Review Report

April 10, 2019
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Actemra 80 mg for Intravenous Infusion Actemra 200 mg for Intravenous Infusion Actemra 400 mg for Intravenous Infusion
Non-proprietary Name	Tocilizumab (Genetical Recombination) (JAN*)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	May 24, 2018
Dosage Form/Strength	A concentrate for a solution for intravenous infusion containing 80 mg, 200 mg, or 400 mg of Tocilizumab (Genetical Recombination) per vial
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug IV

Results of Deliberation

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of adult Still's disease that have not adequately responded to existing therapies, and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indications	○ Treatment of the following diseases in patients who have had an inadequate response to existing therapies: Rheumatoid arthritis (including the inhibition of the progression of structural joint damage), polyarticular-course juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, and adult Still's disease ○ Improvement of various symptoms (e.g., generalised fatigue) and laboratory findings (increased C-reactive protein, increased fibrinogen, increased erythrocyte sedimentation rate, decreased haemoglobin, decreased albumin) associated with Castleman's disease. However, treatment with Actemra should be limited to patients for whom lymph node resection is not indicated.

○ Cytokine release syndrome induced by tumor-specific T cell infusion therapy

(Underline denotes additions.)

Dosage and Administration

○ Rheumatoid arthritis, polyarticular-course juvenile idiopathic arthritis

The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 4 weeks.

○ Systemic juvenile idiopathic arthritis, adult Still's disease, Castleman's disease

The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 2 weeks. The dosing interval may be shortened to a minimum of 1 week according to the patient's symptoms.

○ Cytokine release syndrome

The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) in patients weighing ≥30 kg and 12 mg/kg in patients weighing <30 kg given as an intravenous infusion.

(Underline denotes additions.)

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

March 26, 2019

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

Product Submitted for Approval

Brand Name	Actemra 80 mg for Intravenous Infusion Actemra 200 mg for Intravenous Infusion Actemra 400 mg for Intravenous Infusion
Non-proprietary Name	Tocilizumab (Genetical Recombination)
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Date of Application	May 24, 2018
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Proposed Indications	○ Treatment of the following diseases in patients who have had an inadequate response to existing therapies: Rheumatoid arthritis (including the inhibition of the progression of structural joint damage), polyarticular-course juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, and <u>adult onset Still's disease</u> ○ Improvement of various symptoms (e.g., generalised fatigue) and laboratory findings (increased C-reactive protein, increased fibrinogen, increased erythrocyte sedimentation rate, decreased haemoglobin, decreased albumin) associated with Castleman's disease. However, treatment with Actemra should be limited to patients for whom lymph node resection is not indicated. (Underline denotes additions.)

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○ Rheumatoid arthritis, polyarticular-course juvenile idiopathic arthritis

The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 4 weeks.

○ Systemic juvenile idiopathic arthritis, <u>adult onset Still's disease</u>, Castleman's disease

The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 2 weeks. The dosing interval may be shortened to a minimum of 1 week according to the patient's symptoms.

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

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

Tocilizumab (Genetical Recombination) (hereinafter referred to as "tocilizumab"), which is the active ingredient of "Actemra 80 mg for Intravenous Infusion," "Actemra 200 mg for Intravenous Infusion," and "Actemra 400 mg for Intravenous Infusion," is a humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the immunoglobulin G1 subclass, and was discovered through collaborative research by Osaka University and Chugai Pharmaceutical Co., Ltd. Tocilizumab was approved for the treatment of Castleman's disease in April 2005, and subsequently for the treatment of rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis (sJIA), and other conditions in April 2008.

Still's disease was initially known as a medical condition that developed in children (<16 years of age), characterized by chronic arthritis accompanied by systemic symptoms such as fever and skin rash (*Med Chir Trans.* 1897; 80:47-60.9), and is considered to be roughly synonymous with the current sJIA. However, a disease condition resembling Still's disease was reported to occur in adult life (≥16 years of age) (*Ann Rheum Dis.* 1971;30:121-33); this conditions became known as adult onset Still's disease (AOSD). Due to the resemblance between sJIA and AOSD, sJIA that continues into adulthood and AOSD are collectively referred to as adult Still's disease (ASD). ASD is designated as an intractable disease in Japan (MHLW Ministerial Announcement No. 393 dated October 21, 2014; Ministerial Announcement No. 54). The estimated number of patients with ASD in Japan is 4760, of whom 95% are affected by AOSD (Japan Intractable Diseases Information Center, http://www.nanbyou.or.jp/entry/132).

The clinical symptoms and treatments of AOSD are similar to those of sJIA. AOSD is treated predominantly with systemic corticosteroid therapy; however, no drugs are currently approved for the treatment of AOSD that have not adequately responded to existing therapies. Tocilizumab has been approved for the treatment of sJIA, a disease that is similar to AOSD, and many reports have demonstrated the efficacy of tocilizumab in the treatment of AOSD [see Section 7.R.1.3]. Under these circumstances, an investigator-initiated trial was started in April 2014 at 8 study sites in Japan including Keio University Hospital to evaluate the efficacy and safety of tocilizumab in the treatment of AOSD. Based on the results of that trial and other data, the applicant has filed the present application for partial change approval to add the following indication: AOSD that have not adequately responded to existing therapies.

As of March 2019, tocilizumab is approved in more than 100 countries and regions, including the US and Europe, but has not been approved for the treatment of AOSD in any country or region.

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

Since the present application is for a new indication, no additional data relating to the quality of tocilizumab have been submitted.

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

Although the present application is for a new indication, no additional study data on non-clinical pharmacology have been submitted because the non-clinical pharmacology of tocilizumab was evaluated at the initial approval.

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

Since the present application is for a new indication, no additional study data on non-clinical pharmacokinetics have been submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application is for a new indication, no additional study data relating to the toxicity of tocilizumab have been submitted.

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

Serum tocilizumab concentrations were measured by sandwich enzyme-linked immunosorbent assay (ELISA) with a lower limit of quantification of 100 ng/mL. Serum anti-drug antibody (ADA) concentrations were assayed by bridging ELISA with a detection limit of 15.6 ng/mL for rabbit anti-tocilizumab idiotype antibody.

6.2 Clinical pharmacology

The applicant submitted clinical pharmacological evaluation data, in the form of results data from an investigator-initiated trial in patients with AOSD (Study KCCR-D002 [CTD 5.3.5.1-1]). Unless otherwise specified, doses of Actemra are described as doses of tocilizumab, and pharmacokinetic parameters are expressed as mean ± standard deviation (SD).

6.2.1 Investigator-initiated trial in patients with AOSD (CTD 5.3.5.1-1, Study KCCR-D002, April 2014 to July 2017)

Table 1 shows the trough serum tocilizumab concentrations following repeated intravenous doses of tocilizumab at 8 m/kg every 2 weeks during the double-blind phase of the investigator-initiated trial in patients with AOSD [see Section 7.1.1].

Table 1. Trough serum tocilizumab concentrations following repeated intravenous doses of tocilizumab at 8 mg/kg every 2 weeks in patients with AOSD

Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
15.4 ± 8.2 (13)	15.7 ± 19.4 (13)	29.3 ± 29.6 (11)	40.8 ± 25.6 (10)	56.0 ± 27.6 (9)	57.2 ± 28.1 (9)

µg/mL, mean ± SD (N)
Values below the lower limit of quantification (0.1 µg/mL) were imputed by half the lower limit of quantification.

ADAs were detected in 1 patient in the tocilizumab group and 1 patient in the placebo → tocilizumab group.

The patient in the tocilizumab group was positive for ADAs only on Day 28 of treatment (at the third dose), when the serum tocilizumab concentration was below the lower limit of quantification. This patient did not achieve an ACR 50 response at Week 4, but had an ACR 50 response from Week 6 onward. On Day 42 (at the fourth dose), the patient experienced infusion reaction (preferred term [PT], hypoxia [non-serious]; outcome, resolved), for which a causal relationship to the study drug could not be ruled out. The patient then continued treatment with tocilizumab and had no similar events

The patient in the placebo → tocilizumab group discontinued tocilizumab due to an adverse event (pneumonia) on Day 37 of treatment with tocilizumab (after the third dose), followed by resumption of tocilizumab 185 days after the discontinuation, and experienced an infusion reaction (PT, anaphylactic shock [serious]; outcome, resolved) 22 days after resumption (at the second dose after the resumption [the cumulative fifth dose]). A causal relationship to the study drug could not be ruled out for the infusion reaction. The patient discontinued treatment and underwent an examination 5 days after the onset of the anaphylactic shock. The examination revealed that the patient was positive for ADAs and had a serum tocilizumab concentration below the lower limit of quantification. As for efficacy, the patient had already achieved an ACR 50 response when treatment was resumed.

6.R Outline of the review conducted by PMDA

The applicant explained the pharmacokinetics and the development of ADAs following repeated doses of tocilizumab in patients with AOSD:

The applicant's explanation:

Table 2 shows the trough serum tocilizumab concentrations following repeated doses of tocilizumab at 8 mg/kg every 2 weeks in Study KCCR-D002 in patients with AOSD and a Japanese clinical study in patients with sJIA (Study MRA316JP). The trough serum tocilizumab concentrations from Week 10 onward in patients with AOSD tended to be slightly higher than those in patients with sJIA. Previous clinical study data have suggested that the pharmacokinetics of tocilizumab are affected by gender, age, and body weight[1)] (see "Review Report for Actemra 80 mg for Intravenous Infusion, Actemra 200 mg for Intravenous Infusion, Actemra 400 mg for Intravenous Infusion, dated January 22, 2008"). In view of the differences in patient characteristics between Study KCCR-D002 and Study MRA316JP,[2)] the possibility that these intrinsic factors had affected the pharmacokinetics of tocilizumab could not be ruled out. However, trough serum tocilizumab concentrations did not differ markedly between the 2 studies. Therefore, the applicant considered the trough serum tocilizumab concentrations to be similar in patients with AOSD and patients with sJIA.

1) Serum tocilizumab concentrations tended to be higher in females, males with high body weight, and elderly patients.
2) The patient profiles in Study KCCR-D002 and Study MRA 316JP were as follows: Gender (proportion of males), 23.1% and 35.0%; body weight, 56.1 ± 9.6 kg and 26.5 ± 9.1 kg; and, age, 51.3 ± 20.3 years and 8.0 ± 4.3 years, respectively.

Table 2. Trough serum tocilizumab concentrations in patients with AOSD and patients with sJIA

	Week 6	Week 8	Week 10	Week 12
AOSD (Study KCCR-D002)[a)]	29.3 ± 29.6 (11)	40.8 ± 25.6 (10)	56.0 ± 27.6 (9)	57.2 ± 28.1 (9)
sJIA (Study MRA316JP)	40.1 ± 15.9 (20)	41.9 ± 16.9 (20)	48.2 ± 26.2 (19)	47.6 ± 18.9 (20)

μg/mL, mean ± SD (N)
a) Values below the lower limit of quantification (0.1 μg/mL) were imputed by half the lower limit of quantification.

In Study KCCR-D002, the development of ADAs was confirmed in only 2 patients [see Section 6.2.1]. Therefore, it is difficult to draw any conclusion on the effects of ADAs on the pharmacokinetics, efficacy, or safety of tocilizumab.

PMDA's view:
PMDA accepts the applicant's explanation about the pharmacokinetics of tocilizumab in patients with AOSD. In view of the safety profile of tocilizumab demonstrated by Study KCCR-D002 [see Section 7.R.2], no particular problems with the clinical pharmacology of tocilizumab have not been found in patients with AOSD. Due to the small number of patients testing positive for ADAs in Study KCCR-D002, it is difficult to draw any conclusion on the effects of ADAs on the pharmacokinetics, efficacy, or safety of tocilizumab. However, since the patients positive for ADAs had low serum tocilizumab concentrations and experienced infusion reaction-related adverse events, the safety measures taken for the approved indications should also be implemented in the treatment of AOSD.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from a clinical trial as shown in Table 3.

Table 3. Clinical study on the efficacy and safety of tocilizumab

Phase	Study identifier Data type	Region	Subjects	N	Brief description of dosage regimen	Main endpoints
III	KCCR-D002 Evaluation data	Japan	Patients with AOSD	(i) 13 (ii) 14	Tocilizumab 8 mg/kg (i) or placebo (ii) administered every 2 weeks by intravenous infusion[a)]	Efficacy Safety

a) During the open-label phase, all patients received tocilizumab 8 mg/kg every 2 weeks (The dosing interval could be prolonged or shortened within the range from 1 week to 5 weeks at the discretion of the investigators).

7.1 Phase III study

7.1.1 Investigator-initiated trial in patients with AOSD (CTD 5.3.5.1-1, Study KCCR-D002, April 2014 to July 2017)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of tocilizumab in patients who had active AOSD despite corticosteroid therapy[3)] (target sample size, 34 [17 per group]).

The study was composed of 2 phases: a double-blind phase (Part 1, until Week 4; Part 2, Week 5 to Week 12) and an open-label phase (Part 3, Week 13 to Week 52). Patients who completed Part 1 and met the criteria for escape[4)] were allowed to enter the open-label phase (Part 3) without completing Part 2. Patients received intravenous tocilizumab 8 mg/kg or placebo every 2 weeks during the double-blind phase. All patients received intravenous tocilizumab 8 mg every 2 weeks during the open-label phase.[5)] Corticosteroids were concomitantly administered at a fixed dose from 2 weeks before the start of study treatment to the end of Part 1, and were thereafter increased or decreased according to a predefined rule.[6)]

All of 27 randomized patients[7)] (13 in the tocilizumab group and 14 in the placebo group) received ≥1 dose of the study drug, and were included in the safety analysis set. Of these 27 patients, 1 patient in the placebo group was subsequently diagnosed as non-Hodgkin's lymphoma, rather than AOSD. The remaining 26 patients (13

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3) Key inclusion criteria:
Patients with adult onset Still's disease who met all of inclusion criteria (a) to (e) were eligible for the trial:
(a) Adult onset Still's disease diagnosed according to the criteria by Yamaguchi, *et al.* (1992), as follows: Adult onset Still's disease is diagnosed, if ≥5 criteria are present, ≥2 of which are major criteria, with no exclusion criteria.
Major criteria: (1) Fever ≥39 °C lasting ≥1 week; (2) Articular symptoms lasting ≥2 weeks; (3) Typical skin rash; (4) Leukocytosis ≥10,000/mm^3 with neutrophilia ≥80%
Minor criteria: (1) Sore throat; (2) Lymphadenopathy or splenomegaly; (3) Abnormal liver function tests; (4) Negative tests for rheumatoid factor and antinuclear antibody
Exclusion criteria: (1) Infection (especially sepsis, infectious mononucleosis); (2) Malignancy (especially malignant lymphoma); or, (3) Collagen disorder (especially polyarteritis nodosa and malignant rheumatoid arthritis);
(b) Still's disease onset at ≥16 years of age;
(c) Inadequate response to ≥2 weeks of corticosteroids (equivalent to ≥0.5 mg/kg/day prednisolone), with current corticosteroids (equivalent to ≥10 mg/day of prednisolone) for ≥2 weeks prior to the start of treatment with the study drug;
(d) ≥2 tender joints (in 68 joints) and ≥2 swollen joints (in 66 joints), with ≥1 of the following symptoms: fever; skin rash; lymphadenopathy; hepatomegaly and splenomegaly; and serositis; and,
(e) Erythrocyte sedimentation rate (ESR) of ≥20 mm/h (Westergren method) or C-reactive protein (CRP) ≥1.0 mg/dL

4) Patients who failed to achieve "an ACR 20 response without fever" at the end of Part 1, or failed to achieve "an ACR 50 response without fever" during Part 2, despite an increase in corticosteroid dose to the baseline level.

5) The dosing interval could be reduced to 1 week at the discretion of the investigators. In addition, patients who could reduce their corticosteroid dose to ≤5 mg/day of prednisolone equivalent and maintain the dose for 4 weeks, were allowed to prolong the dosing interval of tocilizumab to a maximum of 5 weeks.

6) Corticosteroid dose reduction rules: In patients who achieved "an ACR 50 response without fever," (a) corticosteroid doses equivalent to ≥30 mg/day of prednisolone were reduced by 5 to 10 mg/day every week, (b) corticosteroid doses equivalent to ≥15 to <30 mg/day of prednisolone were reduced by 2.5 to 5 mg/day every 2 weeks, (c) corticosteroid doses equivalent to ≥7.5 to <15 mg/day of prednisolone were reduced by 1.5 to 2.5 mg/day every 4 weeks, and (d) corticosteroid doses equivalent to <7.5 mg/day of prednisolone were reduced by 0.5 to 1.5 mg/day every 4 weeks. When the corticosteroid dose could be maintained at ≤5 mg/day of prednisolone for 4 weeks, the dosing interval of tocilizumab could be prolonged, with further reduction of corticosteroid doses being left to the discretion of the investigators.
Corticosteroid dose increase rules: Corticosteroid doses could be increased, generally by 50% as a standard, when patients did not maintain "an ACR 50 response without fever" on 2 consecutive visits, or when an obvious exacerbation of the primary disease had been observed at the discretion of the investigators. Dose increases beyond the initial dose as well as the addition of corticosteroids with different routes of administration were prohibited.

7) Due to the slow enrollment of eligible patients, the patient recruitment period was prolonged, and several measures were taken to accelerate enrollment. However, enrollment of the originally planned number of patients in the study was regarded to be difficult, even given the prolonged recruitment period. Accordingly, a blind review was performed, and based on the results, the target number of patients was decreased to 24 patients.

in the tocilizumab group and 13 in the placebo group) were included in the full analysis set (FAS), which was used as the efficacy analysis set.

Treatment discontinuation occurred in 1 patient in the tocilizumab group (hospital transfer) during the double-blind phase, and 1 patient in the tocilizumab group (adverse events) and 3 patients in the placebo → tocilizumab group (adverse events, aggravation of the primary disease, and investigator's judgment in 1 patient each) during the open-label phase. Two patients in the tocilizumab group and 8 patients in the placebo group met the criteria for escape at the end of Part 1, and skipped Part 2 and entered into Part 3 (the open-label phase). In addition, 1 patient in the tocilizumab group met the criteria for escape at Week 6, and switched to Part 3 without completing Part 2.

The ACR 50 response rates at Week 4 (the primary efficacy endpoint) are shown in Table 4.

Table 4. ACR 50 response rates at Week 4 (FAS, non-responder imputation [NRI])

	Tocilizumab	Placebo
ACR 50 response rate	61.5 (8/13)	30.8 (4/13)
[95% CI]	[31.6, 86.1]	[9.1, 61.4]
P-value[a)]	0.238	-

% (n/N)
a) Fisher's exact test, with a 2-sided significance level of 5%

Adverse events were reported by 84.6% (11 of 13) of patients in the tocilizumab group and 57.1% (8 of 14) of patients in the placebo group during the double-blind phase, and in all 12 patients in the tocilizumab group and all 14 patients in the placebo → tocilizumab group during the open-label phase. Common adverse events are shown in Table 5.

No patients died. Serious adverse events were reported by 25.0% (3 of 12) of patients in the tocilizumab group and 28.6% (4 of 14) of patients in the placebo → tocilizumab group during the open-label phase, and a causal relationship to the study drug could not be ruled out for the events in 2 patients in the tocilizumab group (AOSD; cellulitis, nasal abscess, and splenic abscess) and 3 patients in the placebo → tocilizumab group (osteonecrosis; cellulitis; pneumonia and anaphylactic shock). Adverse events led to treatment discontinuation in 1 patient in the tocilizumab group (splenic abscess) and 1 patient in the placebo → tocilizumab group (non-Hodgkin's lymphoma) during the open-label phase. Adverse drug reactions were reported by 61.5% (8 of 13) of patients in the tocilizumab group and 35.7% (5 of 14) of patients in the placebo group during the double-blind phase, and in 75.0% (9 of 12) of patients in the tocilizumab group and 78.6% (11 of 14) of patients in the placebo → tocilizumab group during the open-label phase.

Table 5. Adverse events reported by ≥2 patients in either treatment group (Safety analysis set)

Adverse events	Double-blind phase (Part 1 and Part 2)		Open-label phase (Part 3)	
	Tocilizumab (N = 13)	Placebo (N = 14)	Tocilizumab (N = 12)	Placebo → tocilizumab (N = 14)
Nasopharyngitis	3 (23.1)	0	5 (41.7)	5 (35.7)
Constipation	2 (15.4)	1 (7.1)	1 (8.3)	1 (7.1)
Stomatitis	2 (15.4)	0	1 (8.3)	0
Oral candidiasis	2 (15.4)	0	0	1 (7.1)
Abdominal pain	2 (15.4)	0	0	0
Anaemia	1 (7.7)	0	1 (8.3)	2 (14.3)
Dyslipidaemia	1 (7.7)	1 (7.1)	0	4 (28.6)
Diarrhoea	1 (7.7)	0	0	2 (14.3)
Back pain	1 (7.7)	0	0	2 (14.3)
Drug eruption	0	0	2 (16.7)	2 (14.3)
Headache	0	0	2 (16.7)	1 (7.1)
Insomnia	0	1 (7.1)	1 (8.3)	3 (21.4)
Dermatophytosis of nail	0	0	1 (8.3)	2 (14.3)
Hepatic function abnormal	0	0	1 (8.3)	2 (14.3)
Tinea pedis	0	0	0	2 (14.3)
Hypertension	0	0	0	2 (14.3)
Erythema	0	0	0	2 (14.3)
White blood cell count decreased	0	0	0	2 (14.3)
Cytomegalovirus infection	0	2 (14.3)	0	1 (7.1)

n (%)

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Efficacy in the treatment of AOSD

The applicant's explanation about the efficacy of tocilizumab in the treatment of AOSD:

- **Efficacy endpoints**

Since AOSD is manifested by articular symptoms and systemic symptoms such as fever, skin rash, and lymphadenopathy, both articular and systemic symptoms should be evaluated to assess the efficacy of tocilizumab in the treatment of AOSD. However, there are no established efficacy endpoints for the disease activity of AOSD. Therefore, in Study KCCR-D002, articular symptoms were evaluated based on the ACR core set, and the ACR 50 response rate at Week 4 was employed as the primary endpoint. Systemic symptoms were evaluated using the systemic feature score (SFS), which is composed of clinical features (fever, skin rash, lymphadenopathy, hepatosplenomegaly, and serositis) and laboratory features (ESR, CRP, white blood cell count, haemoglobin, and platelet count). Tocilizumab is expected to be administered to patients with AOSD who are refractory to corticosteroid therapy. Therefore, the effect on corticosteroid tapering was also evaluated.

- **Efficacy in improving articular symptoms**

The ACR 20, ACR 50, and ACR 70 response rates, and the results of the variables of the ACR core set in Study KCCR-D002 are shown in Table 6. A pairwise comparison of ACR 50 response rate at Week 4 (the primary endpoint) revealed no statistically significant difference between the tocilizumab group and the placebo group, but tocilizumab tended to show superior results to placebo in all of the endpoints, and the results of tocilizumab were sustained throughout the tocilizumab treatment period.

Table 6. Efficacy in improving articular symptoms (Study KCCR-D002, FAS)

			Tocilizumab	Placebo	Placebo → tocilizumab
ACR20 response rate		Week 4 (NRI)	76.9 (10/13)	38.5 (5/13)	-
		Week 12 (NRI)	61.5 (8/13)	30.8 (4/13)	-
		End of the open-label phase[a)]	100 (11/11)	-	100 (11/11)
ACR 50 response rate		Week 4 (NRI)	61.5 (8/13)	30.8 (4/13)	-
		Week 12 (NRI)	61.5 (8/13)	30.8 (4/13)	-
		End of the open-label phase[a)]	100 (11/11)	-	100 (11/11)
ACR 70 response rate		Week 4 (NRI)	38.5 (5/13)	30.8 (4/13)	-
		Week 12 (NRI)	46.2 (6/13)	30.8 (4/13)	-
		End of the open-label phase[a)]	72.7 (8/11)	-	72.7 (8/11)
Variables of the ACR core set	Swollen joint count	Baseline	4.2 ± 2.7 (13)	5.7 ± 3.3 (13)	-
		Week 4	1.7 ± 3.1 (13)	5.8 ± 7.3 (13)	-
			−2.5 ± 2.5	0.1 ± 6.9	-
		Week 12 (LOCF)	1.5 ± 3.1 (13)	6.8 ± 7.1 (13)	-
			−2.6 ± 2.7	1.1 ± 7.3	-
		End of the open-label phase[a)]	0.5 ± 0.8 (11)	-	0.3 ± 0.6 (11)
			−3.9 ± 2.5	-	−4.8 ± 3.2
	Tender joint count	Baseline	4.2 ± 3.6 (13)	5.5 ± 3.3 (13)	-
		Week 4	1.0 ± 2.3 (13)	4.2 ± 7.3 (13)	-
			−3.2 ± 1.8	−1.3 ± 7.6	-
		Week 12 (LOCF)	1.0 ± 2.4 (13)	4.7 ± 7.3 (13)	-
			−3.2 ± 2.4	−0.8 ± 7.8	-
		End of the open-label phase[a)]	0.5 ± 0.8 (11)	-	0.5 ± 1.0 (11)
			−3.8 ± 3.3	-	−5.2 ± 3.2
	Patient pain assessment (mm)	Baseline	33.8 ± 30.2 (13)	37.2 ± 26.3 (13)	-
		Week 4	19.6 ± 25.7 (13)	28.4 ± 31.1 (13)	-
			−14.2 ± 23.1	−8.8 ± 41.9	-
		Week 12 (LOCF)	20.8 ± 28.8 (13)	29.0 ± 30.6 (13)	-
			−13.0 ± 28.5	−8.2 ± 45.3	-
		End of the open-label phase[a)]	12.2 ± 21.4 (11)	-	7.5 ± 11.9 (11)
			−24.5 ± 18.3	-	−30.5 ± 28.7
	Patient global assessment (mm)	Baseline	33.7 ± 28.8 (13)	44.5 ± 29.2 (13)	-
		Week 4	19.4 ± 24.3 (13)	28.2 ± 32.5 (13)	-
			−14.3 ± 26.6	−16.4 ± 35.8	-
		Week 12 (LOCF)	22.1 ± 30.9 (13)	30.0 ± 31.7 (13)	-
			−11.6 ± 32.4	−14.5 ± 39.7	-
		End of the open-label phase[a)]	10.4 ± 18.8 (11)	-	8.0 ± 12.3 (11)
			−27.5 ± 21.7	-	−38.2 ± 28.0
	Physician global assessment (mm)	Baseline	38.4 ± 24.5 (13)	42.3 ± 20.1 (12)	-
		Week 4	13.2 ± 15.8 (13)	26.9 ± 24.2 (12)	-
			−25.2 ± 15.1	−15.3 ± 23.8	-
		Week 12 (LOCF)	9.4 ± 14.1 (13)	30.3 ± 23.2 (12)	-
			−29.0 ± 20.1	−12.0 ± 27.1	-
		End of the open-label phase[a)]	6.9 ± 5.7 (11)	-	3.6 ± 3.7 (11)
			−35.5 ± 22.6	-	−40.3 ± 18.5
	HAQ-DI (health assessment questionnaire disability index) (points)	Baseline	0.7 ± 0.9 (13)	1.0 ± 1.0 (13)	-
		Week 4	0.3 ± 0.4 (13)	0.7 ± 0.8 (13)	-
			−0.4 ± 0.9	−0.3 ± 1.0	-
		Week 12 (LOCF)	0.4 ± 0.7 (13)	0.6 ± 0.8 (13)	-
			−0.3 ± 0.9	−0.4 ± 1.0	-
		End of the open-label phase[a)]	0.1 ± 0.2 (11)	-	0.2 ± 0.5 (11)
			−0.4 ± 0.9	-	−0.6 ± 0.5
	CRP (mg/dL)	Baseline	4.2 ± 4.1 (13)	4.7 ± 4.5 (13)	-
		Week 4	0.7 ± 1.1 (13)	2.4 ± 3.6 (13)	-
			−3.5 ± 3.3	−2.3 ± 2.6	-
		Week 12 (LOCF)	0.6 ± 1.2 (13)	2.4 ± 3.0 (13)	-
			−3.6 ± 3.4	−2.3 ± 3.6	-
		End of the open-label phase[a)]	0.0 ± 0.0 (11)	-	0.0 ± 0.0 (11)
			−4.3 ± 4.3	-	−5.1 ± 4.8

ACR response rate, % (n/N); -, not applicable.
Observed case data are present for the categories where "(NRI)" is not written.
Variables of the ACR core set are expressed as mean ± SD (N).
Changes from baseline are shown in shaded columns.
a) The duration of treatment with tocilizumab was from 44 to 52 weeks in the tocilizumab group, and 40 weeks in the placebo → tocilizumab group.

- **Efficacy in improving systemic symptoms**

Table 7 shows efficacy results in terms of improving systemic symptoms other than articular symptom. Tocilizumab tended to show superior results to placebo during the double-blind phase, and the results of tocilizumab were sustained throughout the tocilizumab treatment period.

Table 7. Efficacy in improving systemic symptoms (Study KCCR-D002, FAS)

				Tocilizumab	Placebo	Placebo → tocilizumab
Proportion of patients with a ≥2-point decrease in the SFS including a ≥1-point decrease in clinical features			Week 4 (NRI)	92.3 (12/13)	61.5 (8/13)	-
			Week 12 (NRI)	61.5 (8/13)	30.8 (4/13)	-
			End of the open-label phase[a)]	90.9 (10/11)	-	81.8 (9/11)
SFS (points)			Baseline	4.6 ± 1.7 (13)	5.1 ± 1.4 (13)	-
			Week 4	0.5 ± 0.5 (13)	2.4 ± 1.9 (13)	-
				−4.1 ± 1.7	−2.7 ±2.2	-
			Week 12 (LOCF)	0.7 ± 0.6 (13)	2.5 ± 1.8 (13)	-
				−3.9 ± 1.5	−2.5 ± 2.4	-
			End of the open-label phase[a)]	0.6 ± 0.8 (11)	-	0.5 ± 0.9 (11)
				−4.0 ± 1.7	-	−4.4 ± 1.5
SFS components	Clinical features (proportion of patients)	Fever	Baseline	46.2 (6/13)	46.2 (6/13)	-
			Week 4	0 (0/13)	7.7 (1/13)	-
			Week 12 (LOCF)	0 (0/13)	15.4(2/13)	-
			End of the open-label phase[a)]	0 (0/11)	-	9.1 (1/11)
		Skin rash	Baseline	61.5 (8/13)	53.9 (7/13)	-
			Week 4	15.4 (2/13)	38.5 (5/13)	-
			Week 12 (LOCF)	15.4 (2/13)	38.5 (5/13)	-
			End of the open-label phase[a)]	36.4 (4/11)	—	18.2 (2/11)
		Lymphadenopathy	Baseline	38.5 (5/13)	30.8 (4/13)	-
			Week 4	0 (0/13)	15.4 (2/13)	-
			Week 12 (LOCF)	0 (0/13)	15.4 (2/13)	-
			End of the open-label phase[a)]	9.1 (1/11)	-	9.1 (1/11)
		Hepatosplenomegaly	Baseline	15.4 (2/13)	38.5 (5/13)	-
			Week 4	0 (0/13)	15.4 (2/13)	-
			Week 12 (LOCF)	0 (0/13)	15.4(2/13)	-
			End of the open-label phase[a)]	0 (0/11)	-	9.1 (1/11)
		Serositis	Baseline	7.7 (1/13)	23.1 (3/13)	-
			Week 4	0 (0/13)	7.7 (1/13)	-
			Week 12 (LOCF)	0 (0/13)	7.7 (1/13)	-
			End of the open-label phase[a)]	0 (0/11)	-	0 (0/11)
	Laboratory features	ESR (mm/h)	Baseline	59.5 ± 28.8 (13)	63.8 ± 30.1 (13)	-
			Week 4	8.6 ± 5.1 (13)	42.8 ± 30.4 (13)	-
				−50.9 ± 26.4	−21.0 ± 29.1	-
			Week 12 (LOCF)	8.2 ± 7.8 (13)	45.2 ± 29.2 (13)	-
				−51.4 ± 24.9	−18.6 ± 32.7	-
			End of the open-label phase[a)]	3.2 ± 1.5 (11)	-	3.9 ± 2.6 (11)
				−55.6 ± 27.7	-	−60.9 ± 33.6
		White blood cell count (10^3/μL)	Baseline	17.6 ± 8.9 (13)	11.8 ± 5.0 (13)	-
			Week 4	12.0 ± 5.1 (13)	10.6 ± 5.0 (13)	-
				−5.6 ± 6.4	−1.2 ± 3.7	-
			Week 12 (LOCF)	11.4 ± 7.8 (13)	11.5 ± 5.6 (13)	-
				−6.2 ± 5.7	−0.3 ± 5.2	-
			End of the open-label phase[a)]	7.2 ± 3.6 (11)	-	5.2 ± 2.0 (11)
				−11.9 ± 6.7	-	−6.4 ± 4.9
		haemoglobin (g/dL)	Baseline	11.4 ± 1.6 (13)	10.5 ± 1.9 (13)	-
			Week 4	12.5 ± 1.8 (13)	11.3 ± 1.7 (13)	-
				1.0 ± 0.8	0.8 ± 1.0	-
			Week 12 (LOCF)	12.1 ± 2.3 (13)	11.4 ± 1.8 (13)	-
				0.6 ± 1.7	0.8 ± 1.4	-
			End of the open-label phase[a)]	12.6 ± 2.0 (11)	-	12.9 ± 2.0 (11)
				1.1 ± 1.1	-	2.0 ± 1.7
		Platelet count (10^3/μL)	Baseline	306.4 ± 109.0 (13)	322.3 ± 109.0 (13)	-
			Week 4	223.5 ± 54.6 (13)	309.4 ± 129.1 (13)	-
				−82.9 ± 101.5	−12.9 ± 83.5	-
			Week 12 (LOCF)	240.2 ± 69.2 (13)	306.9 ± 125.1 (13)	-
				−66.2 ± 100.7	−15.4 ± 82.5	-
			End of the open-label phase[a)]	211.1 ± 62.3 (11)	-	221.7 ± 57.4 (11)
				−98.2 ± 68.9	-	−106.6 ± 79.0

% (n/N) or mean ± SD (N); changes from baseline are shown in shaded columns; -, not applicable.
Observed case data are present for the categories where "(NRI)" is not written.
CRP values (a component of the laboratory features) are shown in Table 6.
a) The duration of treatment with tocilizumab was from 44 to 52 weeks in the tocilizumab group, and 40 weeks in the placebo → tocilizumab group.

- **Corticosteroid tapering**

The corticosteroid dose reductions attained in Study KCCR-D002 are summarized in Table 8. The proportion of patients achieving a 20% reduction in corticosteroid dose at Week 12 in the tocilizumab group tended to be higher than that in the placebo group. In addition, the efficacy of tocilizumab in corticosteroid tapering was also seen at the end of the open-label phase.

Table 8. Efficacy in corticosteroid tapering (Study KCCR-D002, FAS)

		Tocilizumab	Placebo	Placebo → tocilizumab
Proportion of patients achieving a 20% reduction in corticosteroid dose at Week 12[a)]		61.5 (8/13)	23.1 (3/13)	-
Proportion of patients achieving a corticosteroid dose reduction to <5 mg/day[c)] at the end of open-label phase[b)]		45.5 (5/11)	-	81.8 (9/11)
Corticosteroid dose (mg/day)	Baseline	23.0 ± 16.2 (13)	32.5 ± 20.4 (13)	-
	Week 4 (OC)	20.9 ± 14.7 (13)	29.0 ± 17.4 (13)	-
		−8.2 ± 11.0	−7.6 ± 10.2	-
	Week 12 (LOCF)	10.6 ± 5.2 (13)	20.6 ± 15.3 (13)	-
		−41.4 ± 27.9	−25.8 ± 32.3	-
	End of the open-label phase[b)] (OC)	6.4 ± 5.1 (11)	-	3.3 ± 2.4 (11)
		−69.8 ± 27.8	-	−86.3 ± 9.6

% (n/N) or mean ± SD (N); changes from baseline are shown in shaded columns; -, not applicable
a) Proportion of patients who achieved "an ACR 50 response without fever" and whose corticosteroid dose was reduced by ≥20% from the baseline dose (NRI)
b) The duration of treatment with tocilizumab was from 44 to 52 weeks in the tocilizumab group, and 40 weeks in the placebo → tocilizumab group.
c) Proportion of patients who achieved "an ACR 50 response without fever" and whose corticosteroid dose was ≤5 mg/day at the end of the open-label phase (OC)

The results of Study KCCR-D002 indicated a trend towards improvement in articular symptoms and systemic symptoms in patients with AOSD treated with tocilizumab, and suggested the possible efficacy of tocilizumab in corticosteroid tapering. In view of these findings, together with the evaluation results in patients with sJIA lasting into adulthood, a similar disease, [see Section 7.R.1.2] and published literature reports [see Section 7.R.1.3], the applicant considers tocilizumab has a certain level of efficacy in the treatment of AOSD.

Study KCCR-D002 failed to demonstrate a statistically significant difference in the pairwise comparison of the primary endpoint between the tocilizumab and placebo groups. The applicant gave the following reasons for the failure:

The applicant had estimated that the ACR 50 response rates at Week 4 in the tocilizumab group and the placebo group of Study KCCR-D002 would be 65% and 15%, respectively, based on the data from clinical studies of tocilizumab in patients with sJIA. However, the ACR 50 response rates actually observed in the tocilizumab group and the placebo group of Study KCCR-D002 were 61.5% and 30.8%, respectively. Thus, the higher than expected ACR 50 response rate in the placebo group was likely to have resulted in the absence of a statistically significant difference between the tocilizumab group and the placebo group. The higher than expected response rate in the placebo group was attributable to the baseline corticosteroid dose (mean ± SD; 32.5 ± 20.4 mg/day in the placebo group, compared to 23.0 ± 16.2 mg/day in the tocilizumab group) and the duration of AOSD at

the time of baseline (median [minimum, maximum]; 0.1 [0.0, 10.8] years in the placebo group, compared to 0.5 [0.1, 23.8] years in the tocilizumab group). The ACR50 response rates at Week 4 adjusted for corticosteroid dose and the duration of AOSD at baseline are shown in Table 9. The difference in the adjusted ACR 50 response rate at Week 4 between the tocilizumab group and the placebo group was greater than that in the unadjusted response rate. Patients with an extremely short AOSD duration are treated with high doses of corticosteroids, and a certain proportion of these patients respond to concomitant corticosteroids. The placebo group included more patients with a short AOSD duration and/or a high baseline corticosteroid dose than the tocilizumab group; this may have resulted in the high response rate in the placebo group.

Table 9. Adjusted ACR 50 response rates at Week 4 (Logistic regression)

Adjustment by logistic regression	Unadjusted	Adjusted for corticosteroid dose (mg) (continuous variable)	Adjusted for duration of AOSD (months) (continuous variable)
Tocilizumab (%)	61.5	65.2	64.8
Placebo (%)	30.8	26.9	25.6
Difference from placebo (%) [95% CI]	30.8 [−6.8, 58.3]	38.3 [−3.8, 65.2]	39.2 [−2.1, 66.1]

Values in each group were calculated based on a least mean square estimate.

7.R.1.2 Efficacy in the treatment of sJIA lasting into adulthood

The applicant explained the efficacy of tocilizumab in the treatment of sJIA (an approved indication) lasting into adulthood, which is a medical condition similar to AOSD in age of onset etc., based on the results of previous clinical studies and the specified use-results survey.

The applicant's explanation:

There are several clinical studies of tocilizumab in patients with sJIA. Among these, a Japanese phase III study (Study MRA324JP[8)]) and a foreign phase III study (Study WA18221[9)]) provide data for evaluating the efficacy of tocilizumab in patients with sJIA lasting into adulthood. Table 10 shows the results of the efficacy endpoints by baseline age (i.e., age at the start of the study) in both studies.

8) An open-label uncontrolled study in patients with sJIA that have not adequately responded to corticosteroid therapy. Tocilizumab was intravenously administered at a dose of 8 mg/kg every 2 weeks.

9) A double-blind parallel-group study in patients with sJIA that have not adequately responded to corticosteroid and nonsteroidal anti-inflammatory drug (NSAID) therapies. Tocilizumab 8 mg/kg (patients weighing ≥30 kg) or 12 mg/kg (patients weighing <30 kg), or placebo was intravenously administered every 2 weeks. The proportion of patients who achieved "a JIA ACR 30 response without fever" at Week 12 (the primary endpoint) was 85.3% (64 of 75) of patients in the tocilizumab group and 24.3% (9 of 37) of patients in the placebo group. A pairwise comparison indicated a statistically significant difference between the 2 groups (P <0.0001).

Table 10. Efficacy of tocilizumab by baseline age in Japanese and foreign clinical studies in patients with sJIA

Timepoint		Baseline		Week 12		Week 52[a)]	
Baseline age		<16 years	≥16 years	<16 years	≥16 years	<16 years	≥16 years
Japanese phase III study (Study MRA324JP)							
Articular symptoms	JIA ACR 30 response rate (OC)	-	-	60.5 (26/43)	50.0 (5/10)	78.4 (29/37)	55.6 (5/9)
	JIA ACR 50 response rate (OC)	-	-	58.1 (25/43)	40.0 (4/10)	73.0 (27/37)	33.3 (3/9)
	JIA ACR 70 response rate (OC)	-	-	34.9 (15/43)	40.0 (4/10)	54.1 (20/37)	33.3 (3/9)
Corticosteroid dose (mg/kg/day)		0.79 ± 0.48 (64)	0.40 ± 0.28 (17)	0.44 ± 0.23 (57)	0.19 ± 0.14 (17)	0.22 ± 0.17 (35)	0.13 ± 0.10 (13)
Foreign phase III study (Study WA18221, tocilizumab 8 mg/kg group)							
Proportion of patients achieving "a JIA ACR 30 response without fever"[b)]		-	-	76.9 (20/26)	72.7 (8/11)	69.2 (18/26)	81.8 (9/11)
Articular symptoms	JIA ACR 30 response rate[b)]	-	-	84.6 (22/26)	81.8 (9/11)	84.6 (22/26)	90.9 (10/11)
	JIA ACR 50 response rate[b)]	-	-	76.9 (20/26)	81.8 (9/11)	84.6 (22/26)	81.8 (9/11)
	JIA ACR 70 response rate[b)]	-	-	73.1 (19/26)	54.5 (6/11)	73.1 (19/26)	63.6 (7/11)
Systemic symptoms	Proportion of patients with fever[c)]	46.2 (12/26)	27.3 (3/11)	15.4 (4/26)	18.2 (2/11)	17.4 (4/23)	18.2 (2/11)
	Proportion of patients with skin rash[c)]	30.8 (8/26)	9.1 (1/11)	15.4 (4/26)	18.2 (2/11)	30.4 (7/23)	27.3 (3/11)
Corticosteroid dose (mg/kg/day)		0.22 ± 0.16 (26)	0.18 ± 0.13 (11)	0.16 ± 0.11 (25)	0.16 ± 0.12 (11)	0.03 ± 0.05 (22)	0.08 ± 0.06 (10)

Response rates and proportions of patients, % (n/N); corticosteroid doses are expressed as mean ±SD (N); -, not applicable
a) At Week 48 for the Japanese phase III study
b) Missing values for the variables of the JIA ACR core set were imputed by last observation carried forward (LOCF). At Week 12, patients who discontinued treatment, patients who entered into escape therapy, and patients whose ACR response was not evaluable were treated as non-responders. At Week 52, patients who discontinued treatment were treated as non-responders.
c) Patients who had the symptom within 14 days before the assessment day or were not evaluable due to insufficient data.

In the specified use-results survey for tocilizumab in patients with sJIA, which was conducted from April 2008 to February 2014, the response rate based on the clinical global impression at Week 52 was 96.4% (217 of 225 patients). The response rate by baseline age (i.e., age at the start of the survey) was 96.3% (182 of 189 patients) at <16 years of age, and 97.2% (35 of 36 patients) at ≥16 years of age. Figure 1 shows the results of efficacy endpoints related to systemic symptoms and mean corticosteroid dose by baseline age.

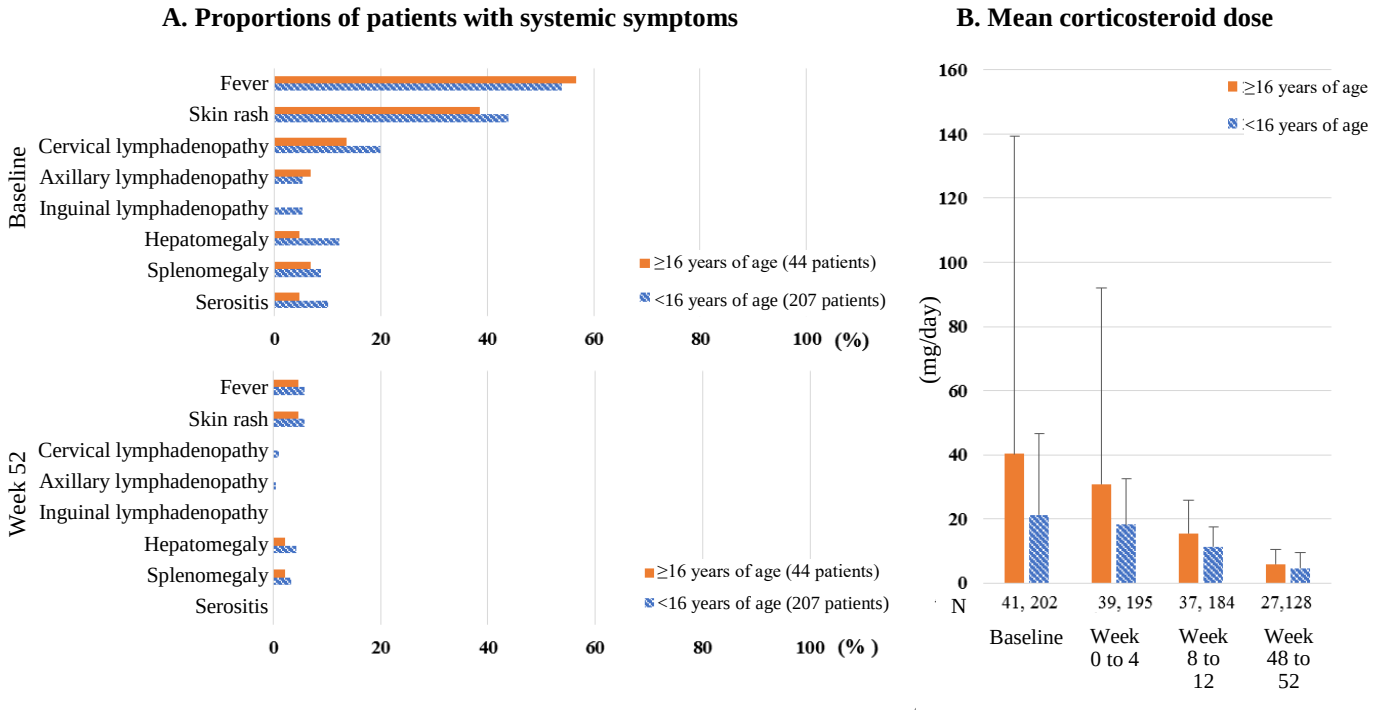

Figure 1. Efficacy of tocilizumab in patients with sJIA by baseline age in the specified use-results survey

Thus, the results of the clinical studies and the specified use-results survey for tocilizumab in patients with sJIA including those with sJIA lasting into adulthood demonstrated that the efficacy of tocilizumab in the treatment of sJIA was independent of baseline age at the start of treatment.

7.R.1.3 Reports in published literature

The applicant's explanation about publications on the use of tocilizumab in patients with AOSD is as follows.

Review papers concerning the treatment of AOSD (*Expert Rev Clin Immunol*. 2017;13:849-66 and *Ther Clin Risk Manag*. 2018;14:167-71) state that the anti-IL-6 antibody products, as well as anti-IL-1 antibody and antitumor necrosis factor preparations, are an important treatment for patients with AOSD that has not adequately responded to existing therapies.

In addition, PubMed, JSTPlus, JMEDPlus, and the Japan Medical Abstracts Society Web were searched using the following conditions (as of December 21, 2017) to investigate the clinical use of tocilizumab in patients with AOSD.

Search conditions:

(a) Search query used for PubMed (from 2008 onward)
tocilizumab [Supplementary Concept] AND ((("adult"[All Fields] AND ("still's"[All Fields] AND "disease"[All Fields])) OR ("still's"[All Fields] AND "disease"[All Fields]))

(b) Search query used for JSTPlus and JMEDPlus
Adult Still's disease AND tocilizumab

(c) Search query used for the Japan Medical Abstracts Society Web (from 2008 onward)
Tocilizumab/TH AND (Still's disease - adult/TH OR adult onset Still's disease/AL) AND (DT=2008:2017) and Tocilizumab/TH AND (adult Still's disease/AL OR Adult Still's disease/AL OR Still's disease/AL OR Still's disease/AL)

A close examination of published reports retrieved under the above search conditions revealed that tocilizumab had been administered to a total of 163 Japanese patients with AOSD or ASD (114 reports), and a total of 121 non-Japanese patients with AOSD or ASD (25 reports). In publications reporting responsiveness to tocilizumab therapy, tocilizumab was effective in improving the clinical features or laboratory features of the disease, corticosteroid tapering, or other efficacy endpoints in 95.6% (152 of 159) of Japanese patients and 79.7% (94 of 118) of non-Japanese patients.

PMDA's view about the efficacy of tocilizumab in the treatment of AOSD or ASD, on the basis of the reviews described in Sections 7.R.1.1 to 7.R.1.3 is as follows.

Currently, there are no established methods to evaluate the efficacy of treatment of AOSD. Study KCCR-D002 therefore had no choice but to use articular symptoms, which are major manifestations of AOSD, as the primary endpoint and other clinical symptoms as secondary endpoints, to comprehensively evaluate the efficacy of tocilizumab in the treatment of AOSD. Study KCCR-D002 failed to demonstrate a statistically significant difference in the primary endpoint between the tocilizumab group and the placebo group. The applicant explained that this failure may have been attributable to imbalances in patient characteristics between the 2groups, such as the duration of AOSD and baseline corticosteroid dose, although the evaluation was limited as it was a post-hoc analysis. This explanation of the applicant was understandable to a certain extent. In view also of the facts presented below, PMDA considered that although Study KCCR-D002 was unable to demonstrate the superiority of tocilizumab to placebo, the results successfully suggested the efficacy of tocilizumab in patients with AOSD. Therefore, PMDA has concluded that tocilizumab is expected to have a certain level of efficacy in the treatment of ASD that have not adequately responded to conventional corticosteroid therapy.

In Study KCCR-D002, the target sample size was changed based on the results of a blind review, although it was not prespecified by the protocol. Although this change may have compromised the credibility of the study results, PMDA considered it to be unavoidable, because enrolling the target number of eligible patients was difficult despite several actions (e.g., prolongation of the enrollment period) taken by the applicant.

<u>Results from Study KCCR-D002</u>

- The results of efficacy endpoints related to articular symptoms (i.e., the primary endpoint of ACR 50 response rate and secondary endpoints) in the tocilizumab group tended to be superior to those in the placebo group, suggesting the efficacy of tocilizumab in improving the articular symptoms of AOSD.

- All the clinical and laboratory features in the SFS tended to be improved in the tocilizumab group, compared with the placebo group, suggesting the efficacy of tocilizumab in improving the systemic symptoms of AOSD.
- The corticosteroid tapering effect tended to be higher in the tocilizumab group than in the placebo group.
- The above trend toward improvement in articular symptoms and systemic symptoms, and the corticosteroid tapering effect were sustained until the end of long-term treatment with tocilizumab.

Other data

- Clinical studies and the specified use-results survey for tocilizumab in patients with sJIA, which is a medical condition resembling AOSD, have demonstrated the efficacy of tocilizumab in patients with sJIA lasting into adulthood.
- Several Japanese and foreign published articles have reported that tocilizumab is effective in patients with AOSD or ASD.

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

7.R.2 Safety

The applicant explained the safety of tocilizumab in patients with AOSD based on the results from an investigator-initiated trial in patients with AOSD (Study KCCR-D002), combined safety results from a foreign study in patients with sJIA (Study WA18221) and 4 Japanese studies in patients with sJIA,[10)] combined safety results from 11 Japanese studies in patients with RA,[11)] results from the specified use-results survey in patients with sJIA, and other data.

The applicant's explanation:

The safety summary of the investigator-initiated trial in patients with AOSD and clinical studies in patients with sJIA or RA is presented in Table 11. The incidences of each adverse event were similar in patients with AOSD, those with sJIA, and those with RA, suggesting no clear differences in the safety profile of tocilizumab among the different patient populations.

10 Studies MRA011JP, MRA316JP, MRA317JP, and MRA324JP
11 Studies MRA002JP, MRA003JP, MRA009JP, MRA010JP, MRA012JP, MRA213JP, MRA214JP, MRA215JP, MRA220JP, MRA221JP, and MRA222JP

Table 11. Safety summary of tocilizumab (safety analysis sets)

	AOSD			sJIA				RA
	Study KCCR-D002 (Japanese)			Study WA18221 (foreign)			4 Japanese sJIA studies combined	11 Japanese RA studies combined
	Double-blind phase (12 weeks)		Entire study period (52 weeks)	Double-blind phase (12 weeks)		Entire study period (104 weeks)		
	Tocilizumab group (N = 13)	Placebo group (N = 14)	Tocilizumab-treated (N = 27)	Tocilizumab group (N = 75)	Placebo group (N = 37)	Tocilizumab-treated (N = 112)	Tocilizumab-treated (N = 128)	Tocilizumab-treated (N = 601)
Total duration of exposure (person-years)	2.54	2.05	21.26	17.19	5.33	202.03	233.91	1891.30
All adverse events	11 (84.6) 433.1	8 (57.1) 390.2	27 (100) 127.0	66 (88.0) 383.9	23 (62.2) 431.5	111 (99.1) 54.9	120 (93.8) 51.3	595 (99.0) 31.5
Serious adverse events	0	0	7 (25.9) 32.9	3 (4.0) 17.5	0	35 (31.3) 17.3	46 (35.9) 19.7	235 (39.1) 12.4
Adverse events leading to drug discontinuation	0	0	2 (7.4) 9.4	1 (1.3) 5.8	0	6 (5.4) 3.0	10 (7.8) 4.3	99 (16.5) 5.2
Adverse drug reactions	8 (61.5) 315.0	5 (35.7) 243.9	23 (85.2) 108.2	25 (33.3) 145.4	6 (16.2) 112.6	84 (75.0) 41.6	115 (89.8) 49.2	585 (97.3) 30.9
Deaths	0	0	0	0	0	3 (2.7) 1.5	2 (1.6) 0.9	0
Anaphylaxis[a)]	0	0	1 (3.7) 4.7	0	0	0	2 (1.6) 0.9	1 (0.2) 0.1
Infusion reaction[b)]	3 (23.1) 118.1	1 (7.1) 48.8	5 (18.5) 23.5	3 (4.0) 17.5	0	10 (8.9) 4.9	22 (17.2) 9.4	89 (14.8) 4.7
Infections[c)]	4 (30.8) 157.5	3 (21.4) 146.3	19 (70.4) 89.4	34 (45.3) 197.8	11 (29.7) 206.4	102 (91.1) 50.5	103 (80.5) 44.0	595 (99.0) 31.5
Serious infections	0	0	3 (11.1) 14.1	2 (2.7) 11.6	0	20 (17.9) 9.9	21 (16.4) 9.0	89 (14.8) 4.7
Interstitial lung diseases[d)]	0	0	0	0	0	0	1 (0.8) 0.4	10 (1.7) 0.5
Gastrointestinal perforation and related diseases[e)]	0	0	0	0	0	0	2 (1.6) 0.9	5 (0.8) 0.3
Haemorrhage[f)]	0	0	2 (7.4) 9.4	4 (5.3) 23.3	1 (2.7) 18.8	34 (30.4) 16.8	27 (21.1) 11.5	160 (26.6) 8.5
Neutrophil count decreased[g)]	0	0	1 (3.7) 4.7	6 (8.0) 34.9	0	28 (25.0) 13.9	17 (13.3) 7.3	32 (5.3) 1.7
Platelet count decreased[h)]	0	0	0	0	0	2 (1.8) 1.0	0	6 (1.0) 0.3
Myocardial infarction/acute coronary syndrome[i)]	0	0	0	0	0	0	0	2 (0.3) 0.1
Malignancies[j)]	0	0	1 (3.7) 4.7	0	0	0	0	17 (2.8) 0.9
Hepatic events[k)]	0	0	0	0	0	0	0	34 (5.7) 1.8
Cerebrovascular disorders[l)]	0	0	0	0	0	0	0	16 (2.7) 0.8
Demyelinating disorders[m)]	0	0	0	0	0	0	0	0
Immunogenicity[n)]	1 (7.7) 39.4	0	2 (7.4) 9.4	1 (1.3) 5.8	0	1 (0.9) 0.5	11 (8.6) 4.7	15 (2.5) 0.8
MAS[o)]	0	0	0	0	0	3 (2.7) 1.5	2 (1.6) 0.9	1 (0.2) 0.1
Dyslipidaemia[p)]	2 (15.4) 78.7	1 (7.1) 48.8	7 (25.9) 32.9	0	0	0	18 (14.1) 7.7	334 (55.6) 17.7

Upper row, n (%); lower row, total exposure-adjusted incidence rate (events per 100 person-years)
(a) Among events in the MedDRA SMQ "Anaphylactic reaction (narrow)," those that occurred within 24 hours after the administration of tocilizumab
(b) Allergy-related events occurring within 24 hours after the administration of tocilizumab (c) Events in the MedDRA SOC "Infection and infestations"
(d) Events in the MedDRA SMQ "Interstitial lung disease (broad)" (e) Events in the MedDRA SMQ "Gastrointestinal perforation (narrow)"
(f) Events in the MedDRA SMQ "Haemorrhage terms (excluding laboratory terms) (broad)" (g) CTCAE Grade ≥3 events (h) CTCAE Grade ≥2 events
(i) Events in the MedDRA SMQ "Myocardial infarction (narrow)"
(j) Events in the MedDRA SMQ "Malignant or unspecified tumors (narrow)"
(k) Events in the MedDRA SMQ "Hepatic failure, hepatic fibrosis, and hepatic cirrhosis and other hepatocellular disturbances (broad)" or "Hepatitis, non-infectious (broad)"
(l) Events in the MedDRA SMQ "Haemorrhagic central nervous system vascular conditions (narrow)" or "Ischaemic central nervous system vascular conditions (narrow)"
(m) Events in the MedDRA SMQ "Demyelination (narrow)"
(n) Patients positive for ADAs (in studies in patients with sJIA [foreign] or AOSD) and patients positive for IgE ADAs (in studies in patients with sJIA [Japanese] or RA)
(o) Events corresponding to the MedDRA PT "Histiocytosis haematophagic" (p) Events in the MedDRA SMQ "Dyslipidaemia (broad)"

The safety summary of the specified use-results survey for tocilizumab in patients with sJIA is presented in Table 12. The incidence of adverse drug reactions was similar in both age groups.

Table 12. Safety summary of the specified use-results survey for tocilizumab in patients with sJIA (Safety analysis set)

	Overall survey population (N = 417)	≥16 years at baseline (N = 85)	<16 years at baseline (N = 332)
Adverse drug reactions	61.2 (255)	51.8 (44)	63.6 (211)
Serious adverse drug reactions	23.7 (99)	17.7 (15)	25.3 (84)
Common adverse drug reactions			
Upper respiratory tract inflammation	14.9 (62)	10.6 (9)	16.0 (53)
Influenza	6.5 (27)	3.5 (3)	7.2 (24)
Hepatic function abnormal	6.2 (26)	3.5 (3)	6.9 (23)
Gastroenteritis	6.0 (25)	1.2 (1)	7.2 (24)
Bronchitis	5.5 (23)	7.1 (6)	5.1 (17)
Histiocytosis haematophagic	5.5 (23)	4.7 (4)	5.7 (19)
Pharyngitis	4.8 (20)	5.9 (5)	4.5 (15)

% (n)

Although limitations are present due to differences in patient characteristics, tocilizumab dose, concomitant medications, and other factors among the studies and survey, comparisons of the safety data did not suggest that the safety profile of tocilizumab in patients with AOSD tended to differ clearly from the safety profiles observed in clinical studies of sJIA or RA, or the specified use-results survey for sJIA, and no new safety concerns were identified. Therefore, the safety risks associated with treatment with tocilizumab in patients with AOSD can be appropriately managed by taking the same safety measures as for the approved indications.

PMDA's view:

(1) Comparisons of the incidences of adverse events identified no new concerns regarding the safety of tocilizumab in patients with AOSD, as compared with patients treated for the approved indications including those with sJIA lasting into adulthood. (2) Tocilizumab therapy may cause serious adverse infections and other events. (3) AOSD, like sJIA, may be complicated by macrophage activation syndrome (MAS), which is potentially fatal. Based on the above (1) to (3), and for other reasons, PMDA has concluded that the same safety measures as for the approved indications including sJIA should be taken in patients with AOSD.

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

7.R.3 Clinical positioning and indication

The applicant's explanation about the clinical positioning of tocilizumab in the treatment of AOSD is as follows.

Basically, AOSD has a favorable prognosis. However, half of patients experience repeated remissions and relapses, and some patients suffer complications that affect their life expectancy. Accordingly, the treatment of AOSD is aimed at preventing relapses and continuously controlling disease activity. The recommended

standard treatment of AOSD is corticosteroid therapy. However, since long-term treatment with corticosteroids is associated with safety concerns, corticosteroid doses are tapered while monitoring disease activity.

The results of Study KCCR-D002 in patients who had active AOSD despite corticosteroid therapy suggested that tocilizumab was effective in improving the clinical symptoms of AOSD and in corticosteroid tapering, while causing no safety problems. Thus, tocilizumab is expected to serve as a new treatment option for patients with AOSD that have not adequately responded to existing therapies.

PMDA's view:
Based on the above explanation of the applicant, as well as the data submitted, discussions in Sections 7.R.1 and 7.R.2, and the fact that the term "adult Still's disease (ASD)" is designated as an intractable disease in Japan, PMDA has concluded that tocilizumab should be positioned as a treatment option for patients with ASD that have not adequately responded to existing therapies, and that the indication should be "adult Still's disease that have not adequately responded to existing therapies."

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

7.R.4 Dosage and administration

PMDA's view:
The dosage regimen used in Study KCCR-D002 was the same as the approved dosage and administration for sJIA. During the double-blind phase of the study, tocilizumab was intravenously administered at 8 mg/kg every 2 weeks, and the results of the phase suggested the efficacy of tocilizumab in the treatment of AOSD [see Section 7.R.1] and identified no new safety concerns [see Section 7.R.2]. In the subsequent open-label phase, shortening the dosing intervals to 1 week was allowed at the discretion of the investigators. Table 13 shows the efficacy and safety data from 6 patients who received tocilizumab at 1-weak intervals. Shortening of the dosing interval tended to ameliorate articular symptoms, systemic symptoms, and CRP, with no particular adverse events occurring more frequently.

Table 13. Efficacy and safety of tocilizumab before and after shortening the dosing interval

	Number of doses[a)]	Before or after the shortening[b)]	ACR 50 response	SFS (points)	CRP (mg/dL)	Adverse events[c)]
3 [redacted] years • [redacted]	3	Before	Not achieved	2	0.1	None
		After	Achieved	1	0	
6 [redacted] years • [redacted]	4	Before	Not achieved	2	1.33	Insomnia, glucose tolerance abnormal, and hepatic dysfunction
		After	Achieved	0	0.01	
3 [redacted] years • [redacted]	4	Before	Not achieved	4	6.31	None
		After	Achieved	1	0.01	
8 [redacted] years • [redacted]	8	Before	Not achieved	2	0.97	Puncture site pain and pyrexia
		After	Not achieved	1	0.06	
4 [redacted] years • [redacted]	25	Before	Achieved	1	3.81	Constipation, purulent mastitis, common cold, keratitis, myalgia, tinnitus, acne on the buttocks, abrasion on the right foot, and rash
		After	Achieved	1	1.13	
4 [redacted] years • [redacted]	33	Before	Achieved	4	7.35	Common cold, folliculitis, and ingrown nail on the right big toe
		After	Achieved	1	0.01	

a) Number of doses administered at shortened (1-week) intervals
b) "Before" represents the assessment timepoint that was before, and closest to, the first dose of 1-week interval treatment. "After" represents the assessment timepoint that was after, and closest to, Day 28 of 1-week interval treatment.
c) Adverse events that occurred between the first dose of 1-week interval treatment and 28 days after the last dose of 1-week interval treatment.

Based on the above, PMDA reached the following conclusion:

The dosage and administration of tocilizumab in the treatment of ASD should be "The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 2 weeks. The dosing interval may be shortened to a minimum of 1 week according to the patient's symptoms," as the applicant proposed. The "Precautions Concerning Dosage and Administration" section of the package insert for ASD, as with that for sJIA, should include a precautionary statement to the effect that the dosing interval may be shortened only when the improvement of symptoms and inhibition of IL-6 (based on CRP levels) are both considered inadequate.

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

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

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

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

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

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection revealed that the clinical studies had been conducted generally in compliance with the GCP. PMDA therefore concluded that there were no obstacles to conducting its review based on the application documents submitted. However, during the inspection, PMDA identified the following finding at a study site, and notified the head of the study site of the finding, although it did not substantially affect the overall evaluation of the clinical studies.

The finding requiring corrective action:

Study site

• Protocol deviation (noncompliance with the rule for the tapering of concomitant medications)

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

On the basis on the data submitted, PMDA has concluded that tocilizumab has efficacy in the treatment of adult Still's disease that have not adequately responded to existing therapies, and that tocilizumab has acceptable safety in view of its benefits. Tocilizumab is clinically meaningful because it offers a new treatment option for patients with adult Still's disease that have not adequately responded to existing therapies.

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

10. Others

The efficacy endpoints used in clinical studies of tocilizumab were defined as follows.

Endpoints	Definitions
ACR 20, ACR 50, or ACR 70 response	≥20%, ≥50%, or ≥70% decreases from baseline in the tender joint count (in 68 joints) and swollen joint count (in 66 joints), and ≥20%, ≥50%, or ≥70% improvements in ≥3 of the following 5 variables of the ACR core set: (a) patient pain assessment (VAS), (b) patient global assessment (VAS), (c) physician global assessment (VAS), (d) patient daily living activity assessment using HAQ-DI (health assessment questionnaire disability index), and (e) CRP
ACR 20, ACR 50, or ACR 70 response rate	The proportion of patients who achieved an ACR 20, ACR 50, or ACR 70 response
JIA ACR 30, ACR 50, or ACR 70 response	≥30%, ≥50%, or 70% improvement in ≥3 of the following 6 variables of the JIA ACR core set, and ≥30%, ≥50% or ≥70% worsening in ≤1 of the 6 variables: (a) physician global assessment (VAS), (b) global assessment (VAS) by patient or patient's parents/legal guardian, (c) function assessment using the Japanese version of the Childhood Health Assessment Questionnaire, (d) number of joints with active arthritis, (e) number of joints with limited range of motion, and (f) ESR
JIA ACR 30, ACR 50, or ACR 70 response rate	The proportion of patients who achieved a JIA ACR 30, ACR 50, or ACR 70 response
SFS	1) Assessment at baseline (maximum of 10 points) (i) Clinical features (Each individual feature is scored as either absent [0 points] or present [1 point].) a) Fever, b) skin rash, c) lymphadenopathy, d) hepatomegaly and splenomegaly, and e) serositis (ii) Laboratory features (Each individual feature is scored as either absent [0 points] or present [1 point]) a) ESR ≥20 mm/h, b) CRP ≥1.0 mg/dL, c) white blood cell count ≥12,000/μL, d) haemoglobin ≤11 g/dL, e) platelet count ≥400,000/μL 2) Assessment at each on-treatment timepoint (maximum of 10 points) (i) Clinical features (Each individual feature is scored as either absent [0 points] or present [1 point].) a) Fever, b) skin rash, c) lymphadenopathy, d) hepatomegaly and splenomegaly, and e) serositis (ii) Laboratory features are assessed according to the following criteria: a) ESR: 0 points if <20 mm/h, or if decreased by ≥30% from baseline; 1 point if increased, or decreased by <30%, from baseline b) CRP: 0 points if <1.0 mg/dL, or if decreased by ≥30% from baseline; 1 point if increased, or decreased by <30%, from baseline c) white blood cell count: 0 points if <12,000/μL, or if decreased by ≥20% from baseline; 1 point if increased, or decreased by <20%, from baseline d) haemoglobin: 0 points if >11 g/dL or if increased by ≥20% from baseline; 1 point if decreased, or increased by <20%, from baseline e) platelet count: 0 points if <400,000/μL, or if decreased by ≥20% from baseline; 1 point if increased, or decreased by <20%, from baseline

Review Report (2)

April 10, 2019

Product Submitted for Approval

Brand Name	Actemra 80 mg for Intravenous Infusion Actemra 200 mg for Intravenous Infusion Actemra 400 mg for Intravenous Infusion
Non-proprietary Name	Tocilizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	May 24, 2018

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy, safety, indication, and dosage and administration

The expert advisors supported PMDA's conclusions about the efficacy, safety, indication, and dosage and administration of tocilizumab presented in the Review Report (1), and made the following comments.

- The absence of a significant difference in ACR 50 response rate at Week 4 (the primary endpoint) between the tocilizumab group and the placebo group in Study KCCR-D002 was attributable primarily to a lack of statistical power, considering that the ACR 50 response rate at Week 4 in the tocilizumab group was approximately 30% higher than that in the placebo group. However, Study KCCR-D002 is an investigator-initiated trial in patients with AOSD, a rare disease, conducted under a situation in which tocilizumab had already been listed by guidelines as a treatment option for AOSD. Therefore, the study had no choice but to enroll only 26 patients.
- Comparisons of the safety of tocilizumab (Table 11) revealed approximately 2-fold differences in the incidences of adverse events or adverse drug reactions between patients with AOSD and patients treated for the approved indications. The effects of total duration of exposure to tocilizumab on these incidences should be examined.

The applicant's explanation:

Table 14 shows a safety summary of Japanese studies involving a 52-week treatment with tocilizumab in

patients with AOSD, sJIA, or RA. Although strict comparisons are difficult because the number of patients with AOSD is small, and because the data from patients treated for the approved indications are from external studies, there were no noteworthy differences in the safety profile of tocilizumab between Japanese patients with AOSD and Japanese patients treated for the approved indications.

Table 14. Safety summary in patients with AOSD and patients treated for the approved indications in Japanese studies (52 weeks)

	AOSD	sJIA	RA
	Study KCCR-D002	Four Japanese sJIA studies combined	Study MRA012JP
	Tocilizumab-treated (N = 27)	Tocilizumab-treated (N = 128)	Tocilizumab group (N = 157)
Total duration of exposure (person-years)	21.26	98.35	144.47
All adverse events	27 (100) 127.0	119 (93.0) 121.0	150 (95.5) 103.8
Serious adverse events	7 (25.9) 32.9	31 (24.2) 31.5	29 (18.5) 20.1
Adverse events leading to drug discontinuation	2 (7.4) 9.4	10 (7.8) 10.2	17 (10.8) 11.8
Adverse drug reactions	23 (85.2) 108.2	114 (89.1) 115.9	139 (88.5) 96.2

Upper row, n (%); lower row, total exposure-adjusted incidence rate (events per 100 person-years)

The above explanation of the applicant is understandable. PMDA has concluded that no new safety concerns have been identified regarding the use of tocilizumab in the treatment AOSD, compared with the approved indications, as described in the Review Report (1).

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and the dosage and administration as follows.

Indications

○ Treatment of the following diseases in patients who have had an inadequate response to existing therapies: Rheumatoid arthritis (including the inhibition of the progression of structural joint damage), polyarticular-course juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, and adult ~~onset~~ Still's disease

○ Improvement of various symptoms (e.g., generalised fatigue) and laboratory findings (increased C-reactive protein, increased fibrinogen, increased erythrocyte sedimentation rate, decreased haemoglobin, decreased albumin) associated with Castleman's disease. However, treatment with Actemra should be limited to patients for whom lymph node resection is not indicated.

○ Cytokine release syndrome induced by tumor-specific T cell infusion therapy

(The strikethrough word is deleted from the proposed text. The dashed line denotes an indication added during the review of the present application.)

Dosage and Administration

○ Rheumatoid arthritis, polyarticular-course juvenile idiopathic arthritis

The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 4 weeks.

○ Systemic juvenile idiopathic arthritis, adult ~~onset~~ Still's disease, Castleman's disease

The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 2 weeks. The dosing interval may be shortened to a minimum of 1 week according to the patient's symptoms.

○ Cytokine release syndrome

The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) in patients weighing ≥30 kg and 12 mg/kg in patients weighing <30 kg given as an intravenous infusion.

(The strikethrough word is deleted from the proposed text. The dashed line denotes a dosage and administration added during the review of the present application.)

Appendix

List of Abbreviations

ACR	American College of Rheumatology
ADA	Anti-drug antibody
AOSD	Adult onset Still's disease
ASD	Adult Still's disease
CI	Confidence interval
CRP	C-reactive protein
CTCAE	Common terminology criteria for adverse events
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
FAS	Full analysis set
GCP	Good clinical practice
Ig	Immunoglobulin
IL	Interleukin
LOCF	Last observation carried forward
MAS	Macrophage activation syndrome
MedDRA	Medical dictionary for regulatory activities
NRI	Non-responder imputation
OC	Observed case
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred term
RA	Rheumatoid arthritis
SFS	Systemic feature score
sJIA	Systemic juvenile idiopathic arthritis
SMQ	Standardized MedDRA queries
SOC	System organ class
VAS	Visual analog scale