)	7 (18.9)	1 (50.0)	0	11 (42.3)	3 (11.5)	0	1 (33.3)	6 (46.2)	4 (36.4)
Hazard ratio[a)] [95% CI]	-		0.36 [0.15, 0.88]		-		0.22 [0.06, 0.82]		-		0.60 [0.17, 2.19]	

-: Not estimable
a) Based on Cox proportional hazard model stratified by allocation factor

- Safety profile:

Table 59 shows the incidence of adverse events by age group in Study SA-307JG. The safety profile of satralizumab did not tend to differ between the age groups, showing no adverse events specific to pediatric patients, though only a small number of patients aged <18 years were studied.

[49)] Not estimable because of the absence of patients who continued the study up to Week 48.

Table 59. Incidence of adverse events by age group (Study SA-307JG, double-blind period)

	<18 years		≥18 years	
	Placebo	Satralizumab	Placebo	Satralizumab
No. of patients evaluated	3	4	39	37
Any adverse event	2 (66.7)	3 (75.0)	38 (97.4)	34 (91.9)
Serious adverse events other than death	0	0	9 (23.1)	7 (18.9)
Adverse events leading to treatment discontinuation	0	0	5 (12.8)	3 (8.1)
Adverse events resulting in death	0	0	0	0
Most common adverse events				
Upper respiratory tract infection	1 (33.3)	0	5 (12.8)	10 (27.0)
Nail infection	1 (33.3)	0	0	0
Nasopharyngitis	1 (33.3)	0	6 (15.4)	10 (27.0)
Rhinitis	0	1 (25.0)	0	2 (5.4)
AST increased	1 (33.3)	0	2 (5.1)	1 (2.7)
ALT increased	1 (33.3)	0	1 (2.6)	1 (2.7)
Haemoglobin decreased	0	1 (25.0)	0	0
Lymphocyte count decreased	0	1 (25.0)	2 (5.1)	0
Serum ferritin decreased	0	1 (25.0)	3 (7.7)	0
Blood fibrinogen increased	1 (33.3)	0	0	0
Lymphopenia	0	1 (25.0)	4 (10.3)	2 (5.4)
Cough	0	1 (25.0)	2 (5.1)	0
Oropharyngeal pain	0	1 (25.0)	1 (2.6)	2 (5.4)
Epistaxis	0	1 (25.0)	0	1 (2.7)
Contusion	0	1 (25.0)	0	0
Headache	0	1 (25.0)	4 (10.3)	9 (24.3)
Dizziness	0	1 (25.0)	1 (2.6)	1 (2.7)
Dysmenorrhoea	0	1 (25.0)	0	0

n (%)

- Based on the above, the applicant considers that there is no problem in specifying the same dosage regimen for pediatrics aged ≥12 years as that for adults.

PMDA's view:

- Study SA-307JG did not show a significant difference in the pharmacokinetics, efficacy, or safety of satralizumab between the pediatric population and adult population. The mean body weight of Japanese children aged 12 years is within the range of the body weight of patients enrolled in Study SA-307JG, and there was no significant difference in efficacy among patients in different body weight groups [see Section 7.R.1.3]. The pathology of NMOSD is similar between pediatrics and adults. Based on the above, there is no problem in specifying the same dosage regimen for pediatrics as that for adults, provided that the body weight of the pediatric patient is similar to that of patients enrolled in the clinical study.

- Satralizumab should be developed without delay for use in pediatric patients aged <12 years according to medical needs. This issue will be finalized together with the appropriateness of the dosage regimen in pediatrics, also taking account of comments raised in the Expert Discussion.

7.R.5.3 Discontinuation of satralizumab

PMDA asked the applicant to explain in what occasions satralizumab should be discontinued.

The applicant's explanation:

- The objective of administering satralizumab to patients with NMOSD is prevention of relapse. A long-term continuous treatment is essential to prevent a relapse which may result in persistent neurological injuries or disabilities. For this objective, it is of clinical significance to continue

administration to prevent the next relapse when the treatment with satralizumab over a certain period has achieved the suppression of relapse, as evidenced by decreased relapse frequency. It is unnecessary to discontinue satralizumab uniformly.

- In patients who experience relapse during treatment with satralizumab, however, satralizumab is expected to be continued or switched to other therapies for relapse prevention, depending on the frequency of relapse prior to treatment with satralizumab and on the timing of the relapse during treatment with satralizumab. In patients showing no response to satralizumab, such as patients who experience more frequent relapses during than before the treatment with satralizumab, discontinuation of satralizumab might be selected, after assessing the risks and benefits of continuing the treatment.

- Based on the above, the package insert will include a precautionary statement advising physicians to investigate the frequency of relapses after a certain period of treatment with satralizumab and then to consider discontinuation of satralizumab in patients with no response to the treatment.

PMDA's view:

- Since the objective of administering satralizumab to patients with NMOSD is prevention of relapses, the applicant's claim that there is no need to discontinue satralizumab uniformly once relapse prevention has been achieved is acceptable.

- Also, there is no problem in deciding whether to discontinue satralizumab by balancing the risks vs. benefits of treatment if relapse occurs in patients during treatment with satralizumab. This precaution should be included in the package insert.

7.R.6 Self-injection

PMDA asked the applicant to explain the possibility of difference in the efficacy and safety of satralizumab between self-injection and injection by a healthcare professional.

The applicant's explanation:

- During the open-label extension period of the global phase III study (CTD 5.3.5.1-1, Study SA-307JG), a healthcare professional explained the method of self-injection to 15 Japanese patients who gave his/her consent to self-injection, after which each patient self-injected, or his/her caregiver injected, satralizumab under the supervision of the investigator or the subinvestigator in each study site. The efficacy and safety of satralizumab during 24 weeks immediately before the start of self-injection were compared to those during 24 weeks after the start of self-injection.

- As for efficacy, a clinical relapse occurred in only 1 patient during the self-injection period. The frequency of relapse did not show a clear increase during the self-injection, albeit based on limited data.

- As for safety, Table 60 shows the incidence of adverse events during the period of injection by a healthcare professional and during the period of self-injection. A serious adverse event (influenza)

occurred in 1 patient during the self-injection period, but its causal relationship to satralizumab was ruled out. No other significant difference was observed in the safety profile between injection by a healthcare professional and self-injection.

- The above results suggest no particular problems in the efficacy or safety in self-injection.

Table 60. Comparison of adverse events during the periods of injection by a healthcare professional and of self-injection (Study SA-307JG, Japanese population)

	Professional injection period	Self-injection period
No. of patients evaluated	15	15
Any adverse event	10 (66.7)	13 (86.7)
Serious adverse events	0	1 (6.7)
Adverse events related to the study drug	0	0
Most common adverse events		
Nasopharyngitis	3 (20.0)	4 (26.7)
Diarrhoea	1 (6.7)	3 (20.0)
Influenza	1 (6.7)	2 (13.3)
Oral herpes	1 (6.7)	2 (13.3)
Complement factor decreased	0	2 (13.3)

n (%)

The package insert will include the following precaution for reasons described below: “In case of delayed administration timing, satralizumab should be injected as soon as possible. The subsequent injection should be given at the prescribed dosing interval starting with the delayed administration.”

- Since relapsed NMOSD is serious, delayed satralizumab should be administered as soon as possible without waiting for the next scheduled date in order to maintain effective serum satralizumab concentration demonstrated by both studies.

- There may be cases of delayed administration due to lapse of memory. In such a case, prompt administration without waiting for the next scheduled timing and the subsequent administration at the prescribed interval starting with the delayed administration will maintain the serum satralizumab concentration with proven good safety profile.

PMDA’s view:

The applicant’s explanation is acceptable. Since NMOSD is a disease that may cause visual impairment, whether to allow patients to self-administer satralizumab should be determined carefully by the physician. Self-injection will be allowed only if patients (or their caregivers) have received adequate education and training, have learned satralizumab-related risks (and how to manage them), and are able to perform self-injection reliably. The self-injection should be performed under the supervision of the physician. The physician should provide the patient appropriate guidance using a patient information leaflet.

7.R.7 Post-marketing investigations

The submitted clinical study data show that only a small number of patients were enrolled in clinical studies, with resultant insufficiency in evaluating the safety profile of satralizumab. PMDA considers that information on the following should be collected in the post-marketing investigation: Infection, reactivation of hepatitis virus B, neutropenia/leukopenia/agranulocytosis, thrombocytopenia,

hypersensitivity, intestinal perforation, hepatic dysfunction, cardiac disorder, interstitial pneumonia, malignant tumor, and immunogenicity.

The applicant's explanation:
In order to assess the safety of satralizumab in clinical practice, a general use-results survey will be conducted in all patients receiving satralizumab (target sample size, 300 patients) with a follow-up period of 2 years and 6 months, as the post-marketing surveillance.

PMDA's view:
The decision on the appropriateness of the post-marketing investigations will be finalized, also taking account of comments raised in the Expert Discussion.

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

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

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in the Review Report (2).

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

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that satralizumab has efficacy in the prevention of relapses of NMOSD, and that satralizumab has acceptable safety in view of its benefits. Satralizumab is clinically meaningful because it offers a new treatment option for patients with NMOSD. Further review at the Expert Discussion will be needed on the efficacy of satralizumab in anti-AQP4 antibody-negative patients, indication, dosage regimen in pediatrics, and the appropriateness of the post-marketing investigations.

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

Review Report (2)

May 11, 2020

Product Submitted for Approval

Brand Name	Enspryng Syringes for Subcutaneous Injection 120 mg
Non-proprietary Name	Satralizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	November 8, 2019

List of Abbreviations
See Appendix.

1. Content of the Review

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

1.1 Efficacy and indication

The efficacy of satralizumab tended to differ between anti-AQP4 antibody-positive patients and negative patients in the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) and foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG). PMDA, therefore, considers that the efficacy in anti-AQP4 antibody-negative patients remains unclear [see Section 7.R.1.1 of the Review Report (1)]. Further, satralizumab should be indicated for anti-AQP4 antibody-positive patients with NMOSD, as a general rule, for the following reasons: (1) The efficacy of satralizumab in anti-AQP4 antibody-negative patients remains unclear, (2) the mechanism of action of satralizumab in anti-AQP4 antibody-negative NMOSD is unknown, and (3) it is therefore unclear whether the benefits of satralizumab overweigh its risks in anti-AQP4 antibody-negative patients [see Section 7.R.4 of the Review Report (1)]. The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

The following comments were raised by expert advisors:

- The detailed pathogenesis of NMOSD in anti-AQP4 antibody-negative patients remains unknown. In addition, whereas anti-AQP4 antibody-positive patients are refractory to corticosteroids but highly responsive to plasmapheresis, anti-AQP4 antibody-negative patients are responsive to corticosteroids. This and other findings suggest that underlying etiologies differ between anti-AQP4 antibody-positive and negative patients, though clinical symptoms are similar in the two patient populations.

- The clinical study data did not demonstrate the efficacy of satralizumab in anti-AQP4 antibody-negative patients, failing to show clinical significance in using satralizumab in this patient population.

- Anti-AQP4 antibody can be measured by an established test easily performed in clinical settings. The test does not take much time and can be performed multiple times.

- When interferon β, a therapeutic agent for multiple sclerosis, was administered to anti-AQP4 antibody-positive patients with NMOSD, symptoms became worsened rather than improved (*2017 Japanese guidelines for multiple sclerosis and neuromyelitis optica* [in Japanese]. Igaku Shoin; 2017). This observation suggests the necessity of careful evaluation on possible adverse effects caused by the use of satralizumab in patients with anti-AQP4 antibody-negative NMOSD with an unknown pathogenesis.

Based on the above, PMDA instructed the applicant to include the following descriptions in the "Precautions Concerning Indication" section of the package insert, to which the applicant took appropriate actions.

Precautions Concerning Indication
There are only limited data showing the efficacy in anti-AQP4 antibody-negative patients. Satralizumab should be administered to anti-AQP4 antibody-positive patients.

1.2 Dosage and administration

Given that the global phase III study (CTD 5.3.5.1-1, Study SA-307JG) and the foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG) demonstrated the efficacy of satralizumab without significant safety concerns, there is no problem in the proposed dosage and administration of satralizumab ("Satralizumab 120 mg is administered every 2 weeks for the first 3 doses, and every 4 weeks thereafter"). In addition, since treatment with satralizumab alone in Study SA-309JG demonstrated the efficacy of satralizumab without any particular safety concerns, the inclusion of satralizumab monotherapy in the dosage regimen is acceptable [see Section 7.R.5.1 of the Review Report (1)]. Further, increases in sIL-6R and IL-6, and a decrease in CRP, were observed up to 16 weeks after the end of treatment with satralizumab in the phase I multiple-dose study (CTD 5.3.3.2-1, Study SA-105JP). The package insert should therefore state that the inhibition of IL-6 signaling continues even after the end of treatment with satralizumab [see Section 6.R.4 of the Review Report (1)].

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Study SA-307JG did not show a significant difference in the pharmacokinetics, efficacy, or safety of satralizumab between the pediatric population and adult population, and the pathology of NMOSD is similar between children and adults. On the basis of the above findings, PMDA considers that there is no problem to specify the same dosage regimen in pediatrics as that in adults, provided that the body weight of the pediatric patient is similar to that of patients enrolled in the clinical study. There is no

need for restricting to pediatrics aged ≥12 years for the dosage and administration [see Section 7.R.5.2 of the Review Report (1)].

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

On the basis of the above, PMDA instructed the applicant to modify the dosage and administration of satralizumab as shown below and include the following descriptions in the "Precautions Concerning Dosage and Administration" and "Important Precautions" sections of the package insert. The applicant took appropriate measures accordingly.

Dosage and Administration
The usual dosage of satralizumab (genetical recombination) for adults and pediatrics is 120 mg administered by subcutaneous injection at Weeks 0, 2, and 4, and every 4 weeks thereafter.

Precautions Concerning Dosage and Administration
In pediatric patients, the eligibility of each patient for the use of satralizumab should be determined by referring to the body weight of patients enrolled in clinical studies.

Important Precautions
Satralizumab has a long elimination half-life; it is eliminated only gradually from blood after treatment discontinuation, with its IL-6 signaling inhibitory activity persisting until complete elimination. Therefore, patients should be carefully monitored for infection and other conditions.

1.3 Risk management plan (draft)

In view of the discussions presented in Section "7.R.7 Post-marketing investigations" in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for satralizumab should include the safety specifications presented in Table 61, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 62.

Table 61. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Infection • Neutropenia/leukopenia/ agranulocytosis • Platelet count decreased	• Hypersensitivity • Hepatic dysfunction • Hepatitis B virus reactivation • Immunogenicity • Cardiac disorder • Malignant tumor • Intestinal perforation • Interstitial pneumonia	Not applicable
Efficacy specification		
Not applicable		

Table 62. 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 • General use-results survey (all-case surveillance) • Post-marketing clinical study[a)]	• Provide information based on the early post-marketing phase vigilance. • Ensure the provision of information on the proper use before the delivery of the product. • Prepare and disseminate information materials for healthcare professionals. • Prepare and disseminate information materials for patients

a) The ongoing Studies SA307-JG and JN41468[50)] will be reclassified as post-marketing clinical studies after approval.

On the basis of the above, PMDA instructed the applicant to conduct a post-marketing surveillance to investigate items described above.

The applicant explained that a general use-results survey shown in Table 63 will be conducted involving patients with NMOSD.

Table 63. Outline of general use-results survey (all-case surveillance) (draft)

Objective	To investigate the safety of satralizumab in clinical practice.
Survey method	All-case surveillance
Population	All patients receiving satralizumab
Observation period	From enrollment until 6 months before the end of the survey period (up to 6 years)
Planned sample size	300
Main survey items	Patient characteristics (age, sex, body weight, relapse, past illness, concurrent diseases, etc.) Prior treatments, concomitant drugs Use state of satralizumab Adverse events Relapse status Incidence of Anti-satralizumab antibody

PMDA accepts the above explanation of the applicant. Information on the results obtained from the survey should be communicated promptly to healthcare professionals.

1.4 Current status of ongoing clinical studies

PMDA asked the applicant to explain the incidences of adverse events observed in the ongoing global phase III study (CTD 5.3.5.1-1, Study SA-307JG) and foreign phase III study (CTD 5.3.5.1-2, Study SA-309JG).

The applicant's explanation:

Among adverse events collected during the period from data cut-off of Study SA-307JG (June 6, 2018) and Study SA-309JG (October 12, 2018) to June 7, 2019, no adverse events resulted in death. Incidences of other serious adverse events are shown in Table 64. Currently, the results do not suggest any safety concerns, compared with the incidence of serious adverse events observed in clinical studies so far conducted [see Sections 7.2.1 and 7.2.2 of the Review Report (1)].

50) A compassionate study mainly consisting of Study SA307-JG.

Table 64. Incidence of serious adverse events other than death

Study	Events
SA-307JG	Pneumonia,* cervical dysplasia, uterine leiomyoma, and cataract in 1 patient each
SA-309JG	Fractured sacrum/uterine leiomyoma, pneumonia, urinary tract infection, ovarian adenoma, and uterine leiomyoma in 1 patient each

* Event for which a causal relationship to the study drug could not be ruled out

PMDA accepts the explanation of the applicant, and considers that there are no new concerns about the long-term safety of satralizumab.

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

2.1 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 document submitted.

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

The new drug application data (CTD 5.3.5.1-1) 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. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following issue at some of the study sites, although it had no significant impact on the overall evaluation of the studies. The head of the relevant medical institutions was notified of the issue as a finding requiring corrective action.

Finding requiring corrective action

Study site:

- Protocol deviation (wrong registration of stratification factors)

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. Since the product is an orphan drug, the re-examination period is 10 years. The product is classified as a biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication Prevention of relapses of neuromyelitis optica spectrum disorder (including neuromyelitis optica)

Dosage and Administration The usual dosage of satralizumab (genetical recombination) for adults and pediatrics is 120 mg administered by subcutaneous injection at Week 0, 2, and 4, and every 4 weeks thereafter.

Approval Conditions

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

2. Because data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey involving all patients treated with the product until data from a specified number of patients have been gathered in order to identify the characteristics of patients using the product, and to promptly collect safety and efficacy data, so that necessary measures are taken to ensure proper use of the product.

Appendix

List of Abbreviations

ADCC	Antibody-Dependent Cellular Cytotoxicity
AEX	Anion Exchange Chromatography
Alemtuzumab	Alemtuzumab (Genetical Recombination)
ALT	Alanine Aminotransferase
AQP4	Aquaporin-4
AST	Aspartate Aminotransferase
AUC	Area Under Concentration-time Curve
CD	Cluster of Differentiation
CDC	Complement-Dependent Cytotoxicity
CEC	Clinical Endpoint Committee
CE-SDS	Capillary gel Electrophoresis with Sodium Dodecyl Sulfate
CHO	Chinese Hamster Ovary
CL	Linear Clearance
C_{max}	Maximum Concentration
CPK	Creatine Phosphokinase
CQA	Critical Quality Attribute
CRP	C-reactive Protein
CSF	Cerebrospinal Fluid
CTD	Common Technical Document
CYP	Cytochrome P450
DNA	Deoxyribonucleic Acid
EC_{50}	Effective Concentration, 50%
ECL	Electrochemiluminescence
Eculizumab	Eculizumab (Genetical Recombination)
EDSS	Expanded Disability Status Scale
ELISA	Enzyme-linked Immunosorbent Assay
E_{min}	Minimum Amount of Active Enzyme Observed in the *in vitro* System
EVA	Ethylene Vinyl Acetate
FcRn	Neonatal Fc Receptor
FcγR	Fcγ Receptor
FSS	Functional System Score
[redacted]	[redacted]
GRP	Glucose-regulated Protein
HCP	Host Cell Protein
IC_{50}	50% Inhibitory Concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IL	Interleukin
IL-6R	Interleukin-6 Receptor
$IndC_{50}$	Concentration of Inducer that Supports the Half Maximal Induction/Suppression
ITT	Intention to Treat
ka	Association Rate Constant
kd	Dissociation Rate Constant
K_D	Dissociation Constant
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MOG	Myelin Oligodendrocyte Glycoprotein
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NMO	Neuromyelitis Optica
NMOSD	Neuromyelitis Optica Spectrum Disorder

NSAIDs	Non-Steroidal Anti-Inflammatory Drug
Panitumumab	Panitumumab (Genetical Recombination)
PBPK	Physiologically Based Pharmacokinetics
PDR	Protocol-defined Relapse
PMDA	Pharmaceuticals and Medical Devices Agency
PPC	Post Process Cells
PT	Preferred Term
Q	Inter-compartmental Clearance
QbD	Quality by Design
Rituximab	Rituximab (Genetical Recombination)
Satralizumab	Satralizumab (Genetical Recombination)
SEC	Size Exclusion Chromatography
SEER	Surveillance Epidemiology and End Results
sIL-6R	Soluble Interleukin 6 Receptor
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
SPR	Surface Plasmon Resonance
$t_{1/2}$	Elimination Half-life
TDAR	T-cell-dependent Antibody Response
Enspryng	Enspryng Syringes for Subcutaneous Injection 120 mg
t_{max}	Time to Reach Maximum Concentration
TNF	Tumor Necrosis Factor
Tocilizumab	Tocilizumab (Genetical Recombination)
Vc	Central Volume of Distribution
Vp	Peripheral Volume of Distribution
WCB	Working Cell Bank
γ-GTP	Gamma-glutamyl transferase