**Review Report**

January 7, 2022
Pharmaceuticals and Medical Devices Agency

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

| | |
|---|---|
| **Brand Name** | Actemra 80 mg for Intravenous Infusion<br>Actemra 200 mg for Intravenous Infusion<br>Actemra 400 mg for Intravenous Infusion |
| **Non-proprietary Name** | Tocilizumab (Genetical Recombination) (JAN*) |
| **Applicant** | Chugai Pharmaceutical Co., Ltd. |
| **Date of Application** | December 13, 2021 |
| **Dosage Form/Strength** | A concentrate for a solution for intravenous infusion containing 80 mg, 200 mg, or 400 mg of Tocilizumab (Genetical Recombination) per vial |
| **Application Classification** | Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage |
| **Items Warranting Special Mention** | The present application underwent a preliminary consultation for the documents, etc. to be submitted and was reviewed on a priority basis, in accordance with "Tentative Procedures for Review of Pharmaceuticals, Medical Devices, In Vitro Diagnostics, and Regenerative Medical Products in Response to Outbreak of COVID-19" (Administrative Notice dated April 13, 2020) and "Procedures for Review of Pharmaceuticals, etc. for COVID-19" (PSEHB/PED Notification No. 0512-4 and PSEHB/MDED Notification No. 0512-1, dated May 12, 2020). |
| **Reviewing Office** | Office of New Drug IV |

**Results of Review**

On the basis of the data submitted, PMDA has concluded that the product, when used in combination with corticosteroids, has efficacy in the treatment of pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection requiring supplemental oxygen, and that the product has acceptable safety in view of its benefits (see Attachment).

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

**Indications**

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

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

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

○Pneumonia caused by SARS-CoV-2 infection (COVID-19) (limited to patients requiring supplemental oxygen)

(Underline denotes additions.)

**Dosage and Administration**

○Rheumatoid arthritis, polyarticular-course juvenile idiopathic arthritis

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

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

The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 2 weeks.

The dosing interval may be shortened to a minimum of 1 week according to the patient's symptoms.

○Cytokine release syndrome

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

○Pneumonia caused by SARS-CoV-2 infection (COVID-19)

The usual adult dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion, in combination with corticosteroids. If clinical symptoms do not improve after the first dose, one additional infusion of Tocilizumab (Genetical Recombination) 8 mg/kg may be administered at least 8 hours after the completion of the initial infusion.

(Underline denotes additions.)

**Approval Condition**

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

**Japanese Accepted Name (modified INN)*

**Attachment**

**Review Report (1)**

December 14, 2021

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

**Product Submitted for Approval**

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|---|---|
| **Brand Name** | Actemra 80 mg for Intravenous Infusion<br>Actemra 200 mg for Intravenous Infusion<br>Actemra 400 mg for Intravenous Infusion |
| **Non-proprietary Name** | Tocilizumab (Genetical Recombination) |
| **Applicant** | Chugai Pharmaceutical Co., Ltd. |
| **Date of Application** | December 13, 2021 |
| **Dosage Form/Strength** | A concentrate for a solution for intravenous infusion containing 80 mg, 200 mg, or 400 mg of Tocilizumab (Genetical Recombination) per vial |

**Proposed Indications**

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

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

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

○<u>Pneumonia caused by SARS-CoV-2 infection (COVID-19) (limited to patients requiring supplemental oxygen)</u>

(Underline denotes additions.)

**Proposed Dosage and Administration**

○Rheumatoid arthritis, polyarticular-course juvenile idiopathic arthritis
The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 4 weeks.

○Systemic juvenile idiopathic arthritis, adult Still's disease, Castleman's disease
The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 2 weeks.

The dosing interval may be shortened to a minimum of 1 week according to the patient's symptoms.

○Cytokine release syndrome

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

○Pneumonia caused by SARS-CoV-2 infection (COVID-19)

The usual adult dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion, in combination with corticosteroids. If clinical symptoms do not improve after the first dose, one additional infusion of Tocilizumab (Genetical Recombination) 8 mg/kg may also be administered at least 8 hours after the completion of the initial infusion.

(Underline denotes additions.)

**Table of Contents**



**List of Abbreviations**

See Appendix.

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

Tocilizumab (Genetical Recombination) (hereinafter referred to as "tocilizumab"), which is the active ingredient of "Actemra 80 mg for Intravenous Infusion," "Actemra 200 mg for Intravenous Infusion," and "Actemra 400 mg for Intravenous Infusion." Tocilizumab is a humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the immunoglobulin G1 subclass discovered in a collaborative research by Osaka University and Chugai Pharmaceutical Co., Ltd. Tocilizumab was approved for the treatment of Castleman's disease in April 2005, and subsequently for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, cytokine release syndrome induced by tumor-specific T cell infusion therapy, and adult Still's disease.

COVID-19 is an infection caused by SARS-CoV-2. In Japan, the first patient infected with SARS-CoV-2 was identified on January 15, 2020. On February 1, 2020, COVID-19[1)] was classified as a Designated Infectious Disease[2)] pursuant to the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Infectious Diseases Control Act) and as a Quarantinable Infectious Disease[3)] pursuant to the Quarantine Act. In Japan, as of December 13, 2021, a total of 1,728,689 people have been infected (positive for polymerase chain reaction [PCR] test), among whom, 18,373 have died.[4)] Reported symptoms of COVID-19 include fever, cough, malaise, dyspnoea, and taste disorder, etc. Approximately 20% of patients experience the progression of pneumonia symptoms. Some patients suffer from respiratory failure due to severe inflammatory conditions characterized by the increased production of multiple cytokines including IL-6. Elevated IL-6 level has been found as one of the prognostic factors for death in patients with COVID-19 (*JAMA.* 2020;324:782-93, *Intensive care Med.* 2020;46:846-8, *Lancet.* 2020;395:1054-62). Furthermore, cytokine release syndrome (CRS) has been reported as the major cause of death in patients infected with MERS-CoV and SARS-CoV (*Science.* 2020;368:473-4).

Tocilizumab inhibits IL-6 receptor-mediated signaling and has demonstrated its efficacy and safety in the treatment of cytokine release syndrome induced by tumor-specific T cell infusion therapy. With an expectation of its efficacy in the treatment of pneumonia caused by SARS-CoV-2 infection (COVID-19) (COVID-19 pneumonia), clinical studies were conducted in Japan and other countries. The studies demonstrated clinical benefits of tocilizumab for the treatment of COVID-19 pneumonia. Based on the study results, etc., the applicant has recently filed a partial change application for tocilizumab for the additional indication of COVID-19 pneumonia.

In EU, F. Hoffmann-La Roche Ltd. filed an application on July 27, 2021 to add an indication for COVID-19 pneumonia based mainly on the results from the RECOVERY study (tocilizumab evaluation cohort), an

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[1)] Limited to the disease caused by the novel coronavirus identified as a member of the genus *Betacoronavirus* (the coronavirus which was reported as transmissible to humans to the World Health Organization [WHO] by the People's Republic of China in January 2020).

[2)] The term Designated Infectious Disease refers to known infectious diseases (excluding Class I Infectious Diseases, Class II Infectious Diseases, Class III Infectious Diseases, and Novel Influenza Infections, etc.) that have been specified by Cabinet Order as a disease that would be likely to seriously affect the health of the public in the event of its spread, if the provisions of the Infectious Diseases Control Act, in whole or in part, did not apply mutatis mutandis (Article 6 of the Infectious Diseases Control Act).

[3)] The term Quarantinable Infectious Disease refers to diseases specified by Cabinet Order as those which require inspection in order to prevent pathogens of infectious diseases not endemic to Japan from entering the country (Article 2, Item 3 of the Quarantine Act).

[4)] Ministry of Health, Labour and Welfare: https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou.html (last accessed on December 13, 2021)

investigator-initiated foreign clinical study, and the application was approved on December 7, 2021. Tocilizumab has been approved for COVID-19 pneumonia in 3 countries/regions as of December 13, 2021. In the US, although yet to be approved for the treatment of COVID-19 pneumonia as of December 13, 2021, tocilizumab obtained an Emergency Use Authorization on June 24, 2021.

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

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

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

Although the present application is intended for a new indication and a new dosage, no additional study data on non-clinical pharmacology were submitted because the non-clinical pharmacology of tocilizumab was evaluated during the initial approval process.

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

Although the present application is intended for a new indication and a new dosage, no additional study data on non-clinical pharmacokinetics were submitted because the non-clinical pharmacokinetics of tocilizumab was evaluated during the initial approval process.

## 5. Toxicity and Outline of the Review Conducted by PMDA

Although the present application is intended for a new indication and a new dosage, no additional study data relating to the toxicity of tocilizumab have been submitted because the toxicity of tocilizumab was evaluated during the initial approval process.

## 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 enzyme-linked immunosorbent assay (ELISA) with a lower limit of quantitation of 0.1 μg/mL.

### 6.2 Clinical pharmacology

The applicant submitted clinical pharmacological evaluation data, in the form of results from a Japanese clinical study in patients with COVID-19 pneumonia (J-COVACTA study; CTD 5.3.5.2-1). The applicant also submitted reference data including the results from foreign studies in non-Japanese patients with COVID-19 pneumonia (phase II, MARIPOSA study [reference data, CTD 5.3.4.2-1]; phase III, COVACTA study [reference data, CTD 5.3.5.1-2]). Unless otherwise specified, the doses are expressed as doses of tocilizumab (genetical recombination), and pharmacokinetic parameters are expressed as mean ± standard deviation.

### 6.2.1 Japanese clinical study (CTD 5.3.5.2-1, J-COVACTA study [May 2020 to December 2020])

A total of 48 patients with COVID-19 pneumonia aged ≥18 years received a single-dose intravenous infusion of tocilizumab 8 mg/kg (maximum dose, 800 mg). If clinical signs or symptoms worsened or remained unimproved, the patients received an additional infusion of tocilizumab 8 mg/kg (maximum dose, 800 mg) 8 to 24 hours after the initial infusion (cases with 2 infusions). Table 1 shows the pharmacokinetic parameters of tocilizumab concentrations in serum of patients treated with 1 or 2 infusions.

Table 1. Pharmacokinetic parameters

| | N | $C_{max}$ μg/mL | $AUC_{inf}$ μg·h/mL | $t_{1/2}$ h | CL L/h | MRT h | Vd L |
|---|---|---|---|---|---|---|---|
| 1 infusion | 41 | 160 ± 27.1 | 21,200 ± 5,230[a)] | 140 ± 59.6[a)] | 0.0285 ± 0.00833[a)] | 195 ± 64.8[a)] | 5.34 ± 1.60[a)] |
| 2 infusions | 7 | 254 ± 54.3 | 47,300 ± 18,600[b)] | 177 ± 101[b)] | — | 264 ± 124[b)] | — |

Mean ± standard deviation; "—," not calculated
a) N = 37
b) N = 6

Figure 1 shows the changes in serum C-reactive protein (CRP) and IL-6 concentrations over time after the infusion of tocilizumab in the overall population treated. The mean CRP concentration decreased after tocilizumab infusion. While the mean IL-6 concentration increased after tocilizumab infusion and then decreased, some patients had increased IL-6 concentration between Days 7 and 14. The applicant explained that based on the information on concomitant drugs and the clinical course, the termination of concomitant corticosteroids may have affected the concentrations in these patients.

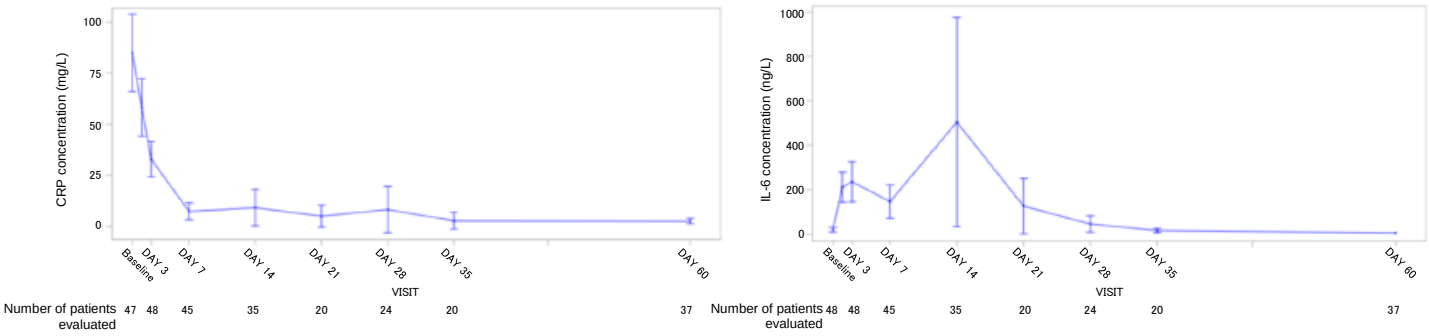


Figure 1. Changes in serum CRP and IL-6 concentrations over time following administration of tocilizumab (mean ± standard deviation)
CRP concentrations (left) and IL-6 concentrations (right)

### 6.2.2 Foreign phase III study (reference data, CTD 5.3.5.1-2, COVACTA study [April 2020 to July 2020])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in patients with COVID-19 pneumonia aged ≥18 years. Patients received a single-dose intravenous infusion of tocilizumab 8 mg/kg (maximum dose, 800 mg) (if clinical signs or symptoms worsened or remained unimproved , patients received an additional infusion of tocilizumab 8 mg/kg 8-24 hours after the initial dose [maximum dose, 800 mg]). Figure 2 shows the change in serum CRP concentrations over time in the tocilizumab and placebo groups (see Table 2 for the change in serum tocilizumab concentrations).

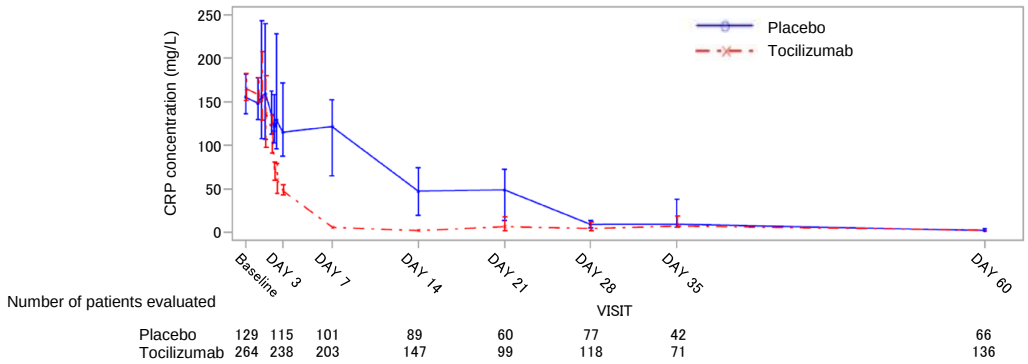


Figure 2. Change in serum CRP concentrations over time following study drug administration (mean ± standard deviation)

### 6.2.3 Difference in pharmacokinetics of tocilizumab between Japanese and non-Japanese populations

The applicant's explanation:

Table 2 shows the changes in serum concentrations over time following the administration of tocilizumab according to the proposed dosage regimen in the Japanese clinical study (J-COVACTA study) and foreign clinical studies (MARIPOSA[5)] and COVACTA studies). The results indicated no clear differences in the pharmacokinetics of tocilizumab in patients with COVID-19 pneumonia between the Japanese and non-Japanese populations.

Table 2 Change in serum tocilizumab concentrations over time

| | | 15 min later | 24 h later | 36 h later | 2 days later | 6 days later | 13 days later | 20 days later | 27 days later | 34 days later |
|---|---|---|---|---|---|---|---|---|---|---|
| J-COVACTA (Japanese clinical study) | 1 infusion | 41 | 41 | 36 | 41 | 38 | 28 | 16 | 32 | 2 |
| | | 160 ± 27.1 | 112 ± 23.2 | 102 ± 20.0 | 86.8 ± 19.0 | 46.2 ± 12.7 | 19.6 ± 6.35 | 8.28 ± 5.27 | 4.83 ± 3.73 | 0.747 ± 0.769 |
| | 2 infusions | 7 | 6 | 5 | 7 | 7 | 7 | 4 | 5 | 1 |
| | | 160 ± 35.0 | 182 ± 87.3 | 203 ± 58.3 | 191 ± 45.9 | 91.1 ± 17.0 | 43.0 ± 21.8 | 27.8 ± 19.4 | 20.0 ± 15.1 | 7.12 |
| MARIPOSA (Foreign clinical study) | 1 infusion | 35 | 32 | — | — | 25 | 19 | 12 | 11 | 4 |
| | | 161 ± 50.2 | 112 ± 27.7 | — | — | 47.2 ± 15.8 | 25.0 ± 28.1 | 7.71 ± 7.40 | 3.51 ± 4.57 | 3.89 ± 3.73 |
| | 2 infusions | 8 | 8 | — | — | 6 | 4 | 4 | 2 | 0 |
| | | 153 ± 75.9 | 174 ± 63.1 | — | — | 65.6 ± 36.1 | 26.8 ± 16.7 | 9.15 ± 8.14 | 2.60 ± 1.90 | N.C. |
| COVACTA (Foreign clinical study) | 1 infusion | 201 | 203 | 142 | 102 | 157 | 114 | 71 | 63 | 16 |
| | | 157 ± 47.7 | 119 ± 34.8 | 101 ± 29.3 | 84.2 ± 27.0 | 43.1 ± 17.4 | 14.2 ± 11.5 | 6.59 ± 7.80 | 3.52 ± 4.01 | 0.884 ± 1.11 |
| | 2 infusions | 86 | 35 | 34 | 20 | 38 | 30 | 22 | 24 | 9 |
| | | 222 ± 100 | 242 ± 84.6 | 250 ± 68.8 | 223 ± 65.3 | 105 ± 36.2 | 43.4 ± 32.0 | 17.2 ± 15.1 | 13.3 ± 11.3 | 6.11 ± 8.29 |

Upper row, N (measurements <lower limit of quantitation are not included); lower row, serum tocilizumab concentration (μg/mL); "—," no measurement was planned; N.C, not calculated
Mean ± standard deviation (individual value is shown for N = 1)

## 6.R Outline of the review conducted by PMDA

PMDA's view:

No particular problems have been suggested with the use of foreign clinical study results as a rationale to evaluate the efficacy and safety of tocilizumab in patients with COVID-19 pneumonia from a pharmacokinetic perspective.

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

The applicant submitted main efficacy and safety data, in the form of clinical study results shown in Table 3.

[5)] Patients with COVID-19 pneumonia received tocilizumab 4 or 8 mg/kg. When symptoms remained unimproved, a second dose was administered at the same dose level 8 to 24 hours after the initial dose.

Table 3. Clinical studies on efficacy and safety

| Data type | Phase | Study identifier | Region | Population | N[a)] | Dosage regimen | Main endpoints |
|---|---|---|---|---|---|---|---|
| Evaluation | III | J-COVACTA | Japan | Patients with COVID-19 pneumonia aged ≥18 years | 49 | In combination with standard of care therapy, a single dose of tocilizumab 8 mg/kg (maximum dose, 800 mg) was intravenously infused. A second dose was allowed in case of no improvement in clinical symptoms. | Efficacy Safety |
| Reference | — | RECOVERY (tocilizumab evaluation cohort) | Foreign | Patients with COVID-19 pneumonia aged ≥18 years | 4,116 (1) 2,022 (2) 2,094 | (1) In combination with standard of care therapy, a single dose of tocilizumab was intravenously infused at the dose determined by body weight on the basis of 8 mg/kg (maximum dose, 800 mg). A second dose was allowed in case of no improvement in clinical symptoms.<br>(2) Standard of care therapy | Efficacy Safety |
| Reference | III | COVACTA | Foreign | Patients with COVID-19 pneumonia aged ≥18 years | 452 (1) 301 (2) 151 | In combination with standard of care therapy, the study drug was intravenously infused. A second dose was allowed in case of no improvement in clinical symptoms.<br>(1) A single dose of tocilizumab 8 mg/kg (maximum dose, 800 mg)<br>(2) Placebo | Efficacy Safety |
| Reference | III | EMPACTA | Foreign | Patients with COVID-19 pneumonia aged ≥18 years | 388 (1) 259 (2) 129 | In combination with standard of care therapy, the study drug was intravenously infused. A second dose was allowed in case of no improvement in clinical symptoms.<br>(1) A single dose of tocilizumab 8 mg/kg (maximum dose, 800 mg)<br>(2) Placebo | Efficacy Safety |
| Reference | III | REMDACTA | Foreign | Patients with COVID-19 pneumonia aged ≥12 years[b)] | 649 (1) 434 (2) 215 | In combination with remdesivir, the study drug was intravenously infused. A second dose was allowed in case of no improvement in clinical symptoms.<br>(1) A single dose of tocilizumab 8 mg/kg (maximum dose, 800 mg)<br>(2) Placebo | Efficacy Safety |

a) The number of participants enrolled for the J-COVACTA study, and the number of randomized participants for the rest of the clinical studies
b) Patients enrolled were all ≥18 years

## 7.1 Japanese clinical study

### 7.1.1 Japanese clinical study (CTD 5.3.5.2-1, J-COVACTA study [May 2020 to December 2020])

An open-label, uncontrolled study was conducted at 11 study sites in Japan to evaluate the efficacy, safety, etc. of tocilizumab in patients with COVID-19 pneumonia aged ≥18 years (target sample size, ≥10 patients). Table 4 summarizes the main inclusion and exclusion criteria of this study.

Table 4. Main inclusion and exclusion criteria

| | |
|---|---|
| Inclusion criteria | 1. Hospitalized with COVID-19 pneumonia identified by PCR with any sample (e.g., respiratory, blood, urine, stool, or other bodily fluid) and subsequently confirmed by chest X-ray or computed tomography (CT) scan<br>2. $SpO_2$ ≤93% or $PaO_2/FiO_2$ <300 mmHg |
| Exclusion criteria | 1. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 10 × the upper limit of normal (ULN)<br>2. Neutrophil count <1,000/μL<br>3. Platelet count <50,000/μL<br>4. Pregnant or breastfeeding women<br>5. Patients who received oral anti-rejection or immunomodulatory drugs (including tocilizumab) within the past 3 months |

Patients received a single-dose intravenous infusion of tocilizumab 8 mg/kg (maximum dose, 800 mg) over 1 hour in combination with standard of care therapy.[6)] A second dose was allowed 8 to 24 hours after the initial dose if clinical symptoms had worsened or remained unimproved.[7)]

[6)] Use of the following concomitant drugs was prohibited: any investigational agent of other studies (except for anti-viral agents against COVID-19), tumor necrosis factor antagonists, anti-IL-6 antibody or anti-IL-6R antibody therapies (except for tocilizumab), Janus kinase (JAK) inhibitors, alkylating agents, thalidomide, intravenous gamma globulin, anti-thymocyte globulin, and azathioprine.
[7)] Defined as a condition with persistent fever (≥38.1°C) or ≥1-category worsening on the 7-category ordinal scale of clinical status.

Of the 49 patients enrolled, 48 patients received tocilizumab and were included in the efficacy analysis set and safety analysis set. Of the 48, 41 patients (85.4%) received 1 dose of tocilizumab and 7 patients (14.6%) received 2 doses of tocilizumab.

Study discontinuation[8)] occurred in 14.6% (7 of 48) of patients. The reasons for discontinuation were death (6 patients) and patient's request for withdrawal (1 patient).

Table 6 shows the clinical status assessed using a 7-category ordinal scale (Table 5) at Day 28, the primary efficacy endpoint. The number of patients who achieved ≥2-category improvement in clinical status (the percentage 95% confidence interval [CI]) was 36 of 48 patients (75.0% [60.40, 86.36], and that of those who achieved ≥1-category improvement was 39 of 48 patients (81.3% [67.37, 91.05]), while ≥1-category worsening in the clinical status occurred in 6 of 48 patients (12.5% [4.73, 25.25]).

Table 5. Seven-category ordinal scale

| Category | Description |
|---|---|
| 1 | Discharged or ready for discharge (normal body temperature and respiratory rate, and stable $SpO_2$ on ambient air or ≤2 L supplemental oxygen) |
| 2 | Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen |
| 3 | Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen |
| 4 | Hospital ward, requiring non-invasive ventilation or high-flow oxygen |
| 5 | ICU, requiring intubation and mechanical ventilation |
| 6 | ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy) |
| 7 | Death |

Table 6. Efficacy results (efficacy analysis set)

| 7-category ordinal scale | N = 48 | |
|---|---|---|
| | Baseline (Day 1) | Day 28 |
| 1 | 0 | 35 (72.9) |
| 2 | 4 (8.3) | 3 (6.3) |
| 3 | 29 (60.4) | 2 (4.2) |
| 4 | 8 (16.7) | 0 |
| 5 | 6 (12.5) | 3 (6.3) |
| 6 | 1 (2.1) | 0 |
| 7 | 0 | 5 (10.4) |

n (%)

Safety data[9)] show that adverse events occurred in 83.3% (40 of 48) of patients. Adverse events occurring in ≥10.0% of patients were constipation (18.8%, 9 of 48 patients), ALT increased (16.7%, 8 of 48 patients), fibrin D dimer increased (16.7%, 8 of 48 patients), hyperuricaemia (16.7%, 8 of 48 patients), AST increased (14.6%, 7 of 48 patients), and liver disorder (10.4%, 5 of 48 patients).

Adverse events led to death in 12.5% (6 of 48) of patients (COVID-19 pneumonia [3 patients]; COVID-19, respiratory failure, and pulmonary infarction [1 patient each]). A causal relationship to tocilizumab was ruled out for all these events.

8) Patients who did not complete the 60-day follow-up period following study drug treatment.
9) Patients were followed for 60 days after the first dose of the study drug.

Serious adverse events occurred in 12.5% (6 of 48) of patients (COVID-19 pneumonia [3 patients]; COVID-19, pneumonia bacterial, respiratory failure, and pulmonary infarction [1 patient each]; some patients had >1 event). A causal relationship to tocilizumab was ruled out for all these events.

No adverse events (except for death) led to study discontinuation.

Adverse drug reactions occurred in 31.3% (15 of 48) of patients.

## 7.2 Foreign clinical studies

### 7.2.1 Investigator-initiated foreign clinical study (reference data, CTD 5.3.5.1-1, RECOVERY study [tocilizumab evaluation cohort] [ongoing since April 2020; data cut-off on March 29, 2021]) (Lancet 2021;397:1637-45)

A randomized, open-label, parallel-group comparative study was conducted at 131 study sites in the UK to evaluate the efficacy, etc. of tocilizumab in patients with COVID-19 pneumonia aged ≥18 years in comparison to the standard of care therapy alone. The target sample size for the tocilizumab evaluation cohort was 4,000 patients[10] (patients were randomized to tocilizumab or the standard of care therapy at a ratio of 1:1).

In the tocilizumab group, the dose was determined by body weight class established on a basis of the approved 8 mg/kg per dose (8 mg/kg for body weight ≤40 kg; 400 mg for body weight >40 kg and ≤65 kg; 600 mg for body weight >65 kg and ≤90 kg; and 800 mg for body weight >90 kg). Tocilizumab was intravenously infused over ≥1 hour in combination with standard of care therapy. If the patient's condition remained unimproved, a second dose was allowed 12 to 24 hours after the initial infusion. In the standard care group, patients continued ongoing standard of care therapies (including the therapy assigned at the first randomization).

Of the patients who were enrolled[11] in the RECOVERY study from April 23, 2020 to January 24, 2021, 4,116 patients were found to be eligible for the inclusion criteria[12] of the tocilizumab evaluation cohort, and were randomized. All the randomized patients (2,022 in the tocilizumab group and 2,094 in the standard care group) were included in the intention-to-treat (ITT) population, which was used as the efficacy analysis set.

The results for all-cause mortality at 28 days after randomization, the primary endpoint, are presented in Table 7 and Figure 3.

Table 7. All-cause mortality at 28 days after randomization (ITT population)

| | Tocilizumab (N = 2,022) | Standard care (N = 2,094) |
|---|---|---|
| All-cause deaths (%) | 621 (31%) | 729 (35%) |
| Hazard ratio[a] [95% CI] | 0.85 [0.76, 0.94] | |
| *P*-value[b] | 0.0028 | |

a) Peto's method
b) Log-rank test

[10] The primary endpoint is all-cause mortality at 28 days after randomization. Based on an assumed all-cause mortality of ≥25% in the standard care group and an all-cause mortality in the tocilizumab group assumed to be one-fifth lower than that in the standard care group, it would be necessary to enroll 4,000 patients for 2 groups to provide ≥90% power at a two-sided significance level of 1%.
[11] Hospitalized patients were eligible if they presented with clinically suspected or laboratory confirmed COVID-19 and had no medical history which was recognized by the treating physician as a significant potential risk in the study.
[12] Eligible patients had $SpO_2$ <92% on room air or receiving oxygen and CRP ≥75 mg/L who were recognized by the treating physician as having no problems with the use of tocilizumab.

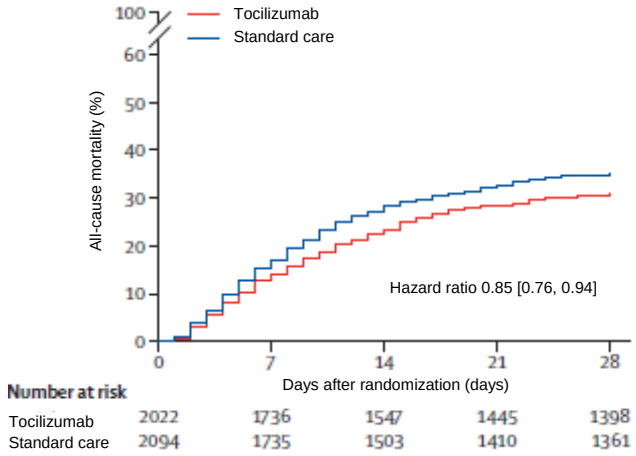


Figure 3. Kaplan-Meier plot of all-cause mortality up to 28 days after randomization (ITT population)

Otitis externa, Staphylococcus aureus bacteraemia, and lung abscess in 1 case each were reported as serious adverse drug reactions that may be related to tocilizumab.

### 7.2.2 Foreign phase III study (CTD 5.3.5.1-2, COVACTA study [April 2020 to July 2020])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted at 62 study sites in 9 countries (the US, Canada, Denmark, France, Germany, Italy, the Netherlands, Spain, and the UK) to evaluate the efficacy, safety, etc. of tocilizumab in patients with COVID-19 pneumonia aged ≥18 years (target sample size, 450 patients[13)] [allocation ratio of 2:1 between tocilizumab and placebo]). Table 8 summarizes the main inclusion and exclusion criteria of this study.

Table 8. Main inclusion and exclusion criteria

| | |
|---|---|
| Inclusion criteria | 1. Hospitalized patients with COVID-19 pneumonia tested positive by PCR of any specimen (e.g., respiratory, blood, urine, stool, or other bodily fluid) and confirmed by chest X-ray or CT scan<br>2. $SpO_2$ ≤93% on room air, or $PaO_2/FiO_2$ <300 mmHg |
| Exclusion criteria | 1. AST or ALT >10 × ULN<br>2. Neutrophil count <1,000/μL<br>3. Platelet count <50,000/μL<br>4. Pregnant or breastfeeding women<br>5. Patients who received oral anti-rejection or immunomodulatory drugs (including tocilizumab) within the past 3 months<br>6. Patients with suspected active bacterial, fungal, or viral (besides SARS-CoV-2) infection<br>7. Progression to death is imminent and inevitable within the next 24 hours |

Tocilizumab 8 mg/kg (maximum dose, 800 mg) or placebo was intravenously infused over 1 hour in combination with standard of care therapy.[14)] If the patient's condition had worsened or remained unimproved,[7)] a second dose was allowed 8 to 24 hours after the initial infusion.

Of the 452 patients (301 in the tocilizumab and 151 in the placebo groups) who were randomized using the stratification factors, i.e., region (North America or Europe) and a history of invasive mechanical ventilation (with or without), 438 patients (294 in the tocilizumab and 144 in the placebo groups) received the study drug and were included in the modified intent-to-treatment (mITT) population, which was used as the efficacy

[13)] The sample size for the 7-category ordinal scale at Day 28, the primary endpoint, was determined as 450 patients (2 groups), which would be required to obtain approximately 90% power based on the odds ratio for tocilizumab vs placebo assumed as 2, at a two-sided significance level of 5%. The proportion of patients on mechanical ventilation at the time of randomization was limited to <50% of the overall population.

[14)] Use of the following concomitant therapies was prohibited: treatment with any investigational agent of other studies (except for anti-viral agents against COVID-19), biologics (tumor necrosis factor antagonists, anti-IL-6 antibody or anti-IL-6R antibody therapies [except for tocilizumab]), JAK inhibitors, alkylating agents, thalidomide, intravenous gamma globulin, anti-thymocyte globulin, and azathioprine.

analysis set. In the mITT population, 1 patient who had been assigned to the placebo group received tocilizumab and was included in the tocilizumab group in the safety analyses. Consequently, the safety analysis set consisted of 295 patients in the tocilizumab group and 143 patients in the placebo group. In total, 230 of 295 patients (78.0%) in the tocilizumab group and 100 of 143 patients (69.9%) in the placebo group received 1 dose of the study drug (tocilizumab or placebo), while 65 of 295 patients (22.0%) in the tocilizumab group and 43 of 143 patients (30.1%) in the placebo group received 2 doses.

Study discontinuation[8)] occurred in 35.4% (104 of 294) of patients in the tocilizumab group, 33.3% (48 of 144) of patients in the placebo group. Main reasons for discontinuation include death (24.1% [71 of 294] of patients in the tocilizumab group and 25.0% [36 of 144] of patients in the placebo group), lost-to-follow-up (7.8% [23 of 294] of patients in the tocilizumab group and 3.5% [5 of 144] of patients in the placebo group), and patient's request for withdrawal (3.4% [10 of 294] of patients in the tocilizumab group and 2.7% [4 of 144] of patients in the placebo group).

Table 9 shows the results of the clinical status assessed using the 7-category ordinal scale at (Table 5) at Day 28, the primary endpoint. No statistically significant differences were observed between the tocilizumab and placebo groups ($P$ = 0.36, at a two-sided significance level of 5%, the Van Elteren test using the stratification factors of region [North America or Europe] and a history of invasive mechanical ventilation [with or without]).

Table 9. Clinical status assessed using the 7-category ordinal scale (mITT population)

| 7-category ordinal scale | Baseline (Day 1) | | Day 28 | |
|---|---|---|---|---|
| | Tocilizumab N = 294 | Placebo N = 144 | Tocilizumab N = 294 | Placebo N = 144 |
| 1 | 0 | 0 | 166 (56.5) | 71 (49.3) |
| 2 | 9 (3.1) | 6 (4.2) | 6 (2.0) | 8 (5.6) |
| 3 | 78 (26.5) | 44 (30.6) | 14 (4.8) | 4 (2.8) |
| 4 | 94 (32.0) | 39 (27.1) | 6 (2.0) | 10 (6.9) |
| 5 | 45 (15.3) | 15 (10.4) | 26 (8.8) | 14 (9.7) |
| 6 | 68 (23.1) | 39 (27.1) | 18 (6.1) | 9 (6.3) |
| 7 | 0 | 1 (0.7)[a)] | 58 (19.7) | 28 (19.4) |

n (%)
a) Died on the day the patient received the study drug

The safety[9)] data show that adverse events occurred in 240 of 295 patients (81.4%) in the tocilizumab group and 118 of 143 patients (82.5%) in the placebo group. Table 10 shows adverse events occurring in ≥3.0% of patients in either group.

Table 10. Adverse events occurring in ≥3.0% of patients in either group (safety analysis set)

| Adverse event | Tocilizumab N = 295 | Placebo N = 143 | Adverse event | Tocilizumab N = 295 | Placebo N = 143 |
|---|---|---|---|---|---|
| COVID-19 pneumonia | 36 (12.2) | 20 (14.0) | Hypotension | 11 (3.7) | 8 (5.6) |
| Urinary tract infection | 24 (8.1) | 5 (3.5) | Thrombocytopenia | 11 (3.7) | 2 (1.4) |
| Acute kidney injury | 21 (7.1) | 7 (4.9) | Pulmonary embolism | 10 (3.4) | 5 (3.5) |
| Hypertension | 21 (7.1) | 3 (2.1) | Deep vein thrombosis | 10 (3.4) | 3 (2.1) |
| Constipation | 18 (6.1) | 8 (5.6) | ALT increased | 10 (3.4) | 2 (1.4) |
| Diarrhoea | 18 (6.1) | 3 (2.1) | Anxiety | 9 (3.1) | 4 (2.8) |
| Pneumonia | 17 (5.8) | 12 (8.4) | Septic shock | 8 (2.7) | 8 (5.6) |
| Anaemia | 17 (5.8) | 10 (7.0) | Hypokalaemia | 7 (2.4) | 6 (4.2) |
| Delirium | 14 (4.7) | 3 (2.1) | Bradycardia | 7 (2.4) | 5 (3.5) |
| COVID-19 | 14 (4.7) | 2 (1.4) | Respiratory failure | 6 (2.0) | 6 (4.2) |
| Atrial fibrillation | 12 (4.1) | 6 (4.2) | Bacteraemia | 5 (1.7) | 6 (4.2) |
| Insomnia | 12 (4.1) | 5 (3.5) | Cardiac arrest | 5 (1.7) | 5 (3.5) |

n (%)

Adverse events led to death in 24.4% (72 of 295) of patients in the tocilizumab group (COVID-19 pneumonia [36 patients]; COVID-19 [13 patients]; multiple organ dysfunction syndrome [5 patients]; respiratory failure [3 patients]; septic shock, acute respiratory distress syndrome, cardiac arrest, and retroperitoneal haemorrhage [2 patients each]; acute respiratory failure, pulmonary embolism, shock haemorrhagic, haemorrhage, coagulopathy, haemorrhagic transformation stroke, and acute kidney injury [1 patient each]); and in 25.2% (36 of 143) of patients in the placebo group (COVID-19 pneumonia [20 patients]; respiratory failure [3 patients]; COVID-19, acute respiratory distress syndrome and acute respiratory failure [2 patients each]; septic shock, pneumonia bacterial, pulmonary embolism, aspiration, lung consolidation, cardiac arrest, and shock haemorrhagic [1 patient each]). A causal relationship to the study drug could not be ruled out for events in 3 patients in the tocilizumab group (multiple organ dysfunction syndrome, retroperitoneal haemorrhage, and septic shock in 1 patient each).

Serious adverse events occurred in 39.3% (116 of 295) of patients in the tocilizumab group and 44.8% (64 of 143) of patients in the placebo group. Table 11 shows serious adverse events occurring in ≥1.0% of patients in either group. A causal relationship to the study drug could not be ruled out for the events in 18 patients in the tocilizumab group (neutropenia [4 patients]; septic shock and pneumonia bacterial [3 patients each]; bacteraemia and pneumonia [2 patients each]; pneumonia escherichia, Citrobacter test positive, bacterial sepsis, cytomegalovirus hepatitis, Enterobacter pneumonia, lower gastrointestinal haemorrhage, urinary tract infection, multiple organ dysfunction syndrome, sepsis, retroperitoneal haemorrhage, and pancreatitis [1 patient each]; some patients had more than 1 event) and in 13 patients in the placebo group (septic shock and pneumonia [3 patients each]; candida infection, thrombocytopenia, Stenotrophomonas infection, pancytopenia, pneumonia bacterial, bacteraemia, sepsis, cholecystitis, respiratory failure, urosepsis, and pseudomonal sepsis [1 patient each]; some patients had more than 1 event).

Table 11. Serious adverse events occurring in ≥1.0% of patients in either group (safety analysis set)

| Adverse event | Tocilizumab N = 295 | Placebo N = 143 | Adverse event | Tocilizumab N = 295 | Placebo N = 143 |
|---|---|---|---|---|---|
| COVID-19 pneumonia | 36 (12.2) | 20 (14.0) | Acute respiratory distress syndrome | 4 (1.4) | 2 (1.4) |
| COVID-19 | 14 (4.7) | 2 (1.4) | Neutropenia | 4 (1.4) | 0 |
| Acute kidney injury | 10 (3.4) | 4 (2.8) | Atrial fibrillation | 3 (1.0) | 0 |
| Septic shock | 7 (2.4) | 7 (4.9) | Sepsis | 3 (1.0) | 4 (2.8) |
| Pneumonia | 7 (2.4) | 4 (2.8) | Bacteraemia | 3 (1.0) | 3 (2.1) |
| Pneumonia bacterial | 6 (2.0) | 2 (1.4) | Bacterial sepsis | 3 (1.0) | 0 |
| Respiratory failure | 5 (1.7) | 6 (4.2) | Acute respiratory failure | 2 (0.7) | 2 (1.4) |
| Pulmonary embolism | 5 (1.7) | 2 (1.4) | Pulseless electrical activity | 2 (0.7) | 2 (1.4) |
| Multiple organ dysfunction syndrome | 5 (1.7) | 1 (0.7) | Renal failure | 2 (0.7) | 2 (1.4) |
| Cardiac arrest | 4 (1.4) | 5 (3.5) | Hypoxia | 0 | 3 (2.1) |
| Pneumothorax | 4 (1.4) | 3 (2.1) | Pharyngeal haemorrhage | 0 | 2 (1.4) |

n (%)

No adverse events (except for death) led to study discontinuation in either group.

Adverse drug reactions occurred in 18.3% (54 of 295) of patients in the tocilizumab group and 18.2% (26 of 143) of patients in the placebo group.

### 7.2.3 Foreign phase III study (reference data, CTD 5.3.5.1-3, EMPACTA study [May 2020 to September 2020])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted at 42 study sites in 6 countries (the US, Mexico, Kenya, South Africa, Peru, and Brazil) to evaluate the efficacy, safety, etc. of tocilizumab in patients with COVID-19 pneumonia aged ≥18 years (target sample size, 379 patients[15)] [allocation ratio of 2:1 between tocilizumab and placebo]). Table 12 summarizes the main inclusion and exclusion criteria of this study.

Table 12. Main inclusion and exclusion criteria

| | |
|---|---|
| Inclusion criteria | 1. Hospitalized patients with COVID-19 pneumonia tested positive by PCR of any specimen (e.g., respiratory, blood, urine, stool, or other bodily fluid) and confirmed by chest X-ray or CT scan<br>2. $SpO_2$ <94% on room air |
| Exclusion criteria | 1. Patients requiring continuous positive airway pressure (CPAP), bilevel positive airway pressure (BIPAP), or invasive mechanical ventilation<br>2. AST or ALT >5 × ULN<br>3. Neutrophil count <1,000/μL<br>4. Platelet count <50,000/μL<br>5. Pregnant or breastfeeding women<br>6. Patients who received oral anti-rejection or immunomodulatory drugs (including tocilizumab) within the past 3 months<br>7. Patients with any history of intestinal perforation<br>8. Patients with suspected active bacterial, fungal, or viral (besides SARS-CoV-2) infection<br>9. Progression to death is imminent and inevitable within the next 24 hours |

A single dose of tocilizumab 8 mg/kg (maximum dose, 800 mg) or placebo was infused intravenously over 1 hour in combination with standard of care therapy.[14)] A second dose was allowed 8 to 24 hours after the initial infusion if clinical signs or symptoms had worsened or remained unimproved.[7)]

Of the 388 patients (259 patients in the tocilizumab group and 129 patients in the placebo group) who were randomized by stratification factors of country and age (≤60 years or >60 years), 377 patients (249 patients in the tocilizumab group and 128 patients in the placebo group) received the study drug and were included in the mITT group, which was used as the efficacy analysis set. Of the mITT population, 1 patient who had been assigned to placebo received tocilizumab and the data were included in the tocilizumab group in the safety analyses. Consequently, the safety analysis set consisted of 250 patients in the tocilizumab group and 127 patients in the placebo group. In total, 182 of 250 patients (72.8%) in the tocilizumab group and 92 of 127 patients (72.4%) in the placebo group received 1 dose of the study drug (tocilizumab or placebo), while 68 of 250 patients (27.2%) in the tocilizumab group and 35 of 127 patients (27.6%) in the placebo group received 2 doses.

Study discontinuation occurred in 9.6% (24 of 249) of patients in the tocilizumab group and 10.2% (13 of 128) of patients in the placebo group. Reasons for discontinuation include death (9.6% [24 of 249] of patients in the tocilizumab group and 8.6% [11 of 128] of patients in the placebo group]).

The primary efficacy endpoint was the use of mechanical ventilation or death by Day 28. The results are presented in Table 13 and Figure 4. The difference between the tocilizumab and placebo groups was statistically significant.

[15)] The sample size was determined as 379 patients (2 groups) to obtain approximately 80% power, under the assumption of cumulative event (mechanical ventilation or death) rates of 25% in the tocilizumab group and 40% in the placebo group at Day 28, at a two-sided 5% significance level, with a dropout rate of 10% taken into account.

Table 13. Use of mechanical ventilation or death by Day 28 (mITT population)

| | | Tocilizumab N = 249 | Placebo N = 128 |
|---|---|---|---|
| Mechanical ventilation or death,[a] n (%) | | 29 (11.6) | 24 (18.8) |
| | Death, n (%) | 9 (3.6) | 8 (6.3) |
| | Mechanical ventilation use, n (%) | 20 (8.0) | 16 (12.5) |
| Hazard ratio[b] [95% CI] | | 0.56 [0.33, 0.97] | |
| *P*-value[c] | | 0.0360 | |

a) Patients who experienced both mechanical ventilation and death by Day 28 were included in the earlier event.
b) A stratified Cox proportional-hazard model with a stratification factor of age group (≤60 years or >60 years)
c) Two-sided 5% significance level; a stratified log-rank test with a stratification factor of age group (≤60 years or >60 years)

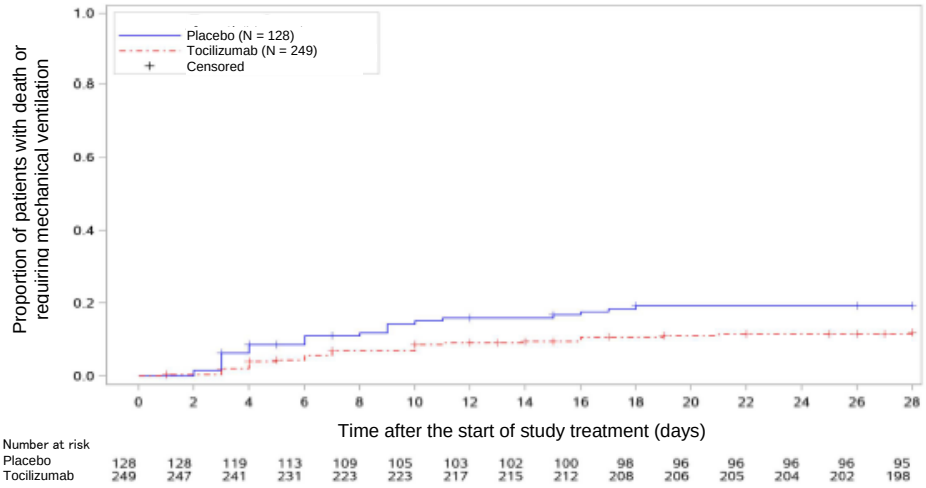


Figure 4. Kaplan-Meier plot of use of mechanical ventilation or death by Day 28 of study drug treatment (mITT population)

Safety[9] data show that adverse events occurred in 50.8% (127 of 250) of patients in the tocilizumab group and 52.8% (67 of 127) of patients in the placebo group. Adverse events occurring in ≥3.0% of patients in either group were constipation (6.4% [16 of 250] of patients in the tocilizumab group and 3.1% [4 of 127] patients in the placebo group), anxiety (6.0% [15 of 250] of patients and 3.1% [4 of 127] of patients), headache (3.2% [8 of 250] of patients and 2.4% [3 of 127] of patients), fatigue (1.2% [3 of 250] of patients and 3.9% [5 of 127] of patients), acute kidney injury (1.6% [4 of 250] of patients and 3.1% [4 of 127] of patients), hyperglycaemia (1.2% [3 of 250] of patients and 3.1% [4 of 127] of patients), and pneumonia (0.8% [2 of 250] of patients and 3.1% [4 of 127] of patients).

Adverse events led to death in 11.2% (28 of 250) of patients in the tocilizumab group (acute respiratory distress syndrome [5 patients]; acute respiratory failure and respiratory failure [4 patients each]; COVID-19 pneumonia, septic shock, cardiac arrest, and cardio-respiratory arrest [2 patients each]; COVID-19, pneumonia staphylococcal, acute myocardial infarction, brain stem stroke, cerebrovascular accident, intestinal perforation, and multiple organ dysfunction syndrome [1 patient each]) and in 10.2% (13 of 127) of patients in the placebo group (COVID-19 pneumonia [3 patients]; acute respiratory failure and respiratory failure [2 patients each]; acute respiratory distress syndrome, respiratory distress, septic shock, pneumonia bacterial, atrial fibrillation, and myocardial infarction [1 patient each]). A causal relationship to the study drug could not be ruled out for the event of pneumonia staphylococcal (1 patient) in the tocilizumab group.

Serious adverse events occurred in 15.2% (38 of 250) of patients in the tocilizumab group and 19.7% (25 of 127) of patients in the placebo group. Serious adverse events occurring in ≥1.0% of patients in either group were septic shock (2.0% [5 of 250] of patients in the tocilizumab group and 2.4% [3 of 127] of patients in the placebo group), acute respiratory distress syndrome (2.0% [5 of 250] of patients and 0.8% [1 of 127] of patients), acute respiratory failure (1.6% [4 of 250] of patients and 2.4% [3 of 127] of patients), respiratory failure (1.6% [4 of 250] of patients and 1.6% [2 of 127] of patients), pulmonary embolism (1.2% [3 of 250] of patients and 0.8% [1 of 127] of patients), COVID-19 pneumonia (0.8% [2 of 250] of patients and 2.4% [3 of 127] of patients), acute kidney injury (0.4% [1 of 250] of patients and 2.4% [3 of 127] of patients), pneumonia (0 and 2.4% [3 of 127] of patients), and pneumonia bacterial (0 and 1.6% [2 of 127] of patients). A causal relationship to the study drug could not be ruled out for the following events in the 3 patients in the tocilizumab group: bacteraemia, cholecystitis infective, device related infection, and pneumonia staphylococcal in 1 patient each (1 patient had 2 events).

No adverse events (except for death) led to study discontinuation in either group.

Adverse drug reactions occurred in 12.8% (32 of 250) of patients in the tocilizumab group and 3.9% (5 of 127) of patients in the placebo group.

### 7.2.4 Foreign phase III study (CTD 5.3.5.1-4, REMDACTA study [June 2020 to March 2021])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in 53 study sites in 4 countries (the US, Brazil, Russia, and Spain) to evaluate the efficacy, safety, etc. of tocilizumab in patients with COVID-19 pneumonia aged ≥12 years[16)] (target sample size,[17)] 650 patients [allocation ratio of 2:1 between tocilizumab and placebo]). Table 14 shows the main inclusion and exclusion criteria for this study.

Table 14. Main inclusion and exclusion criteria

| | |
|---|---|
| Inclusion criteria | 1. Hospitalized patients with COVID-19 pneumonia tested positive by PCR of any specimen (e.g., respiratory, blood, urine, stool, or other bodily fluid) and confirmed by chest X-ray or CT scan<br>2. Requiring > 6 L/min oxygen to maintain $SpO_2$ >93% |
| Exclusion criteria | 1. AST or ALT >5 × ULN<br>2. Neutrophil count <1,000/μL<br>3. Platelet count <50,000/μL<br>4. Pregnant or breastfeeding women<br>5. Patients who received oral anti-rejection or immunomodulatory drugs (including tocilizumab) within the past 3 months<br>6. Patients who received >2 doses of remdesivir<br>7. Estimated glomerular filtration rate (eGFR) of <30 mL/min or patients receiving hemodialysis<br>8. Body weight <40 kg<br>9. Patients with suspected active bacterial, fungal, or viral (besides COVID-19) infection<br>10. Progression to death is imminent and inevitable within the next 24 hours |

Tocilizumab 8 mg/kg (maximum dose, 800 mg) or placebo was intravenously infused over 1 hour in combination with remdesivir. A second dose was allowed 8 to 24 hours after the initial infusion if clinical signs or symptoms had worsened or remained unimproved.[7)] Remdesivir was administered intravenously once daily

[16)] Patients enrolled in the REMDACTA study were all ≥18 years.

[17)] The primary endpoint was time from randomization to hospital discharge or "ready for discharge" up to Day 28. Assuming a median time of 11 days for the placebo group and a hazard ratio of 1.3 for time to hospital discharge or ready for discharge between groups (corresponding to approximately 2.5 days difference in median time between the tocilizumab and placebo groups), approximately 520 events would be required to provide approximately 80% power at two-sided significance level of 5%, and approximately 650 participants would be required (for 2 groups) for the number of events. The proportion of patients meeting the category 6 criteria was limited to a maximum of 25%.

at 200 mg on Day 1 and 100 mg from Days 2 to 10. Treatment was discontinued when patients were discharged from the hospital.

A total of the 649 patients (434 patients in the tocilizumab group and 215 patients in the placebo group) were randomized by stratification factors of region (North America, Europe, or other) and disease severity (Category 4, 5, or 6 on the 7-category ordinal scale in Table 5). Of these, 640 patients who received the study drug (430 patients in the tocilizumab group and 210 patients in the placebo group) were included in the mITT population, which was used as the efficacy analysis set. All 642 patients who received remdesivir or the study drug (tocilizumab or placebo) were included in the safety analysis set. Of the patients allocated to tocilizumab, 1 patient received placebo by mistake and 2 patients received remdesivir without receiving the study drug, and they were included in the placebo group in the safety analyses. The safety analysis set therefore consisted of 429 patients in the tocilizumab group and 213 patients in the placebo group. In total, 344 of 429 patients (80.2%) in the tocilizumab group and 163 of 211 patients (77.3%) in the placebo group received 1 dose of the study drug (tocilizumab or placebo), while 85 of 429 patients (19.8%) in the tocilizumab group and 48 of 211 patients (22.7%) in the placebo group received 2 doses of the study drug.

Study discontinuation[8)] occurred in 30.5% (131 of 430) of patients in the tocilizumab group and 33.3% (70 of 210) of patients in the placebo group. Reasons for discontinuation include death (22.3% [96 of 430] of patients in the tocilizumab group and 25.7% [54 of 210] of patients in the placebo group), lost-to-follow-up (5.3% [23 of 430] of patients in the tocilizumab group and 5.7% [12 of 210] of patients in the placebo group), and patient's request for withdrawal (2.1% [9 of 430] of patients in the tocilizumab group and 1.9% [4 of 210] of patients in the placebo group).

The results of efficacy primary endpoint, time from randomization to hospital discharge or "ready for discharge" by Day 28, are presented in Table 15 and Figure 5. No statistically significant differences were observed between the groups.

Table 15. Time from randomization to hospital discharge or ready for discharge by Day 28 (mITT population)

| | Tocilizumab N = 430 | Placebo N = 210 |
|---|---|---|
| Patients who were discharged or ready for discharge, n (%) | 284 (66.0%) | 141 (67.1%) |
| Time to discharge or ready for discharge, median [95% CI] (days) | 14.0 [12.0, 15.0] | 14.0 [11.0, 16.0] |
| Hazard ratio[a)] [95% CI] | 0.965 [0.78, 1.19] | |
| *P*-value[b)] | 0.7414 | |

a) A stratified Cox proportional-hazard model with stratification factors of region (North America, Europe, or other) and disease severity (Category 4, 5, or 6 on the 7-category ordinal scale in Table 5)
b) Two-sided 5% significance level; a stratified log-rank test with stratification factors of region (North America, Europe, or other) and disease severity (Category 4, 5, or 6 on the 7-category ordinal scale)

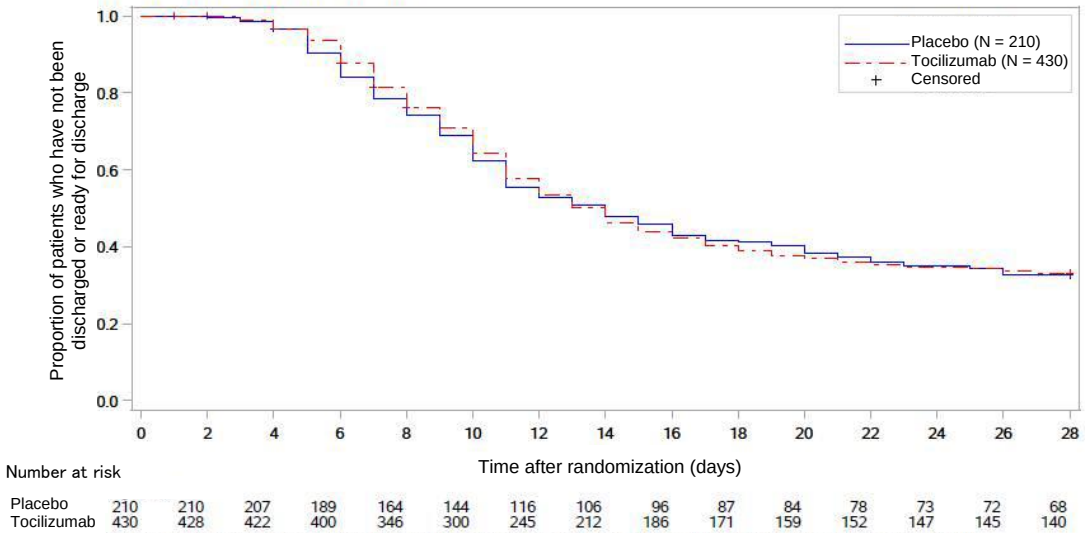


Figure 5. Kaplan-Meier plot of time from randomization to hospital discharge or ready for discharge up to Day 28 (mITT population)

Safety data[9)] show that adverse events occurred in 77.4% (332 of 429) of patients in the tocilizumab group and 71.8% (153 of 213) of patients in the placebo group. Table 16 shows adverse events occurring in ≥3.0% of patients in either group.

Table 16. Adverse events occurring in ≥3.0% of patients in either group (safety analysis set)

| Adverse event | Tocilizumab N = 429 | Placebo N = 213 | Adverse event | Tocilizumab N = 429 | Placebo N = 213 |
|---|---|---|---|---|---|
| Constipation | 54 (12.6) | 25 (11.7) | Anaemia | 15 (3.5) | 14 (6.6) |
| Acute kidney injury | 44 (10.3) | 24 (11.3) | COVID-19 | 14 (3.3) | 8 (3.8) |
| COVID-19 pneumonia | 36 (8.4) | 27 (12.7) | Delirium | 14 (3.3) | 8 (3.8) |
| Pneumonia | 33 (7.7) | 10 (4.7) | Anxiety | 14 (3.3) | 4 (1.9) |
| Transaminases increased | 26 (6.1) | 13 (6.1) | Hypoglycaemia | 14 (3.3) | 2 (0.9) |
| Urinary tract infection | 24 (5.6) | 14 (6.6) | Thrombocytopenia | 14 (3.3) | 2 (0.9) |
| Septic shock | 24 (5.6) | 10 (4.7) | Hyperkalaemia | 13 (3.0) | 10 (4.7) |
| Hypotension | 23 (5.4) | 16 (7.5) | Pneumothorax | 13 (3.0) | 6 (2.8) |
| Hypokalaemia | 23 (5.4) | 6 (2.8) | Pain | 13 (3.0) | 2 (0.9) |
| Hyperglycaemia | 22 (5.1) | 9 (4.2) | Sepsis | 12 (2.8) | 7 (3.3) |
| Insomnia | 21 (4.9) | 7 (3.3) | Bradycardia | 8 (1.9) | 7 (3.3) |
| Atrial fibrillation | 19 (4.4) | 9 (4.2) | Pneumonia bacterial | 8 (1.9) | 7 (3.3) |
| Nausea | 19 (4.4) | 7 (3.3) | | | |

n (%)

Adverse events led to death in 22.6% (97 of 429) of patients in the tocilizumab group (COVID-19 pneumonia [35 patients]; COVID-19 [14 patients]; septic shock [13 patients]; pneumonia [6 patients]; sepsis [5 patients]; pneumonia acinetobacter, shock, shock haemorrhagic, cardiogenic shock, and death [2 patients each]; haemorrhagic stroke, cerebrovascular accident, embolic stroke, pneumonia klebsiella, pulmonary sepsis, bradycardia, supraventricular tachycardia, intestinal ischaemia, retroperitoneal haemorrhage, multiple organ dysfunction syndrome, pulmonary embolism, pneumonia aspiration, pneumothorax, and brain herniation [1 patient each]), and in 25.8% (55 of 213) of patients in the placebo group (COVID-19 pneumonia [26 patients]; COVID-19 [8 patients]; septic shock [3 patients]; sepsis, haemorrhagic stroke, and multiple organ dysfunction syndrome [2 patients each]; pneumonia, pneumonia bacterial, urosepsis, death, brain death, haemorrhage intracranial, hypoxic-ischaemic encephalopathy, haemodynamic instability, intestinal ischaemia, colitis, pulmonary embolism, and acute kidney injury [1 patient each]). A causal relationship to the study drug could not be ruled out for the events in 9 patients in the tocilizumab group (septic shock [3 patients]; sepsis, pneumonia, pneumonia acinetobacter, pneumonia klebsiella, intestinal ischaemia, and multiple organ

dysfunction syndrome [1 patient each]) and in 2 patients in the placebo group (septic shock and urosepsis [1 patient each]).

Serious adverse events occurred in 32.9% (141 of 429) of patients in the tocilizumab group and 35.7% (76 of 213) of patients in the placebo group. Table 17 shows serious adverse events occurring in ≥1.0% of patients in either group. A causal relationship to the study drug could not be ruled out for the events in 34 patients in the tocilizumab group (pneumonia [12 patients]; septic shock [7 patients]; sepsis [5 patients]; urinary tract infection [4 patients]; pneumonia bacterial, acute kidney injury, and liver injury [2 patients each]; renal impairment, intestinal ischaemia, pneumonia klebsiella, tracheobronchitis, multiple organ dysfunction syndrome, Enterobacter infection, catheter site haemorrhage, shock, bacterial sepsis, pneumothorax, pneumonia acinetobacter, and platelet count decreased [1 patient each]; some patients had more than 1 event) and in 16 patients in the placebo group (septic shock and pneumonia [4 patients each]; sepsis, tracheobronchitis, and systemic candida [2 patients each]; urinary tract infection, Enterobacter bacteraemia, pneumonia bacterial, Staphylococcal infection, pneumonia acinetobacter, hepatic enzyme increased, hepatic failure, urosepsis, pulmonary sepsis, hepatitis acute, diverticular perforation, bacteraemia, device related sepsis, and pneumonia klebsiella [1 patient each]; some patients had more than 1 event).

Table 17. Serious adverse events occurring in ≥1.0% of patients in either group (safety analysis set)

| Adverse event | Tocilizumab N = 429 | Placebo N = 213 | Adverse event | Tocilizumab N = 429 | Placebo N = 213 |
|---|---|---|---|---|---|
| COVID-19 pneumonia | 36 (8.4) | 27 (12.7) | Cerebrovascular accident | 5 (1.2) | 2 (0.9) |
| Septic shock | 23 (5.4) | 10 (4.7) | Encephalopathy | 5 (1.2) | 1 (0.5) |
| Acute kidney injury | 21 (4.9) | 14 (6.6) | Pneumomediastinum | 5 (1.2) | 1 (0.5) |
| Pneumonia | 21 (4.9) | 6 (2.8) | Renal failure | 5 (1.2) | 0 |
| COVID-19 | 14 (3.3) | 8 (3.8) | Hypotension | 4 (0.9) | 4 (1.9) |
| Sepsis | 11 (2.6) | 6 (2.8) | Urinary tract infection | 4 (0.9) | 3 (1.4) |
| Pneumothorax | 7 (1.6) | 1 (0.5) | Cardiac arrest | 2 (0.8) | 3 (1.4) |
| Pneumonia bacterial | 5 (1.2) | 4 (1.9) | Renal impairment | 1 (0.2) | 5 (2.3) |
| Pulmonary embolism | 5 (1.2) | 3 (1.4) | Transaminases increased | 1 (0.2) | 3 (1.4) |

n (%)

Adverse events (except for death) led to study discontinuation in 0.5% (2 of 429) of patients in the tocilizumab group (cerebrovascular accident and acute kidney injury [1 patient each]). A causal relationship to the study drug was ruled out for both events.

Adverse drug reactions occurred in 14.9% (64 of 429) of patients in the tocilizumab group and 12.7% (27 of 213) of patients in the placebo group.

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Efficacy and clinical positioning

The applicant's explanation about the efficacy of tocilizumab:

The RECOVERY study (tocilizumab evaluation cohort) was an investigator-initiated foreign clinical study conducted primarily in patients with COVID-19 pneumonia requiring oxygen, with the sample size considered sufficient to provide a certain level of statistical power for the evaluation of all-cause mortality. The results showed decreased all-cause mortality in patients treated with tocilizumab (see Table 7 and Figure 3). The

analysis by concomitant use of corticosteroid[18] at baseline shows that the hazard ratio [95% CI] for all-cause mortality comparing tocilizumab to the standard of care therapy by Day 28 after randomization was 0.79 [0.70, 0.89] among patients receiving corticosteroids and 1.16 [0.91, 1.48] among patients not receiving corticosteroids, with the latter being >1. Table 18 shows the results of all-cause mortality at Day 28 in the RECOVERY study (tocilizumab evaluation cohort) and 3 foreign studies conducted by the applicant (COVACTA, EMPACTA, and REMDACTA studies).

The results of all-cause mortality at Day 28 are not consistent among the 3 foreign studies. Each study had limited number of patients evaluated and thus did not provide adequate statistical power to evaluate the efficacy of tocilizumab based on the data of all-cause mortality. In addition, the types of standard of care therapy varied depending on when the studies were conducted, causing different proportions of patients administered with concomitant corticosteroids and varied disease severity among patients enrolled. These factors may have led the inconsistency in all-cause mortality among the studies.

A meta-analysis of 27 randomized comparative studies was conducted by WHO to estimate the association between all-cause mortality and IL-6 antagonist treatment in hospitalized patients with COVID-19. The overall all-cause mortality odds ratio [95% CI] at Day 28 among patients who received IL-6 antagonist as compared to those who received standard of care therapy or placebo was 0.86 [0.79, 0.95]. The odds ratio [95% CI] was 0.78 [0.69, 0.88] for patients receiving corticosteroids at baseline vs 1.09 [0.91, 1.30] for those not receiving (*JAMA.* 2021;326:499-518). Based on the data for tocilizumab from 19 studies, the overall odds ratio [95% CI] was 0.83 [0.74, 0.92] while the odds ratio [95% CI] was 0.77 [0.68, 0.87] for those receiving corticosteroids at baseline vs 1.06 [0.85, 1.33] for those not receiving, suggesting that tocilizumab, in combination with corticosteroids, may decrease all-cause mortality (*JAMA.* 2021;326:499-518). In the RECOVERY study (tocilizumab evaluation cohort), eligible patients had CRP ≥75 mg/L. In the WHO meta-analysis based on data from 14 studies evaluating tocilizumab, no effects of baseline CRP levels on the odds ratio for all-cause mortality at Day 28 were indicated[19] (*JAMA.* 2021;326:499-518).

[18] Information on concomitant use of corticosteroids was collected from June 18, 2020 onward. Patients who underwent the first randomization before this date and were not allocated to dexamethasone and are assumed not to have received corticosteroids.

[19] The analysis results of 14 studies in which baseline CRP values are available. The odds ratios [95% CI] were 0.848 [0.484, 1.487], 0.769 [0.640, 0.923], and 0.902 [0.756, 1.076] for baseline CRP <75 μg/mL, baseline CRP ≥75 μg/mL and <150 μg/mL, and baseline CRP ≥150 μg/mL, respectively.

Table 18. All-cause mortality by Day 28 in the RECOVERY study (tocilizumab evaluation cohort) and the 3 foreign studies[a)]

| | Overall population | | Patients receiving corticosteroids at baseline[b)] | | Patients not receiving corticosteroids at baseline[b)] | |
|---|---|---|---|---|---|---|
| | Tocilizumab | Control | Tocilizumab | Control | Tocilizumab | Control |
| All categories | | | | | | |
| RECOVERY | 30.7 (621/2,022) | 34.8 (729/2,094) | 29.0 (482/1,664) | 34.9 (600/1,721) | 38.9 (139/357) | 34.6 (127/367) |
| | 0.85 [0.76, 0.94] | | 0.79 [0.70, 0.89] | | 1.16 [0.91, 1.48] | |
| COVACTA | 19.7 (58/294) | 19.4 (28/144) | 24.6 (14/57) | 29.3 (12/41) | 18.6 (44/237) | 15.5 (16/103) |
| | 1.07 [0.68, 1.67] | | 0.91 [0.41, 2.01] | | 1.30 [0.73, 2.31] | |
| EMPACTA | 10.4 (26/249) | 8.6 (11/128) | 12.6 (23/183) | 11.0 (10/91) | 4.5 (3/66) | 2.7 (1/37) |
| | 1.20 [0.61, 2.38] | | 1.10 [0.52, 2.33] | | 1.64 [0.17, 15.85] | |
| REMDACTA | 18.1 (78/430) | 19.5 (41/210) | 19.3 (69/358) | 21.5 (39/181) | 12.5 (9/72) | 6.9 (2/29) |
| | 0.95 [0.65, 1.39] | | 0.89 [0.60, 1.32] | | 1.55 [0.32, 7.39] | |
| Category 3[c), d)] | | | | | | |
| RECOVERY | 19.3 (180/935) | 22.9 (214/933) | 16.4 (126/769) | 22.6 (173/767) | 32.5 (54/166) | 24.8 (41/165) |
| COVACTA | 11.5 (9/78) | 4.5 (2/44) | 9.1 (1/11) | 8.3 (1/12) | 11.9 (8/67) | 3.1 (1/32) |
| EMPACTA | 7.5 (12/161) | 4.9 (4/81) | 9.4 (11/117) | 5.3 (3/57) | 2.3 (1/44) | 4.2 (1/24) |
| REMDACTA | 3.4 (1/29) | 0 (0/13) | 7.1 (1/14) | 0 (0/2) | 0 (0/15) | 0 (0/11) |
| Category 4[c), e)] | | | | | | |
| RECOVERY | 37.9 (310/819) | 42.2 (366/867) | 36.4 (259/711) | 40.9 (300/733) | 47.7 (51/107) | 50.0 (65/130) |
| COVACTA | 19.1 (18/94) | 30.8 (12/39) | 23.5 (4/17) | 40.0 (4/10) | 18.2 (14/77) | 27.6 (8/29) |
| EMPACTA | 21.9 (14/64) | 19.4 (7/36) | 21.4 (12/56) | 24.1 (7/29) | 25.0 (2/8) | 0 (0/7) |
| REMDACTA | 14.6 (49/336) | 19.4 (34/175) | 14.3 (41/286) | 20.1 (32/159) | 16.0 (8/50) | 12.5 (2/16) |
| Category 5[c), f)] | | | | | | |
| RECOVERY | 48.9 (131/268) | 50.7 (149/294) | 52.7 (97/184) | 57.5 (127/221) | 40.5 (34/84) | 29.2 (21/72) |
| COVACTA | 11.4 (5/44) | 20.0 (3/15) | 15.4 (2/13) | 33.3 (1/3) | 9.7 (3/31) | 16.7 (2/12) |
| EMPACTA | — | — | — | — | — | — |
| REMDACTA | 43.6 (17/39) | 22.2 (2/9) | 48.6 (17/35) | 28.6 (2/7) | 0 (0/4) | 0 (0/2) |
| Category 6[c)] | | | | | | |
| RECOVERY | — | — | — | — | — | — |
| COVACTA | 37.7 (26/69) | 25.6 (10/39) | 53.8 (7/13) | 41.7 (5/12) | 33.9 (19/56) | 18.5 (5/27) |
| EMPACTA | — | — | — | — | — | — |
| REMDACTA | 42.3 (11/26) | 38.5 (5/13) | 43.5 (10/23) | 38.5 (5/13) | 33. 3 (1/3) | — |

Data in all categories (upper row) and Categories 3 to 6, all-cause mortality, % (n/N); all categories (lower row), hazard ratio [95% CI] (Peto's method was used in the RECOVERY study. Other studies employed a stratified Cox proportional hazard model with stratification factors specified for each study [only age was used in the EMPACTA study]); "—," not applicable

a) Analyses were performed on the ITT population for the RECOVERY study and on the mITT population for the other studies.

b) The status of corticosteroid use at baseline is not clear for 1 patient in the tocilizumab group and 6 patients in the standard care group in the RECOVERY study.

c) Category 2 consisted of 9 patients in the tocilizumab group and 6 patients in the placebo in the COVACTA study; and 24 patients in the tocilizumab group and 11 patients in the placebo in the EMPACTA study. No all-cause deaths were reported up to Day 28.

d) The RECOVERY study included patients who did not undergo respiratory support other than supplemental oxygen therapy, and 4 patients in the tocilizumab group and 5 patients in the placebo group who did not even undergo supplemental oxygen therapies.

e) The RECOVERY study included patients who were under non-invasive ventilation.

f) The RECOVERY study included patients who underwent mechanical ventilation (including extracorporeal membrane oxygenation [ECMO]) and patients who would be classified as Category 6.

Table 19 shows the results for main efficacy endpoints other than all-cause mortality in the following studies: RECOVERY (tocilizumab evaluation cohort), COVACTA, EMPACTA, and REMDACTA.

Table 19. The results of main efficacy endpoints other than all-cause mortality in the RECOVERY study (tocilizumab evaluation cohort) and the 3 foreign studies[a)]

| | | Overall population | | Patients receiving corticosteroids at baseline[b)] | | Patients not receiving corticosteroids at baseline[b)] | |
|---|---|---|---|---|---|---|---|
| | | Tocilizumab | Control | Tocilizumab | Control | Tocilizumab | Control |
| Time to hospital discharge or ready for discharge through Day 28[c)] | | | | | | | |
| RECOVERY | Patients discharged from hospital, n/N (%) | 1,150/2,022 (56.9) | 1,044/2,094 (49.9) | 987/1,664 (59.3) | 873/1,721 (50.7) | 162/357 (45.4) | 168/367 (45.8) |
| | Median time to discharge [95% CI] (days) | 19 [16, 21] | NE [24, NE] | 16 [14, 18] | 26 [22, NE] | NE [28, NE] | NE [26, NE] |
| | Hazard ratio[d)] | 1.22 [1.12, 1.33] | | 1.27 [1.16, 1.40] | | 0.98 [0.79, 1.22] | |
| COVACTA | Patients discharged or ready for discharge from hospital, n/N (%) | 167/294 (56.8) | 72/144 (50.0) | 25/57 (43.9) | 18/41 (43.9) | 142/237 (59.9) | 54/103 (52.4) |
| | Median time to discharge or ready for discharge [95% CI] (days) | 20.0 [17.0, 27.0] | 28.0 [20.0, NE] | NE [17.0, NE] | NE [19.0, NE] | 19.0 [15.0, 25.0] | 26.0 [18.0, NE] |
| | Hazard ratio[e)] | 1.35 [1.02, 1.79] | | 1.21 [0.65, 2.26] | | 1.35 [0.98, 1.86] | |
| EMPACTA | Patients discharged or ready for discharge from hospital, n/N (%) | 217/249 (87.1) | 106/128 (82.8) | 157/183 (85.8) | 75/91 (82.4) | 60/66 (90.9) | 31/37 (83.8) |
| | Median time to discharge or ready for discharge [95% CI] (days) | 6.0 [6.0, 7.0] | 7.5 [7.0, 9.0] | 6.0 [6.0, 7.0] | 8.0 [6.0, 10.0] | 5.5 [4.0, 8.0] | 7.0 [7.0, 11.0] |
| | Hazard ratio[e)] | 1.16 [0.91, 1.48] | | 1.10 [0.82, 1.48] | | 1.34 [0.84, 2.12] | |
| REMDACTA | Patients discharged or ready for discharge from hospital, n/N (%) | 284/430 (66.0) | 141/210 (67.1) | 234/358 (65.4) | 117/181 (64.6) | 50/72 (69.4) | 24/29 (82.8) |
| | Median time to discharge or ready for discharge [95% CI] (days) | 14.0 [12.0, 15.0] | 14.0 [11.0, 16.0] | 14.0 [12.0, 15.0] | 15.0 [12.0, 19.0] | 12.0 [10.0, 16.0] | 11.0 [10.0, 14.0] |
| | Hazard ratio[e)] | 0.97 [0.78,1.19] | | 1.00 [0.80, 1.26] | | 0.83 [0.49, 1.41] | |
| Proportion of patients who required mechanical ventilation or who died by Day 28[f)] | | | | | | | |
| RECOVERY | Proportion of patients who required mechanical ventilation or died by Day 28, %, (n/N) | 35.3 (619/1,754) | 41.9 (754/1,800) | 33.4 (495/1,480) | 41.1 (617/1,500) | 45.4 (124/273) | 46.1 (136/295) |
| | Risk ratio | 0.84 [0.77, 0.92] | | 0.81 [0.74,0.89] | | 0.99 [0.82,1.18] | |
| COVACTA | Proportion of patients who required mechanical ventilation or died by Day 28, %, (n[g)]/N) | 27.9 (51/183) | 36.7 (33/90) | 31.0 (9/29) | 37.5 (9/24) | 27.3 (42/154) | 36.4 (24/66) |
| | Risk ratio[h)] | 0.76 [0.53, 1.08] | | 0.82 [0.39, 1.75] | | 0.75[0.50, 1.13] | |
| EMPACTA | Proportion of patients who required mechanical ventilation or died by Day 28, %, (n[g)]/N) | 11.6 (29/249) | 18.8 (24/128) | 14.2 (26/183) | 17.6 (16/91) | 4.5 (3/66) | 21.6 (8/37) |
| | Risk ratio[h)] | 0.63 [0.39, 1.02] | | 0.84 [0.49, 1.44] | | 0.21 [0.06, 0.74] | |
| REMDACTA | Proportion of patients who required mechanical ventilation or died by Day 28, %, (n[g)]/N) | 27.5 (102/371) | 29.8 (56/188) | 27.3 (83/304) | 32.3 (52/161) | 28.4 (19/67) | 14.8 (4/27) |
| | Risk ratio[h)] | 0.93[0.71, 1.22] | | 0.85 [0.64, 1.13] | | 1.67 [0.64, 4.35] | |

NE, not estimated
a) The RECOVERY study, ITT population; other studies, mITT population
b) The status of corticosteroid use at baseline is not clear for 1 patient in the tocilizumab group and 6 patients in the standard care group in the RECOVERY study.
c) The RECOVERY study, time to hospital discharge
d) Peto's method
e) A stratified Cox proportional hazard ratio model with stratification factors specified for each study (only age was used in the EMPACTA study)
f) Patients who were not on mechanical ventilation (including ECMO) at randomization were included.
g) Data include patients who discontinued the study by Day 28
h) Analysis by Mantel-Haenszel method with stratification factors specified for each study (only age was used in the EMPACTA)

Based on the results of the RECOVERY study (tocilizumab evaluation cohort), etc., the applicant considers that in combination with corticosteroids, tocilizumab has a certain level of efficacy in the treatment of patients with COVID-19 pneumonia requiring supplemental oxygen. In the US, tocilizumab, in combination with corticosteroids, obtained an Emergency Use Authorization on June 24, 2021. In the EU, tocilizumab was approved on December 7, 2021 for the treatment of patients with COVID-19 pneumonia requiring supplemental oxygen.

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

Remdesivir, dexamethasone (corticosteroid), baricitinib, casirivimab/imdevimab, and sotrovimab are mentioned in Japan in the Japanese treatment guidelines for COVID-19 as approved drugs. However, only limited treatment options are available for patients with COVID-19 pneumonia requiring supplemental oxygen.

To date, no clinical studies have been conducted to evaluate the efficacy and safety of tocilizumab in comparison with standard of care therapy or placebo in Japanese patients with COVID-19 pneumonia. However, the following observations indicates that tocilizumab's clinical benefits for Japanese patients can be evaluated based on the clinical study results in non-Japanese patients:

- There have been no clear differences among countries/regions in the symptoms of COVID-19, risk factors for severe COVID-19, etc ("*Clinical Management of Patients with COVID-19: A guide for front-line healthcare workers*, Version 6.0"; National Institutes of Health, *Coronavirus Disease 2019 (COVID-19) Treatment Guidelines*; National Institute for Health and Care Excellence, *COVID-19 rapid guideline: Managing COVID-19*).
- In countries and regions participating in the 3 foreign studies and in the UK where the RECOVERY study was conducted to evaluate tocilizumab, patients with COVID-19 infection have been treated with supplemental oxygen, mechanical ventilation, or ECMO according to severity, neutralizing antibodies such as casirivimab and imdevimab and other pharmacotherapies including remdesivir and corticosteroids according to severity, as well as prophylaxis of thrombosis and complication management (e.g., "*Clinical Management of Patients with COVID-19: A guide for front-line healthcare workers*, Version 6.0"; National Institutes of Health, *Coronavirus Disease 2019 (COVID-19) Treatment Guidelines*; National Institute for Health and Care Excellence, *COVID-19 rapid guideline: Managing COVID-19*). The therapeutic strategies for COVID-19 infection in Japan thus do not differ significantly from those in other countries.
- The results of clinical studies in Japan and other countries that evaluated the pharmacokinetics of tocilizumab revealed no evident differences in the pharmacokinetics of Japanese patients with COVID-19 pneumonia from that of non-Japanese patients [see Section 6.2.3].
- Safety data of tocilizumab in patients with COVID-19 pneumonia show no new safety concerns in Japanese patients different from those observed in non-Japanese patients [see Section 7.R.2].
- Tocilizumab has been approved in countries/regions including Japan for the treatment of cytokine release syndrome induced by tumor-specific T cell infusion therapy. No evident differences have been suggested in efficacy and safety between Japanese and non-Japanese patients with this pathological condition (Review Report for Actemra [CRS]).

The data including the results from the RECOVERY study (tocilizumab evaluation cohort) have demonstrated that tocilizumab has a certain level of efficacy and were well tolerated in patients with COVID-19 pneumonia. Thus tocilizumab, in combination with corticosteroids, can offer a treatment option for patients with COVID-19 pneumonia requiring supplemental oxygen.

PMDA's view:

The RECOVERY study yielded limited efficacy, safety, and other information as compared to typical clinical studies, leading to limited amount and accuracy of data of individual patients. Nevertheless, its approach is strategically acceptable to some extent for a large-scale randomized study under the pandemic of COVID-19 infection. Although the RECOVERY study was conducted in an unblinded manner, the efficacy was evaluated based on all-cause mortality that is an objective outcome and in a large-scale efficacy analysis set with approximately 4,000 patients (approximately 2,000 patients/group). Thus all-cause mortality results is evaluable to some degree using the data from the study.

Based on the above conclusion and given the limited treatment options currently available for patients with COVID-19 pneumonia requiring supplemental oxygen, the applicant's explanation about the efficacy and clinical positioning of tocilizumab is considered reasonable. Furthermore, in light of the findings on the difference between Japanese and non-Japanese populations in the efficacy and safety of tocilizumab for the treatment of cytokine release syndrome induced by tumor-specific T cell infusion therapy as well as the approval of tocilizumab in EU on the basis of the results from the RECOVERY study, although for different patient population, tocilizumab used in combination with corticosteroids can offer a treatment option for patients with COVID-19 pneumonia requiring supplemental oxygen.

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

### 7.R.2 Safety

#### 7.R.2.1 Safety profile

The applicant's explanation about the safety profile of tocilizumab:

The safety of tocilizumab was evaluated based on the pooled data from the 3 foreign studies and data from the Japanese clinical study in patients with COVID-19 pneumonia. Table 20 summarizes safety data from these clinical studies.

Table 20. Safety summary (safety analysis set)

| | Overall population | | | Patients receiving corticosteroids at baseline | | |
|---|---|---|---|---|---|---|
| | Pooled data from 3 foreign studies | | Japanese clinical study | Pooled data from 3 foreign studies | | Japanese clinical study |
| | Tocilizumab N = 974 | Placebo N = 483 | N = 48 | Tocilizumab N = 597 | Placebo N = 315 | N = 34 |
| All adverse events | 699 (71.8) | 338 (70.0) | 40 (83.3) | 425 (71.2) | 217 (68.9) | 27 (79.4) |
| Grade ≥3 adverse events | 385 (39.5) | 204 (42.2) | 12 (25.0) | 213 (35.7) | 127 (40.3) | 10 (29.4) |
| Adverse events resulting in death | 197 (20.2) | 104 (21.5) | 6 (12.5) | 126 (21.1) | 75 (23.8) | 6 (17.6) |
| Serious adverse events | 295 (30.3) | 165 (34.2) | 6 (12.5) | 175 (29.3) | 108 (34.3) | 6 (17.6) |
| Adverse events leading to study discontinuation[a)] | 2 (0.2) | 0 | 0 | 2 (0.3) | 0 | 0 |
| Adverse drug reactions | 194 (19.9) | 78 (16.1) | 15 (31.3) | 114 (19.1) | 49 (15.6) | 9 (26.5) |

n (%)

a) Except for death

In the overall population of the 3 foreign studies in the pooled data, an adverse event reported with a ≥2.0% higher incidence in the tocilizumab group than in the placebo group was hypertension (3.6% [35 of 974] of patients in the tocilizumab group and 1.4% [7 of 483] of patients in the placebo group). Adverse events leading to death reported with a ≥0.5% higher incidence in the tocilizumab group than in the placebo group were COVID-19 (2.9% [28 of 974] of patients and 2.1% [10 of 483] of patients) and septic shock (1.7% [17 of 974]

of patients and 1.0% [5 of 483] of patients). Serious adverse events reported with a ≥0.5% higher incidence in the tocilizumab group than in the placebo group were COVID-19 (3.0% [29 of 974] of patients and 2.1% [10 of 483] of patients), bacterial sepsis (0.5% [5 of 974] of patients and 0 patients), and retroperitoneal haemorrhage (0.5% [5 of 974] of patients and 0 patients). No Grade ≥3 adverse events were reported with a ≥2.0% higher incidence in the tocilizumab group than in the placebo group.

The data from the tocilizumab group in the overall population of the 3 foreign studies in the pooled data were compared with the Japanese clinical study data. Adverse events reported with a ≥5.0% higher incidence in the Japanese clinical study than in the overall population of the 3 foreign studies in the pooled data were constipation (18.8% [9 of 48] of patients in the Japanese clinical study and 9.0% [88 of 974] of patients in the pooled data from the 3 foreign studies), ALT increased (16.7% [8 of 48] of patients and 2.3% [22 of 974] of patients), fibrin D dimer increased (16.7% [8 of 48] of patients and 1.0% [10 of 974] of patients), hyperuricaemia (16.7% [8 of 48] of patients and 0 patients), AST increased (14.6% [7 of 48] of patients and 1.6% [16 of 974] of patients), liver disorder (10.4% [5 of 48] of patients and 0 patients), hepatic function abnormal (6.3% [3 of 48] of patients and 0.6% [6 of 974] of patients), skin exfoliation (8.3% [4 of 48] of patients and 0 patients), and dermatitis (6.3% [3 of 48] of patients and 0.2% [2 of 974] of patients). The Japanese clinical study reported no Grade ≥3 adverse events, adverse events resulting in death, or serious adverse events occurring in ≥2 patients at a ≥2.0% higher incidence than in the tocilizumab group in the overall population of the 3 foreign studies in the pooled data. Laboratory test result-related events such as ALT increased and fibrin D dimer increased tended to occur more frequently in the Japanese clinical study than in the tocilizumab group in the overall population of the 3 foreign studies in the pooled data, which may be partly attributable to the higher testing frequency in the former group than in the latter group.

Table 21 shows the incidence of events specified as important identified risks associated with the use of tocilizumab in the review process for the previously approved indication[20)] (serious infections, intestinal perforation, serious hypersensitivity such as anaphylaxis, hepatitis B virus reactivated, neutropenia/leukopenia/agranulocytosis, thrombocytopenia, hepatic dysfunction, and interstitial pneumonia).

[20)] Events were defined as follows: infections: Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) "infections and infestations"; intestinal perforation: "gastrointestinal perforation"(standardized MedDRA queries [SMQ] narrow); serious hypersensitivity such as anaphylaxis: "anaphylactic reaction" (SMQ narrow), "hypersensitivity" (preferred term [PT]) and "infusion related reaction" (PT); hepatitis B: PTs "acute hepatitis B," "chronic hepatitis B," "congenital hepatitis B infection," "HBV-DNA polymerase increased," "hepatitis B," "hepatitis B antibody abnormal," "hepatitis B antibody positive," "hepatitis B core antibody positive," "hepatitis B core antigen positive," "hepatitis B DNA assay positive," "hepatitis B DNA increased," "hepatitis B e antibody positive," "hepatitis B e antigen positive," "hepatitis B surface antibody positive," "hepatitis B surface antigen positive," "hepatitis B virus test positive," "perinatal HBV infection," and "hepatitis B reactivation," neutropenia/leukopenia/agranulocytosis: "neutropenias"(high level term [HLT]), "leukopenias NEC" (HLT), "neutrophil count decreased" (PT), "white blood cell count decreased" (PT), and "granulocyte count decreased" (PT); thrombocytopenia: "thrombocytopenias" (HLT) and "platelet count decreased" (PT); hepatic dysfunction: "hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions" (SMQ narrow); "liver related investigations, signs and symptoms" (SMQ narrow), "cholestasis and jaundice of hepatic origin" (SMQ narrow), and "hepatocellular damage and hepatitis NEC" (HLT); interstitial pneumonia: "interstitial lung disease" (SMQ narrow).

Table 21. The incidence of events[a)] listed as important identified risks (safety analysis set)

| | | Overall population | | | Patients receiving corticosteroids at baseline | | |
|---|---|---|---|---|---|---|---|
| | | Pooled data from 3 foreign studies | | Japanese clinical study N = 48 | Pooled data from 3 foreign studies | | Japanese clinical study N = 34 |
| | | Tocilizumab N = 974 | Placebo N = 483 | | Tocilizumab N = 597 | Placebo N = 315 | |
| Serious infections | All adverse events | 181 (18.6) | 110 (22.8) | 4 (8.3) | 108 (18.1) | 72 (22.9) | 4 (11.8) |
| | Adverse events resulting in death | 134 (13.8) | 71 (14.7) | 4 (8.3) | 81 (13.6) | 48 (15.2) | 4 (11.8) |
| | Serious adverse events | 181 (18.6) | 110 (22.8) | 4 (8.3) | 108 (18.1) | 72 (22.9) | 4 (11.8) |
| Intestinal perforation | All adverse events | 5 (0.5) | 3 (0.6) | 0 | 3 (0.5) | 1 (0.3) | 0 |
| | Adverse events resulting in death | 1 (0.1) | 0 | 0 | 1 (0.2) | 0 | 0 |
| | Serious adverse events | 4 (0.4) | 1 (0.2) | 0 | 3 (0.5) | 1 (0.3) | 0 |
| Serious hypersensitivity such as anaphylaxis | All adverse events | 4 (0.4) | 0 | 0 | 3 (0.5) | 0 | 0 |
| | Adverse events resulting in death | 2 (0.2) | 0 | 0 | 2 (0.3) | 0 | 0 |
| | Serious adverse events | 4 (0.4) | 0 | 0 | 3 (0.5) | 0 | 0 |
| Neutropenia/ leukopenia/ agranulocytosis | All adverse events | 20 (2.1) | 2 (0.4) | 2 (4.2) | 7 (1.2) | 1 (0.3) | 1 (2.9) |
| | Adverse events resulting in death | 0 | 0 | 0 | 0 | 0 | 0 |
| | Serious adverse events | 4 (0.4) | 0 | 0 | 0 | 0 | 0 |
| Thrombocytopenia | All adverse events | 29 (3.0) | 6 (1.2) | 3 (6.3) | 17 (2.8) | 3 (1.0) | 2 (5.9) |
| | Adverse events resulting in death | 0 | 0 | 0 | 0 | 0 | 0 |
| | Serious adverse events | 6 (0.6) | 1 (0.2) | 0 | 4 (0.7) | 0 | 0 |
| Hepatic dysfunction | All adverse events | 114 (11.7) | 49 (10.1) | 18 (37.5) | 70 (11.7) | 32 (10.2) | 10 (29.4) |
| | Adverse events resulting in death | 0 | 0 | 0 | 0 | 0 | 0 |
| | Serious adverse events | 12 (1.2) | 8 (1.7) | 0 | 8 (1.3) | 6 (1.9) | 0 |
| Interstitial pneumonia | All adverse events | 10 (1.0) | 1 (0.2) | 0 | 5 (0.8) | 1 (0.3) | 0 |
| | Adverse events resulting in death | 0 | 0 | 0 | 0 | 0 | 0 |
| | Serious adverse events | 4 (0.4) | 1 (0.2) | 0 | 2 (0.3) | 1 (0.3) | 0 |

n (%)

a) No adverse events related to "hepatitis B virus reactivated" were reported. No adverse events led to study discontinuation for any event.

Checking through the occurrence of adverse events reported in the clinical studies, PMDA's review primarily focused on bleeding events. Although bleeding events were not listed as important identified risks associated with the use of tocilizumab in the review process for the previously approved indication, the pooled data from the 3 foreign studies reveals the occurrence of serious bleeding events at a higher incidence in the tocilizumab group than in the placebo group.

### 7.R.2.2 Bleeding events

The applicant's explanation:

Table 22 shows the incidences of bleeding-related events (PTs included in the results of broad search on SMQ "haemorrhages" were gathered).

Table 22. Incidence of bleeding-related events (safety analysis set)

| | Overall population | | | Patients receiving corticosteroids at baseline | | |
|---|---|---|---|---|---|---|
| | Pooled data from 3 foreign studies | | Japanese clinical study | Pooled data from 3 foreign studies | | Japanese clinical study |
| | Tocilizumab N = 974 | Placebo N = 483 | N = 48 | Tocilizumab N = 597 | Placebo N = 315 | N = 34 |
| All adverse events | 120 (12.3) | 50 (10.4) | 9 (18.8) | 72 (12.1) | 36 (11.4) | 5 (14.7) |
| Grade ≥3 adverse events | 47 (4.8) | 25 (5.2) | 0 | 24 (4.0) | 17 (5.4) | 0 |
| Adverse events resulting in death | 10 (1.0) | 4 (0.8) | 0 | 5 (0.8) | 4 (1.3) | 0 |
| Serious adverse events | 28 (2.9) | 15 (3.1) | 0 | 16 (2.7) | 12 (3.8) | 0 |
| Adverse events leading to study discontinuation[a)] | 0 | 0 | 0 | 0 | 0 | 0 |
| Main adverse events[b)] | | | | | | |
| Epistaxis | 16 (1.6) | 12 (2.5) | 0 | 13 (2.2) | 9 (2.9) | 0 |
| Fibrin D dimer increased | 10 (1.0) | 2 (0.4) | 8 (16.7) | 6 (1.0) | 0 | 4 (11.8) |
| Haematuria | 9 (0.9) | 3 (0.6) | 0 | 4 (0.7) | 3 (1.0) | 0 |
| Haematoma | 8 (0.8) | 3 (0.6) | 0 | 4 (0.7) | 3 (1.0) | 0 |
| Melaena | 7 (0.7) | 1 (0.2) | 1 (2.1) | 2 (0.3) | 0 | 1 (2.9) |
| Mouth haemorrhage | 6 (0.6) | 3 (0.6) | 0 | 5 (0.8) | 2 (0.6) | 0 |
| Contusion | 6 (0.6) | 1 (0.2) | 0 | 5 (0.8) | 1 (0.3) | 0 |
| Haemoptysis | 5 (0.5) | 1 (0.2) | 1 (2.1) | 3 (0.5) | 1 (0.3) | 0 |
| Rectal haemorrhage | 5 (0.5) | 1 (0.2) | 0 | 2 (0.3) | 0 | 0 |
| Lower gastrointestinal haemorrhage | 5 (0.5) | 0 | 0 | 1 (0.2) | 0 | 0 |
| Retroperitoneal haemorrhage | 5 (0.5) | 0 | 0 | 4 (0.7) | 0 | 0 |
| Catheter site haemorrhage | 4 (0.4) | 4 (0.8) | 0 | 4 (0.7) | 2 (0.6) | 0 |
| Haematochezia | 4 (0.4) | 1 (0.2) | 0 | 4 (0.7) | 1 (0.3) | 0 |
| Blood loss anaemia | 4 (0.4) | 1 (0.2) | 0 | 4 (0.7) | 1 (0.3) | 0 |
| Coagulopathy | 4 (0.4) | 1 (0.2) | 0 | 2 (0.3) | 1 (0.3) | 0 |
| Ecchymosis | 4 (0.4) | 1 (0.2) | 0 | 2 (0.3) | 1 (0.3) | 0 |
| Shock haemorrhagic | 4 (0.4) | 1 (0.2) | 0 | 2 (0.3) | 1 (0.3) | 0 |
| Gastrointestinal haemorrhage | 3 (0.3) | 6 (1.2) | 0 | 1 (0.2) | 4 (1.3) | 0 |

n (%)
a) Except for death
b) Events that occurred in ≥4 patients in either of the 2 groups of the pooled data from the foreign phase III studies, or in the Japanese clinical study

In the pooled data of the 3 foreign studies, bleeding events resulting in death in the tocilizumab group were retroperitoneal haemorrhage and shock haemorrhagic (3 patients each); haemorrhagic stroke, haemorrhagic transformation stroke, haemorrhage, and coagulopathy (1 patient each), while those in the placebo group were haemorrhagic stroke (2 patients); and haemorrhage intracranial and shock haemorrhagic (1 patient each). A causal relationship to the study drug could not be ruled out for retroperitoneal haemorrhage (1 patient) in the tocilizumab group.

Serious bleeding events shown in the pooled data from the 3 foreign studies were as follows: in the tocilizumab group, retroperitoneal haemorrhage (5 patients); shock haemorrhagic (4 patients); melaena, haematoma, haemorrhagic transformation stroke, and catheter site haemorrhage (2 patients each); lower gastrointestinal haemorrhage, mouth haemorrhage, rectal haemorrhage, arterial haemorrhage, haemorrhage, haemorrhagic stroke, cerebral haemorrhage, blood loss anaemia, coagulopathy, disseminated intravascular coagulation, epistaxis, haemothorax, and post procedural haemorrhage (1 patient each); and in the placebo group, gastrointestinal haemorrhage, haemorrhagic stroke, haemorrhage intracranial, and pharyngeal haemorrhage (2 patients each); melaena, abdominal wall haematoma, mesenteric haematoma, upper gastrointestinal haemorrhage, shock haemorrhagic, haematoma, subarachnoid haemorrhage, blood loss anaemia, and catheter site haemorrhage (1 patient each). A causal relationship to the study drug could not be ruled out for lower gastrointestinal haemorrhage, retroperitoneal haemorrhage, and catheter site haemorrhage (1 patient each) in the tocilizumab group.

Thrombotic complications occur frequently in patients with COVID-19 pneumonia, and antithrombotic treatment is one standard of care therapy recommended for these conditions in treatment guidelines in various countries and regions (e.g., "*Clinical Management of Patients with COVID-19: A guide for front-line healthcare workers*, Version 6.0"). The pooled data from the 3 foreign studies show that antithrombotic drugs[21)] were used in 922 of 974 patients (94.7%) in the tocilizumab group, 459 of 483 patients (95.0%) in the placebo group, and 34 of 48 patients (70.8%) in the Japanese clinical study. All the patients who experienced serious bleeding events in the clinical studies received antithrombotic drugs either before or at the onset of the events. Bleeding events that occurred in the group of patients who were not receiving antithrombotic drugs were bloody stool (1 patient) in the tocilizumab group of the pooled data from the 3 foreign studies, fibrin D dimer increased and haemoptysis (1 patient each) in the Japanese clinical study.

According to the safety database (as of November 12, 2021), bleeding-related events following the administration of tocilizumab to patients with COVID-19 pneumonia were reported in 14 patients in Japan (13 serious events and 13 non-serious event),[22)] and 89 patients in other countries (96 serious events and 8 non-serious events).[23)] No events were found to have any clear association with tocilizumab.

The currently available findings above do not indicate the need for cautionary advice regarding bleeding events associated with tocilizumab treatment.

PMDA accepted the applicant's explanation, and concluded that obvious bleeding-related risks associated with tocilizumab treatment are not suggested at present.

PMDA's view based on the above discussion:
The safety profile for tocilizumab based on the obtained clinical study results does not tend to differ markedly from that for the previously approved indications. In addition, although the limited number of patients evaluated in the Japanese clinical study, etc. preclude a strict comparison between Japanese and non-Japanese populations, the obtained clinical study results have identified no new safety concerns in Japanese patients different from those observed in non-Japanese patients.

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

### 7.R.3 Indications

The applicant's explanation about the indication of tocilizumab:

[21)] Drugs classified as "B01A antithrombotic agents" in the anatomical therapeutic chemical (ATC) classification system.
[22)] Serious events occurring in ≥2 cases were blood fibrinogen decreased, disseminated intravascular coagulation, and fibrin D dimer increased (2 cases each). Non-serious events occurring in ≥2 cases were prothrombin time prolonged (5 cases); activated partial thromboplastin time prolonged and international normalised ratio increased (3 cases each).
[23)] Serious events occurring in ≥2 cases were hypofibrinogenaemia (19 cases); gastrointestinal haemorrhage (8 cases); haemorrhage (7 cases); disseminated intravascular coagulation (5 cases); fibrin D dimer increased and melaena (4 cases each); cerebral haemorrhage, retroperitoneal haemorrhage, and epistaxis (3 cases each); haematoma, haemoglobin decreased, hypocoagulable state, rectal haemorrhage, shock haemorrhagic, haemorrhage intracranial, gastric ulcer haemorrhage, coagulopathy, haemorrhagic stroke, mouth haemorrhage, and haemoptysis (2 cases each). Non-serious events occurring in ≥2 cases were fibrin D dimer increased and post procedural haemorrhage (2 cases each).

Data including the results from the RECOVERY study (tocilizumab evaluation cohort) have demonstrated that tocilizumab has a certain level of efficacy in the treatment of patients with COVID-19 pneumonia requiring supplemental oxygen, and tocilizumab was considered to be well tolerated in these patients. The indication was thus defined as "COVID-19 pneumonia (limited to patients requiring supplemental oxygen)." In addition, to make clear the intended population of tocilizumab therapy, the "Precautions Concerning Indication" section will provide a cautionary statement, i.e., "tocilizumab should be administered to hospitalized patients who require supplemental oxygen, mechanical ventilation management, or introduction of extracorporeal membrane oxygenation (ECMO)."

In view of the submitted data and the reviews presented in Sections 7.R.1 and 7.R.2, PMDA considers that it is appropriate to define the indication and give the cautionary advice in the "Precautions Concerning Indication" section as proposed by the applicant.

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

### 7.R.4 Dosage and administration

The applicant's explanation about the dosage regimen for tocilizumab:

Based on the approved dosage regimen for the treatment of cytokine release syndrome induced by tumor-specific T cell infusion therapy in patients weighing ≥30 kg and on the experience in the use of tocilizumab in China (*Proc Natl Acad Sci USA.* 2020;117:10970-5), the dosage regimen for the 3 foreign studies and 1 Japanese clinical study was determined: tocilizumab 8 mg/kg (maximum dose, 800 mg), given as an intravenous infusion over 1 hour, and 1 additional dose can be given 8 to 24 hours after the initial infusion if clinical signs or symptoms worsen or remain unimproved. This is generally the same as the dosage regimen used in the RECOVERY study (tocilizumab evaluation cohort). The currently available study results have demonstrated that tocilizumab, in combination with corticosteroids, has a certain level of efficacy in the treatment of patients with COVID-19 pneumonia requiring supplemental oxygen, and was well tolerated [see Sections 7.R.1 and 7.R.2]. Therefore, the proposed dosage regimen is "the usual adult dosage is 8 mg/kg of tocilizumab (genetical recombination) given as an intravenous infusion, in combination with corticosteroids. If clinical symptoms do not improve after the first dose, one additional infusion of tocilizumab (genetical recombination) 8 mg/kg may also be administered ≥8 hours after the completion of the initial infusion."

The applicant's explanation about the use of tocilizumab in combination with remdesivir or baricitinib, both of which are approved for the treatment of patients with COVID-19 requiring supplemental oxygen:

In the pooled data from the 3 foreign studies, remdesivir was used in combination in 587 of 974 patients in the tocilizumab group and 297 of 483 patients in the placebo group. In the Japanese clinical study, remdesivir was used in combination in 23 of 48 patients. Table 23 shows the safety summary of tocilizumab used with or without remdesivir. The data shows no particular safety concern associated with the combination use of remdesivir.

Table 23. Safety summary with or without combination use of remdesivir (safety analysis set)

| | With remdesivir | | | Without remdesivir | | |
|---|---|---|---|---|---|---|
| | Pooled data from 3 foreign studies | | Japanese clinical study | Pooled data from 3 foreign studies | | Japanese clinical study |
| | Tocilizumab N = 587 | Placebo N = 297 | N = 23 | Tocilizumab N = 387 | Placebo N = 186 | N = 25 |
| All adverse events | 432 (73.6) | 203 (68.4) | 18 (78.3) | 267 (69.0) | 135 (72.6) | 22 (88.0) |
| Grade ≥3 adverse events | 209 (35.6) | 109 (36.7) | 7 (30.4) | 176 (45.5) | 95 (51.1) | 5 (20.0) |
| Adverse events resulting in death | 125 (21.3) | 61 (20.5) | 3 (13.0) | 72 (18.6) | 43 (23.1) | 3 (12.0) |
| Serious adverse events | 177 (30.2) | 91 (30.6) | 3 (13.0) | 118 (30.5) | 74 (39.8) | 3 (12.0) |
| Adverse events leading to study discontinuation[a)] | 2 (0.3) | 0 | 0 | 0 | 0 | 0 |
| Adverse drug reactions | 132 (22.5) | 50 (16.8) | 9 (39.1) | 62 (16.0) | 28 (15.1) | 6 (24.0) |

n (%)
a) Except for death

The Japanese clinical study and the 3 foreign studies prohibited the concomitant use of baricitinib or other JAK inhibitors with tocilizumab because of their partially overlapping action mechanisms. In the clinical studies conducted in patients with COVID-19 pneumonia, 1 patient[24)] was found to have used tocilizumab with baricitinib. Due to extremely limited experience in the concomitant use of baricitinib, the use of tocilizumab in combination with baricitinib is not recommended.

PMDA's view:
While the applicant's explanation about the dosage regimen is acceptable, and the proposed dosage and administration should be modified as shown below. Given that concomitant use of JAK inhibitors was prohibited in the clinical studies and that data on the concomitant use in patients with COVID-19 pneumonia are extremely limited, the package insert should present a cautionary statement to the effect that the efficacy and safety of tocilizumab in combination with baricitinib have not been established.

**Dosage and administration**
The usual adult dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion, in combination with corticosteroids. If clinical symptoms do not improve after the first dose, one additional infusion of Tocilizumab (Genetical Recombination) 8 mg/kg may be administered ≥8 hours after the completion of the initial infusion.

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

### 7.R.5 Post-marketing investigations

The applicant's explanation:
The safety profile of tocilizumab was compared with that for its approved indications. The results indicated no new events that warrant caution in the use of tocilizumab in patients with COVID-19 pneumonia. Thus no new safety specifications have been identified for the partial change application. Given a substantial amount of safety data of tocilizumab available from Japanese patients treated for the previously approved indications, it

[24)] Data from the REMDACTA study confirmed that baricitinib was coadministered with tocilizumab in 1 patient in the tocilizumab group. This patient, a woman aged 73 years, received baricitinib 4 mg once daily for 4 days, from 2 days prior to the treatment with tocilizumab. The patient died of septic shock at 8 days after the start of tocilizumab treatment. A causal relationship to tocilizumab was ruled out.

is not necessary at this time to implement another post-marketing surveillance targeting patients with COVID-19 pneumonia.

PMDA accepted the applicant's explanation.

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

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

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

The inspections are ongoing. The results and PMDA's conclusion will be reported in the Review Report (2).

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

The inspections are ongoing. The results and PMDA's conclusion will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that tocilizumab, in combination with corticosteroids, has efficacy in the treatment of COVID-19 pneumonia requiring supplemental oxygen, and that tocilizumab has acceptable safety in view of its benefits. Tocilizumab is clinically meaningful because it offers a new treatment option for patients with COVID-19 pneumonia requiring supplemental oxygen.

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.

**Review Report (2)**

January 7, 2022

**Product Submitted for Approval**

| | |
|---|---|
| Brand Name | Actemra 80 mg for Intravenous Infusion<br>Actemra 200 mg for Intravenous Infusion<br>Actemra 400 mg for Intravenous Infusion |
| Non-proprietary Name | Tocilizumab (Genetical Recombination) |
| Applicant | Chugai Pharmaceutical Co., Ltd. |
| Date of Application | December 13, 2021 |

**List of Abbreviations**

See Appendix.

## 1. Content of the Review

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

### 1.1 Efficacy, safety, clinical positioning, indication, and dosage and administration

At the Expert Discussion, the expert advisors supported the PMDA's conclusions on the efficacy, safety, clinical positioning, indication, and dosage and administration of tocilizumab presented in Review Report (1), and also made the following comments:

- The following information should be provided: In the RECOVERY study (tocilizumab evaluation cohort), patients with COVID-19 pneumonia with elevated CRP levels were enrolled; tocilizumab was found to have efficacy in combination with corticosteroids; and among patients who had not received corticosteroids, all-cause mortality in those who were treated with tocilizumab tended to be higher than those who were not.
- Given no evidence of significant decrease in all-cause mortality in patients treated with tocilizumab in the 3 foreign studies and the likely insignificant effect of tocilizumab on all-cause mortality indicated in the meta-analysis (*Lancet.* 2021;397:1637-45) of clinical studies including the RECOVERY study (tocilizumab evaluation cohort), the contribution of tocilizumab alone to patients' survival is not considered very promising.

Based on the discussion at the Expert Discussion, PMDA has concluded that the "Indication," "Precautions Concerning Indication," "Dosage and Administration," and "Precautions Concerning Dosage and Administration" should be described as follows:

**Indication**

Pneumonia caused by SARS-CoV-2 infection (COVID-19) (limited to patients requiring supplemental oxygen)

**Precautions Concerning Indication**

- Tocilizumab should be administered to hospitalized patients who require supplemental oxygen, mechanical ventilation management, or introduction of extracorporeal membrane oxygenation (ECMO).
- The investigator-initiated foreign clinical study was conducted in patients with pneumonia caused by SARS-CoV-2 infection (COVID-19) who had blood oxygen saturation ($SpO_2$) of <92% on room air or were on supplemental oxygen and had a CRP of ≥7.5 mg/dL. The results demonstrated the efficacy of tocilizumab in combination with corticosteroids. Eligible patients for tocilizumab treatment should be selected with a thorough understanding of the efficacy and safety of tocilizumab based on the adequate knowledge from the study.

**Dosage and Administration**

The usual adult dosage is 8 mg/kg of tocilizumab (genetical recombination) given as an intravenous infusion, in combination with corticosteroids. If clinical symptoms do not improve after the first dose, one additional infusion of tocilizumab (genetical recombination) 8 mg/kg may be administered at least 8 hours after the completion of the initial infusion.

**Precautions Concerning Dosage and Administration**

- In the investigator-initiated foreign clinical study, all-cause mortality tended to be higher in tocilizumab-treated patients among those who had not received corticosteroids in combination.
- The efficacy and safety of tocilizumab used in combination with baricitinib have not been established.

### 1.2 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported the PMDA's conclusions on the post-marketing investigations presented in the Review Report (1), and also made the following comments:

- Tocilizumab has already been widely used in clinical practice for the treatment of COVID-19 pneumonia, and therefore gathering information through post-marketing surveillance may have little significance.

In view of the above discussion, PMDA has concluded that the risk management plan (draft) for tocilizumab should include the safety specification presented in Table 24, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 25.

Table 24. Safety and efficacy specifications in the risk management plan (draft)

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| • Serious infections<br>• Intestinal perforation<br>• Serious hypersensitivity such as anaphylaxis (including administration reactions)<br>• Neutropenia/leukopenia/agranulocytosis<br>• Thrombocytopenia<br>• Interstitial pneumonia<br>• Hepatitis B virus reactivated<br>• Hepatic dysfunction | • Malignant tumor<br>• Demyelinating disease<br>• Immunogenicity<br>• Cardiac disorder/cardiac failure<br>• Pleurisy | None |
| Efficacy specification | | |
| • The efficacy of Actemra subcutaneous injection in patients with Takayasu's arteritis or giant cell arteritis in clinical practice<br>• The efficacy of Actemra intravenous infusion in patients with cytokine release syndrome | | |

(No change)

Table 25. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

| Additional pharmacovigilance activities | Efficacy survey and studies | Additional risk minimization activities |
|---|---|---|
| • Early post-marketing phase vigilance (COVID-19 pneumonia)<br>• Specified use-results survey (long-term) in patients with Takayasu's arteritis or giant cell arteritis | • Specified use-results survey (long-term) in patients with Takayasu's arteritis or giant cell arteritis<br>• Post-marketing database survey in patients who developed cytokine release syndrome | • Disseminate data gathered during early post-marketing phase vigilance (COVID-19 pneumonia)<br>• Ensure that information on proper use is provided before delivery<br>• Prepare and disseminate written information for healthcare professionals (Takayasu's arteritis and giant cell arteritis)<br>• Prepare and disseminate written information for patients (Takayasu's arteritis and giant cell arteritis)<br>• Disseminate information on self-administration (subcutaneous injection formulation) |

(Underline denotes additions for the present application.)

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

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

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

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

The new drug application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

## 3. Overall evaluation

As a result of the above review, PMDA has concluded that the product may be approved with the indications and the dosage and administration shown below, with the following approval condition. The re-examination

period for the present application should be the remainder of ongoing re-examination period for cytokine release syndrome induced by tumor-specific T cell infusion therapy (until March 25, 2023).

**Indications**

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

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

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

○Pneumonia caused by SARS-CoV-2 infection (COVID-19) (limited to patients requiring supplemental oxygen)

(No change is made to the proposed text)

**Dosage and Administration**

○Rheumatoid arthritis, polyarticular-course juvenile idiopathic arthritis

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

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

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

○Cytokine release syndrome

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

○Pneumonia caused by SARS-CoV-2 infection (COVID-19)

The usual adult dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion, in combination with corticosteroids. If clinical symptoms do not improve after the first dose, one additional infusion of Tocilizumab (Genetical Recombination) 8 mg/kg may ~~also~~ be administered at least 8 hours after the completion of the initial infusion.

(The strikethrough word is deleted from the proposed text.)

**Approval Condition**

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

**Appendix**

**List of Abbreviations**

| | |
|---|---|
| Actemra | Actemra 80 mg for Intravenous Infusion, Actemra 200 mg for Intravenous Infusion, Actemra 400 mg for Intravenous Infusion |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| ATC | Anatomical therapeutic chemical |
| Casirivimab/ imdevimab | Casirivimab (Genetical Recombination) and Imdevimab (Genetical Recombination) |
| CI | Confidence interval |
| CRP | C-reactive protein |
| ECMO | extracorporeal membrane oxygenation |
| $FiO_2$ | fraction of inspiratory oxygen |
| HLT | high level term |
| ICU | intensive care unit |
| IL-6 | interleukin-6 |
| ITT | intent-to-treat |
| JAK | Janus kinase |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MERS-CoV | Middle East respiratory syndrome coronavirus |
| mITT | modified intent-to-treatment |
| $PaO_2$ | partial pressure of oxygen |
| PCR | polymerase chain reaction |
| PK | pharmacokinetics |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PT | preferred terms |
| Review Report for Actemra (CRS) | Review Report for Actemra 80 mg for Intravenous Infusion, Actemra 200 mg for Intravenous Infusion, Actemra 400 mg for Intravenous Infusion, dated February 6, 2019 |
| SARS-CoV | severe acute respiratory syndrome coronavirus |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| sIL-6R | soluble interleukin-6 receptor |
| SMQ | standardized MedDRA queries |
| SOC | system organ class |
| $SpO_2$ | blood oxygen saturation |
| Tocilizumab | Tocilizumab (Genetical Recombination) |
| Treatment guidelines for COVID-19 | Guidelines Development Committee, *Clinical Management of Patients with COVID-19: A guide for front-line healthcare workers,* Version 6.0 [in Japanese] |
| WHO | World Health Organization |
| 3 foreign studies | The COVACTA, EMPACTA, and REMDACTA studies, which were conducted by the applicant |