Report on the Deliberation Results

August 10, 2017

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

Brand Name	Actemra 162 mg Syringe for SC Injection Actemra 162 mg Auto-injector for SC Injection
Non-proprietary Name	Tocilizumab (Genetical Recombination) (JAN*)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	November 30, 2016

Results of Deliberation

In its meeting held on July 27, 2017, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years.

Condition of Approval

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

**Japanese Accepted Name (modified INN)*

Review Report

July 11, 2017
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Actemra 162 mg Syringe for SC Injection Actemra 162 mg Auto-injector for SC Injection
Non-proprietary Name	Tocilizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	November 30, 2016
Dosage Form/Strength	Injection: each 0.9 mL syringe contains 162 mg of Tocilizumab (Genetical Recombination). Injection: each 0.9 mL auto-injector contains 162 mg of Tocilizumab (Genetical Recombination).
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
Items Warranting Special Mention	Orphan drug (Drug Designation No. 340 of 2014 [*26 yaku*]; PFSB/ELD Notification No. 0611-1 dated June 11, 2014, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of Takayasu's arteritis or giant cell arteritis that has 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 indications and dosage and administration shown below, with the following condition. The safety and efficacy of the product in clinical use should be further investigated via post-marketing surveillance.

Indications ○ Treatment of the following diseases in patients who have had an inadequate response to existing therapies:

Rheumatoid arthritis (including the inhibition of progression of structural joint damage)

Takayasu's arteritis or giant cell arteritis

(Underlines denote additions.)

Dosage and Administration ○ Rheumatoid arthritis

The usual adult dosage is 162 mg of Tocilizumab (Genetical Recombination) administered subcutaneously every 2 weeks. The dosing interval may be reduced to a minimum of 1 week in patients with an inadequate response.

○ Takayasu's arteritis or giant cell arteritis

The usual dosage is 162 mg of Tocilizumab (Genetical Recombination) administered subcutaneously once weekly.

(Underlines denote additions[1].)

Condition of Approval

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

[1] The dotted underline denotes additions made as of June 26, 2017, the approval date of another partial change application for the product.

Attachment

Review Report (1)

June 16, 2017

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

Product Submitted for Approval	
Brand Name	Actemra 162 mg Syringe for SC Injection Actemra 162 mg Auto-injector for SC Injection
Non-proprietary Name	Tocilizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	November 30, 2016
Dosage Form/Strength	Injection: each 0.9 mL syringe contains 162 mg of Tocilizumab (Genetical Recombination). Injection: each 0.9 mL auto-injector contains 162 mg of Tocilizumab (Genetical Recombination).
Proposed Indications	○ Treatment of rheumatoid arthritis with an inadequate response to existing therapies (including the inhibition of progression of structural joint damage) ○ Treatment of large vessel vasculitis (Takayasu's arteritis or giant cell arteritis) (Underlines denote additions.)
Proposed Dosage and Administration	○ Rheumatoid arthritis The usual adult dosage is 162 mg of Tocilizumab (Genetical Recombination) administered subcutaneously every 2 weeks. ○ Large vessel vasculitis (Takayasu's arteritis or giant cell arteritis) The usual dosage is 162 mg of Tocilizumab (Genetical Recombination) administered subcutaneously once weekly. (Underlines denote additions.)

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List of Abbreviations

BLQ	Below the lower limit of quantification
CRP	C-reactive protein
DMARDs	Disease-modifying antirheumatic drugs
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
Fab	Fragment, antigen binding
IgE	Immunoglobulin E
IL-6	Interleukin-6
Intravenous tocilizumab	Actemra 80 mg for Intravenous Infusion, Actemra 200 mg for Intravenous Infusion, Actemra 400 mg for Intravenous Infusion
ITT	Intention-to-treat
Japanese clinical practice guidelines	Guidelines for management of vasculitis syndrome 2008 by the joint working groups: The Japanese Circulation Society, The Japan Radiological Society, The Japanese Association for Thoracic Surgery, The Japanese Society for Vascular Surgery, The Japan Pediatric Society, The Japanese Society of Nephrology, The Japanese Society for Cardiovascular Surgery, The Japanese College of Cardiology, The Japanese Society of Pathology, The Japanese College of Angiology, and The Japan College of Rheumatology
MTX	Methotrexate
NE	Not estimable
NRI	Non-responder imputation
PMDA	Pharmaceuticals and Medical Devices Agency
PMR	Polymyalgia rheumatica
RA	Rheumatoid arthritis
SAA	Serum amyloid A
sIL-6R	Soluble interleukin-6 receptor
TNF	Tumor necrosis factor

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

Tocilizumab (Genetical Recombination) (hereinafter referred to as tocilizumab) is the active ingredient of "Actemra 162 mg Syringe for SC Injection and Actemra 162 mg Auto-injector for SC Injection" (subcutaneous tocilizumab) and "Actemra 80 mg for Intravenous Infusion, Actemra 200 mg for Intravenous Infusion, and Actemra 400 mg for Intravenous Infusion" (intravenous tocilizumab). Tocilizumab 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. Subcutaneous tocilizumab has been approved for the "treatment of rheumatoid arthritis with an inadequate response to existing therapies (including the inhibition of progression of structural joint damage)," and intravenous tocilizumab for the "treatment of the following diseases in patients who have had an inadequate response to existing therapies: Rheumatoid arthritis (including the inhibition of progression of structural joint damage), polyarticular-course juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis" and other indications.

Vasculitis syndromes are inflammatory diseases involving systemic or local blood vessels, and are classified according to the size of the predominantly affected vessels. Vasculitis occurring in the aorta and its major branches to the extremities, the head, and the neck are classified as large vessel vasculitis, which includes Takayasu's arteritis and giant cell arteritis (Japanese clinical practice guidelines). Takayasu's arteritis often develops in young individuals (the most common age of onset is around 20 years old) and predominantly affects the mesenteric arteries. Giant cell arteritis often develops in individuals ≥60 years of age and predominantly affects the temporal arteries (*Respiration Research.* 2014;33:1082-95). Since both Takayasu's arteritis and giant cell arteritis affect the subclavian arteries and the renal arteries, with no significant differences in the histopathology of the lesions, several reports have suggested that they are the same disease (e.g., *Arthritis Rheum.* 2013;65:1-11, *Ann Rheum Dis.* 2012;71:1329-34, and *Infection, Inflammation & Immunity*. 2012;42:265-7). Both Takayasu's arteritis and giant cell arteritis (a) cause symptoms such as fever, weight loss, anemia, and arthralgia, (b) lead to arterial stenosis, intermittent claudication, aneurysm, etc. as a result of the inflammation of blood vessels, and (c) sometimes result in serious organ damage, such as cerebral infarction, heart valve disorder, renal impairment, and visual loss, depending on the location of the lesion. Both Takayasu's arteritis and giant cell arteritis were designated as intractable diseases on October 21, 2014, by the Ministry of Health, Labour and Welfare (MHLW) Ministerial Announcement No. 393 of 2014. In Japan, there are an estimated approximately 6420 patients with Takayasu's arteritis (based on the number of patients who received the Medical Care Certificate for Specific Diseases in fiscal 2014, showing an increase by 100 to 200 patients every year) and an estimated approximately 690 patients with giant cell arteritis who are treated at hospitals (according to the epidemiologic study conducted in 1998 by the Epidemiologic Study Group and the Intractable Vasculitis Study Group of the Ministry of Health and Welfare).

Oral corticosteroid therapy is the first-line treatment for both diseases; however, some patients experience relapse during oral corticosteroid tapering after remission induction, or cannot continue treatment due to serious adverse reactions associated with long-term oral corticosteroid therapy (Japanese clinical practice guidelines, and *Arthritis Rheum.* 2007;56:1000-9). Such patients receive cyclophosphamide or an immunosuppressant (e.g., azathioprine) in combination with oral corticosteroid therapy. Despite these available treatments, approximately half of the patients with the diseases will require surgical treatment such as revascularization and percutaneous transluminal angioplasty (*Rheumatology.* 2012;51:882-6 and *Athritis Rheum.* 2003;49:703-8).

The etiology of Takayasu's arteritis and giant cell arteritis has not been fully elucidated, although stressors such as viral infection may trigger inflammation through immune system responses, and the production of cytokines such as IL-6 may play a central role in the pathogenesis of the diseases (*Curr Opin Rheumatol.* 2014;26:7-15 and *Circ J.* 2011;75:474-503). Against this background, the development of tocilizumab for the treatment of Takayasu's arteritis and giant cell arteritis that have not adequately responded to oral corticosteroid therapy, the standard treatment, was launched.

Outside Japan, the clinical development of tocilizumab for the treatment of giant cell arteritis started in July 2013. Tocilizumab was approved in the U.S. for the treatment of giant cell arteritis in May 2017, and is under review in Europe as of June 2017.

In Japan, the clinical development of tocilizumab for the treatment of Takayasu's arteritis started in September 2014. The present partial change application was filed based on the results of a Japanese clinical study in patients with Takayasu's arteritis and a foreign clinical study in patients with giant cell arteritis.

Tocilizumab was designated as an orphan drug on June 11, 2014 with the intended indication of "large vessel vasculitis" (Drug Designation No. 340 of 2014 [*26 yaku*]).

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

Since the present application is for a new indication and a new dosage, no data relating to the quality of tocilizumab were submitted.

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

Although the application is for a new indication and a new dosage, no new study data on non-clinical pharmacology were submitted because the non-clinical pharmacology of tocilizumab had been evaluated at the previous applications.

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

Although the application is for a new indication and a new dosage, no new study data on non-clinical pharmacokinetics were submitted because the non-clinical pharmacokinetics of tocilizumab had been evaluated at the previous applications.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application is for a new indication and a new dosage, no data relating to the toxicity of tocilizumab were 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 an enzyme-linked immunoassay (ELISA) (lower limit of quantitation, 0.1 μg/mL). Serum antibodies against tocilizumab (i.e., anti-tocilizumab antibodies, anti-tocilizumab-antigen-binding fragment [Fab] antibodies, anti-tocilizumab neutralizing antibodies, and anti-tocilizumab immunoglobulin E [IgE] antibodies) were measured by ELISA.

6.2 Clinical pharmacology

The applicant submitted evaluation data: the results from a Japanese clinical study in patients with Takayasu's arteritis (CTD 5.3.5.1-1, -4, -5, and -7) and a foreign clinical study in patients with giant cell arteritis (CTD 5.3.5.1-3). Unless otherwise specified, the doses of Actemra are described as the doses of tocilizumab (genetical recombination) and pharmacokinetic parameters are expressed as mean ± standard deviation.

6.2.1 Patients with Takayasu's arteritis (CTD 5.3.5.1-1, -4, -5, and -7; Study MRA632JP, ongoing since September 2014 [cutoff date, November 2016])

In a placebo-controlled, randomized, double-blind, parallel-group study in 36 patients with Takayasu's arteritis conducted in Japan, tocilizumab 162 mg was administered subcutaneously once weekly. Table 1 shows changes in serum tocilizumab trough concentrations. At baseline, 1 of 18 patients in the tocilizumab group was positive for anti-tocilizumab antibodies. After the start of tocilizumab therapy, no patients (including the patient with positive anti-tocilizumab antibodies at baseline) tested positive for anti-tocilizumab antibodies, anti-tocilizumab-Fab antibodies, or anti-tocilizumab IgE antibodies at any assessment points.

Table 1. Serum tocilizumab trough concentrations in patients with Takayasu's arteritis who received subcutaneous tocilizumab 162 mg once weekly (μg/mL)

Double-blind phase[a)]									
Weeks after the start of double-blind phase		1	2	4	8	12	24	48	At relapse[b)]
Tocilizumab	n (n with a BLQ value)	18 (0)	18 (0)	17 (0)	15 (0)	14 (0)	7 (0)	1 (0)	14 (0)
	Serum concentration	12.4 ± 6.06	21.7 ± 8.20	36.1 ± 16.0	53.2 ± 24.4	52.8 ± 27.3	56.6 ± 20.1	23.8	69.3 ± 19.7

Open-label phase[c)]										
Weeks after the start of open-label phase		1	2	4	8	12	24	48	52	At relapse[b)]
Ex-tocilizumab	n (n with a BLQ value)	18 (0)	18 (0)	18 (0)	17 (0)	17 (0)	17 (0)	16 (0)	16 (0)	4 (0)
	Serum concentration	57.1 ± 19.6	57.1 ± 18.4	57.2 ± 21.2	58.5 ± 17.3	60.1 ± 22.5	61.9 ± 28.8	69.8 ± 33.8	70.4 ± 34.3	91.3 ± 18.7
Ex-placebo	n (n with a BLQ value)	17 (0)	17 (0)	18 (0)	17 (0)	17 (0)	15 (0)	14 (0)	13 (0)	23 (1)
	Serum concentration	9.92 ± 4.93	18.4 ± 8.29	33.5 ± 14.6	47.6 ± 20.0	50.6 ± 21.5	55.1 ± 25.7	58.4 ± 28.3	60.1 ± 25.2	44.3 ± 14.6[d)]

Mean ± standard deviation
BLQ, below the lower limit of quantitation (<0.1 μg/mL)
a) Tocilizumab or placebo was administered until Takayasu's arteritis relapsed or until a total of 19 events had occurred in the tocilizumab and placebo groups combined.
b) Summary statistics of data collected at all relapses
c) All the patients who completed the double-blind phase received open-label tocilizumab.
d) Excluding data from patients with a BLQ value

6.2.2 Patients with giant cell arteritis (CTD 5.3.5.1-3; Study WA28119, ongoing since July 2013 [cutoff date, April 2016])

In a placebo-controlled, randomized, double-blind, parallel-group study in 250 patients with giant cell arteritis conducted outside Japan, tocilizumab 162 mg was administered subcutaneously once weekly or every 2 weeks. Table 2 shows changes in serum tocilizumab trough concentrations. At baseline, some patients were positive for anti-tocilizumab antibodies: 1 of 99 patients in the tocilizumab once-weekly dosing (QW) group; 4 of 47 patients in the tocilizumab every-2-weeks dosing (Q2W) group; and 1 of 49 patients in the placebo + 52-week oral corticosteroid (CS) taper group. After the start of treatment, several patients developed anti-tocilizumab antibodies: 1 of 95 patients in the QW group, 3 of 46 patients in the Q2W group, 1 of 49 patients in the placebo + 26-week CS taper group, and 1 of 47 patients in the placebo + 52-week CS taper group. Among these patients, 1 in the QW group and 3 in the Q2W group were positive for anti-tocilizumab neutralizing antibodies. No patients developed anti-tocilizumab IgE antibodies. None of the patients who developed anti-tocilizumab antibodies after the start of treatment experienced administration-related systemic reactions, administration site reactions, or anaphylaxis that were considered attributable to immunoreactions. No patients discontinued the study treatment due to inadequate response.

Table 2. Serum tocilizumab trough concentrations in patients with giant cell arteritis who received repeated subcutaneous administration of tocilizumab 162 mg (μg/mL)

Weeks after the start of treatment		1	2	8	16	24	36	48	52
QW (N = 100)	n (n with a BLQ value)	98 (0)	96 (0)	92 (0)	89 (0)	87 (0)	81 (0)	81 (0)	72 (0)
	Serum concentration	8.84 ± 5.99	15.7 ± 8.1	45.2 ± 22.1	63.5 ± 29.3	68.2 ± 30.7	68.4 ± 33.7	70.5 ± 32.8	67.9 ± 34.4
Q2W (N = 49)	n (n with a BLQ value)	43 (0)	39 (0)	45 (0)	45 (0)	41 (0)	39 (0)	40 (0)	33 (0)
	Serum concentration	8.34 ± 5.15	2.48 ± 3.27	8.37 ± 7.28	11.6 ± 10.0	12.5 ± 9.8	13.8 ± 10.5	13.5 ± 11.5	12.2 ± 10.0

Mean ± standard deviation
BLQ, below the lower limit of quantitation (<0.1 μg/mL)

6.R Outline of the review conducted by PMDA

6.R.1 Impact of ethnicity and patient characteristics on the pharmacokinetics of tocilizumab

The efficacy and safety of tocilizumab in patients with Takayasu's arteritis were evaluated in a Japanese clinical study (Study MRA632JP), but the efficacy and safety in patients with giant cell arteritis were evaluated only in a foreign clinical study (Study WA28119). PMDA asked the applicant to explain the effects of the disease type, Takayasu's arteritis or giant cell arteritis, on the pharmacokinetics of tocilizumab, in consideration of the impact of ethnic factors upon serum tocilizumab concentration, blood IL-6 concentration, and blood soluble interleukin-6 receptor (sIL-6R) concentration.

The applicant's explanation:

Among the clinical studies of tocilizumab in patients with active rheumatoid arthritis (RA) conducted in Japan and other countries, the results of a Japanese phase I/II study (Study MRA227JP[2]) and a foreign phase I study (NP22623[3]) were compared because both studies enrolled patients with similar characteristics. The results suggested that ethnic factors were unlikely to affect the pharmacokinetics of tocilizumab, for the following reasons.

- The steady-state serum tocilizumab trough concentrations in patients receiving tocilizumab 162 mg once weekly were similar in both studies: 26.6 ± 14.8 μg/mL (Week 13) in Study MRA227JP and 27.9 ± 14.7 μg/mL (Week 12) in Study NP22623.
- The time course of blood IL-6 concentration was similar in both studies: after the start of tocilizumab therapy, blood IL-6 concentrations transiently increased (Study MRA227JP, 322 ± 365 pg/mL (Day 7); Study NP22623, 199 ± 214 pg/mL [Day 4]), then decreased, and finally attained a similar level in both studies around the time when serum tocilizumab trough concentrations reached a steady state (Study MRA227JP, 81.8 ± 79.3 pg/mL [Week 13]; Study NP22623, 71.9 ± 37.4 pg/mL [Week 12]).
- The time course of blood sIL-6R concentrations was similar in both studies: blood sIL-6R concentrations elevated to a certain level with an increase in serum tocilizumab concentrations after

[2] An open -label, dose-escalation study to evaluate the safety, pharmacokinetics, and efficacy of subcutaneous tocilizumab in patients with active RA
[3] A randomized, open-label, parallel-group study to evaluate the safety, pharmacokinetics, and efficacy of subcutaneous tocilizumab in patients with active RA

repeated doses of tocilizumab (Study MRA227JP, 524 ± 111 ng/mL [Week 9]; Study NP22623, 624 ± 173 ng/mL [Week 9]).

Table 3 shows serum tocilizumab trough concentrations, blood IL-6 concentrations, and blood sIL-6R concentrations in patients with Takayasu's arteritis (Study MRA632JP) or giant cell arteritis (Study WA28119) who received subcutaneous tocilizumab 162 mg once weekly. The time course of serum tocilizumab concentrations and blood sIL-6R concentrations did not differ substantially between patients with Takayasu's arteritis and those with giant cell arteritis. Both patient groups had a similar time course of blood IL-6 concentration (i.e., a transient increase followed by a gradual decrease), though simple comparison may be meaningless because of the difference in the protocol-specified use of oral corticosteroids between the studies.

These data suggest that disease type, Takayasu's arteritis or giant cell arteritis, is unlikely to affect the pharmacokinetics of tocilizumab.

Table 3. Serum tocilizumab trough concentrations, blood IL-6 concentrations, and blood sIL-6R concentrations in patients with Takayasu's arteritis or giant cell arteritis who received subcutaneous tocilizumab 162 mg once weekly

	Assessment points	Study MRA632JP	Study WA28119
		Takayasu's arteritis (N = 18)	Giant cell arteritis (N = 100)
Serum tocilizumab trough concentration (μg/mL)	Week 2	21.7 ± 8.20 (18)	15.7 ± 8.09 (96)
	Week 4[a)]	36.1 ± 16.0 (17)	22.5 ± 11.1 (94)
	Week 16	49.5 ± 28.1 (10)	63.5 ± 29.3 (89)
Blood IL-6 concentration (pg/mL)	Week 2	56.6 ± 82.9 (18)	111 ± 106 (96)
	Week 4[a)]	78.8 ± 149 (18)	118 ± 131 (94)
	Week 16	64.5 ± 71.7 (10)	106 ± 125 (89)
Blood sIL-6R concentration (ng/mL)	Week 2	355 ± 54.5 (18)	371 ± 103 (97)
	Week 4[a)]	459 ± 88.0 (18)	426 ± 113 (93)
	Week 16	533 ± 108 (10)	671 ± 164 (89)

Mean ± standard deviation (n)
a) Week 3 for Study WA28119

PMDA accepted the applicant's explanation.

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

The applicant submitted evaluation data: the results from a Japanese clinical study in patients with Takayasu's arteritis (CTD 5.3.5.1-1 and -7, Study MRA632JP) and a foreign double-blind study in patients with giant cell arteritis (CTD 5.3.5.1-3, Study WA28119) (Table 4).

Table 4. Clinical studies on the efficacy and safety of tocilizumab

Data type	Region	Study identifier	Phase	Subjects	No. of patients enrolled	Dosage regimen	Main endpoints
Evaluation data	Japan	MRA632JP	III	Patients with Takayasu's arteritis	36 ((a) 18, (b) 18)	Administered subcutaneously once weekly (a) Tocilizumab 162 mg (b) Placebo	Efficacy Safety
	Foreign	WA28119	III	Patients with giant cell arteritis	251 ((a) 100, (b) 50, (c) 50, (d) 51)	(a) Tocilizumab 162 mg administered subcutaneously once weekly[a)] (b) Tocilizumab 162 mg administered subcutaneously every 2 weeks[a)] (c) Placebo administered subcutaneously once weekly[a)] (d) Placebo administered subcutaneously once weekly[b)]	Efficacy Safety

a) Oral corticosteroid was tapered over 26 weeks.
b) Oral corticosteroid was tapered over 52 weeks.

7.1 Clinical studies

7.1.1 Phase III study in patients with Takayasu's arteritis (CTD 5.3.5.1-1 and -7: Study MRA632JP [ongoing since September 2014 [cutoff date, November 2016])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in Japan, to evaluate the efficacy and safety of tocilizumab in patients with Takayasu's arteritis aged ≥12 years who experienced relapse of the disease within 12 weeks before randomization despite oral corticosteroid therapy (≥0.2 mg/kg/day prednisolone equivalent) (target sample size, 34 patients [17 per group]) [for the definition of relapse, see Section "10. Others"].

Patients received subcutaneous tocilizumab 162 mg or placebo once weekly. The treatment was continued until Takayasu's arteritis relapsed or the study was completed[4)] (double-blind phase). In both the tocilizumab and placebo groups, the oral corticosteroid was gradually reduced according to the pre-specified tapering regimen.[5)] All patients who completed the double-blind phase rolled over to the open-label phase to receive tocilizumab 162 mg subcutaneously once weekly (the ongoing open-label phase).

A total of 36 patients were stratified by oral corticosteroid dose at baseline (<0.6 mg/kg/day, ≥0.6 mg/kg/day and <0.8 mg/kg/day, or ≥0.8 mg/kg/day prednisolone equivalent) and randomly assigned[6)] to tocilizumab or placebo (18 patients each). All 36 patients received the study drug, and were included in the safety analysis set and the intention-to-treat (ITT) population. The efficacy analysis set was the ITT population.

During the double-blind phase, no patients discontinued the study treatment. All 36 patients (18 in the tocilizumab group and 18 in the placebo group) completed the double-blind phase and rolled over to the

[4] The study had to be terminated at the point in time when a total of 19 events of relapse had occurred in the tocilizumab and placebo groups combined, or when the sponsor had declared discontinuation of the study based on the recommendation of the independent data monitoring committee.
[5] In the double-blind phase, the initial oral corticosteroid dose was maintained for the first 4 weeks of study treatment and then tapered by 10% weekly to 0.1 mg/kg/day (prednisolone equivalent). Patients experiencing relapse of Takayasu's arteritis during the double-blind phase were required to increase their oral corticosteroid dose in the open-label phase. In the open-label phase, oral corticosteroid dose could be changed at the discretion of investigators.
[6] Patients in sustained remission of Takayasu's arteritis were randomized if they were receiving an oral corticosteroid, for at least 1 week before the first dose of study drug, administered once daily at a fixed dose that was more than twice the dose administered at relapse of the disease.

open-label phase. In the open-label phase, 19.4% (7 of 36) of the patients discontinued treatment with tocilizumab because of inadequate response (3 patients), use of prohibited concomitant therapies (2 patients), treatment refusal/poor cooperation (1 patient), and consent withdrawal (1 patient).

The primary endpoint in the double-blind phase of the study was relapse of Takayasu's arteritis. An interim analysis was conducted as planned after at least 12 events were collected, to determine whether the study should be terminated early for efficacy or futility. The probability of a type I error for early termination for efficacy was adjusted using the O'Brien-Fleming α-spending function, and the boundary for early termination for futility was calculated according to the O'Brien-Fleming β-spending function. The results of interim analysis did not suggest early termination for efficacy or futility. In the sections below, therefore, the results of the final analysis are described.

Table 5 shows the time to relapse of Takayasu's arteritis, the primary endpoint, and Figure 1 shows the Kaplan-Meier curves. A pairwise comparison revealed no statistically significant difference between the tocilizumab and placebo groups, thus showing no superiority of tocilizumab to placebo.

Table 5. Time to relapse of Takayasu's arteritis (ITT population)

	Tocilizumab (N = 18)	Placebo (N = 18)
Number of patients without relapse (%)	10 (55.6)	7 (38.9)
Median time to relapse (weeks)[a)] [95% CI][b)]	NE [12.1, NE]	12.1 [10.7, 16.0]
Hazard ratio [95.41% CI][c)] *P* value[d) e)]	0.41 [0.15, 1.10] *P* = 0.0596	

a) Kaplan-Meier method
b) Brookmeyer-Crowley method (log-log transformation)
c) Cox proportional hazards model stratified by age category (<18, ≥18 and <65, or ≥65 years old)
d) Log-rank test stratified by age category (<18, ≥18 and <65, or ≥65 years old)
e) The final analysis used a 2-sided significance level of 0.0459 based on the O'Brien-Fleming α-spending function.

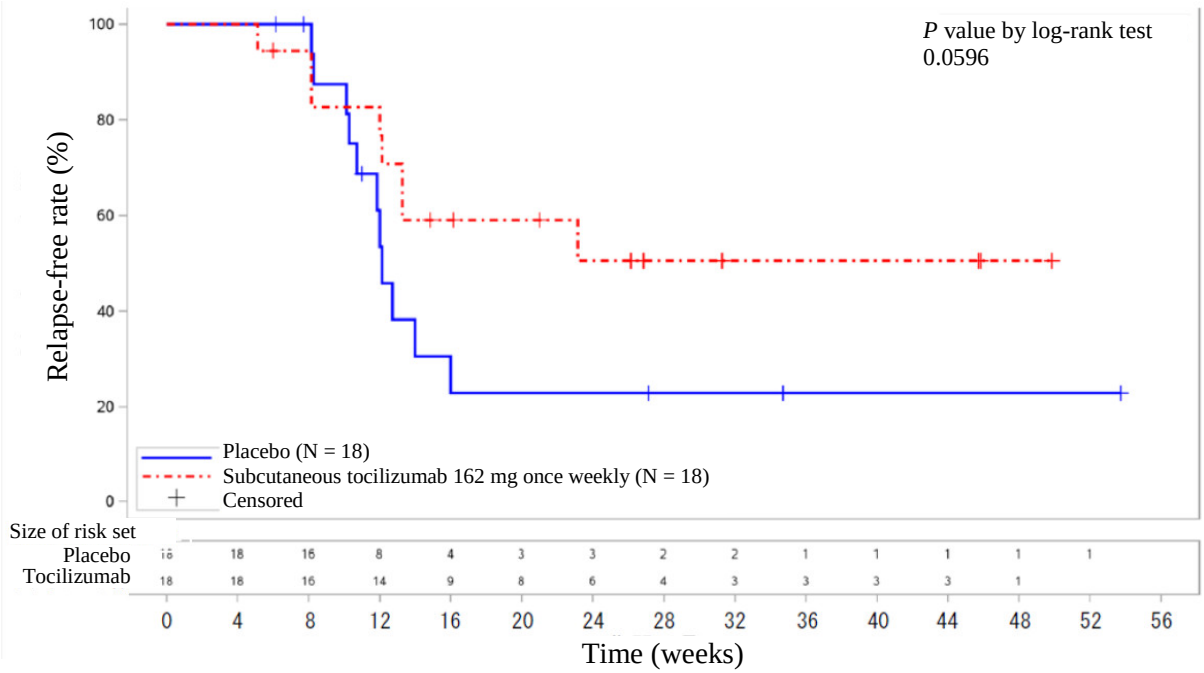

Figure 1. Kaplan-Meier curves for the time to first relapse of Takayasu's arteritis (ITT population)

The incidences of adverse events in the double-blind phase were 77.8% (14 of 18 patients) in the tocilizumab group and 61.1% (11 of 18 patients) in the control group. Table 6 shows the common adverse events. No deaths occurred in the double-blind phase. The incidences of serious adverse events were 5.6% (1 of 18 patients; cataract) in the tocilizumab group and 11.1% (2 of 18 patients: cataract in one patient; shock haemorrhagic and gastric ulcer haemorrhage in the other); a causal relationship to the study drug was ruled out for all of the events. No patients discontinued the study treatment due to adverse events.

The incidences of adverse drug reactions were 27.8% (5 of 18 patients) in the tocilizumab group and 16.7% (3 of 18 patients) in the placebo group in the double-blind phase.

Table 6. Adverse events reported in ≥2 patients in either group during the double-blind phase (safety analysis set)

	Tocilizumab (N = 18)	Placebo (N = 18)
Nasopharyngitis	6 (33.3)	3 (16.7)
Upper respiratory tract infection	3 (16.7)	0
Gastroenteritis	2 (11.1)	0
Pharyngitis	2 (11.1)	0
Oropharyngeal pain	0	2 (11.1)
Weight increased	0	2 (11.1)

n (%)

Adverse events occurred in 94.4% (34 of 36) of patients receiving tocilizumab during the entire study period (see Table 7 for the common adverse events). There were no deaths. Serious adverse events occurred in 16.7% (6 of 36) of patients receiving tocilizumab during the entire study period. The serious adverse events in 5 of the 6 patients occurred during the open-label phase (pyelonephritis acute,

pneumonia, dental caries, pulmonary infarction, and complex regional pain syndrome in 1 patient each); and a causal relationship to the study drug could not be ruled out for pyelonephritis acute, pneumonia, and complex regional pain syndrome. No patients discontinued the study treatment due to adverse events throughout the entire study period.

Adverse drug reactions occurred in 50.0% (18 of 36) of patients receiving tocilizumab during the entire study period.

Table 7. Adverse events reported in ≥2 patients during the entire study period (safety analysis set)

	Patients receiving tocilizumab (N = 36)		Patients receiving tocilizumab (N = 36)
Nasopharyngitis	18 (50.0)	Headache	3 (8.3)
Pharyngitis	7 (19.4)	Contusion	3 (8.3)
Upper respiratory tract infection	7 (19.4)	Influenza	2 (5.6)
Gastroenteritis	5 (13.9)	Vulvovaginal candidiasis	2 (5.6)
Enteritis infectious	4 (11.1)	Sinusitis	2 (5.6)
Diarrhoea	4 (11.1)	Cheilitis	2 (5.6)
Myalgia	4 (11.1)	Stomatitis	2 (5.6)
Back pain	4 (11.1)	Abdominal discomfort	2 (5.6)
Oral herpes	3 (8.3)	Eczema	2 (5.6)
Cystitis	3 (8.3)	Rash	2 (5.6)
Nausea	3 (8.3)	Dry skin	2 (5.6)
Abdominal pain	3 (8.3)	Urticaria	2 (5.6)
Dental caries	3 (8.3)	Pain in extremity	2 (5.6)
Acne	3 (8.3)	Hypoaesthesia	2 (5.6)
Haemorrhage subcutaneous	3 (8.3)	Rib fracture	2 (5.6)
Presyncope	3 (8.3)	Pulmonary infarction	2 (5.6)

n (%)

7.1.2 Phase III study in patients with giant cell arteritis (CTD 5.3.5.1-3: Study WA28119 [ongoing since July 2013 [cutoff date, April 2016])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 14 foreign countries, including the U.S., Germany, and Belgium, to evaluate the efficacy and safety of tocilizumab in patients with giant cell arteritis[7)] (target sample size, 250 patients).

Patients received 52-week administration of subcutaneous tocilizumab 162 mg once weekly or every 2 weeks, or subcutaneous placebo once weekly. In both the tocilizumab and placebo groups, the oral corticosteroid was gradually reduced according to the pre-specified tapering regimen.[8)]

[7] Patients were enrolled in the study, if they met the following criteria: (a) ≥50 years old, (b) a history of ESR ≥50 mm/h (if past ESR data were available, CRP ≥2.45 mg/dL), (c) unequivocal cranial symptoms of giant cell arteritis or symptoms of PMR, (d) a diagnosis of giant cell arteritis based on temporal artery biopsy, angiography, or other imaging techniques, (e) new onset of giant cell arteritis (diagnosed within 6 weeks before baseline) or relapse of giant cell arteritis (diagnosed >6 weeks before baseline and previously treated with ≥40 mg/day of oral corticosteroids for at least 2 consecutive weeks), (f) giant cell arteritis was confirmed to be active within 6 weeks before baseline (cranial symptoms or symptoms/signs of PMR, with ESR ≥30 mm/h or CRP ≥1 mg/dL [excluding positive results of temporal artery biopsy conducted within 6 weeks before baseline]).

[8] The baseline prednisone dose, 20 to 60 mg/day, was tapered over 26 weeks in the tocilizumab groups or over 26 or 52 weeks in the placebo groups (tapered to 20 mg/day in an open-label manner, then to 0 mg/day in a double-blind manner). If a patient experienced a relapse of giant cell arteritis during the tapering period [for the definition of relapse, see Section "10. Others"] or could not continue the tapering according to the pre-specified tapering regimen, the oral corticosteroid therapy was unblinded and the oral corticosteroid dose was adjusted at the discretion of the investigator.

A total of 251 patients were stratified by prednisone dose at baseline (≤30 mg/day or >30 mg/day) and randomly assigned, in a 2:1:1:1 ratio, to (a) the tocilizumab once weekly + 26-week oral corticosteroid (CS) taper group (the QW group), (b) the tocilizumab every 2 weeks + 26-week CS taper group (the Q2W group), (c) the placebo + 26-week CS taper group, or (d) the placebo + 52-week CS taper group. Of the 251 patients, 1 did not receive study treatment. The remaining 250 patients (100 in the QW group, 49 in the Q2W group, 50 in the placebo + 26-week CS taper group, and 51 in the placebo + 52-week CS taper group) were included in the safety analysis set and the ITT population. The efficacy analysis set was the ITT population. Treatment was discontinued in 18.0% (18 of 100) of patients in the QW group, 18.4% (9 of 49) of patients in the Q2W group, 18.0% (9 of 50) of patients in the placebo + 26-week CS taper group, and 9.8% (5 of 51) of patients in the placebo + 52-week CS taper group. The common reasons for treatment discontinuation were adverse events (9 patients in the QW group, 3 in the Q2W group, and 3 in the placebo + 26-week CS taper group).

The primary efficacy endpoint was the proportion of patients who achieved remission [for the definition of remission, see Section "10. Others"] within 12 weeks after the start of study treatment, successfully underwent oral corticosteroid tapering according to the pre-specified tapering regimen, and remained in remission at Week 52 (relapse-free rate at Week 52). Table 8 shows the results. Pairwise comparisons revealed statistically significant differences between the placebo + 26-week CS taper group and the QW or Q2W group. Tocilizumab 162 mg once weekly and every 2 weeks was thus superior to placebo.

Table 8. Relapse-free rates at Week 52 (ITT population, NRI)

	QW	Q2W	Placebo + 26-week CS taper	Placebo + 52-week CS taper
Relapse-free rate	56.0 (56/100)	53.1 (26/49)	14.0 (7/50)	17.6 (9/51)
Difference from placebo + 26-week CS taper [99.5% CI] *P* value[a) b)]	42.0 [18.0, 66.0] *P* < 0.0001	39.1 [12.5, 65.7] *P* < 0.0001		
Difference from placebo + 52-week CS taper [99.5% CI]	38.4 [17.9, 58.8]	35.4 [10.4, 60.4]		

% (n/N)
a) Cochran-Mantel-Haenszel test stratified by prednisone dose at baseline (≤30 mg/day or >30 mg/day)
b) Multiplicity was adjusted using the Bonferroni method, with a 2-sided significance level of 0.01.

The incidence of adverse events was 98.0% (98 of 100 patients) in the QW group, 95.9% (47 of 49 patients) in the Q2W group, 96.0% (48 of 50 patients) in the placebo + 26-week CS taper group, and 92.2% (47 of 51 patients) in the placebo + 52-week CS taper group (see Table 9 for the common adverse events). No deaths occurred. The incidence of serious adverse events was 15.0% (15 of 100 patients) in the QW group, 14.3% (7 of 49 patients) in the Q2W group, 22.0% (11 of 50 patients) in the placebo + 26-week CS taper group, and 25.5% (13 of 51 patients) in the placebo + 52-week CS taper group. The common serious adverse events were hypertensive crisis (2 patients in the QW group), temporal arteritis (1 patient each in the QW, placebo + 26-week CS taper, and placebo + 52-week CS taper groups), gastroenteritis (1 patient in the QW group and 2 patients in the placebo + 52-week CS taper group), and herpes zoster (1 patient in the QW group and 2 patients in the placebo + 52-week CS taper group). The incidence of adverse events leading to study drug discontinuation was 11.0% (11 of 100 patients) in the

QW group, 10.2% (5 of 49 patients) in the Q2W group, and 6.0% (3 of 50 patients) in the placebo + 26-week CS taper group.

The incidence of adverse drug reactions was 52.0% (52 of 100 patients) in the QW group, 53.1% (26 of 49 patients) in the Q2W group, 42.0% (21 of 50 patients) in the placebo + 26-week CS taper group, and 35.3% (18 of 51 patients) in the placebo + 52-week CS taper group.

Table 9. Adverse events with an incidence of ≥5% in any group (safety analysis set)

	QW (N = 100)	Q2W (N = 49)	Placebo + 26-week CS taper (N = 50)	Placebo + 52-week CS taper (N = 51)
Nasopharyngitis	29 (29.0)	12 (24.5)	9 (18.0)	13 (25.5)
Headache	27 (27.0)	10 (20.4)	16 (32.0)	12 (23.5)
Oedema peripheral	16 (16.0)	12 (24.5)	8 (16.0)	6 (11.8)
Back pain	14 (14.0)	7 (14.3)	7 (14.0)	10 (19.6)
Arthralgia	13 (13.0)	8 (16.3)	11 (22.0)	8 (15.7)
Musculoskeletal pain	12 (12.0)	6 (12.2)	5 (10.0)	2 (3.9)
Hypertension	12 (12.0)	6 (12.2)	4 (8.0)	4 (7.8)
Diarrhoea	12 (12.0)	3 (6.1)	8 (16.0)	5 (9.8)
Upper respiratory tract infection	10 (10.0)	6 (12.2)	5 (10.0)	7 (13.7)
Urinary tract infection	10 (10.0)	4 (8.2)	2 (4.0)	4 (7.8)
Myalgia	9 (9.0)	4 (8.2)	4 (8.0)	4 (7.8)
Fatigue	8 (8.0)	5 (10.2)	8 (16.0)	3 (5.9)
Pain in extremity	8 (8.0)	5 (10.2)	5 (10.0)	5 (9.8)
Bronchitis	8 (8.0)	4 (8.2)	5 (10.0)	5 (9.8)
Nausea	8 (8.0)	2 (4.1)	5 (10.0)	4 (7.8)
Rash	7 (7.0)	5 (10.2)	4 (8.0)	2 (3.9)
Oropharyngeal pain	7 (7.0)	4 (8.2)	5 (10.0)	8 (15.7)
Osteoarthritis	7 (7.0)	2 (4.1)	3 (6.0)	4 (7.8)
Fall	7 (7.0)	2 (4.1)	2 (4.0)	2 (3.9)
Cystitis	7 (7.0)	0	2 (4.0)	3 (5.9)
Dizziness	6 (6.0)	10 (20.4)	6 (12.0)	8 (15.7)
Rhinitis	6 (6.0)	4 (8.2)	2 (4.0)	3 (5.9)
Cough	6 (6.0)	3 (6.1)	7 (14.0)	3 (5.9)
Neck pain	6 (6.0)	1 (2.0)	2 (4.0)	4 (7.8)
Alopecia	5 (5.0)	7 (14.3)	3 (6.0)	5 (9.8)
Asthenia	5 (5.0)	3 (6.1)	5 (10.0)	0
Haematoma	5 (5.0)	3 (6.1)	3 (6.0)	1 (2.0)
Alanine aminotransferase increased	5 (5.0)	2 (4.1)	2 (4.0)	0
Herpes zoster	5 (5.0)	2 (4.1)	0	2 (3.9)
Cataract	5 (5.0)	1 (2.0)	3 (6.0)	5 (9.8)
Muscle spasms	4 (4.0)	6 (12.2)	6 (12.0)	4 (7.8)
Oral herpes	4 (4.0)	5 (10.2)	3 (6.0)	2 (3.9)
Paraesthesia	4 (4.0)	2 (4.1)	5 (10.0)	4 (7.8)
Insomnia	4 (4.0)	1 (2.0)	4 (8.0)	4 (7.8)
Conjunctivitis	4 (4.0)	1 (2.0)	4 (8.0)	1 (2.0)
Pharyngitis	4 (4.0)	0	1 (2.0)	3 (5.9)
Gastroenteritis	3 (3.0)	4 (8.2)	4 (8.0)	4 (7.8)
Dyspnoea	3 (3.0)	4 (8.2)	1 (2.0)	3 (5.9)
Sinusitis	3 (3.0)	4 (8.2)	1 (2.0)	2 (3.9)
Abdominal pain upper	3 (3.0)	3 (6.1)	3 (6.0)	4 (7.8)
Depression	3 (3.0)	2 (4.1)	3 (6.0)	1 (2.0)
Anxiety	3 (3.0)	1 (2.0)	6 (12.0)	1 (2.0)
Epistaxis	3 (3.0)	1 (2.0)	4 (8.0)	0
Pruritus	2 (2.0)	4 (8.2)	1 (2.0)	1 (2.0)
Hypercholesterolaemia	2 (2.0)	3 (6.1)	0	1 (2.0)
Dry skin	2 (2.0)	3 (6.1)	0	0
Palpitations	2 (2.0)	2 (4.1)	4 (8.0)	2 (3.9)
Vomiting	2 (2.0)	2 (4.1)	2 (4.0)	3 (5.9)
Vertigo	2 (2.0)	1 (2.0)	3 (6.0)	1 (2.0)
Bursitis	1 (1.0)	4 (8.2)	2 (4.0)	1 (2.0)
Night sweats	1 (1.0)	3 (6.1)	1 (2.0)	1 (2.0)
Dry eye	1 (1.0)	3 (6.1)	1 (2.0)	1 (2.0)
Sleep disorder	1 (1.0)	3 (6.1)	1 (2.0)	1 (2.0)
Non-cardiac chest pain	1 (1.0)	2 (4.1)	1 (2.0)	3 (5.9)
Dyspnoea exertional	1 (1.0)	0	3 (6.0)	1 (2.0)
Ecchymosis	0	2 (4.1)	1 (2.0)	3 (5.9)
Constipation	0	1 (2.0)	3 (6.0)	4 (7.8)
Hypokalaemia	0	1 (2.0)	0	3 (5.9)
Dyspepsia	0	0	4 (8.0)	1 (2.0)
Tremor	0	0	3 (6.0)	3 (5.9)

n (%)

7.2 Publications

7.2.1 Takayasu's arteritis

A literature search of PubMed (queries, "tocilizumab" + "takayasu arteritis"), Embase (queries, "tocilizumab" + "aorta arch syndrome"), and *Igaku Chuo Zasshi* (queries, "tocilizumab" + "Takayasu's arteritis") was conducted. Among the 44 publications found in PubMed, 168 in Embase, and 33 in *Igaku Chuo Zasshi* (June 22, 2016), 10 Japanese case reports and 4 reviews on tocilizumab therapy for patients with Takayasu's arteritis were submitted for the present application. The Japanese case reports on tocilizumab therapy in patients with Takayasu's arteritis are summarized below.

	Source	Patients	Dosing regimen	Efficacy	Safety
1	*J Jpn Coll Angiol.* 2015;55:S97	9 patients with corticosteroid-resistant Takayasu's arteritis (Case reports)	Tocilizumab 8 mg/kg every 4 weeks for ≥1 year (12 to 88 doses)	Nine patients continuously treated with tocilizumab showed favorable response in terms of the clinical symptoms, serum CRP and SAA levels, IL-6 concentration, the dose of corticosteroids required for sustained remission, and image findings. The CRP and SAA levels were rapidly normalized and the mean dose of prednisolone was reduced from 17.2 mg/day to 4.8 mg/day. In all the patients, serum IL-6 concentration tended to transiently increase after the start of tocilizumab therapy and decrease thereafter. In 4 patients, the regression of vascular hypertrophy was noted on images when serum IL-6 concentration was decreasing.	Not described
2	*Int J Cardiol*. 2015;187: 319-21	1 patient with refractory Takayasu's arteritis (Case report)	Tocilizumab 8 mg/kg every 4 weeks for 26 months	The CRP and SAA levels normalized following a single dose of tocilizumab. The dose of prednisolone was reduced from 18.75 to 3 mg/day, without any signs of relapse. After the completion of tocilizumab therapy (a total of 20 doses), the prednisolone dose was increased to 5 mg/day. At 9 weeks after the completion of tocilizumab therapy, the patient experienced dry cough with increased CRP and SAA levels. The prednisolone dose was increased to 10 mg/day, but the symptoms did not resolve. Tocilizumab therapy was therefore resumed. Within 1 month after resumption, dry cough resolved, and the CRP and SAA levels normalized again. Subsequently, prednisolone was tapered to 5 mg/day and MTX was started, and then tocilizumab therapy was completed without relapse. During a 2-year follow-up, no signs of relapse were noted.	Not described
3	*Shinzo.* 2014;46: 1585-91	1 patient with refractory Takayasu's arteritis (Case report)	Tocilizumab 8 mg/kg every 4 weeks, ↓ 8 mg/kg every 2 weeks for 6 months ↓ 8 mg/kg every 4 to 5 weeks for approximately 1 year	The patients started to receive tocilizumab 8 mg/kg/day every 4 weeks, showing transient improvement in symptoms. However, a reduction in methylprednisolone dose to 8 mg/day led to a recurrence of pyrexia and chest/back pain, suggesting dilatation and inflammation of the ascending aorta. In addition to methylprednisolone 24 mg/day and MTX 12 mg/week, the dosing interval of tocilizumab 8 mg/kg was reduced from 4 weeks to 2 weeks; patient-reported symptoms and FDG-PET findings then improved. Subsequently, the methylprednisolone dose could be reduced without dilatation of the ascending aorta. The patient received tocilizumab every 2 weeks for 6 months, then the dosing interval was prolonged to every 4 to 5 weeks. The patient is currently on tocilizumab every 4 to 5 weeks.	No safety concerns such as infections have been noted.
4	Program and abstracts of the 24th Annual Meeting of Pediatric Rheumatology Association of Japan. 2014;118	2 patients with Takayasu's arteritis (including 1 pediatric patient) (Case reports)	Unknown	Patient A: After the start of tocilizumab therapy, the prednisolone dose could be reduced from 25 to 8.5 mg/day because of improvement in clinical symptoms, white blood cell count, CRP, ESR, etc. At 2 years after the start of tocilizumab therapy, FDG-PET revealed abnormal accumulation in the right and left common carotid arteries, and contrast-enhanced CT revealed exacerbation of right common carotid artery stenosis. Patient B (pediatric): After the start of tocilizumab therapy, the prednisolone dose could be reduced to 15 mg/day because of improvement in clinical symptoms, white blood cell count, CRP, ESR, etc. Six months later, FDG-PET revealed accumulation in the ascending aorta to the aortic arch, the right and left common carotid arteries, and the left subclavian artery, and contrast-enhanced CT revealed exacerbation and enlarged areas of bilateral common carotid artery stenosis.	Not described

	Source	Patients	Dosing regimen	Efficacy	Safety
5	Program and abstracts of the 58th Annual General Assembly and Scientific Meeting of Japan College of Rheumatology/ International Rheumatology Symposium. 2014;413	4 patients with refractory Takayasu's arteritis (Case reports)	Unknown	Four patients with secondary failure to infliximab were treated with tocilizumab, and 3 of the patients achieved remission. No patients discontinued tocilizumab therapy after the remission. The doses of the corticosteroids could be reduced because of tocilizumab.	No patients discontinued tocilizumab due to adverse reactions.
6	Program and abstracts of the 58th Annual General Assembly and Scientific Meeting of Japan College of Rheumatology /International Rheumatology Symposium. 2014; 713	1 patient with anti-TNF therapy-resistant Takayasu's arteritis (Case report)	Dose and treatment duration unknown ↓ 8 mg/kg every 4 weeks	Tocilizumab monotherapy was started in a patient who had experienced multiple relapses of Takayasu's arteritis while receiving monotherapy or combination therapy with oral corticosteroids, MTX, cyclophosphamide, tacrolimus, etc. Pyoderma gangrenosum occurred immediately after the start of tocilizumab, resulting in the discontinuation of treatment. Takayasu's arteritis relapsed, and tocilizumab was resumed (8 mg/kg every 4 weeks) in combination with MTX. A subcutaneous tumor developed in the right heel and was treated with antibiotics, but tocilizumab was continued thereafter. Subsequently, tacrolimus was added and the corticosteroid dose could be reduced, without relapse of the disease.	Not described
7	*Int Heart J.* 2013; 54: 405-11	4 patients with refractory Takayasu's arteritis (Case reports)	Tocilizumab 8 mg/kg every 4 weeks, 24 to 51 doses in total	Tocilizumab therapy rapidly normalized the clinical symptoms, IL-6 concentration, and CRP and SAA levels; and reduced the mean dose of prednisolone from 21.3 to 1.5 mg/day. The sIL-6R concentration was transiently elevated in all the patients after several doses of tocilizumab, but it gradually returned to the initial level. Two patients exhibited decreased arterial hypertrophy as well as decreased serum IL-6 concentration. Tocilizumab was thus effective in patients with refractory Takayasu's arteritis.	Tocilizumab was well-tolerated, and no new adverse reactions were identified.
8	Program and abstracts of the 23rd Annual Meeting of the Pediatric Rheumatology Association of Japan. 2013;87	2 pediatric patients with Takayasu's arteritis (Case reports)	Unknown	Patient A: After the start of tocilizumab therapy, the cervical bruit and inflammatory reactions improved without any increases in inflammatory markers. Patient B: After the start of tocilizumab therapy, inflammatory reactions improved without relapse of the reactions.	Not described
9	Program and abstracts of the 23rd Annual Meeting of the Pediatric Rheumatology Association of Japan. 2013;87	6 (pediatric) patients with refractory Takayasu's arteritis (Case reports)	Tocilizumab 8 to 10 mg/kg every 2 weeks for a mean duration of 24 months (range, 6 to 58 months)	After the start of tocilizumab therapy, the symptoms of pyrexia, myalgia, headache, hypertension, and abdominal pain improved. The mean ESR level decreased from 36.1 mm/h (range, 11 to 58 mm/h) to 3.2 mm/h (range, 1 to 6 mm/h). The mean daily dose of prednisolone was reduced from 24.3 mg/day (range, 11 to 45 mg/day) to 5.7 mg/day (range, 5 to 6.5 mg/day) at 24 months. The mean serum IL-6 concentration peaked at 166.7 pg/mL (range, 20.7 to 548.1 pg/mL) at 2 to 3 months and then decreased to 33.3 pg/mL (range, 7.1 to 54.8 mg/mL) at 6 months. Imaging revealed improvement in vascular hypertrophy and stenosis in 3 patients.	Not described
10	*Arthritis Rheum.* 2008; 58: 1197-200	1 patient with refractory Takayasu's arteritis (Case report)	Tocilizumab 4 mg/kg once weekly, 6 doses ↓ 4 mg/kg every 2 weeks ↓ 8 mg/kg every 3 weeks after Week 46; (total treatment duration, ≥45 months)	Within 3 weeks of the start of tocilizumab therapy, the CRP level completely normalized. After 1 month of treatment, fibrinogen and SAA levels normalized. The neck pain, chest pain, and episodes of syncope disappeared. The prednisolone dose could be tapered from 60 mg/day at the start of tocilizumab therapy to 7.5 mg/day at the final follow-up, without relapse of the disease.	Tocilizumab therapy caused no adverse drug reactions, except for viral enterocolitis. No antibodies against tocilizumab were detected at any time during a >5-year period.

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FDG-PET, ^{18}F-fluorodeoxy glucose positron emission tomography; MTX, methotrexate; SAA, serum amyloid A; TNF, tumor necrosis factor

7.2.2 Giant cell arteritis

A literature search of PubMed (queries, "tocilizumab" + "giant cell arteritis"), Embase (queries, "tocilizumab" + "giant cell arteritis" or "temporal arteritis"), and *Igaku Chuo Zasshi* (queries, "tocilizumab" + "giant cell arteritis") was conducted. Among the 47 publications found in PubMed, 159 in Embase, and 14 in *Igaku Chuo Zasshi* (June 22, 2016), 1 Japanese case report was submitted for the present application. In addition, a report regarding a Japanese prospective clinical study presented at the 18th International Vasculitis & ANCA Workshop held on March 2017, was submitted. The Japanese reports on tocilizumab therapy in patients with giant cell arteritis are summarized below.

	Source	Patients	Dosing regimen	Efficacy	Safety
1	Abstracts of the 610th Kanto Regional Meeting of the Japanese Society of Internal Medicine. 2014;31	1 patient with giant cell arteritis requiring reduction in the oral corticosteroid due to type 2 diabetes mellitus and lumbar compression fracture (Case report)	Unknown	After the start of tocilizumab therapy, the prednisolone dose was reduced from 40 to 10 mg/day, while remission was sustained. Although tocilizumab therapy was not resumed after the occurrence of decreased peripheral neutropenia count, the reduced dose of prednisolone could be maintained without relapse of giant cell arteritis.	At approximately 3 weeks after the start of tocilizumab therapy, the peripheral neutrophil count decreased to <500/μL and granulocyte colony-stimulating factor agent was administered,
2	*Rheumatology*. (Oxford) 2017; 56: 59	2 patients with active giant cell arteritis (Prospective study)	Tocilizumab monotherapy; dose unknown, every 2 weeks for 2 months, followed by every 4 weeks for 10 months	Remission was induced at 12 weeks after the start of tocilizumab monotherapy. At 52 weeks, arterial wall hypertrophy disappeared.	There were no clinically important adverse events.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Efficacy for Takayasu's arteritis

The applicant's explanation about the efficacy of tocilizumab in patients with Takayasu's arteritis based on the results of the Japanese phase III study (Study MRA632JP):

• Study design

As Takayasu's arteritis may result in irreversible outcomes such as vascular fibrosis, the study was designed to enroll patients who had achieved remission. The mean body weight in both male and female populations aged ≥12 years is >40 kg, which did not largely differ from the mean body weight of the subjects enrolled in the Japanese clinical studies of tocilizumab for RA. Study MRA632JP therefore enrolled patients aged ≥12 years, in order to evaluate the efficacy of tocilizumab at the same dose used in the Japanese studies of RA.

The therapeutic purpose of tocilizumab for patients with Takayasu's arteritis is the prevention of relapse with tapering of oral corticosteroids, the first-line treatment. Therefore, the study was designed to evaluate the efficacy of tocilizumab based on the period of sustained remission with corticosteroid tapering according to the pre-specified tapering regimen; the primary endpoint was the time to remission of Takayasu's arteritis. "Relapse of Takayasu's arteritis" was defined based primarily on Kerr's criteria proposed by the National Institutes of Health (*Ann Intern Med.* 1994;120:919-29), which are most widely used, and based on the remission assessment criteria used in clinical practice and the Indian

Takayasu Clinical Activity Score 2010 (*Rheumatology*. 2013;52:1795-801) [for the details of each definition, see Section "10. Others"] (Table 10).

Table 10. Definitions of relapse of Takayasu's arteritis in Study MRA632JP

		Components						Definition of relapse
		Systemic symptoms by objective assessment	Systemic symptoms by subjective assessment	Increases in inflammatory markers	Vascular lesions	Ischemic symptoms with organ lesions	Image findings	
Primary endpoint	Relapse of Takayasu's arteritis	✓	✓	✓	✓	✓	✗	≥2 of the 5 components are present.
Secondary endpoints	Relapse of Takayasu's arteritis according to Kerr's criteria	✓		✓	✓		✓	≥2 of the 4 components are present.
	Relapse of Takayasu's arteritis based solely on clinical symptoms	✓	✓	✗	✓	✓	✗	≥1 of the 4 components is present.

✓: Components included in the assessment of relapse;
✗: Components not included in the assessment of relapse

• Time to relapse

Table 5 [see Section 7.1.1] shows the time to relapse of Takayasu's arteritis (the primary endpoint), and Table 11 shows the time to relapse of Takayasu's arteritis according to other definitions (secondary endpoints) in Study MRA632JP. Pairwise comparisons revealed no statistically significant differences between the tocilizumab and placebo groups in any endpoints, but the time to relapse tended to be longer in the tocilizumab group than the placebo group. The difference in relapse-free rate between the tocilizumab and placebo groups was appreciably smaller than that estimated at planning[9)] of Study MRA632JP. This was probably due to the following differences between Study MRA632JP and the published studies used to estimate the relapse-free rate (*Autoimmun Rev*. 2013;12: 1143-9 and *Int J Rheum Dis*. 2013;16:754-61).

- The protocol of Study MRA632JP specifies that oral corticosteroids should be reduced at a constant rate, regardless of symptoms.
- In Study MRA632JP, the proportion of patients aged <18 years, who predominantly present with nonspecific clinical symptoms (e.g., hypertension, headache, pyrexia, and weight loss) (*Rheumatology*. 2010;49:1806-14 and *Int J Rheum Dis*. 2016;19:116-26), was higher in the tocilizumab group (22.2% [4 of 18 patients]) than the placebo group (11.1% [2 of 18 patients]).
- Concomitant immunosuppressants were prohibited in Study MRA632JP.

[9] When Study MRA632JP was planned, the relapse-free rate at Week 24 was estimated to be 75% in the tocilizumab group and 25% in the placebo group, with a hazard ratio of 0.2075, based on which the target sample size and the number of events were set.

Table 11. Time to relapse of Takayasu's arteritis, secondary endpoints, in Study MRA632JP (ITT population)

	Tocilizumab (N = 18)	Placebo (N = 18)
Median time to relapse according to Kerr's criteria (weeks)[a] [95% CI][b]	NE [12.1, NE]	12.1 [10.7, 16.0]
Hazard ratio [95.41% CI][c]	0.41 [0.15, 1.10]	
Median time to relapse based solely on clinical symptoms (weeks)[a] [95% CI][b]	16.0 [8.1, NE]	12.0 [8.3, 16.0]
Hazard ratio [95.41% CI][c]	0.70 [0.29, 1.70]	

a) Kaplan-Meier method
b) Brookmeyer-Crowley method (log-log transformation)
c) Cox proportional hazards model stratified by age category (<18, ≥18 and <65, or ≥65 years old)

• Time to relapse of each component of the definition of relapse of Takayasu's arteritis

Table 12 shows the time to relapse of each component of the definition of relapse of Takayasu's arteritis in Study MRA632JP. The risk of relapse tended to be lower in the tocilizumab group than in the placebo group.

Table 12. Time to relapse of each component of the definition of Takayasu's arteritis in Study MRA632JP (ITT population)

Components	Tocilizumab	Placebo	Hazard ratio [95% CI][b]
	Time to relapse[a] (Number of patients with relapse)		
Systemic symptoms by objective assessment	NE (2/18)	NE (5/18)	0.27 [0.05, 1.45]
Systemic symptoms by subjective assessment	NE (7/18)	89.0 (9/18)	0.51 [0.18, 1.45]
Increases in inflammatory markers	NE (1/18)	NE (4/18)	0.17 [0.02, 1.55]
Vascular lesions	162.0 (9/18)	85.0 (10/18)	0.54 [0.21, 1.39]
Ischemic symptoms with organ lesions	NE (2/18)	NE (2/18)	0.97 [0.13, 6.98]
Image findings	NE (4/18)	NE (3/18)	0.69 [0.13, 3.55]

Median (days)
a) Kaplan-Meier method
b) Cox proportional hazards model stratified by age category (<18, ≥18 and <65, or ≥65 years old)

• Relapse rate

The relapse rates of Takayasu's arteritis in the double-blind phase were 44.4% (8 of 18 patients, 101.1 patients per 100 person-years) in the tocilizumab group and 66.7% (12 of 18 patients, 203.1 patients per 100 person-years); thus, the relapse rate per 100 person-years adjusted for total exposure period in the tocilizumab group was approximately half that in the placebo group. The relapse rate in the open-label phase was 22.2% (8 of 36 patients, 23.6 patients per 100 person-years).

• Effects on oral corticosteroid tapering

In the double-blind phase of Study MRA632JP, the dose of oral corticosteroid at relapse or the final assessment tended to be lower in the tocilizumab group than the placebo group, and the proportion of patients who were receiving ≤10 mg/day oral corticosteroid at relapse or the final assessment tended to be higher in the tocilizumab group than the placebo group (Table 13). In total, 83.3% (30 of 36) of patients reached "the target tapered dose of oral corticosteroid" (i.e., a ≤10 mg/day dose, which must be below the dose at the most recent relapse before enrollment) at least once after the start of tocilizumab therapy. Of the 30 patients, 25 did not increase the oral corticosteroid dose for relapse or the signs of relapse. The 25 patients maintained the target tapered dose for 379 [84, 630] days (median [minimum, maximum]).

Table 13. Oral corticosteroid doses and the number of patients who were receiving ≤10 mg/day at relapse or the final assessment in the double-blind phase of Study MRA632JP (prednisolone equivalent, ITT population)

	Tocilizumab (N = 18)	Placebo (N = 18)
Median dose of oral corticosteroid at baseline [minimum, maximum] (mg/day)	26.5 [20.0, 100.0]	30.0 [20.0, 45.0]
Median dose of oral corticosteroid at relapse or the final assessment [minimum, maximum] (mg/day)	9.1 [4.0, 32.0]	11.9 [4.0, 20.0]
Number (%) of patients on oral corticosteroid ≤10 mg/day at relapse or the final assessment	11 (61.1)	7 (38.9)

As described above, tocilizumab reduced the relapse of Takayasu's arteritis and led to reduction in oral corticosteroid doses. Tocilizumab has therefore clinically significant efficacy for the treatment of Takayasu's arteritis.

PMDA's view:
Study MRA632JP failed to demonstrate the superiority of tocilizumab to placebo in time to relapse, the primary endpoint. The applicant explained that the failure may have been attributable to overestimation of the difference in relapse-free rate between the tocilizumab and placebo groups (relapse-free rate was estimated when the study was designed); this explanation is understandable. The results of Study MRA652JP alone have not conclusively demonstrated the efficacy of tocilizumab; however, the time to relapse of Takayasu's arteritis, the primary endpoint, tended to be longer in the tocilizumab group than the placebo group. In addition, the results of secondary endpoints (e.g., relapse rate, components of the definition of relapse, and reduction in oral corticosteroid dose) tended to be better in the tocilizumab group than the placebo group. These differences between the tocilizumab and placebo groups indicate a certain level of clinical significance. Tocilizumab is thus expected to be effective for the treatment of Takayasu's arteritis.

In Japanese and foreign clinical studies, only a small number of pediatric patients received tocilizumab, with no clinical experience in those <12 years old. The efficacy and other aspects of tocilizumab should be further investigated in pediatric patients by post-marketing surveillance, etc.

PMDA will draw a final conclusion based on the discussion at the Expert Discussion.

7.R.1.2 Efficacy for giant cell arteritis

The applicant's explanation about the efficacy of tocilizumab in patients with giant cell arteritis:

• Study design

The efficacy of tocilizumab in Japanese patients with giant cell arteritis was evaluated based on the results of a foreign clinical study in patients with giant cell arteritis (Study WA28119) as well as a Japanese clinical study in patients with Takayasu's arteritis (Study MRA632JP), because the 2 disease are considered to be similar (see below for detailed discussion).

- In the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, large vessel vasculitis, a category of vasculitis, has 2 major variants, Takayasu's

arteritis and giant cell arteritis. Since these diseases are not easily distinguishable based on histopathological findings, some reports have suggested that Takayasu's arteritis and giant cell arteritis are the same disease (e.g., *Arthritis Rheum.* 2013;65:1-11, *Ann Rheum Dis.* 2012;71:1329-34, and *Infection, Inflammation & Immunity*. 2012;42:265-7).

- In Japan, the number of patients with giant cell arteritis is estimated to be approximately 690. Of these, patients eligible for tocilizumab therapy, that is, patients with giant cell arteritis that has not adequately responded to oral corticosteroids are expected to be even fewer.
- The pathology, clinical features, diagnostic criteria, and therapeutic system of giant cell arteritis do not differ between Japan and other countries.
- No significant differences have been observed in the pharmacokinetics and the inhibitory effects on IL-6 signaling, of tocilizumab among ethnic groups [see Section 6.R.1].

The study was designed on the assumption that tocilizumab would show similar efficacy in patients with new-onset and relapsing giant cell arteritis. In view of the current standard treatment for giant cell arteritis, the study was designed to initiate oral corticosteroid therapy in the screening period, to induce remission within 12 weeks of randomization.

As with Takayasu's arteritis, the therapeutic purpose of tocilizumab for patients with giant cell arteritis is to prevent relapse of the disease, and to simultaneously taper oral corticosteroids, the first-line treatment. Therefore, the study was designed to evaluate the efficacy of tocilizumab based on the proportion of patients achieving sustained remission despite corticosteroid tapering according to the pre-specified tapering regimen; the primary endpoint was the proportion of patients in sustained remission at Week 52.

• Proportion of patients in sustained remission at Week 52

Study WA28119 demonstrated the superiority of tocilizumab 162 mg once weekly or every 2 weeks to placebo in the proportion of patients in sustained remission at Week 52, the primary endpoint (Table 8) [see Section 7.1.2]. In addition, pairwise comparisons of the secondary endpoints between the QW or Q2W group and the placebo + 52-week CS taper group showed that the proportion of patients in sustained remission at Week 52 tended to be higher in the QW or Q2W group than the placebo + 52-week CS taper group. For the primary endpoint, remission was defined as the absence of relapse and normalization of C-reactive protein (CRP) (<1 mg/dL). When remission was defined only by the signs/symptoms of giant cell arteritis, regardless of CRP, taking account of the impact of the pharmacodynamic actions of tocilizumab, similar results were obtained for the proportion of patients in sustained remission (Table 14).

Table 14. Proportion of patients in sustained remission at Week 52, when remission was defined by only clinical symptoms/signs (ITT population, NRI)

	QW	Q2W	Placebo + 26-week CS taper	Placebo + 52-week CS taper
Proportion of patients in sustained remission at Week 52	59.0 (59/100)	55.1 (27/49)	20.0 (10/50)	33.3 (17/51)
Difference from placebo + 26-week CS taper [99.5% CI][a)]	39.0 [14.8, 63.2]	35.1 [7.8, 62.4]		
Difference from placebo + 52-week CS taper [99.5% CI][a)]	25.7 [2.6, 48.8]	21.8 [−5.5, 49.0]		

% (n/N)
a) Cochran-Mantel-Haenszel test stratified by baseline prednisone dose (≤30 mg/day or >30 mg/day).

• Time to relapse and the cumulative dose of oral corticosteroid

Table 15 shows the time to relapse of giant cell arteritis, a secondary endpoint, and Figure 2 shows the Kaplan-Meier curves for relapse-free rates. The time to relapse tended to be longer in the QW and Q2W groups than the 2 placebo groups. The median cumulative doses of oral corticosteroid[10)] [95% confidence interval] were 1862 [1582, 1942] mg in the QW group and 1862 [1568, 2240] mg in the Q2W group, as compared with 3296 [2730, 4024] mg in the placebo+ 26-week CS taper group and 3818 [2818, 4426] mg in the placebo + 52-week CS taper group; thus, the cumulative doses of oral corticosteroid tended to be lower in the QW and Q2W groups than the 2 placebo groups.

Table 15. Time to relapse of giant cell arteritis (ITT population, NRI)

	QW (N = 100)	Q2W (N = 49)	Placebo + 26-week CS taper (N = 50)	Placebo + 52-week CS taper (N = 51)
Median time to relapse (days) [99% CI][a)]	NE [NE, NE]	NE [NE, NE]	165.0 [120.0, 260.0]	295.0 [168.0, NE]
Hazard ratio relative to placebo + 26-week CS taper [99% CI][b)]	0.23 [0.11, 0.46]	0.28 [0.12, 0.66]		
Hazard ratio relative to placebo + 52-week CS taper [99% CI][b)]	0.39 [0.18, 0.82]	0.48 [0.20, 1.16]		

Patients who failed to achieve remission were censored on Day 1.
Patients who were withdrawn from the study by Week 52 were censored at the time of withdrawal.
a) Kaplan-Meier method
b) Cox proportional hazards model stratified by baseline prednisone dose (≤30 mg/day or >30 mg/day)

[10] The cumulative dose includes (a) the prednisone dose administered after unblinding of oral corticosteroid therapy and (b) the dose of other over-the-counter oral corticosteroids used during the study.

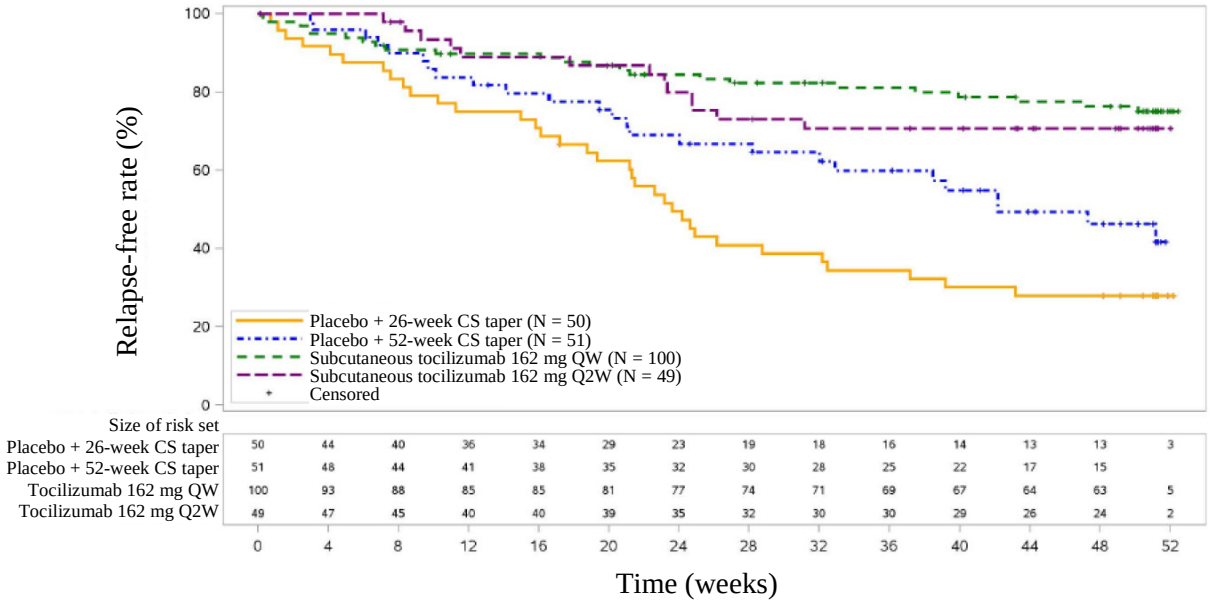

Figure 2. Kaplan-Meier curves for the time to first relapse of giant cell arteritis (ITT population)

PMDA's view:

In Study WA28119, tocilizumab 162 mg once weekly or every 2 weeks was shown to be superior to placebo in the proportion of patients with sustained remission at Week 52, the primary endpoint, and the results of secondary endpoints tended to be better with tocilizumab 162 mg once weekly or every 2 weeks than with placebo. These results indicate the efficacy of tocilizumab for the treatment of giant cell arteritis. No clinical study data from Japanese patients with giant cell arteritis are available; however, tocilizumab is expected to be effective also in Japanese patients with giant cell arteritis, since its efficacy has been suggested by a Japanese clinical study in patients with Takayasu's arteritis, a disease resembling giant cell arteritis in pathology. As tocilizumab has not been administered to Japanese patients with giant cell arteritis, the efficacy and other aspects of tocilizumab for giant cell arteritis should be further investigated in Japanese patients by post-marketing surveillance.

PMDA will draw a final conclusion based on the discussion at the Expert Discussion.

7.R.2 Safety

The applicant's explanation about the safety of tocilizumab in patients with Takayasu's arteritis or giant cell arteritis:

Tables 16 and 17 show the incidences of adverse events during the double-blind phase of a Japanese phase III study in patients with Takayasu's arteritis (Study MRA632JP), Japanese clinical studies in

patients with RA (Studies MRA231JP[11)] and MRA229JP[12)]), a foreign phase III study in patients with giant cell arteritis (Study WA28119), and foreign clinical studies in patients with RA (Studies WA22762[13)] and NA25220[14)]). Although direct comparisons among the studies involving several differences (e.g., patient characteristics and concomitant medications) have limitations, no new concerns about the safety profile of tocilizumab were noted in patients with Takayasu's arteritis or giant cell arteritis as compared with patients with RA.

Thus, the risks associated with tocilizumab in patients with Takayasu's arteritis or giant cell arteritis are controllable by continuing the safety measures currently taken for the approved indications.

[11] A randomized, double-blind, parallel-group study in patients with RA who had an inadequate response to subcutaneous tocilizumab 162 mg every 2 weeks, to evaluate the efficacy and safety of subcutaneous tocilizumab 162 mg once weekly versus control (i.e., subcutaneous tocilizumab 162 mg every 2 weeks).

[12] A randomized, double-blind, parallel-group study in patients with RA who had an inadequate response to DMARDs or biological products, to evaluate the efficacy and safety of subcutaneous tocilizumab 162 mg every 2 weeks versus control (i.e., intravenous tocilizumab 8 mg/kg every 4 weeks).

[13] A randomized, double-blind, parallel-group study in patients with RA who had an inadequate response to DMARDs or anti-TNFs, to evaluate the efficacy and safety of subcutaneous tocilizumab 162 mg once weekly versus control (i.e., intravenous tocilizumab 8 mg/kg every 4 weeks).

[14] A placebo-controlled, randomized, double-blind, parallel-group study in patients with RA who had an inadequate response to DMARDs or anti-TNFs, to evaluate the efficacy and safety of subcutaneous tocilizumab 162 mg every 2 weeks.

Table 16. Comparison of the incidences of adverse events between patients with Takayasu's arteritis and those with RA (double-blind phase of Japanese clinical studies, safety analysis set)

	Takayasu's arteritis		RA			
	Study MRA632JP (Subcutaneous)		Study MRA231JP (Subcutaneous)		Study MRA229JP	
	Tocilizumab (N = 18)	Placebo (N = 18)	Tocilizumab once weekly (N = 21)	Tocilizumab every 2 weeks (N = 21)	Subcutaneous tocilizumab every 2 weeks (N = 173)	Intravenous tocilizumab (N = 173)
Total duration of exposure (person-years)	7.9	5.9	4.53	4.23	77.43	77.29
Summary of adverse events						
All adverse events	14 (77.8) 177.22	11 (61.1) 186.44	15 (71.4) 331.13	14 (66.7) 330.97	154 (89.0) 198.89	157 (90.8) 203.13
Serious adverse events	1 (5.6) 12.66	2 (11.1) 33.90	1 (4.8) 22.07	1 (4.8) 23.66	13 (7.5) 16.79	10 (5.8) 12.94
Deaths	0	0	1 (4.8) 22.07	0	0	0
Adverse events leading to drug discontinuation	0	0	1 (4.8) 22.07	1 (4.8) 23.66	3 (1.7) 3.87	9 (5.2) 11.64
Adverse drug reactions	5 (27.8) 63.29	3 (16.7) 50.85	10 (47.6) 220.75	11 (52.4) 260.05	144 (83.2) 185.97	149 (86.1) 192.78
Adverse events of interest						
Infections	9 (50.0) 113.92	6 (33.3) 101.69	6 (28.6) 132.42	7 (33.3) 165.59	72 (41.6) 92.99	78 (45.1) 100.92
Serious infections	0	0	1 (4.8) 22.07	0	2 (1.2) 2.58	5 (2.9) 6.47
Haemorrhage	2 (11.1) 25.32	3 (16.7) 50.85	1 (4.8) 22.07	1 (4.8) 23.66	0	0
Gastrointestinal perforation and associated disorders	0	0	0	0	0	1 (0.6) 1.29
Malignant tumors	0	0	0	1 (4.8) 23.66	0 [c)]	0
Anaphylaxis	0	0	0	0	0	1 (0.6) 1.29
Administration-related systemic reactions	0	0	1 (4.8) 22.07	1 (4.8) 23.66	6 (3.5) 7.75	12 (6.9) 15.53
Administration site reactions	0	0	0	0	21 (12.1) 27.12	9 (5.2) 11.64
Interstitial lung disease	0	0	0	0	0	0
Neutrophil count decreased[a)]	0	0	0	0	5 (2.9) 6.46	5 (2.9) 6.47
Platelet count decreased[b)]	0	0	0	0	1 (0.6) 1.29	0
Hepatic disease	0	0	0	0	1 (0.6) 1.29	3 (1.7) 3.88
Stroke	0	0	0	0	0	0
Myocardial infarction/acute coronary syndrome	0	0	0	0	0	0
Demyelinating disease	0	0	0	0	0	0

Upper row, n (%);
Lower row, incidence rate per 100 person-years, adjusted for the total duration of exposure
a) CTCAE Grade ≥3,
b) CTCAE Grade ≥2,
c) A case of benign neoplasm was excluded.
CTCAE; Common toxicity criteria for adverse events (ver.4 [Studies MRA632JP and MRA231JP], ver.3 [Study MRA229JP])

Table 17. Comparison of the incidences of adverse events between patients with giant cell arteritis and those with RA (double-blind phase of foreign clinical studies, safety analysis set)

	Giant cell arteritis				RA			
	Study WA28119 (Subcutaneous)				Study WA22762		Study NA25220 (Subcutaneous)	
	QW (N = 100)	Q2W (N = 49)	Placebo + 26-week CS taper (N = 50)	Placebo + 52-week CS taper (N = 51)	Subcutaneous tocilizumab once weekly (N = 631)	Intravenous tocilizumab (N = 631)	Tocilizumab every 2 weeks (N = 437)	Placebo (N = 218)
Total duration of exposure (person-years)	92.89	45.57	47.44	48.06	289.82	288.39	182.68	81.8
Summary of adverse events								
All adverse events	98 (98.0) 105.50	47 (95.9) 103.14	48 (96.0) 101.18	47 (92.2) 97.79	481 (76.2) 165.97	486 (77.0) 168.52	274 (62.7) 149.99	126 (57.8) 154.03
Serious adverse events	15 (15.0) 16.15	7 (14.3) 15.36	11 (22.0) 23.19	13 (25.5) 27.05	29 (4.6) 10.01	33 (5.2) 11.44	20 (4.6) 10.95	8 (3.7) 9.78
Deaths	0	0	0	0	0	1 (0.2) 0.35	3 (0.7) 1.64	0
Adverse events leading to drug discontinuation	11 (11.0) 11.84	5 (10.2) 10.97	3 (6.0) 6.32	0	30 (4.8) 10.35	41 (6.5) 14.22	9 (2.1) 4.93	3 (1.4) 3.67
Adverse drug reactions	52 (52.0) 55.98	26 (53.1) 57.06	21 (42.0) 44.27	18 (35.3) 37.45	305 (48.3) 105.24	277 (43.9) 96.05	145 (33.2) 79.37	47 (21.6) 57.46
Adverse events of interest								
Infections	75 (75.0) 80.74	36 (73.5) 79.00	38 (76.0) 80.10	33 (64.7) 68.66	227 (36.0) 78.32	247 (39.1) 85.65	131 (30.0) 71.71	61 (28.0) 74.57
Serious infections	7 (7.0) 7.54	2 (4.1) 4.39	2 (4.0) 4.22	6 (11.8) 12.48	9 (1.4) 3.11	9 (1.4) 3.12	9 (2.1) 4.93	4 (1.8) 4.89
Serious haemorrhage	0	0	0	0	1 (0.2) 0.35	4 (0.6) 1.39	1 (0.2) 0.55	0
Serious gastrointestinal perforation and associated disorders	0	0	0	0	0	0	0	0
Malignant tumors	1 (1.0) 1.08	0	1 (2.0) 2.11	1 (2.0) 2.08	4 (0.6) 1.38	2 (0.3) 0.69	3 (0.7) 1.64	0
Anaphylaxis	0	0	0	0	0	0	0	0
Administration-related systemic reactions	11 (11.0) 11.84	6 (12.2) 13.17	6 (12.0) 12.65	3 (5.9) 6.24	44 (7.0) 15.18	73 (11.6) 25.31	19 (4.3) 10.40	8 (3.7) 9.78
Administration site reactions	6 (6.0) 6.46	7 (14.3) 15.36	5 (10.0) 10.54	1 (2.0) 2.08	64 (10.1) 22.08	15 (2.4) 5.20	31 (7.1) 16.97	9 (4.1) 11.00
Interstitial lung disease	1 (1.0) 1.08	0	1 (2.0) 2.11	0	1 (0.2) 0.35	1 (0.2) 0.35	1 (0.2) 0.55	0
Neutrophil count decreased[a)]	4 (4.0) 4.31	2 (4.1) 4.39	0	0	18 (2.9) 6.21	20 (3.2) 6.94	16 (3.7) 8.76	0
Platelet count decreased[b)]	0	0	0	0	1 (0.2) 0.35	3 (0.5) 1.04	2 (0.4) 1.09	0
Serious hepatic disease	0	0	0	0	0	1 (0.2) 0.35	0	0
Serious stroke	0	1 (2.0) 2.19	0	1 (2.0) 2.08	0	4 (0.6) 1.39	0	0
Serious myocardial infarction/acute coronary syndrome	0	0	0	0	1 (0.2) 0.35	0	0	1 (0.5) 1.22
Serious demyelinating disease	0	0	0	0	0	0	0	0

Upper row, n (%);
Lower row, incidence rate per 100 person-years, adjusted for the total duration of exposure
a) CTCAE Grade ≥3,
b) CTCAE Grade ≥2
CTCAE; Common toxicity criteria for adverse events (ver.4 [Studies WA28119 and WA22762], ver.3 [Study NA25220])

PMDA's view:

Although the number of patients evaluated in the data submitted for the present application was limited, no new safety concerns have been identified in patients with Takayasu's arteritis or giant cell arteritis as compared with those with RA; therefore, similar safety measures taken for the approved indications

should be adopted for the treatment of Takayasu's arteritis and giant cell arteritis. Tocilizumab is assumed to be used in combination with intermediate to high doses of oral corticosteroids, which may increase the risk of infections or other complications. The applicant should therefore inform healthcare professionals and patients that tocilizumab must be used under the supervision of physicians with sufficient knowledge about tocilizumab and experience of treating Takayasu's arteritis or giant cell arteritis.

In addition, the safety of tocilizumab, including serious infections, should be further investigated by post-marketing surveillance, in view of the following findings.

- The incidence of serious infections tends to be higher in patients with giant cell arteritis than those with RA (Table 17).
- In Study WA28119, the incidence of serious infections tended to be higher in the QW group than the placebo + 26-week CS taper group or the Q2W group, although the 3 groups underwent the same corticosteroid tapering regimen.
- Patients with Takayasu's arteritis or giant cell arteritis are expected to more commonly use concomitant oral corticosteroids, which may increase the risk of infections, than those using tocilizumab for the approved indications.
- Only a limited number of Japanese patients with Takayasu's arteritis or giant cell arteritis have been evaluated.

Tocilizumab has not been administered to pediatric patients aged <12 years. The package insert or other materials should include a precautionary statement that the safety of tocilizumab has not been established in pediatric patients aged <12 years. The safety of tocilizumab for pediatric patients should be investigated by post-marketing surveillance, etc.

7.R.3 Clinical positioning

The applicant's explanation about the clinical positioning of tocilizumab:

The basic treatment strategy for Takayasu's arteritis or giant cell arteritis is to induce remission with high doses of an oral corticosteroid at the initial onset or relapse, followed by corticosteroid dose tapering while monitoring disease activity, to prevent safety problems associated with long-term oral corticosteroid therapy (e.g., increased risk of serious infections, progression of osteoporosis in elderly patients, dwarfism in pediatric patients). Patients with Takayasu's arteritis or giant cell arteritis who are resistant to oral corticosteroids have been treated with concomitant disease-modifying antirheumatic drugs (DMARDs; e.g., immunosuppressants and MTX) or biological products indicated for RA or other diseases (Japanese clinical practice guidelines and *Ann Rheum Dis.* 2009;68:318-323).

In Study WA28119, the efficacy tended to be higher in the QW or Q2W group with a 26-week (a shorter term) oral corticosteroid taper, than in the placebo + 52-week oral corticosteroid taper group. In the

open-label phase of Study MRA632JP, several patients accomplished withdrawal of oral corticosteroid therapy. In Study WA28119, the efficacy of tocilizumab was also demonstrated by sustained corticosteroid-free remission in patients undergoing the 26-week corticosteroid taper.

According to a report, tocilizumab monotherapy without any corticosteroids or immunosuppressants successfully induced remission of Takayasu's arteritis (Program and abstracts of the 60th Annual General Assembly and Scientific Meeting of the Japan College of Rheumatology. 2016;4:331).

In view of the above results, tocilizumab is expected to acquire a position similar to that of DMARDs (e.g., immunosuppressants and MTX) or biological products indicated for RA or other diseases, and it is also expected to be used in patients who are resistant to oral corticosteroids, patients (including pediatric patients) who require early reduction in oral corticosteroid dose, or patients who are intolerant to oral corticosteroids due to adverse drug reactions or other reasons.

PMDA's view:
Based on the data and other materials submitted, PMDA concludes that tocilizumab can be administered in combination with oral corticosteroids, the standard treatment of Takayasu's arteritis or giant cell arteritis, to patients resistant to oral corticosteroids, those requiring early reduction of oral corticosteroids for safety reasons, and other patients. Since only limited data are available from clinical studies, more information on the combination therapy with tocilizumab and other drugs should be collected by post-marketing surveillance, etc.

This conclusion will be discussed at the Expert Discussion.

7.R.4 Indications

Based on the data submitted, and as a result of its review described in Sections 7.R.1, 7.R.2, and 7.R.3, PMDA concluded that the proposed indications should be modified as shown below and the following precautionary statements should be included in the "Precautions for Instructions" section.

Indications

Treatment of <u>the following diseases</u> in patients who have had an inadequate response to existing therapies:
Rheumatoid arthritis (including the inhibition of progression of structural joint damage)
<u>Takayasu's arteritis or giant cell arteritis</u>

(Underlines denote additions.)

Precautions for Indications

- Tocilizumab should be administered to patients with rheumatoid arthritis who have had an inadequate response to appropriate treatment with at least 1 antirheumatic agent.

- Tocilizumab should be administered, as a rule, to patients with Takayasu's arteritis or giant cell arteritis who have active disease despite appropriate corticosteroid therapy, or who cannot continue corticosteroid therapy.

(Underline denotes additions.)

These conclusions will be discussed at the Expert Discussion.

7.R.5 Dosage and administration

The applicant's explanation of the dosage and administration of tocilizumab:

In patients with Takayasu's arteritis or giant cell arteritis, inflammation should be suppressed continuously and effectively because inflammation of the aorta or ophthalmic arteries may result in serious and irreversible disorders. In Study MRA632JP in patients with Takayasu's arteritis, a dose of 162 mg once weekly was used because this dosage was expected to sufficiently inhibit IL-6 receptor-mediated signaling; as a result, tocilizumab 162 mg once weekly tended to be superior in efficacy to placebo in Study MRA632JP. In Study WA28119, the proportion of patients in sustained remission at Week 52, the primary endpoint, was 56.0% (56 of 100 patients) in the QW group and 53.1% (26 of 49 patients) in the Q2W group, and the results of the secondary endpoints (e.g., time to relapse) tended to be better in the QW group than the Q2W group [see Section 7.R.1.2].

Based on these results, the applicant has proposed the following dosage and administration for Takayasu's arteritis and giant cell arteritis: "The usual dosage is 162 mg of Tocilizumab (Genetical Recombination) administered subcutaneously once weekly."

PMDA's conclusion:

Based on the data submitted, and as a result of its review described in Sections 7.R.1 and 7.R.2, PMDA concluded that the proposed dosage and administration of tocilizumab 162 mg once weekly for the treatment of Takayasu's arteritis or giant cell arteritis is acceptable.

7.R.6 Post-marketing investigations

Based on the reviews in Sections 7.R.1 and 7.R.2, PMDA concluded that post-marketing surveillance should be conducted to investigate (a) the efficacy of tocilizumab in Japanese patients with giant cell arteritis and Japanese pediatric patients and (b) the safety of tocilizumab in patients with Takayasu's arteritis or giant cell arteritis in clinical practice, including the incidences of serious infections and other adverse events.

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

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

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

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

The new drug application data (CTD 5.3.5.1-1 and CTD 5.3.5.1-7) 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.

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

On the basis of the data submitted, PMDA has concluded that tocilizumab has efficacy in the treatment of Takayasu's arteritis or giant cell arteritis, and that tocilizumab has acceptable safety in view of its benefits. Tocilizumab is clinically meaningful because it offers a new therapeutic option to patients with Takayasu's arteritis or giant cell arteritis who have had an inadequate response to existing therapies. PMDA considers that the safety of tocilizumab in clinical practice should be further investigated by post-marketing surveillance.

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 table below shows the definitions of the endpoints used in the Japanese phase III study (Study MRA632JP) and the foreign phase III study (Study WA28119).

Endpoints	Definition
Study MRA632JP	
Components of relapse of Takayasu's arteritis	(a) Systemic symptoms by objective assessment At least one of the following: • Pyrexia ≥38.0°C; • Weight loss of >2 kg in the past 4 weeks; or • Arthritis symptoms (spontaneous pain, swelling, tenderness) involving ≥2 joints. (b) Systemic symptoms by subjective assessment An increase in CTCAE grade of malaise, myalgia, headache, or dizziness. (c) Increases in inflammatory markers At least one of the following: • CRP ≥1.0 mg/dL with ESR ≥30 mm/h; • SAA ≥20 μg/mL with ESR ≥30 mm/h; or • White blood cell count ≥10,000/μL with a ≥1.3-fold increase from baseline (d) Vascular lesions At least one of the following: • Renovascular hypertension; • New vascular bruits; • New pulse loss; • Newly identified difference in blood pressure between the right and left arms; • Tenderness or spontaneous pain of the carotid arteries; • Spontaneous chest/back pain; or • Aortic valve incompetence (e) Ischemic symptoms with organ lesions An increase in CTCAE grade of abdominal pain, stroke, epileptic seizure, syncope, intermittent claudication, ischaemic cardiac pain, or myocardial infarction (f) Image findings Deterioration from baseline
Relapse of Takayasu's arteritis	In principle, relapse is defined as having ≥2 of the 5 components (a) to (e) listed above, but is also defined as having either of the following conditions without any other components: • Severe aortic valve incompetence accompanied by cardiac failure symptoms in component (d); or • An increase to CTCAE grade ≥2 (grade ≥3 for myocardial infarction) in component (e)
Remission of Takayasu's arteritis	Remission is defined as having none of the 5 components (a) to (e) listed above.
Relapse of Takayasu's arteritis according to Kerr's criteria	In principle, relapse is defined as having ≥2 of the 4 components [(a) or (b); (c); (d) or (e); and (f)] listed above, but is also defined as having either of the following conditions without any other components: • Severe aortic valve incompetence accompanied by cardiac failure symptoms in component (d); or • An increase to CTCAE grade ≥2 (grade ≥3 for myocardial infarction) in component (e)
Relapse of Takayasu's arteritis based solely on clinical symptoms	Relapse is defined as having ≥1 of the 4 components (a), (b), (d), and (e) listed above.
Study WA28119	
Relapse of giant cell arteritis	Relapse is defined as having (a) a relapse of the following signs/symptoms or (b) ESR ≥30 mm/h due to giant cell arteritis, as assessed by the investigator. • Fever (≥38°C or ≥100.4°F) • Symptoms of polymyalgia rheumatica (PMR) (morning stiffness or pain in the shoulder or girdle) • Localized headache, pain of temporal arteries, or tenderness of scalp • Visual symptoms/signs, such as acute or subacute visual loss due to arteritic anterior ischemic optic neuropathy and transient blurry vision (monocular conditions in general, or monocular conditions that may potentially result in binocular conditions) • Pain in the jaw or mouth • New onset or deterioration of intermittent claudication in extremities • Other characteristics consistent with the relapse of giant cell arteritis or PMR, as assessed by the investigator
Remission of giant cell arteritis	Remission is defined as CRP <1.0 mg/dL in patients who do not meet any of the criteria for the relapse of giant cell arteritis (shown in the above column).

Review Report (2)

July 10, 2017

Product Submitted for Approval

Brand Name	Actemra 162 mg Syringe for SC Injection
	Actemra 162 mg Auto-injector for SC Injection
Non-proprietary Name	Tocilizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	November 30, 2016

1. Content of the Review

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

1.1 Efficacy, safety, clinical positioning, indications, and dosage and administration

At the Expert Discussion, the expert advisors largely supported the PMDA's conclusions on the efficacy, safety, clinical positioning, indications, and dosage and administration of Actemra 162 mg Syringe for SC Injection and Actemra 162 mg Auto-injector for SC Injection (hereinafter collectively referred to as "tocilizumab"), described in Review Report (1).

1.2 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported the PMDA's conclusion on the safety measures after the market launch, described in Review Report (1), and offered the following comments.

- When using tocilizumab for the treatment of Takayasu's arteritis or giant cell arteritis, similar safety measures as for the approved indications should be taken, for example, ensuring that tocilizumab is administered by physicians with sufficient knowledge of tocilizumab and experience of treating Takayasu's arteritis or giant cell arteritis.
- Since only a limited number of patients with Takayasu's arteritis or giant cell arteritis were evaluated in clinical studies, further information should be collected by post-marketing surveillance and the collected information should be provided to healthcare professionals. Clinical data from pediatric patients are particularly limited; therefore, the proper dosing regimen, etc. for pediatric patients should be further investigated by collecting information by post-marketing surveillance.

Based on the review described in Section "7.R.6 Post-marketing investigations" in Review Report (1) and the comments regarding pediatric patients from the Expert Discussion, PMDA has concluded that the risk management plan (draft) for tocilizumab should include the safety and efficacy specifications presented in Table 18, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 19. PMDA instructed the applicant to conduct post-marketing surveillance that allows the evaluation of these specifications.

Table 18. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Serious infections • Intestinal perforation • Serious hypersensitivity such as anaphylaxis (including administration reactions) • Neutropenia/leukopenia/agranulocytosis • Thrombocytopenia • Interstitial pneumonia • Hepatitis B virus reactivated	• Hepatic function abnormal • Malignant tumor • Demyelinating disease • Immunogenicity • Cardiac disorder/cardiac failure • Pleurisy	• None
Efficacy specification		
・Efficacy in patients with rheumatoid arthritis in clinical practice ・Efficacy in patients with Takayasu's arteritis or giant cell arteritis in clinical practice		

Table 19. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Use-results survey in patients with Takayasu's arteritis or giant cell arteritis • Post-marketing clinical study (extension study of the phase III study) in patients with Takayasu's arteritis[a)]	• Ensure that information on proper use is disseminated before delivery of the product to medical institutions. • Provide information for healthcare professionals. • Provide information for patients. • Disseminate information on self-administration.

a) The ongoing Study MRA632JP will be reclassified as a post-marketing clinical study after approval of the proposed indications, and continued until tocilizumab becomes available for routine clinical practice at each study site.

The applicant's explanation about the main investigations in the post-marketing settings:

As shown in Table 20, a use-results survey will be performed to evaluate the safety and efficacy of tocilizumab in clinical practice. The target sample size is 120 patients with Takayasu's arteritis and 120 patients with giant cell arteritis. The observation period is 52 weeks. The key survey items are serious infections, intestinal perforation, serious hypersensitivity such as anaphylaxis (including administration reactions), neutropenia/leukopenia/agranulocytosis, thrombocytopenia, interstitial pneumonia, hepatic function abnormal, malignant tumor, cardiac disorder/cardiac failure, hepatitis B virus reactivated, and lipid test abnormal. Since only a limited number of pediatric patients were evaluated in clinical studies, pediatric patients (target, approximately 5 patients) will be enrolled to further investigate the safety and efficacy of tocilizumab in this population.

Table 20. Outline of the use-result survey of patients with Takayasu's arteritis or giant cell arteritis (draft)

Objective	To collect and evaluate information on the safety and efficacy of tocilizumab in clinical use
Survey method	Central registration system
Population	Patients with Takayasu's arteritis or giant cell arteritis
Observation period	52 weeks
Planned sample size	120 patients with Takayasu's arteritis (100 for the safety analysis set), including approx. 5 pediatric patients aged <15 years; 120 patients with giant cell arteritis (100 for the safety analysis set)
Main survey items	• Key survey items: serious infections, intestinal perforation, serious hypersensitivity such as anaphylaxis (including administration reactions), neutropenia/leukopenia/agranulocytosis, thrombocytopenia, interstitial pneumonia, hepatic function abnormal, malignant tumor, cardiac disorder/cardiac failure, hepatitis B virus reactivated, and lipid test abnormal • Patient characteristics (e.g., body weight, age, severity, duration of the disease, prior treatment, complications) • Exposure to tocilizumab (e.g., dosing interval) • Concomitant medications/therapies • Laboratory data • Adverse events • Efficacy

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved, provided that the proposed indications and the dosage and administration are modified as follows, with the condition of approval shown below. The product is designated as an orphan drug for the proposed indications and the dosage and administration; therefore, the re-examination period is 10 years.

Indications

○ Treatment of the following diseases ~~rheumatoid arthritis with~~ in patients who have had an inadequate response to existing therapies:

Rheumatoid arthritis (including the inhibition of progression of structural joint damage)

~~○ Treatment of large vessel vasculitis (~~Takayasu's arteritis or giant cell arteritis~~)~~

(Underline denotes additions to the applicant's proposal. Crossed-out words are deleted from the applicant's proposal.)

Dosage and Administration

○ Rheumatoid arthritis

The usual adult dosage is 162 mg of Tocilizumab (Genetical Recombination) administered subcutaneously every 2 weeks. The dosing interval may be reduced to a minimum of 1 week in patients with an inadequate response.

○ ~~Large vessel vasculitis (~~Takayasu's arteritis or giant cell arteritis~~)~~

The usual dosage is 162 mg of Tocilizumab (Genetical Recombination) administered subcutaneously once weekly.

(Underline denotes additions to the applicant's proposal.[15)] Crossed-out words are deleted from the applicant's proposal.)

[15] The dotted underline denotes additions made as of June 26, 2017, the approval date of another partial change application for the product.

Condition of Approval

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