Report on the Deliberation Results

April 21, 2021

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	Olumiant Tablets 2 mg
	Olumiant Tablets 4 mg
Non-proprietary Name	Baricitinib (JAN*)
Applicant	Eli Lilly Japan K.K.
Date of Application	December 25, 2020

Results of Deliberation

In its meeting held on April 21, 2021, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period for the present partial change application represents the remainder of the ongoing re-examination period for the initial approval (until July 2, 2025).

Approval Conditions

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

**Japanese Accepted Name (modified INN)*

Review Report

April 12, 2021
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	Olumiant Tablets 2 mg Olumiant Tablets 4 mg
Non-proprietary Name	Baricitinib
Applicant	Eli Lilly Japan K.K.
Date of Application	December 25, 2020
Dosage Form/Strength	Each tablet contains 2 or 4 mg of baricitinib.
Application Classification	Prescription drug, (4) Drug with a new indication and (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 remdesivir, 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. However, the safety and other

aspects of the product in clinical practice should be further evaluated through post-marketing surveillance, etc.

Indications

The following diseases in patients who have had an inadequate response to conventional treatments:

Rheumatoid arthritis (including the prevention of structural joint damage)

Atopic dermatitis

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

(Underline denotes additions. Double underline denotes additions made on December 25, 2020.)

Dosage and Administration

Rheumatoid arthritis, atopic dermatitis

The usual adult dosage is 4 mg of baricitinib administered orally once daily. The dose should be reduced to 2 mg according to the patient's condition.

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

The usual adult dosage is 4 mg of baricitinib administered orally once daily, in combination with remdesivir. The total duration of baricitinib therapy should be ≤14 days.

(Underline denotes additions.)

Approval Conditions

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

Attachment

Review Report (1)

March 9, 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.

Product Submitted for Approval	
Brand Name	Olumiant Tablets 2 mg Olumiant Tablets 4 mg
Non-proprietary Name	Baricitinib
Applicant	Eli Lilly Japan K.K.
Date of Application	December 25, 2020
Dosage Form/Strength	Each tablet contains 2 or 4 mg of baricitinib.
Proposed Indications	Rheumatoid arthritis in patients who have had an inadequate response to conventional treatments (including the prevention of structural joint damage) Disease caused by SARS-CoV-2 infection (COVID-19) (Underline denotes additions.)
Proposed Dosage and Administration	Rheumatoid arthritis The usual adult dosage is 4 mg of baricitinib administered orally once daily. The dose should be reduced to 2 mg according to the patient's condition. Disease caused by SARS-CoV-2 infection (COVID-19) The usual dosage for adult patients and pediatric patients ≥9 years of age is 4 mg of baricitinib administered orally once daily, in combination with remdesivir. The usual dosage for pediatric patients ≥2 years to <9 years of age is 2 mg of baricitinib administered orally once daily, in combination with remdesivir. Baricitinib therapy may continue for ≤14 days or until hospital discharge, whichever occurs first. (Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

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

Baricitinib, the active ingredient of Olumiant Tablets 2 mg and Olumiant Tablets 4 mg, is a Janus kinase (JAK) inhibitor developed by Incyte Corporation in the US. In Japan, baricitinib was approved for "the treatment of rheumatoid arthritis in patients who have had an inadequate response to conventional treatments (including the prevention of structural joint damage)" in July 2017. In December 2020, "the treatment of atopic dermatitis" was added to the indication.

Coronavirus disease 2019 is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19). 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)] based on 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)] based on the Quarantine Act. In Japan, as of February 16, 2021, a total of 415,565 people have been infected with SARS-CoV-2, among whom 7013 have died.[4)] A wide range of symptoms such as pyrexia, cough, malaise, dyspnoea, taste disorder, and smell disorder are reported in many patients with COVID-19. Approximately 20% of patients experience the progression of their symptoms to severe pneumonia. Some patients suffer from respiratory failure due to severe inflammatory conditions characterized by the increased production of multiple cytokines. Increases in interleukin (IL)-6 and other cytokines have been reported to be prognostic factors of death in patients with COVID-19 (*JAMA.* 2020;324:782-93, *Intensive care Med.* 2020;46:846-8, *Lancet.* 2020;395:1054-62).

Baricitinib inhibits the JAK-STAT (signal transducer and activator of transcription) signaling pathway, which is involved in the signaling of pro-inflammatory cytokines such as IL-6. With the expectation that this drug might exhibit clinical benefits in the treatment of COVID-19, the US National Institute of Allergy and Infectious Disease (NIAID) started an investigator-initiated global clinical trial (the Adoptive COVID-2 Treatment Trial [ACTT-2]) in May 2020 in multiple countries including Japan. The ACTT-2 study was a randomized, double-blind, placebo-controlled, parallel-group study that was conducted in patients with COVID-19 aged ≥18 years to evaluate the efficacy and safety of baricitinib in combination with remdesivir. With the results of the ACTT-2 study serving as pivotal data, Eli Lilly Japan K.K. has recently filed a partial change application for baricitinib, to extend its indications to include "the treatment of COVID-19."

As of February 2021, baricitinib has not been approved for the treatment of COVID-19 in any country or region; however, it was granted an Emergency Use Authorization on November 19, 2020 in the US.

---

1) Limited to the disease caused by the novel coronavirus identified as a member of the genus Betacoronaviru (the coronavirus which was reported as transmissible to humans to the 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 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/newpage_16856.html (last accessed on February 16, 2021)

The applicant is conducting a global clinical study in patients with COVID-19 aged ≥18 years to evaluate the efficacy and safety of baricitinib (the KHAA study[5)]), and is planning a clinical study of baricitinib in patients with COVID-19 aged <18 years.

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

Although the present application is intended for the addition of a new indication and a new dosage, results from a study evaluating the stability and other properties of baricitinib dispersed in water have been submitted. The details are described in Section 7.R.5.

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

Although the present application is intended for the addition of a new indication and a new dosage, no new data on non-clinical pharmacology have been submitted. The non-clinical pharmacology of baricitinib was evaluated during the review of the initial application.

3.R Outline of the review conducted by PMDA

3.R.1 Inhibitory effects of baricitinib on the Numb-associated kinases (NAKs)

The applicant's explanation:

In addition to showing anti-inflammatory activity through the blockade of the JAK-STAT pathway, baricitinib inhibits NAK family members that promote the endocytosis of SARS-CoV-2, according to the following reports:

- A kinase assay was performed to determine the affinities of baricitinib for NAKs (AP2-associated protein kinase [AAK1], BMP2-inducible kinase [BIKE], cyclin G-associated kinase [GAK], and serine/threonine kinase 16 [STK16]). The equilibrium dissociation constant (K_d) values of baricitinib for AAK1, BIKE, GAK, and STK16 were 8.2, 20, 120, and 1100 nmol/L, respectively (*EMBO Mol Med.* 2020;12:e12697).
- When SARS-CoV-2 was incubated with IFN-α2 in organotypic 3D cultures of primary human liver cells, IFN-α2 increased the expression of angiotensin-converting enzyme 2 (ACE2), a SARS-CoV-2 receptor, and SARS-CoV-2 nucleocapsid protein. The expression of these proteins was inhibited by baricitinib (100 nmol/L) (*Sci Adv.* 2021;7:eabe4724).

Based on the above reports, the applicant provided the following explanation about the effects of baricitinib on COVID-19 through the inhibition of NAKs:

SARS-CoV-2 is thought to enter into host cells for viral replication through NAKs-dependent, ACE2 receptor-mediated endocytosis (*Eur J Pharmacol.* 2021;891:173748, *Lancet.* 2020;395:e30-1, *Int Immunopharmacol.* 2020;86:106749, etc). In addition, in view of the fact that the 50% inhibitory concentration (IC_{50}) values of baricitinib against JAK1 and JAK2 (5.9 and 5.7 nmol/L, respectively ["Review Report for Olumiant Tablets 2 mg and Olumiant Tablets 4 mg, dated on May 19, 2017"] are similar to the K_d values for AAK1, etc., baricitinib may suppress the replication of SARS-CoV-2 by reducing viral cell-to-cell movement in hosts through the inhibition of NAKs. However, the results of the ACTT-2 study does not serve to evaluate the

[5)] The KHAA study does not require the use of concomitant remdesivir.

inhibitory effect of baricitinib on the JAK-STAT pathway separately from its inhibitory effect on NAKs. Further, concomitant remdesivir was used in the ACTT-2 study. These issues precluded a precise evaluation of the inhibitory effect of baricitinib on viral replication.

PMDA's view:

Baricitinib may be effective in the treatment of COVID-19 because it inhibits not only the JAK-STAT pathway but also NAKs. However, the inhibitory effect of baricitinib on NAKs has only been investigated in *in vitro* studies. In view of this and other facts, the action mechanisms of baricitinib by which the JAK-STAT pathway and NAKs are inhibited, including the extent of the contribution of each inhibitory activity to the efficacy of baricitinib in the treatment of COVID-19, remains unclear.

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

Although the present application is intended for the addition of a new indication and a new dosage, no new data on non-clinical pharmacokinetics have been submitted. The non-clinical pharmacokinetics of baricitinib were evaluated during the review of the initial application.

5. Toxicity and Outline of the Review Conducted by PMDA

Although the present application is intended for the addition of a new indication and a new dosage, results from a toxicity study in juvenile rats have been submitted.

5.1 Study in juvenile rats

A repeated oral dose toxicity study was conducted in juvenile rats (Table 1). The common toxicological or abnormal findings include immunosuppression, decreased erythrocyte parameters, and renal tubular/pelvis dilatation. Effects on bone tissues were toxicological findings newly identified in juvenile rats, but were not observed in adult rats receiving repeated doses of baricitinib. Abnormal test results and findings related to immune system cells were considered to be changes associated with JAK inhibition by baricitinib. A male rat in the 25 mg/kg group had a suspected fracture in the right hindlimb, and was thus euthanized on Postnatal Day (PND) 20. The rat was found to have a secondary femur fracture attributable to neutrophil inflammation associated with bacterial infection. The no-observed adverse effect level (NOAEL) in rats receiving repeated doses of baricitinib from PND 10 to PND 90 was 1 mg/kg/day (for both male and female rats). The $AUC_{0\text{-}24}$ values (PND 90) in male and female rats at the NOAEL were 286 ng·h/mL and 267 ng·h/mL, respectively, both of which were approximately 0.8-fold the estimated blood exposure (geometric mean AUC_{tau} = 380.2 ng·h/mL[6)]) in children treated with baricitinib.

[6)] The AUC of baricitinib administered at a dose of 4 mg once daily was 380.2 ng•h/mL in a phase III clinical study in adult patients with atopic dermatitis. The dose for children was selected to achieve an AUC value comparable to that observed in adults receiving baricitinib 4 mg once daily. The AUC of baricitinib in patients with atopic dermatitis was assumed to be similar to that in patients with COVID-19.

Table 1. Summary of the results of a repeated oral dose toxicity study in juvenile rats

Test system	Route of administration	Treatment duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg/day)	Submitted data CTD
Male and female juvenile rats (Sprague -Dawley)	Oral gavage	PND 10 to PND 90 (once-daily dosing)	0[a], 1, 5, 25	**Death** 25 mg/kg: 1 male; swelling of the right hindlimb, fracture of the right distal tibia, joint enlargement and neutrophilic inflammation with bacteria in the right tibia (fracture site), bone loss and production and neutrophilic inflammation with bacteria in the left distal femur, and curvature of the ulna and radius **Systemic toxicity (surviving animals)** ≥1 mg/kg: Decreased body weight, body weight gain, and food consumption,[b] decreased leucocytes, lymphocytes, and T-lymphocytes in blood, decreased relative spleen weight, and inflammation/hyperplasia in the cecum (males and females); and, decreased basophil, helper T-cell, and tissue-toxic T-cell counts in blood, and decreased lymphocyte, helper T-cell, and B-cell counts in the spleen (females) ≥5 mg/kg: Decreased B-cell count in blood, decreased T-cell and tissue-toxic T-cell counts in the spleen, decreased anti-KLH-IgG antibody production, decreased relative thymus and adrenal gland weights, decreased myelopoietic cell count, decreased lymphoid follicle counts in splenic lymph nodes, and renal tubular dilatation (males and females); decreased basophil, helper T-cell, and tissue-toxic T-cell counts in blood, decreased lymphocyte, helper T-cell, B-cell, and NK cell counts in the spleen, decreased lymphoid follicle count in the thymus, and colon dilatation (males); and, decreased NK cell count in blood, increased ratio of helper T-cells to tissue-toxic T-cells in blood, decreased anti-KLH-IgM antibody production, small spleen, and renal pelvis dilatation (females) 25 mg/kg: Decreased hemoglobin, increased blood urea, increased ratio of helper T-cells to tissue-toxic T-cells in the spleen, decreased lymphocyte, T-cell, helper T-cell, tissue-toxic T-cell, CD3+CD4+CD8a+ cell, and CD3-CD4+CD8a+ cell counts in the thymus, and decreased lymphoid follicle counts in the submaxillary and mesenteric lymph nodes (males and females); increased glucose and inorganic phosphate in blood, decreased NK-cell count in blood, increased ratio of helper T-cells to tissue-toxic T-cells in blood, decreased anti-KLH-IgM antibody production, small spleen, and renal pelvis dilatation (males); and, decreased eosinophil and erythrocyte counts, and decreased hematocrit in blood, decreased B-cell and NK-cell counts in the spleen, decreased lymphoid follicle count in the thymus, and colon dilatation (females)	1	4.2.3.5.4.2
				Bone tissue effects (surviving animals) PND 30 ≥5 mg/kg: Bone production of the humerus and tibia (females) 25 mg/kg: Bone loss in the femur (males and females), bone production of the humerus and tibia, and curvature of the tibia (males); cortical irregularity and increased cortical thickness of the tibia (females) PND 42 25 mg/kg: Bone loss in the femur, bone production of the humerus and tibia (males and females); curvature of the tibia (males) PND 65 ≥5 mg/kg: Bone production of the humerus and tibia (males and females); curvature of the tibia (males) 25 mg/kg: Morphological defect of the acetabulum, bone loss in the femur, and increased cortical thickness in the tibia (males and females); curvature and cortical irregularity of the tibia (males)		

Table 1. Summary of the results of a repeated oral dose toxicity study in juvenile rats (continued)

Test system	Route of administration	Treatment duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg/day)	Submitted data CTD
Male and female juvenile rats (Sprague-Dawley)	Oral gavage	PND 10 to PND 90 (once-daily dosing)	0[a)], 1, 5, 25	PND 91 ≥1 mg/kg: Increased woven bone of the tibia (males and females); decreased bone area, cortical bone mineral content (BMC), and cortical bone mineral density (BMD) of the diaphysis site of the femur, and decreased total vertebral area (males); and, bone production of the tibia (females) ≥5 mg/kg: Decreased length of the femur, decreased BMC of the vertebral trabecular bones, cartilage loss in the proximal femur and proximal humerus, and bone production of the humeral trabecular bone (males and females); decreased thickness, total metaphyseal area, and trabecular area of the femur, decreased total diaphyseal area and cortical thickness of the femur, decreased diaphyseal periosteum, endosteal perimeter, and moment of inertia of the femur, decreased length and thickness of the tibia, decreased total area and BMC of the vertebrae, and joint degeneration in the proximal femur (males); and, bone production of the humerus (females) 25 mg/kg: Decreased cortex/subcortical BMD of the metaphysis site of the femur, morphological defect of the acetabulum, bone loss in the femur, increased cortical thickness of the tibia, degeneration/atrophy of the proximal femur, and increased woven bone of the humerus (males and females); decreased total BMC and BMD, and decreased trabecular BMC and BMD of the metaphysis site of the femur, bone production of the humerus and tibia, abnormal shape of the humerus, and curvature of the tibia (males); and, decreased thickness of the femur, decreased diaphyseal total area, cortical area, BMC, BMD, and cortical thickness of the femur, decreased diaphyseal endosteal, perimeter, and moment of inertia of the diaphysis site of the femur, decreased length and thickness of the tibia, decreased BMC of the vertebrae, cortical irregularity of the tibia, joint degeneration in the proximal femur, and increased cortical thickness of the tibia (females)	1	4.2.3.5.4.2

a) 0.5% Methylcellulose solution
b) The findings in the 1 mg/kg group were considered to be of little toxicological significance, because these were transient changes, which were associated with no relevant abnormalities or toxicological findings.

5.R Outline of the review conducted by PMDA

5.R.1 Effects on the immune system

PMDA's view:

JAK inhibition-related effects on lymphoid cells observed in juvenile rats receiving repeated doses of baricitinib are similar to the profile observed in adult animals chronically treated with baricitinib. Given that the duration of treatment with baricitinib in patients with COVID-19 is as short as ≤14 days, and that the changes in animals were reversible after the completion of treatment, the immunosuppressive effects of baricitinib in patients with COVID-19 are limited and are unlikely to pose any concern to pediatric patients. However, to allow the long-term use of baricitinib in children, the tolerability of baricitinib in terms of the lymphocytic effects should be evaluated based on data regarding the immunosuppressive effects of baricitinib assessed in long-term pediatric clinical studies.

5.R.2 Effects on the kidney

The applicant's explanation:

The dilatation of the renal tubules and pelvis observed in juvenile rats receiving repeated doses of baricitinib was unlikely to be harmful, because these findings were associated with no abnormalities in tubular epithelial cells or changes in laboratory test results that were suggestive of abnormal renal function, and they were reversible.

PMDA accepted the applicant's explanation.

5.R.3 Effects on bone

The applicant's explanation:

Bone effects were observed in juvenile rats receiving repeated doses of baricitinib, but were not noted in adult animals. The bone effects are unlikely to pose any safety concern about the use of baricitinib in pediatric patients with COVID-19, for the following reasons:

- The dose that caused baricitinib-related toxic bone changes was considered to be 25 mg/kg, and the exposure at 25 mg/kg ($AUC_{0\text{-}24}$ on PND 10 was 25,400 ng·h/mL in males and 22,200 ng·h/mL in females; $AUC_{0\text{-}24}$ on PND 90 was 8420 ng·h/mL in males and 9850 ng·h/mL in females) was 24- to 62-fold the estimated exposure in children treated with baricitinib (AUC_{tau}, 380.2 ng·h/mL[6)]).
- Baricitinib was administered as repeated doses for up to 9 months to young dogs with open growth plates, which are thought to have bones that physiologically and anatomically resemble human bones (*Endocrinology.* 1998;139:663-70, *Vet Pathol.* 2015;52:842-50). Results showed that baricitinib caused no abnormalities in the femur head, suggesting that baricitinib has no effects on actively growing bone tissues.
- The marked bone effects were seen in juvenile animals receiving repeated doses of baricitinib for 80 days. In view of the fact that the duration of baricitinib therapy in patients with COVID-19 will be as short as ≤14 days, and the fact that the bone remodeling period in humans is 10 to 60 days (*Bone.* 2000;26:103-9), baricitinib is unlikely to adversely affect bone growth in childhood.

PMDA's view:

Peficitinib, an inhibitor of JAK1, JAK2, and JAK3, caused necrotic changes in the femoral metaphysis in a repeated-dose toxicity study in rats ["Review Report for Smyraf Tablets 50 mg and Smyraf Tablets 100 mg, dated May 31, 2019"]. Further, all of the oral JAK inhibitors approved in Japan have been shown to cause fetal skeletal abnormalities ["Review Report for Xeljanz Tablets 5 mg, dated February 28, 2013," "Review Report for Olumiant Tablets 2 mg and Olumiant Tablets 4 mg, dated May 19, 2017," "Review Report for Smyraf Tablets 50 mg and Smayraf Tablets 100 mg, dated May 31, 2019," "Review Report for Rinvoq Tablets 7.5 mg and Rinvoq Tablets 15 mg, dated November 14, 2019," and "Review Report for Jyseleca Tablets 100 mg and Jyseleca Tablets 200 mg, dated August 26, 2020"]. The systemic inhibition of the JAK-STAT signaling pathway may thus affect bone development or growth in rodents. In contrast, the bone effects of baricitinib observed in rats are unlikely to be relevant to humans, because baricitinib has been shown to have no effects on bone tissues in young dogs with open growth plates, which have bones physiologically and anatomically resembling human bones. The short duration of baricitinib therapy for COVID-19 is another reason to conclude that the bone effects of baricitinib are limited and unlikely to pose any safety concern to pediatric patients with COVID-19. However, no definite conclusion has been drawn regarding whether the bone effects observed in rats receiving long-term treatment with baricitinib is relevant to humans. Therefore, long-term systemic treatment with JAK-STAT signaling inhibitors, including baricitinib, in children with active bone growth should call for safety considerations.

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

Although the present application is intended for the addition of a new indication and new dosage, no new data on biopharmaceutic studies or associated analytical methods have been submitted. The biopharmaceutic studies and associated analytical methods for baricitinib were evaluated during the review of the initial application.

6.2 Clinical pharmacology

Although the present application is intended for the addition of a new indication and new dosage, no new data on the clinical pharmacology of baricitinib have been submitted. The clinical pharmacology of baricitinib were evaluated during the review of the initial application.

6.R Outline of the review conducted by PMDA

6.R.1 Pharmacokinetic interactions between baricitinib and remdesivir

In the ACTT-2 study, patients with COVID-19 were to receive baricitinib in combination with remdesivir. The applicant's explanation about the potential for pharmacokinetic interactions between baricitinib and remdesivir is shown below.

Effects of remdesivir on the pharmacokinetics of baricitinib

The available *in vitro* study results have shown that baricitinib is a substrate of cytochrome P450 (CYP) 3A4, organic anion transporter (OAT) 3, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug and toxin extrusion (MATE2)-K. These results, along with the results of a mass balance study and drug interaction studies, suggest that the co-administration of baricitinib and a potent OAT3 inhibitor (e.g., probenecid) increases exposure to baricitinib, thus having clinically significant effects on the pharmacokinetics of baricitinib. It is therefore recommended that the dose of baricitinib be reduced by half, when a potent OAT3 inhibitor is coadministered with baricitinib ["Review Report for Olumiant Tablets 2 mg and Olumiant Tablets 4 mg, dated May 19, 2017"].

According to the available product information for remdesivir (from the labels for Veklury for Intravenous Injection in Japan and the US), remdesivir has no inhibitory effect on OAT3, indicating that remdesivir is unlikely to affect the pharmacokinetics of baricitinib.

Effects of baricitinib on the pharmacokinetics of remdesivir

According to the available product information for remdesivir (from the labels for Veklury for Intravenous Injection in Japan and the US), remdesivir is a substrate of CYP2C8, CYP2D6, CYP3A4, OATP1B1, and P-gp, and GS-704277, a metabolite of remdesivir, is a substrate of OATP1B1 and OATP1B3.

Given the results of *in vitro* studies and the exposure to baricitinib administered at the recommended clinical dose, baricitinib is unlikely to have substantial effects on the pharmacokinetics of drugs that are substrates of

CYP2C8, CYP2D6, CYP3A4, OATP1B1, OATP1B3, or P-gp ["Review Report for Olumiant Tablets 2 mg and Olumiant Tablets 4 mg, dated May 19, 2017"]. Baricitinib is thus unlikely to affect the pharmacokinetics of remdesivir or its metabolite.

PMDA accepted the applicant's explanation.

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

The applicant submitted efficacy and safety evaluation data, in the form of results from the clinical study shown in Table 2.

Table 2. Submitted evaluation data

Phase	Study identifier	Region	Patient Population	No. of randomized patients	Dosage regimen (Orally or through a nasogastric tube*)	Primary endpoints
III	ACTT-2 study (Study I4V-MC-K001)	Global	Patients with COVID-19	(a) 515 patients (b) 518 patients	In combination with remdesivir: (a) Baricitinib group: Baricitinib 4 mg once daily orally for ≤14 days (b) Placebo group: Placebo once daily orally for ≤14 days	Efficacy Safety

* For patients who were unable to swallow whole baricitinib tablets or matched placebo, the tablets were dispersed in water and then given by mouth or nasogastric tube.

7.1 Phase III studies

7.1.1 Global clinical study (CTD 5.3.5.1.1; ACTT-2 [I4V-MC-K001] study, May 2020 to July 2020)

A randomized, double-blind, placebo-controlled, parallel-group study was conducted at 78 sites in 8 countries (Japan, the US, Singapore, South Korea, Mexico, Spain, the UK, and Denmark) to evaluate the efficacy and safety of baricitinib in combination with remdesivir in patients aged ≥18 years with COVID-19 (target sample size, 1032 patients[7)] [516 per group]). Table 3 shows the key inclusion and exclusion criteria.

7) Assuming a hazard ratio of 1.25 for the incidence of the primary endpoint in the baricitinib group versus the placebo group, a total of 723 events would be needed to achieve a hypothesis test with 85% power and a 2-sided significance level of 0.05, and the sample size required to achieve these 723 events would be 1032 patients.

Table 3. Key inclusion and exclusion criteria

Inclusion criteria	1. Currently hospitalized with symptoms suggestive of COVID-19 2. Has laboratory-confirmed SARS-CoV-2 infection, as determined by polymerase chain reaction (PCR) or other assays, as documented by either of the following: ・ PCR positive in a sample collected <72 hours prior to randomization; OR ・ PCR positive in a sample collected ≥72 hours prior to randomization, documented inability to obtain a repeat sample, AND a progressive disease suggestive of an ongoing SARS-CoV-2 infection 3. At least 1 of the following are met: ・ Imaging findings of COVID-19 pneumonia by chest x-ray, CT scan, etc.; OR ・ Saturation pulse oxygen (SpO_2) ≤94% on room air; OR ・ Requiring supplemental oxygen; OR ・ Requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
Exclusion criteria	1. Aspartate aminotransferase (ALT) or Alanine aminotransferase (AST) >5 times the upper limit of normal (ULN) 2. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, or the patient is receiving hemodialysis or hemofiltration 3. Absolute neutrophil count <1000/mm^3 4. Absolute lymphocyte count <200/mm^3 5. Pregnancy or breast feeding 6. Received ≥3 doses of remdesivir, including a loading dose, outside of the study under the EUA (or similar mechanism) for COVID-19 7. Received convalescent plasma or intravenous immunoglobulin for COVID-19 (i.e., the current illness) 8. Received small molecule tyrosine kinase inhibitors (e.g., baricitinib, imatinib, gefinitib) in the 1 week prior to screening 9. Received monoclonal antibodies targeting cytokines (e.g., TNF inhibitors, anti-IL-1, anti-IL-6 [tocilizumab or sarilumab]) or T-cells (e.g., abatacept) in the 4 weeks prior to screening 10. Received monoclonal antibodies targeting B-cells (e.g., rituximab, and including any targeting multiple cell lines including B-cells) in the 3 months prior to screening 11. Received ≥20 mg/day of prednisone or equivalent corticosteroid for ≥14 consecutive days within 4 weeks prior to screening

Patients received oral doses of baricitinib 4 mg[8] or placebo once daily for ≤14 days,[9][10] in combination with remdesivir, which was intravenously administered at 200 mg on Day 1, followed by 100 mg once daily on Days 2 to 10.[11] Any treatment with baricitinib, placebo, or remdesivir was discontinued upon hospital discharge.

Randomization was stratified by study site and disease severity (moderate disease, National Institute of Allergy and Infectious Disease Ordinal Scale [NIAID-OS; see Table 4 for the definition] = 4 or 5; severe disease, NIAID-OS = 6 or 7). All 1033 randomized patients (515 in the baricitinib group and 518 in the placebo group, including 1 Japanese patient in the placebo group) were included in the intention-to-treat (ITT) population. The efficacy analysis set was the ITT population. Of these 1033 patients, 17 did not receive the study drug, and the remaining 1016 (507 in the baricitinib group and 509 in the placebo group, including 1 Japanese patient in the placebo group) were included in the safety analysis set.

The study treatment was discontinued in 16.3% (84 of 515) of patients in the baricitinib group and 21.2% (110 of 518) of patients in the placebo group. The common reasons for discontinuation were death (4.5% [23 of 515 patients] in the baricitinib group, 6.9% [36 of 518 patients] in the placebo group), lost to follow-up (7.8% [40

8) Two 2-mg tablets of baricitinib were administered. The baricitinib dose for patients with an eGFR of ≥30 to <60 mL/min/1.73 m^2 was 2 mg.
9) For patients who were unable to swallow whole tablets of baricitinib or matched placebo, the tablets were dispersed in water and then given by mouth or nasogastric tube.
10) The study treatment was discontinued if the patient had any of the following events: total white blood cells of <1000/mm^3, an absolute neutrophil count of 500/mm^3, ALT or AST of >5 × ULN, an eGFR of <30 mL/min/1.73 m^2, or an infection considered to be related to the study drug.
11) If patients had already received the loading dose (200 mg) of remdesivir before enrollment, they were allowed to start the protocol-specified remdesivir treatment at 100 mg once daily. The allowable maximum doses of remdesivir, including those administered before enrollment and during the study period, was 10 doses, with a maximum of 2 doses before enrollment.

of 515 patients], 7.9% [41 of 518 patients]), and the patient's voluntary discontinuation (1.6% [8 of 515 patient], 3.1% [16 of 518 patients]).

The primary efficacy endpoint was time to recovery[12)] within 28 days after randomization. An interim analysis allowing early termination for efficacy was planned, and the interim analysis and the final analysis were to be performed when 239 and 723 cases of recovery, respectively, had been observed. An α-spending function of the O'Brien-Fleming type was used to control the probability of a type I error associated with the interim analysis. The 2-sided significance level was set at 0.0007 for the interim analysis and 0.05 for the final analysis.

The interim analysis was performed when 286 case of recovery had been observed; based on the results of the interim analysis, the study proceeded without early termination for efficacy. The final analysis was performed when 817 cases of recovery had been observed. Table 5 and Figure 1 present the results for time to recovery within 28 days after randomization. The results demonstrated the superiority of baricitinib in combination with remdesivir over remdesivir alone (hazard ratio [95% confidence interval (CI)], 1.15 [1.00 to 1.31]; stratified log-rank test; 2-sided *P*-value = 0.047; 2-sided significance level = 0.05).

Table 4. NIAID-OS

Score	Definition
1	Not hospitalized, no limitations on activities
2	Not hospitalized, limitation on activities and/or requiring home oxygen
3	Hospitalized, not requiring supplemental oxygen—no longer requires ongoing medical care
4	Hospitalized, not requiring supplemental oxygen—requiring ongoing medical care (COVID-19 related or otherwise)
5	Hospitalized, requiring supplemental oxygen
6	Hospitalized, on non-invasive ventilation or high flow oxygen devices
7	Hospitalized, on invasive mechanical ventilation or ECMO
8	Death

Table 5. Results of the final analysis of time to recovery within 28 days after randomization (ITT population)

	Baricitinib	Placebo
N	515	518
No. of patients who recovered (%)	433 (84.1%)	406 (78.4%)
Median time to recovery [95% CI], days	7.0 [6.0, 8.0]	8.0 [7.0, 9.0]
Hazard ratio [95% CI][*1]	1.15 [1.00, 1.31]	
2-sided *P*-value[*2]	0.047	

*1, Cox proportional hazards model stratified by disease severity (moderate vs. severe)
*2, Log-rank test stratified by disease severity (moderate vs. severe) with a 2-sided significance level of 0.05

12) Recovery was documented if an NIAID-OS score of 1, 2, or 3 was attained. Patients who died before recovery were censored at the end of the full evaluation period (i.e., 28 days after randomization).

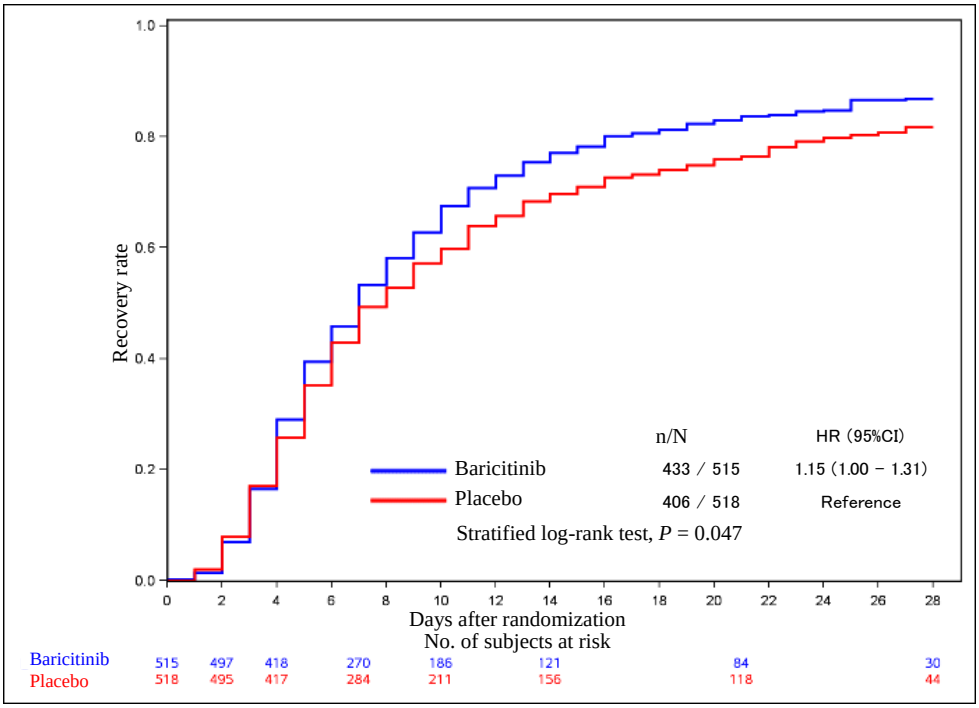


Figure 1. Kaplan-Meier curves for the time to recovery within 28 days after randomization (ITT population)

Adverse events[13)] were reported in 41.4% (210 of 507) of patients in the baricitinib group and 47.5% (242 of 509) of patients in the placebo group. Table 6 shows the common adverse events.

Table 6. Adverse events reported in ≥2% of patients in either group (safety analysis set)

Events	Baricitinib N = 507	Placebo N = 509
Any adverse event	210 (41.4)	242 (47.5)
Glomerular filtration rate decreased	49 (9.7)	42 (8.3)
Haemoglobin decreased	30 (5.9)	30 (5.9)
Hyperglycaemia	25 (4.9)	40 (7.9)
Anaemia	25 (4.9)	33 (6.5)
Respiratory failure	24 (4.7)	39 (7.7)
Lymphocyte count decreased	24 (4.7)	35 (6.9)
Blood glucose increased	22 (4.3)	27 (5.3)
Acute kidney injury	20 (3.9)	36 (7.1)
Acute respiratory failure	16 (3.2)	15 (2.9)
Respiratory distress	13 (2.6)	15 (2.9)
Pneumonia	12 (2.4)	21 (4.1)
Deep vein thrombosis	12 (2.4)	10 (2.0)
Lymphopenia	11 (2.2)	24 (4.7)
Hypertension	11 (2.2)	6 (1.2)
AST increased	9 (1.8)	18 (3.5)
Hypotension	9 (1.8)	18 (3.5)
ALT increased	6 (1.2)	12 (2.4)
Sepsis	4 (0.8)	11 (2.2)

n (%)

[13)] In view of the patient population eligible for the ACTT-2 study, patients had been presumed to have many symptoms, abnormal vital signs, and abnormal laboratory test results. Therefore, adverse events collected in the study were grade 3 and 4 adverse events, in addition to the following specified events (a) and (b): (a) Grade ≥2 hypersensitivity reactions that were considered related to the study drug, and (b) venous thromboembolism (VTE)-related events reported during the study period.

Adverse events led to death in 3.7% (19 of 507) of patients in the baricitinib group (respiratory failure in 5 patients; acute respiratory failure in 3 patients; septic shock in 2 patients; and hypoxia, pneumonia aspiration, respiratory arrest, respiratory distress, cardiac arrest, cardio-respiratory arrest, pulseless electrical activity, sinus tachycardia, and gastrointestinal haemorrhage in 1 patient each) and 6.1% (31 of 509) of patients in the placebo group (respiratory failure in 7 patients; acute respiratory failure in 5 patients; acute respiratory distress syndrome in 4 patients; multiple organ dysfunction syndrome in 3 patients; cardiac arrest in 2 patients; and hypoxia, respiratory arrest, respiratory distress, pulmonary embolism, cardio-respiratory arrest, left ventricular failure, septic shock, subdural haematoma, encephalopathy, and shock in 1 patient each). A causal relationship to the study drug was ruled out for all of the events.

Serious adverse events were reported in 15.2% (77 of 507) of patients in the baricitinib group and 20.2% (103 of 509) of patients in the placebo group. Table 7 shows the common serious adverse events. A causal relationship to the study drug could not be ruled out in 6 patients in the baricitinib group (pulmonary embolism in 4 patients, acute kidney injury in 1 patient, and intervertebral discitis in 1 patient) and 5 patients in the placebo group (lung abscess, hepatitis, oedema peripheral, hypersensitivity, and ALT increased in 1 patient each).

Table 7. Serious adverse events reported by ≥5 patients in either group (safety analysis set)

Events	Baricitinib N = 507	Placebo N = 509
Any serious adverse event	77 (15.2)	103 (20.2)
Respiratory failure	24 (4.7)	37 (7.3)
Acute respiratory failure	16 (3.2)	9 (1.8)
Acute kidney injury	5 (1.0)	11 (2.2)
Hypotension	5 (1.0)	5 (1.0)
Pulmonary embolism	5 (1.0)	1 (0.2)
Acute respiratory distress syndrome	4 (0.8)	9 (1.8)
Septic shock	4 (0.8)	8 (1.6)
Respiratory distress	4 (0.8)	6 (1.2)
Pneumonia	2 (0.4)	8 (1.6)
Multiple organ dysfunction syndrome	1 (0.2)	6 (1.2)
Renal failure	0	5 (1.0)

n (%)

Adverse events led to study drug discontinuation in 34 patients (6.7%) in the baricitinib group and 59 patients (11.6%) in the placebo group. Table 8 shows the common adverse events leading to study drug discontinuation. A causal relationship to the study drug could not be ruled out in 7 patients in the baricitinib group (ALT increased, AST increased, and pulmonary embolism in 2 patients each; transaminases increased, acute kidney injury, and deep vein thrombosis in 1 patient each [some patients reported ≥2 events]) and 15 patients in the placebo group (deep vein thrombosis in 5 patients; and ALT increased, transaminases increased, acute kidney injury, axillary vein thrombosis, peripheral ischaemia, thrombosis, neutropenia, vomiting, hepatitis, hypersensitivity, and rash in 1 patient each [some patients reported ≥2 events]).

Adverse drug reactions were reported in 5.1% (26 of 507) of patients in the baricitinib group and 6.1% (31 of 509) of patients in the placebo group.

Table 8. Adverse events that led to study drug discontinuation in ≥2 patients in either group (safety analysis set)

Events	Baricitinib N = 507	Placebo N = 509
Any adverse event leading to study drug discontinuation	34 (6.7)	59 (11.6)
Acute kidney injury	7 (1.4)	18 (3.5)
Deep vein thrombosis	6 (1.2)	6 (1.2)
AST increased	3 (0.6)	2 (0.4)
Transaminases increased	2 (0.4)	3 (0.6)
Respiratory failure	2 (0.4)	3 (0.6)
ALT increased	2 (0.4)	2 (0.4)
Septic shock	2 (0.4)	2 (0.4)
Pulmonary embolism	2 (0.4)	0
Glomerular filtration rate decreased	1 (0.2)	3 (0.6)
Pneumonia	1 (0.2)	2 (0.4)
Renal failure	0	3 (0.6)

n (%)

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

The ACTT-1 study successfully demonstrated the clinical benefits, such as reduced time to recovery, of remdesivir, an antiviral agent, in patients with COVID-19 (*N Engl J Med.* 2020;383:1813-26). In response to the outcomes of the ACTT-1 study, the ACTT-2 study was conducted as a global clinical trial to evaluate the efficacy and safety of baricitinib, an anti-inflammatory drug, in combination with remdesivir. The applicant has submitted the results of the ACTT-2 study as evaluation data for the present partial change application, although the study enrolled only 1 Japanese patient assigned to placebo.[14)]

The applicant's explanation about the reasons for concluding that the efficacy and safety of baricitinib in patients with COVID-19, including Japanese patients, can be evaluated based on the results of the ACTT-2 study:

Although the morbidity and mortality of COVID-19 per 100,000 persons vary across countries and regions (World Health Organization; WHO Coronavirus Disease [COVID-19] Dashboard[15)]), no clear differences in the symptoms of COVID-19, risk factors for severe COVID-19, etc. have been identified across countries and regions (Guidelines Development Committee, *Clinical Management of Patients with COVID-19: A guide for front-line healthcare workers*, Version 4.2 [In Japanese]; National Institutes of Health, *Coronavirus Disease 2019 [COVID-19] Treatment Guidelines*). Further, in the countries or regions participating in the ACTT-2 study, patients with COVID-19 are treated according to disease severity, with a wide range of modalities, including respiratory management (supplemental oxygen, mechanical ventilation, or ECMO), pharmacotherapies (e.g., remdesivir and corticosteroids[16)]), prophylaxis of thrombosis, and complication

[14)] A 6[redacted]-year-old male patient who had severe COVID-19 (NIAID-OS = 6) at baseline, and recovered to NIAID-OS = 2 at 14 days after randomization.

[15)] The number of patients with COVID-19 per 100,000 persons is 8250.54 patients in the US, 5948.33 patients in the UK, 6505.12 patients in Spain, 328.74 patients in Japan, 163.59 patients in South Korea, and 1022.16 patients in Singapore. The number of deaths per 100,000 persons is 145.15 deaths in the US, 172.59 deaths in the UK, 137.35 deaths in Spain, 5.5 deaths in Japan, 2.98 deaths in South Korea, and 0.5 deaths in Singapore (https://covid19.who.int; Data since January 3, 2020, as of February 16, 2021).

[16)] The results of the RECOVERY study that evaluated the efficacy of dexamethasone in the treatment of COVID-19 was published through a press release from the University of Oxford on June 16, 2020, midway through the ACTT-2 study.

management; thus, no large differences in therapeutic strategies for COVID-19 are thought to exist across countries and regions.

Considering the situations above-mentioned and the following facts regarding the pharmacokinetics of baricitinib and the efficacy and safety of baricitinib for other indications, the efficacy and safety of baricitinib in the treatment of patients with COVID-19, including Japanese patients, can be evaluated based on the results of the ACTT-2 study.

- The pharmacokinetics of baricitinib was analyzed in healthy volunteers, patients with rheumatoid arthritis, patients with atopic dermatitis, etc. The analysis identified renal function as the sole intrinsic factor that might affect the pharmacokinetics of baricitinib, and revealed no clear ethnic differences between Japanese and non-Japanese populations, which might affect the efficacy or safety of baricitinib in the treatment of rheumatoid arthritis or atopic dermatitis [see "Review Report for Olumiant Tablets 2 mg and Olumiant Tablets 4 mg, dated May 19, 2017" and "Review Report for Olumiant Tablets 2 mg and Olumiant Tablets 4 mg, dated November 25, 2020"].
- Baricitinib is currently approved for the treatment of rheumatoid arthritis and atopic dermatitis. For both of the approved indications, pivotal clinical studies were conducted as global clinical studies, including Japan, and the results of the studies demonstrated no clear differences in the efficacy or safety of baricitinib between the Japanese and non-Japanese populations [see "Review Report for Olumiant Tablets 2 mg and Olumiant Tablets 4 mg, dated May 19, 2017" and "Review Report for Olumiant Tablets 2 mg and Olumiant Tablets 4 mg, dated November 25, 2020"].

In Japan, the number of patients newly diagnosed with COVID-19 (approximately 55 patients per day, on average)[17] was decreasing during the patient enrollment period of the ACTT-2 study (May to June 2020), with fewer patients with severe COVID-19. This is one reason for the extremely limited enrollment of Japanese patients in the study.

PMDA's view:
The ACTT-2 study included only one Japanese patient who was assigned to placebo, and thus yielded no clinical data from Japanese patients treated with baricitinib for COVID-19. However, no large differences between Japanese and non-Japanese populations exist in terms of the symptoms of and therapeutic strategies for COVID-19, risk factors for severe COVID-19, and other aspects, and limited treatment options are available for the patient population eligible for the ACTT-2 study in the current COVID-19 pandemic situation. In view of the above, along with (a) the accumulated knowledge regarding differences in the efficacy or safety of baricitinib in the treatment of other diseases (rheumatoid arthritis and atopic dermatitis) between Japanese and non-Japanese populations; (b) a certain amount of clinical experience with the use of baricitinib for the approved indications in Japan; and (c) the fact that the dosage regimen of baricitinib used in the ACTT-2 study

[17] Ministry of Health, Labour and Welfare; Novel Coronavirus (COVID-19), Current Situation in Japan in 2021 (https://www.mhlw.go.jp/content/pcr_positive_daily.csv confirmed on February 10, 2021). The number of patients with newly diagnosed COVID-19 during the patient enrollment period (May to June 2020) represents the average of the daily number of patients throughout the period.

was identical to the approved dosage regimen in Japan; the clinical benefits of baricitinib in patients with COVID-19, including Japanese patients, can be evaluated based on the results of the ACTT-2 study.

7.R.2 Efficacy

7.R.2.1 Efficacy endpoints

The applicant's explanation:

In the ACTT-2 study, the primary endpoint was time to recovery within 28 days after randomization,[18] and the key secondary endpoint was clinical status according to the NIAID-OS at 14 days after randomization. The primary endpoint and the key secondary endpoint are clinically important efficacy endpoints, as stated by the US Food and Drug Administration (FDA) guidance document.[19]

PMDA's view:

The choice of time to recovery within 28 days after randomization, an endpoint indicating the improvement of clinical status, as the primary endpoint of the ACTT-2 study is acceptable. However, the efficacy evaluation should focus on the effects of baricitinib on the deterioration of clinical status, as well as those on the improvement of clinical status. For this and other reasons, the efficacy of baricitinib should be comprehensively evaluated based on the outcome of clinical status according to NIAID-OS, deaths, and other study results.

7.R.2.2 Efficacy evaluation results

The applicant's explanation about the efficacy of baricitinib based on the results of the ACTT-2 study:

The results of the ACTT-2 study demonstrated the superiority of baricitinib in combination with remdesivir over remdesivir alone in terms of time to recovery within 28 days after randomization as the primary endpoint [see Section 7.1.1]. Disease severity (moderate COVID-19 or severe COVID-19) was misclassified in 44 patients among the ITT population. Specifically, 42 patients with moderate COVID-19 were stratified as having severe COVID-19 and 2 patients with severe COVID-19 were stratified as having moderate COVID-19, and they were incorrectly randomized. However, a sensitivity analysis by true disease severity yielded a 2-sided *P*-value of 0.035 by stratified log-rank test and a hazard ratio [95% CI] of 1.16 [1.01, 1.32] by stratified Cox proportional hazards model, which were similar to the results of the primary analysis.

In the ACTT-2 study, the use of concomitant corticosteroids for indications other than COVID-19 was allowed. The use of concomitant biological products or investigational drugs (including the off-label use of marketed medications) intended as a treatment for COVID-19 was also permitted, if local guidelines, etc. recommended them as the standard of care for COVID-19. Patients who reported the use of any of the concomitant medications that might affect the efficacy evaluation for baricitinib ("medications of interest")[20] were censored

[18] The ACTT studies, including the ACTT-2 study share a common primary endpoint. In the ACTT-1 study evaluating the efficacy and safety of remdesivir versus placebo, the primary endpoint was planned at the start of the study to be clinical status, based on the NIAID-OS at 14 days after randomization. Subsequently, accumulated evidence showed that the course of COVID-19 would be longer than initially expected. The original primary endpoint was then changed to a secondary endpoint, and time to recovery within 28 days after randomization was defined as the new primary endpoint.

[19] COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guideline for Industry (U.S. Department of Health and Human Services Food and Drug Administration, May 2020)

[20] Among medications used in the study, the following medications were tabulated as those that might affect the efficacy evaluation for baricitinib ("medications of interest"): corticosteroids, potential treatments for COVID-19 (e.g., hydroxychloroquine), anti-inflammatory drugs (e.g., immunoglobulins), and antivirals (protease inhibitors). Corticosteroids, potential treatments for COVID-19, anti-inflammatory drugs, and antivirals

at the time they started treatment with the "medications of interest," and a sensitivity analysis was performed. The results of the sensitivity analysis, as presented in Table 9 (hazard ratio [95% CI] by stratified Cox proportional hazards model; 1.15 [0.99, 1.33] in the overall population, 1.08 [0.91, 1.29] in patients with moderate COVID-19, and 1.34 [1.00, 1.80] in patients with severe COVID-19), were similar to those of the primary analysis.

Table 9. Results of a sensitivity analysis of time to recovery within 28 days after randomization by concomitant drug use (ITT population)

	Overall population		Moderate COVID-19		Severe COVID-19	
	Baricitinib	Placebo	Baricitinib	Placebo	Baricitinib	Placebo
N	515	518	339	327	176	191
No. of patients using any medication of interest[*1]	118	136	65	65	53	71
No. of patients who recovered (%)	358 (69.5%)	322 (62.2%)	260 (76.7%)	243 (74.3%)	98 (55.7%)	79 (41.4%)
Median time to recovery [95% CI] (days)	6.0 [6.0, 7.0]	7.0 [6.0, 8.0]	5.0 [5.0, 6.0]	5.0 [5.0, 6.0]	10.0 [9.0, 14.0]	15.0 [11.0, 20.0]
Hazard ratio [95% CI][*2]	1.15 [0.99, 1.33]		1.08 [0.91, 1.29]		1.34 [1.00. 1.80]	

*1, Patients using any medication of interest were censored at the time they started treatment with the medication.
*2, Cox proportional hazards model stratified by disease severity (moderate vs. severe)

In addition to the results for the primary endpoint, those for all-cause mortality at 14 days and 28 days after randomization, clinical status based on the NIAID-OS at 14 days after randomization, and time to death tended to be favorable in the baricitinib group as compared with the placebo group (see Table 10 and Figure 2). These results supported the efficacy of baricitinib.

Table 10. All-cause mortality and clinical status based on NIAID-OS at 14 days after randomization (ITT population)

		Baricitinib N = 515	Placebo N = 518
All-cause mortality	14 days after randomization	1.6% (n = 8)	2.9% (n = 15)
	28 days after randomization	4.7% (n = 24)	7.1% (n = 37)
Proportional odds ratio* [95% CI] of clinical status based on NIAID-OS at 14 days after randomization		1.26 [1.01,1.57]	

* Proportional odds model with disease severity (moderate vs. severe) as a covariate

were used in 106 patients, 15 patients, 8 patients, and 2 patients, respectively, in the baricitinib group, and 118 patients, 15 patients, 5 patients, and 7 patients, respectively, in the placebo group.

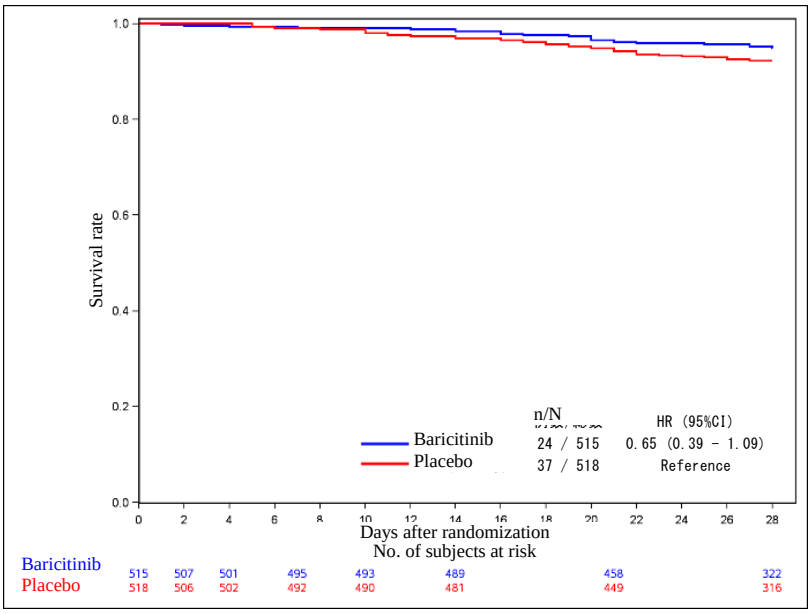


Figure 2. Kaplan-Meier curves for time to death within 28 days after randomization (ITT population)

The results for time to recovery, clinical status, and time to death by baseline NIAID-OS, based on true disease severity are presented in Table 11, as well as

Figure 3, Figure 4, and Figure 5. In patients categorized as NIAID-OS = 4 at baseline, no add-on effect of baricitinib to remdesivir was seen; treatment with baricitinib is therefore not recommended in the patient population.

Table 11. Time to recovery within 28 days after randomization, all-cause mortality, and clinical status based on NIAID-OS at 14 days after randomization by baseline NIAID-OS[*1] (ITT population)

		NIAID-OS = 4 at baseline		NIAID-OS = 5 at baseline	
		Baricitinib N = 70	Placebo N = 72	Baricitinib N = 288	Placebo N = 276
Time to recovery within 28 days after randomization	No. of patients who recovered	67	69	262	243
	Median time to recovery [95% CI] (days)	5.0 [4.0, 6.0]	4.0 [4.0, 6.0]	5.0 [5.0, 6.0]	6.0 [5.0, 6.0]
	Hazard ratio[*2] [95% CI]	0.88 [0.62, 1.23]		1.17 [0.98, 1.39]	
All-cause mortality	14 days after randomization	0	0	1.0% (n = 3)	1.4% (n = 4)
	28 days after randomization	0	0	1.7% (n = 5)	4.3% (n = 12)
Proportional odds ratio of clinical status based on NIAID-OS at 14 days after randomization[*3] [95% CI]		0.58 [0.31, 1.10]		1.19 [0.88, 1.62]	
		NIAID-OS = 6 at baseline		NIAID-OS = 7 at baseline	
		Baricitinib N = 103	Placebo N = 113	Baricitinib N = 54	Placebo N = 57
Time to recovery within 28 days after randomization	No. of recovered patients	82	73	22	21
	Median time to recovery [95% CI] (days)	10.0 [9.0, 13.0]	18.0 [13.0, 21.0]	NE [25.0, NE]	NE [26.0, NE]
	Hazard ratio[*2] [95% CI]	1.51 [1.10, 2.08]		1.08 [0.59, 1.97]	
All-cause mortality	14 days after randomization	1.0% (n = 1)	4.4% (n = 5)	7.4% (n = 4)	10.5% (n = 6)
	28 days after randomization	6.8% (n = 7)	11.5% (n = 13)	22.2% (n = 12)	21.1% (n = 12)
Proportional odds ratio of clinical status based on NIAID-OS at 14 days after randomization[*3] [95% CI]		2.25 [1.39, 3.64]		1.67 [0.82, 3.42]	

NE: Not evaluable

*1 True NIAID-OS data at baseline

*2 Cox proportional hazards model stratified by disease severity (moderate vs. severe), or Cox proportional hazards model for the results by disease severity and NIAID-OS

*3 Proportional odds model with disease severity (moderate vs. severe) as a covariate

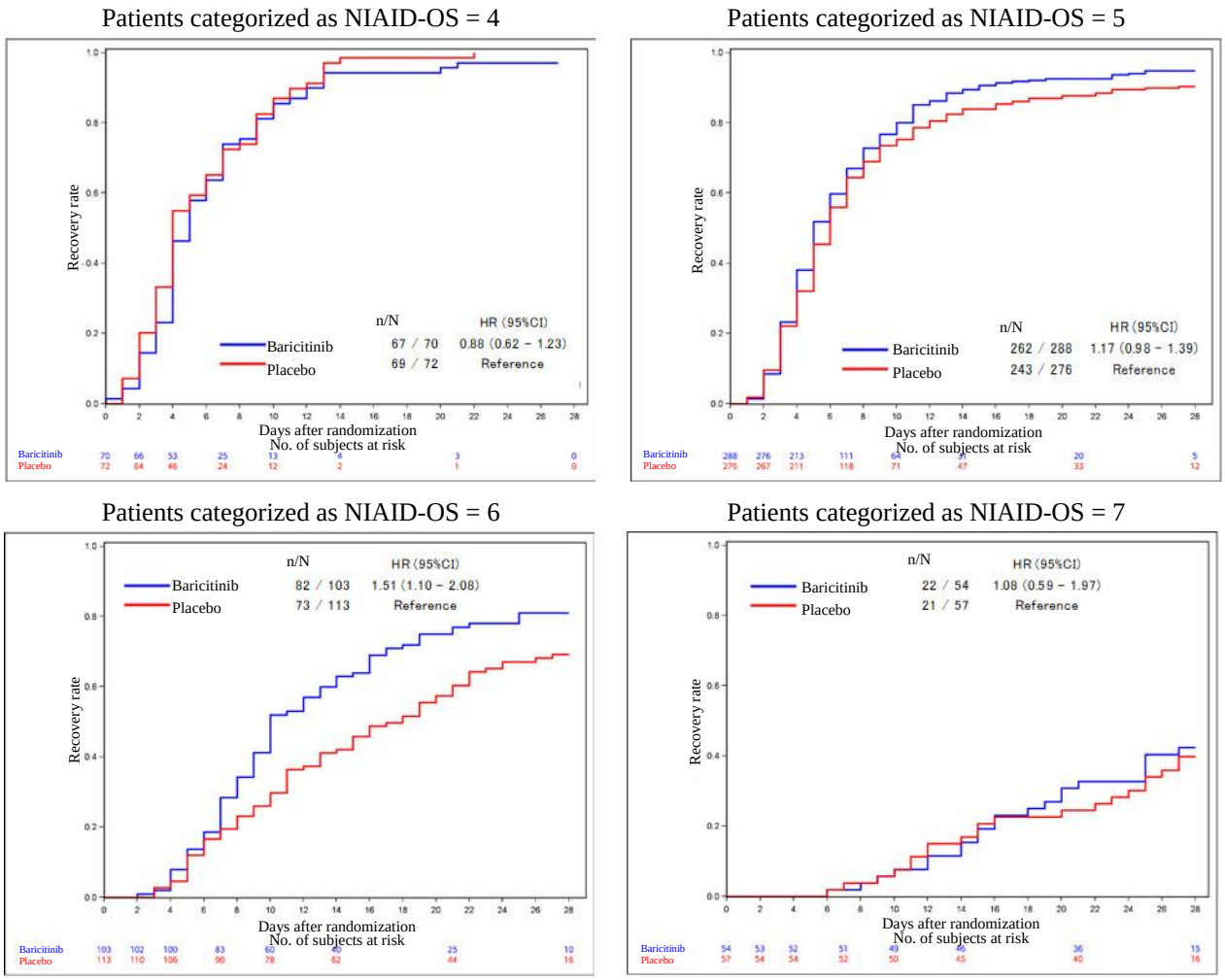


Figure 3. Kaplan-Meier curves for time to recovery within 28 days after randomization by baseline NIAID-OS (ITT population)

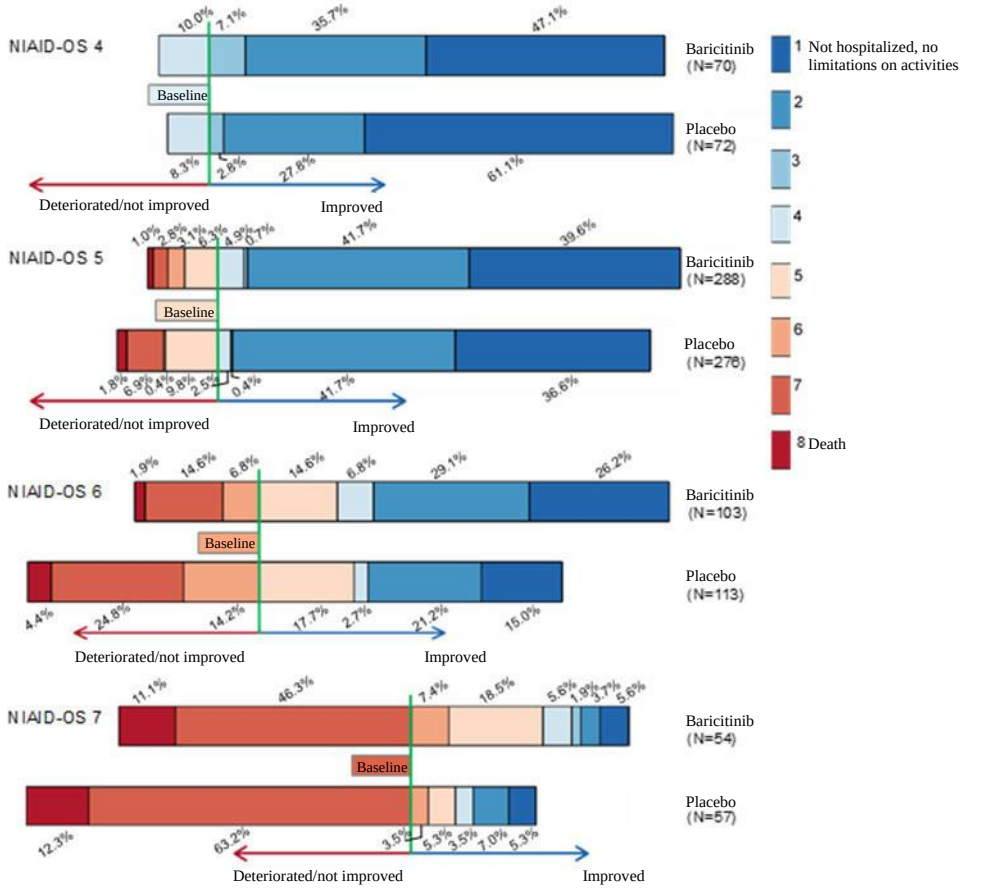
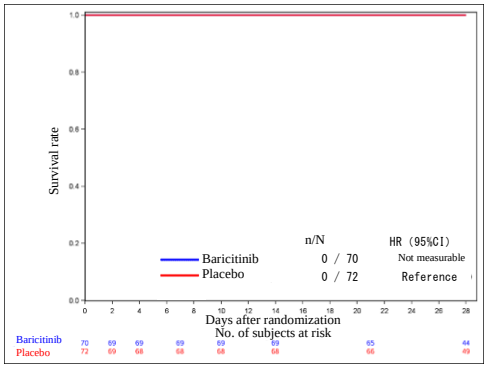
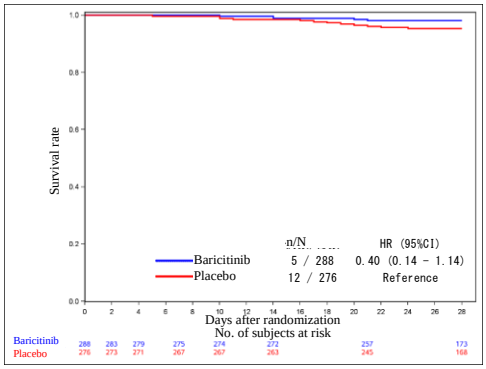


Figure 4. Clinical status at 14 days after randomization by baseline NIAID-OS (ITT population)

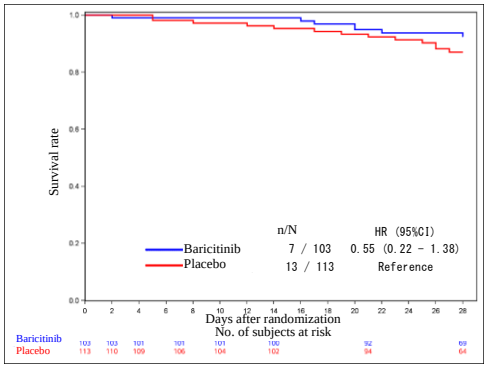
Patients categorized as NIAID-OS = 4



Patients categorized as NIAID-OS = 5



Patients categorized as NIAID-OS = 6



Patients categorized as NIAID-OS = 7

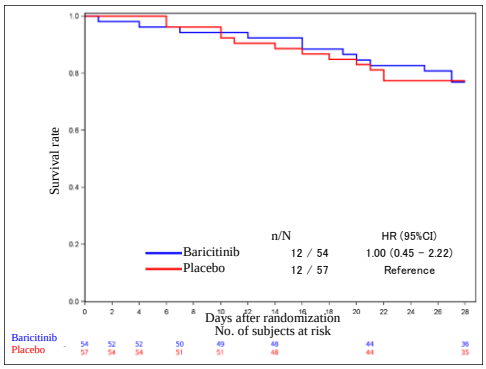
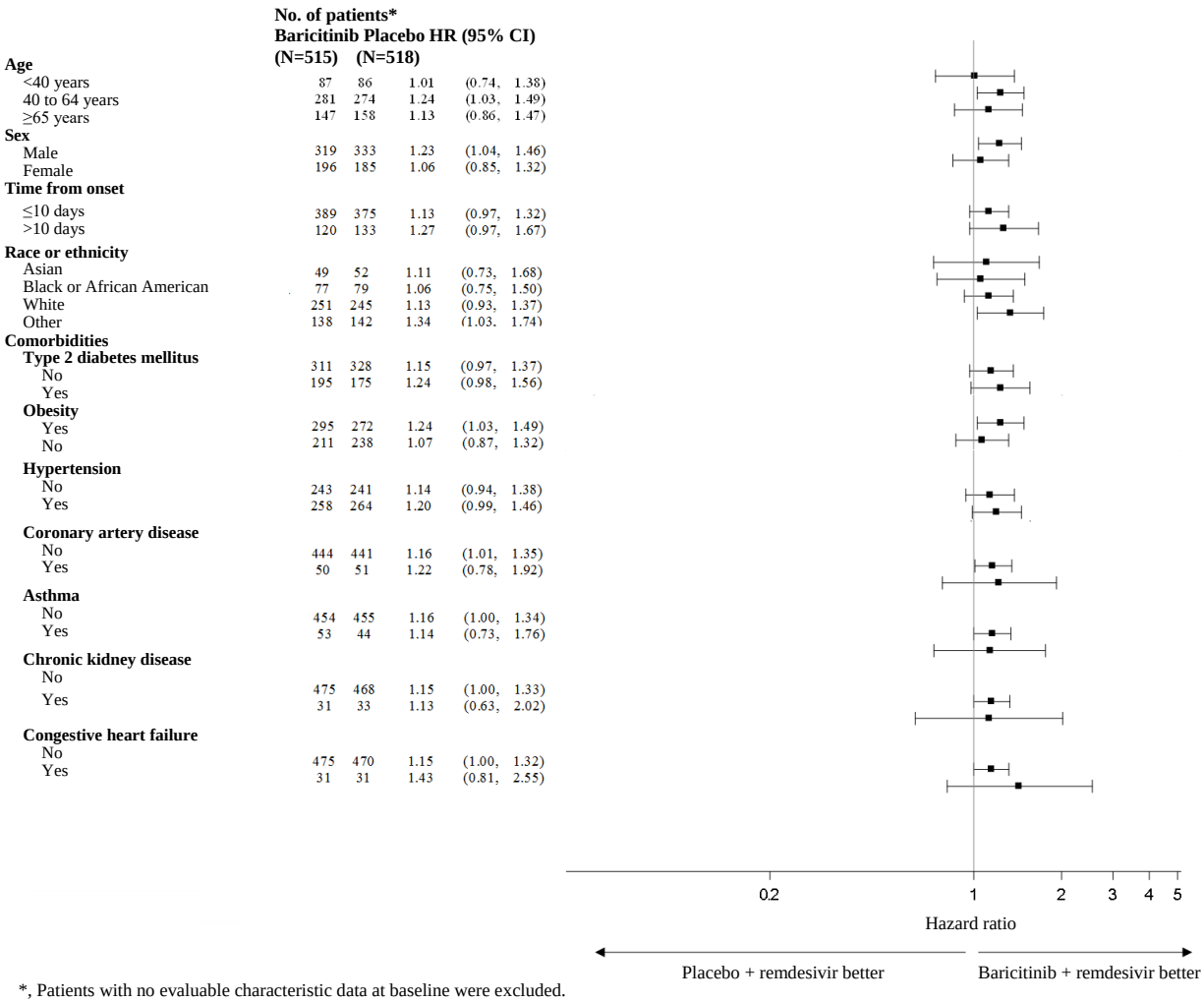


Figure 5. Kaplan-Meier curves for time to death within 28 days after randomization by baseline NIAID-OS (ITT population)

Figure 6 shows the results for the primary endpoint by patient characteristics other than baseline NIAID-OS in the ACTT-2 study.



*, Patients with no evaluable characteristic data at baseline were excluded.

Figure 6. Results of subgroup analysis by patient characteristics

PMDA's view:

It is understandable that the impact of the misclassification that occurred in stratified randomization in the ACTT-2 study was assessed by conducting a sensitivity analysis based on true severity classification according to the ITT principle, rather than by changing the primary analysis. The results of the sensitivity analysis were consistent with those of the primary analysis, supporting the statistically significant difference in the primary endpoint between the placebo group and the baricitinib group. Baricitinib also tended to be superior over placebo in other efficacy endpoints, such as all-cause mortality and improvement in clinical status. These study results are considered to support the efficacy of baricitinib in the treatment of COVID-19. Despite difficulties in making a precise evaluation, a subgroup analysis of patients categorized as NIAID-OS = 4 at baseline revealed no tendency for baricitinib to be superior over placebo, in terms of the primary endpoint or any of the

secondary endpoints. The applicant therefore considered that the results of the ACTT-2 study had failed to demonstrate the promising efficacy of baricitinib in patients categorized as NIAID-OS = 4 at baseline, and that the use of baricitinib in this patient population would not be recommended. The applicant's decision is acceptable.

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

7.R.3 Safety

7.R.3.1 Safety profile

The applicant provided the following explanation about the safety of baricitinib, based on the results of the ACTT-2 study:

Adverse events collected in the ACTT-2 study consisted of those classified as Grade 3 or 4 according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Event, version 2.1, and those shown below. Table 12 presents a summary of the safety data from the ACTT-2 study.

- Grade ≥2 hypersensitivity reactions that were considered to be related to the study drug
- Venous thromboembolism (VTE)-related events reported during the study period

Table 12. Safety summary in the ACTT-2 study

	Baricitinib N = 507	Placebo N = 509
All adverse events	210 (41.4)	242 (47.5)
Adverse events leading to death	19 (3.7)	31 (6.1)
Serious adverse events	77 (15.2)	103 (20.2)
Adverse events leading to study drug discontinuation	34 (6.7)	59 (11.6)
Adverse drug reactions	26 (5.1)	31 (6.1)

n (%)

Serious adverse events reported with a ≥0.5% higher incidence in the baricitinib group than in the placebo group were acute respiratory failure[21)] and pulmonary embolism (Table 7). No adverse events were reported with a ≥5% higher incidence in the baricitinib group than in the placebo group. No adverse events led to death or study drug discontinuation with a ≥0.5% higher incidence in the baricitinib group than in the placebo group.

[21)] The incidence of serious respiratory failure was ≥ 0.5% higher in the baricitinib group than in the placebo group.

Table 13 presents the incidences of the events listed as important identified risks[22] of baricitinib (herpes zoster, serious infection, gastrointestinal perforation, hepatitis B virus reactivation, interstitial pneumonia, neutrophil count decreased, lymphocyte count decreased, haemoglobin decreased, hepatic function disorder, and VTE) during the reviews for the approved indications.

Table 13. Incidences of events listed as the important identified risks of baricitinib in the ACTT-2 study[*1]

		Baricitinib (N = 507)	Placebo (N = 509)
Serious infection[*2]	All adverse events	11 (2.2%)	19 (3.7%)
	Adverse events leading to death	2 (0.4%)	1 (0.2%)
	Serious adverse events	11 (2.2%)	19 (3.7%)
	Adverse events leading to study drug discontinuation	3 (0.6%)	5 (1.0%)
Neutrophil count decreased	All adverse events	1 (0.2%)	0
	Adverse events leading to death	0	0
	Serious adverse events	0	0
	Adverse events leading to study drug discontinuation	0	0
Lymphocyte count decreased	All adverse events	24 (4.7%)	35 (6.9%)
	Adverse events leading to death	0	0
	Serious adverse events	1 (0.2%)	0
	Adverse events leading to study drug discontinuation	0	0
Haemoglobin decreased	All adverse events	30 (5.9%)	30 (5.9%)
	Adverse events leading to death	0	0
	Serious adverse events	0	1 (0.2%)
	Adverse events leading to study drug discontinuation	0	0
Hepatic function disorder	All adverse events	22 (4.3%)	37 (7.3%)
	Adverse events leading to death	0	0
	Serious adverse events	0	4 (0.8%)
	Adverse events leading to study drug discontinuation	6 (1.2%)	7 (1.4%)
VTE	All adverse events	21 (4.1%)	16 (3.1%)
	Adverse events leading to death	0	1 (0.2%)
	Serious adverse events	7 (1.4%)	4 (0.8%)
	Adverse events leading to study drug discontinuation	10 (2.0%)	9 (1.8%)

n (%)

*1 No events related to herpes zoster, gastrointestinal perforation, hepatitis B virus reactivation, or interstitial pneumonia were reported.

*2 "Infection" events were reported in 40 patients (7.9%) in the baricitinib group and 60 patients (11.8%) in the placebo group. "Infection" events reported by ≥5 patients in the baricitinib group were pneumonia in 12 patients, septic shock in 7 patients, and urinary tract infection in 6 patients. "Infection" events reported by ≥5 patients in the placebo group were pneumonia in 21 patients, sepsis in 11 patients, septic shock in 10 patients, pneumonia bacterial in 9 patients, and bacteraemia in 5 patients.

[22] "Herpes zoster" events were defined as events coded to "herpes zoster (preferred term [PT])" or "varicella zoster (lowest level term [LLT])." "Serious infection" events were defined as events coded to "infections and infestations (system organ class [SOC])," and as being serious. "Gastrointestinal perforation" events were defined as events coded to "gastrointestinal perforation (standard MedDRA queries [SMQ] [narrow])." "Hepatitis B virus reactivation" events were defined as events coded to the following PTs: "asymptomatic viral hepatitis," "chronic hepatitis B," "HBV-DNA polymerase increased," "hepatitis B," "hepatitis B antigen," "hepatitis B antigen positive," "hepatitis B core antigen," "hepatitis B core antigen positive," "hepatitis B DNA assay," "hepatitis B DNA assay positive," "hepatitis B DNA increased," "hepatitis B e antigen," "hepatitis B e antigen positive," hepatitis B reactivation," "hepatitis B surface antigen," "hepatitis B surface antigen positive," "hepatitis B virus test," "hepatitis B virus test positive," "hepatitis A," "hepatitis post-transfusion," "hepatitis viral," or "withdrawal hepatitis." "Interstitial pneumonia" events were defined as events coded to "interstitial lung disease (PT)." "Neutrophil count decreased" events were defined as events coded to "neutrophil count decreased (PT)." "Lymphocyte count decreased" events were defined as events coded to "lymphocyte count decreased (PT)." "Haemoglobin decreased" events were defined as events coded to "haemoglobin decreased (PT)." "Hepatic function disorder" events were defined as events coded to "liver-related investigations, signs and symptoms (SMQ)," acute hepatic failure (PT)," "chronic hepatic failure (PT)," "hepatic failure (PT)," or "subacute hepatic failure (PT)." "Venous thromboembolism" events were adjudicated based on the review of a medical expert at the US NIH.

The ACTT-2 study included patients with a lymphocyte count of 200 to 500/mm^3 and those with a haemoglobin level of <8 g/dL, who had been excluded from clinical studies in patients with rheumatoid arthritis or atopic dermatitis.

The numbers of patients with a lymphocyte count of 200 to 500 /mm^3 enrolled in the ACTT-2 study were 39 patients in the baricitinib group and 33 patients in the placebo group, and those of patients with a haemoglobin level of <8 g/dL were 6 patients and 8 patients, respectively. Table 14 shows the incidences of adverse events by baseline lymphocyte count. In the subgroup of patients with a baseline lymphocyte count of 200 to 500/mm^3, no tendency of particular concern was identified. Three of the 6 patients with a baseline haemoglobin level of <8 g/dL in the baricitinib group had adverse events (glomerular filtration rate decreased, anaemia, and blood creatinine increased in 1 patient each), all of which were categorized as being non-serious.

Table 14. Incidences of adverse events by baseline lymphocyte count*

	Lymphocyte count 200 to 500/mm^3		Lymphocyte count ≥500/mm^3	
	Baricitinib N = 39	Placebo N = 33	Baricitinib N = 460	Placebo N = 473
All adverse events	21 (53.8)	25 (75.8)	186 (40.4)	214 (45.2)
Adverse events leading to death	3 (7.7)	5 (15.2)	15 (3.3)	25 (5.3)
Serious adverse events	9 (23.1)	12 (36.4)	67 (14.6)	90 (19.0)
Adverse events leading to study drug discontinuation	5 (12.8)	7 (21.2)	28 (6.1)	50 (10.6)
Infection-related adverse events	7 (17.9)	7 (21.2)	33 (7.2)	50 (10.6)
Infection-related serious adverse events	3 (7.7)	3 (9.1)	8 (1.7)	15 (3.2)

n (%)
* Eight patients in the baricitinib group and 1 patient in the placebo group had no evaluable lymphocyte count data at baseline, and 2 patients in the placebo group had a lymphocyte count of <200/mm^2 at baseline.

PMDA's view:

In the ACTT-2 study which was conducted amid the COVID-19 pandemic, Grade ≥3 events were mainly collected, precluding a precise evaluation of adverse events of lower severity. However, the results of the ACTT-2 study identified no events that would require additional attention. The assessment of the serious adverse events reported in the ACTT-2 study revealed a higher incidence of pulmonary embolism in the baricitinib group than in the placebo group. Since VTE, including pulmonary embolism, is a comorbidity requiring attention in patients with COVID-19 (The Japanese Society on Thrombosis and Hemostasis; *Warnings regarding the increased potential risk of thrombosis associated with SARS-CoV-2 infection* [in Japanese][23)]), VTE is investigated further in Section 7.R.3.2.

7.R.3.2 Venous thromboembolism

The applicant's explanation:

Based on the results of clinical studies for the approved indications and other data, baricitinib is expected to be associated with the risk of VTE. In the ACTT-2 study, VTE prophylaxis was recommended for all patients but those with a past history of active bleeding events or heparin-induced thrombosis in whom such measures were contraindicated. The prophylaxis was to follow the local standard of care, with no specific procedure specified by the protocol.

[23)] The Japanese Society on Thrombosis and Hemostasis: http://www.jsth.org/wordpress/wp-content/uploads/2020/05/20200513_2.pdf

Table 15 shows the incidences of VTE-related events[22)] in the ACTT-2 study.

Table 15. Incidences of VTE-related events

	Baricitinib (N = 507)	Placebo (N = 509)
Any adverse event	21 (4.1%)	16 (3.1%)
Adverse events leading to death	0	1 (0.2%)
Serious adverse events	7 (1.4%)	4 (0.8%)
Adverse events leading to study drug discontinuation	10 (2.0%)	9 (1.8%)
Deep vein thrombosis	12 (2.4%)	10 (2.0%)
Pulmonary embolism	5 (1.0%)	2 (0.4%)
Thrombosis	2 (0.4%)	2 (0.4%)
Cerebrovascular accident	1 (0.2%)	1 (0.2%)
Embolism venous	1 (0.2%)	1 (0.2%)
Peripheral artery occlusion	1 (0.2%)	0
Axillary vein thrombosis	0	1 (0.2%)
Brachiocephalic vein thrombosis	0	1 (0.2%)

n (%)

Serious VTE-related adverse events reported in the baricitinib group were pulmonary embolism in 5 patients, deep vein thrombosis in 1 patient, and cerebrovascular accident in 1 patient, while those in the placebo group were deep vein thrombosis, pulmonary embolism, cerebrovascular accident, and venous thrombosis in 1 patient each. A causal relationship to the study drug could not be ruled out for pulmonary embolism (4 patients) in the baricitinib group.

VTE-related adverse events that led to study drug discontinuation in the baricitinib group were deep vein thrombosis in 6 patients, pulmonary embolism in 2 patients, and embolism venous and cerebrovascular accident in 1 patient each, while those in the placebo group were deep vein thrombosis in 6 patients, and embolism venous, axillary vein thrombosis, and thrombosis in 1 patient each. A causal relationship to the study drug could not be ruled out for the following events: pulmonary embolism (2 patients) and deep vein thrombosis (1 patient) in the baricitinib group, and deep vein thrombosis (5 patients), axillary vein thrombosis (1 patient), and thrombosis (1 patient) in the placebo group.

Table 16 shows the incidences of VTE-related events by risk factors for thrombosis.

Table 16. Incidences of VTE-related events by risk factors for thrombosis

	With risk factors		Without risk factors*	
	Baricitinib	Placebo	Baricitinib	Placebo
Any risk factor	21/428 (4.9)	16/416 (3.8)	0/79	0/93
Obesity	11/293 (3.8)	10/271 (3.7)	10/214 (4.7)	6/238 (2.5)
Age (≥65 years)	10/144 (6.9)	5/155 (3.2)	11/363 (3.0)	11/354 (3.1)
Smoking	2/18 (11.1)	3/29 (10.3)	19/489 (3.9)	13/480 (2.7)
Prolonged immobility	0/11	0/13	21/496 (4.2)	16/496 (3.2)
Past history of VTE	0/11	0/11	21/496 (4.2)	16/498 (3.2)
Concurrent VTE	1/11 (9.1)	0/18	20/496 (4.0)	16/491 (3.3)
Concurrent cancer	1/19 (5.3)	0/17	20/488 (4.1)	16/492 (3.3)
Coronary artery disease	3/49 (6.1)	2/51 (3.9)	18/458 (3.9)	14/458 (3.1)
Congestive heart failure	5/31 (16.1)	1/30 (3.3)	16/476 (3.4)	15/479 (3.1)
Chronic respiratory disease	4/39 (10.3)	1/30 (3.3)	17/468 (3.6)	15/479 (3.1)
Type II diabetes mellitus	10/193 (5.2)	7/174 (4.0)	11/314 (3.5)	9/335 (2.7)
Immune deficiency	0/17	0/13	21/490 (4.3)	16/496 (3.2)

n/N (%)

* Patients with any of the risk factors, except for age, were classified as having the risk factor, while others were classified as not having the risk factor.

In the ACTT-2 study, information on VTE prophylaxis was not collected and the details of the measures used in the study were thus unknown. The concomitant medications used were summarized for those categorized into "B01A antithrombotic agents" according to the Anatomical Therapeutic Chemical (ATC) Classification System because such agents were presumed to have been used for VTE prophylaxis. The results revealed that thrombotic agents were used at baseline or during the study period in 495 of 507 patients (97.6%) in the baricitinib group and 498 of 509 patients (97.8%) in the placebo group for prophylactic or other purposes.[24)] As shown in Table 17, the most commonly used antithrombotic agent was heparin, including low-molecular-weight heparin. The antithrombotic agents listed include both drugs used for prophylaxis and those used for treatment because they could not be distinguished by intended use.

Table 17. Antithrombotic agents used at baseline or during the study period[*1]

	Baricitinib (N = 507)	Placebo (N = 509)
Use of any antithrombotic agent	495 (97.6)	498 (97.8)
Use of any antithrombotic agent since before enrollment	398 (78.5)	413 (81.1)
Enoxaparin	314 (61.9)	325 (63.9)
Acetylsalicylic acid	79 (15.6)	82 (16.1)
Heparin[*2]	32 (6.3)	48 (9.4)
Nadroparin	22 (4.3)	21 (4.1)
Apixaban	12 (2.4)	14 (2.8)
Clopidogrel	11 (2.2)	12 (2.4)
Use of any antithrombotic agent after enrollment (except use for treatment of adverse events)	97 (19.1)	84 (16.5)
Enoxaparin	92 (18.1)	72 (14.1)
Heparin[*2]	9 (1.8)	20 (3.9)

n (%)

*1 If used in ≥2% of patients in either group, the individual drug names were listed in the table.

*2 Unfractionated heparin and low-molecular-weight heparin (for drugs not listed in the table).

The safety of baricitinib was demonstrated by the results of the ACTT-2 study, in which VTE prophylaxis was recommended. In principle, VTE prophylaxis should be recommended when baricitinib is administered to

[24)] The use of an anticoagulant was reported in 492 of 507 patients (97.0%) in the baricitinib group and 496 of 509 patients (97.4%) in the placebo group.

patients with COVID-19, unless the drugs used for prophylaxis are contraindicated. This precautionary advice will be included in the package insert.

PMDA's view:
In the ACTT-2 study, VTE prophylaxis was recommended and thus most study participants used antithrombotic agents. The results of the study showed that the incidences of VTE-related events tended to be consistently higher in the baricitinib group than in the placebo group, including the incidences of the events in subgroups of patients with and without risk factors for thrombosis. In view of the above results, and given that serious VTE-related events for which a causal relationship to baricitinib could not be ruled out were reported, and that COVID-19 is itself associated with an increased risk of thrombosis (The Japanese Society on Thrombosis and Hemostasis; *Warnings regarding the increased potential risk of thrombosis associated with SARS-CoV-2 infection* [in Japanese][23)]), patients with COVID-19 during treatment with baricitinib should be carefully monitored for the development of VTE. Accordingly, the package insert should include a precautionary statement to the effect that VTE prophylaxis should be administered to patients with COVID-19 during treatment with baricitinib, whenever possible, and should provide information on the use of antithrombic agents and the incidence of VTE-related events in the ACTT-2 study. Given the fact that no clinical data are available from Japanese patients treated with baricitinib for COVID-19, the incidence of VTE, and the relationship between drugs used for VTE prophylaxis and the incidence of VTE should continue to be evaluated in the post-marketing setting. Any new information should be appropriately communicated to healthcare professionals when it becomes available.

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

7.R.4 Clinical positioning and indication

The applicant's explanation about the clinical positioning and indication of baricitinib:
Although "*Clinical Management of Patients with COVID-19: A guide for front-line healthcare workers*, Version 4.2 [in Japanese], dated February 29, 2021" recommends remdesivir and dexamethasone (a corticosteroid) as pharmacotherapies for COVID-19 that are approved in Japan, only limited options for the treatment of COVID-19 are currently available.

The results of the ACTT-2 study in patients with COVID-19 demonstrated the efficacy and acceptable tolerability of baricitinib, when added to remdesivir, indicating the potential of baricitinib to offer a new treatment option to patients with COVID-19. However, the results of the ACTT-2 study demonstrated no add-on effect of baricitinib to remdesivir in patients categorized as NIAID-OS = 4 (i.e., hospitalized, not requiring supplemental oxygen—requiring ongoing medical care [COVID-19 related or otherwise]) [see Section 7.R.2]; the use of baricitinib in patients categorized as NIAID-OS = 4 is therefore not recommended.

The proposed indication was "disease caused by SARS-CoV-2 infection (COVID-19)," but has been changed to "disease caused by SARS-CoV-2 infection (COVID-19) requiring supplemental oxygen" to clarify the

intended population of baricitinib therapy. In addition, the following precautionary statement is included in the "Precautions Concerning Indications" section: "Baricitinib is indicated for hospitalized patients requiring supplemental oxygen, invasive mechanical ventilation, or ECMO."

PMDA's view:
In view of the submitted data, the reviews presented in Sections 7.R.2 and 7.R.3, and the fact that the patient population eligible for the ACTT-2 study was patients who presented with pneumonia, baricitinib can offer a treatment option for patients with pneumonia caused by SARS-CoV-2 infection who require supplemental oxygen (categorized as NIAID-OS = 5 to 7). Accordingly, baricitinib should be indicated for the treatment of "pneumonia caused by SARS-CoV-2 infection (limited to patients requiring supplemental oxygen)."

Dexamethasone is another anti-inflammatory drug that is recommended for the treatment of COVID-19. However, no data is available from a clinical study evaluating the efficacy and safety of baricitinib versus dexamethasone, and the clinical positioning of baricitinib, as compared with dexamethasone, is thus unknown. If new information regarding the efficacy or safety of baricitinib, as compared with corticosteroids is obtained in the post-marketing setting, the applicant should communicate the information to healthcare professionals or take other appropriate actions.

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

7.R.5 Dosage and administration

7.R.5.1 Dosage and administration for adults

The applicant's explanation about the dosage regimen for adults:
A clinical study of baricitinib in patients with rheumatoid arthritis (the JADN study) showed a dose-dependent decrease in blood IL-6 levels in patients receiving baricitinib 1 to 8 mg once daily (*EMBO Mol Med.* 2020;12:e12697). In addition, the approved dosage regimen of baricitinib for the treatment of rheumatoid arthritis is 4 mg administered orally once daily. Based on these facts and the available information on the use of baricitinib in patients hospitalized for COVID-19,[25)] the ACTT-2 study employed a dosage regimen of baricitinib 4 mg once daily orally, with a total treatment duration of ≤14 days. Treatment with baricitinib was discontinued upon hospital discharge.

Since the results of the ACTT-2 study successfully demonstrated the efficacy and safety of baricitinib in combination with remdesivir, the dose of baricitinib 4 mg once daily orally, in combination with remdesivir, has been selected as the dosage regimen for adults, with a total treatment duration of ≤14 days or until hospital discharge, whichever occurs first.

[25)] A report on a study evaluating the safety and other aspects of baricitinib compared with a standard of care therapy (the fixed-dose combination of ritonavir + lopinavir and hydroxychloroquine), which served as the control. Baricitinib was administered at a dose of 4 mg once daily for 14 days, in combination with the fixed-dose combination of ritonavir + lopinavir, to 12 patients with COVID-19 who were hospitalized from March 16 to 30, 2020 (*J Infect.* 2020;81:318-56).

The applicant also provided the following explanation about the combination of baricitinib with corticosteroids, including dexamethasone, which is recommended for the treatment of COVID-19 in Japan:

Since the use of concomitant corticosteroids for treating COVID-19 was prohibited in the ACTT-2 study, no sufficient information regarding the efficacy or safety of baricitinib in combination with corticosteroids is available. However, the use of concomitant corticosteroids for indications other than COVID-19 was permitted in the ACTT-2 study, and 105 patients in the baricitinib group and 118 patients in the placebo group used a corticosteroid during the study.[26)] Table 18 presents a summary of the safety data in the ACTT-2 study by the use of concomitant corticosteroids. Adverse events occurred more frequently in patients receiving concomitant corticosteroids than in those receiving no concomitant corticosteroids, in both the baricitinib group and the placebo group. Among patients receiving concomitant corticosteroids, the adverse event reported with a ≥5% higher incidence in the baricitinib group than in the placebo group was glomerular filtration rate decreased, which was reported as non-serious. The KHAA study, which is an ongoing clinical study evaluating the efficacy and safety of baricitinib in patients with COVID-19, allows the use of concomitant corticosteroids, including dexamethasone, for the treatment of COVID-19. This study will provide new information regarding the safety and other aspects of baricitinib in combination with corticosteroids.

Table 18. Safety summary by use of corticosteroids (safety analysis set)

	With use of corticosteroids		Without use of corticosteroids	
	Baricitinib N = 105	Placebo N = 118	Baricitinib N = 402	Placebo N = 391
Any adverse event	75 (71.4)	89 (75.4)	135 (33.6)	153 (39.1)
Adverse events leading to death	11 (10.5)	20 (16.9)	8 (2.0)	11 (2.8)
Serious adverse events	42 (40.0)	57 (48.3)	35 (8.7)	46 (11.8)
Adverse events leading to study drug discontinuation	14 (13.3)	27 (22.9)	20 (5.0)	32 (8.2)
Common adverse events*				
Respiratory failure	17 (16.2)	23 (19.5)	7 (1.7)	16 (4.1)
Lymphocyte count decreased	17 (16.2)	22 (18.6)	7 (1.7)	13 (3.3)
Glomerular filtration rate decreased	16 (15.2)	10 (8.5)	33 (8.2)	32 (8.2)
Anaemia	14 (13.3)	18 (15.3)	11 (2.7)	15 (3.8)
Hyperglycaemia	13 (12.4)	17 (14.4)	12 (3.0)	23 (5.9)
Haemoglobin decreased	13 (12.4)	14 (11.9)	17 (4.2)	16 (4.1)
Blood glucose increased	12 (11.4)	14 (11.9)	10 (2.5)	13 (3.3)
Lymphopenia	9 (8.6)	12 (10.2)	2 (0.5)	12 (3.1)
Acute respiratory failure	9 (8.6)	9 (7.6)	7 (1.7)	6 (1.5)
Respiratory distress	9 (8.6)	8 (6.8)	4 (1.0)	7 (1.8)
Acute kidney injury	7 (6.7)	18 (15.3)	13 (3.2)	18 (4.6)
Deep vein thrombosis	7 (6.7)	5 (4.2)	5 (1.2)	5 (1.3)
Pneumonia	6 (5.7)	15 (12.7)	6 (1.5)	6 (1.5)
Septic shock	6 (5.7)	8 (6.8)	1 (0.2)	2 (0.5)
Hypotension	2 (1.9)	11 (9.3)	7 (1.7)	7 (1.8)
Sepsis	2 (1.9)	6 (5.1)	2 (0.5)	5 (1.3)
Multiple organ dysfunction syndrome	1 (1.0)	6 (5.1)	1 (0.2)	1 (0.3)
Renal failure	0	6 (5.1)	0	0

n (%)

* Events occurring in ≥5% of patients in either group

PMDA's view:

In view of the submitted data and the reviews presented in Sections 7.R.2 and 7.R.3, the efficacy and safety of baricitinib in combination with remdesivir has been demonstrated. It is appropriate to recommend the following

[26)] The use of concomitant dexamethasone was reported in 41 patients in the baricitinib group and 56 patients in the placebo group.

dosage for adults: 4 mg of baricitinib administered orally once daily in combination with remdesivir, with a total treatment duration of ≤14 days. Based on the above, the proposed dosage and administration for adults should be modified as presented below. In contrast, the use of concomitant corticosteroids, including dexamethasone, for the treatment of COVID-19 was prohibited in the ACTT-2 study, and no information regarding the amount, treatment duration, etc., of concomitant corticosteroids were collected in the study. These facts preclude the safety of baricitinib in combination with corticosteroids in the treatment of COVID-19 from being evaluated based on the safety information from patients receiving corticosteroids in the ACTT-2 study. Thus, the efficacy and safety of baricitinib in combination with corticosteroids, including dexamethasone, remain unknown. The applicant should appropriately inform healthcare professionals that the efficacy and safety of baricitinib in combination with corticosteroids in the treatment of COVID-19 was not demonstrated in the ACTT-2 study. Furthermore, the applicant should collect information regarding the efficacy and safety of baricitinib in combination with corticosteroids through the ongoing KHAA study, etc. in the post-marketing setting, and should take appropriate actions, such as communicating new findings to healthcare professionals.

Dosage and administration

The usual adult dosage is 4 mg of baricitinib administered orally once daily, in combination with remdesivir. The total duration of baricitinib therapy should be ≤14 days.

7.R.5.2 Dose adjustment for patients with renal impairment

The applicant's explanation about the necessity of dose adjustment for baricitinib in patients with renal impairment:

The exposure to baricitinib (AUC) tends to increase with an increase in the severity of renal impairment [see "Review Report for Olumiant Tablets 2 mg and Olumiant Tablets 4 mg, dated May 19, 2017"], and a reduced dose of baricitinib (2 mg) is recommended in patients with rheumatoid arthritis who have moderate renal impairment (eGFR, 30 to 60 mL/min/1.73 m^2). Based on these facts, baricitinib was administered at a dose of 2 mg to patients with moderate renal impairment (eGFR, 30 to 60 mL/min/1.73 m^2) in the ACTT-2 study.

Data from the ACTT-2 study were analyzed by renal function. Table 19 shows time to recovery within 28 days after randomization by baseline eGFR, and Table 20 presents a summary of the safety data by baseline eGFR.

Table 19. Time to recovery within 28 days after randomization by baseline eGFR* (ITT population)

	30 ≤ eGFR < 60		60 ≤ eGFR < 90		90 ≤ eGFR	
	Baricitinib N = 57	Placebo N = 58	Baricitinib N = 149	Placebo N = 147	Baricitinib N = 298	Placebo N = 303
No. of patients who recovered (%)	37 (64.9)	37 (63.8)	126 (84.6)	110 (74.8)	268 (89.9)	259 (85.5)
Median time to recovery [95% CI] (days)	12.0 [8.0, 25.0]	15.0 [7.0, 25.0]	8.0 [6.0, 9.0]	10.0 [8.0, 13.0]	6.0 [6.0, 7.0]	7.0 [6.0, 8.0]

* Eleven patients in the baricitinib group and 9 patients in the placebo group had no evaluable eGFR data at baseline, and 1 patient in the placebo group had an eGFR <30 mL/min/1.73 m^2 at baseline.

Table 20. Safety summary by baseline eGFR* (safety analysis set)

	30 ≤ eGFR < 60		60 ≤ eGFR < 90		90 ≤ eGFR	
	Baricitinib N = 56	Placebo N = 58	Baricitinib N = 149	Placebo N = 147	Baricitinib N = 298	Placebo N = 303
Any adverse event	34 (60.7)	37 (63.8)	65 (43.6)	76 (51.7)	109 (36.6)	128 (42.2)
Adverse events leading to death	5 (8.9)	12 (20.7)	7 (4.7)	10 (6.8)	6 (2.0)	9 (3.0)
Serious adverse events	18 (32.1)	22 (37.9)	26 (17.4)	36 (24.5)	32 (10.7)	45 (14.9)
Adverse events leading to study drug discontinuation	10 (17.9)	12 (20.7)	13 (8.7)	26 (17.7)	10 (3.4)	21 (6.9)

n (%)

* Four patients in the baricitinib group had no evaluable eGFR data at baseline, and 1 patient in the placebo group had an eGFR <30 mL/min/1.73 m^2 at baseline.

The use of baricitinib for the approved indications is contraindicated in patients with severe renal impairment (eGFR, 15 to 30 mL/min/1.73 m^2), and the ACTT-2 study excluded such patients. However, taking into account the seriousness of COVID-19, and given that the duration of baricitinib therapy for COVID-19 is as short as ≤14 days, the potential benefits of baricitinib are likely to outweigh its potential risks in such patients. In view of the following investigations, a dosage regimen of baricitinib 2 mg every 48 hours is recommended in patients with severe renal impairment.

- The results of a clinical study in patients with renal impairment (the JADL study) revealed that the exposure to baricitinib ($AUC_{0-\infty}$) was approximately 4 times higher in subjects with severe renal impairment (eGFR, 15 to 30 mL/min/1.73 m^2) than in subjects with normal renal function, while the effect of renal impairment on the C_{max} of baricitinib was small. The C_{max} value in subjects with severe renal was only 1.4 times higher than that in subjects with normal renal function [see "Review Report for Olumiant Tablets 2 mg and Olumiant Tablets 4 mg, dated May 19, 2017"].
- A population pharmacokinetic (PPK) analysis was performed based on data from 5 phase I and II studies, including a clinical study in patients with renal impairment (the JADL study). Figure 7 presents the estimated blood baricitinib concentrations following multiple doses of baricitinib 4 mg once daily in subjects with normal renal function, and those following multiple doses of baricitinib 2 mg every 48 hours in subjects with severe renal impairment.

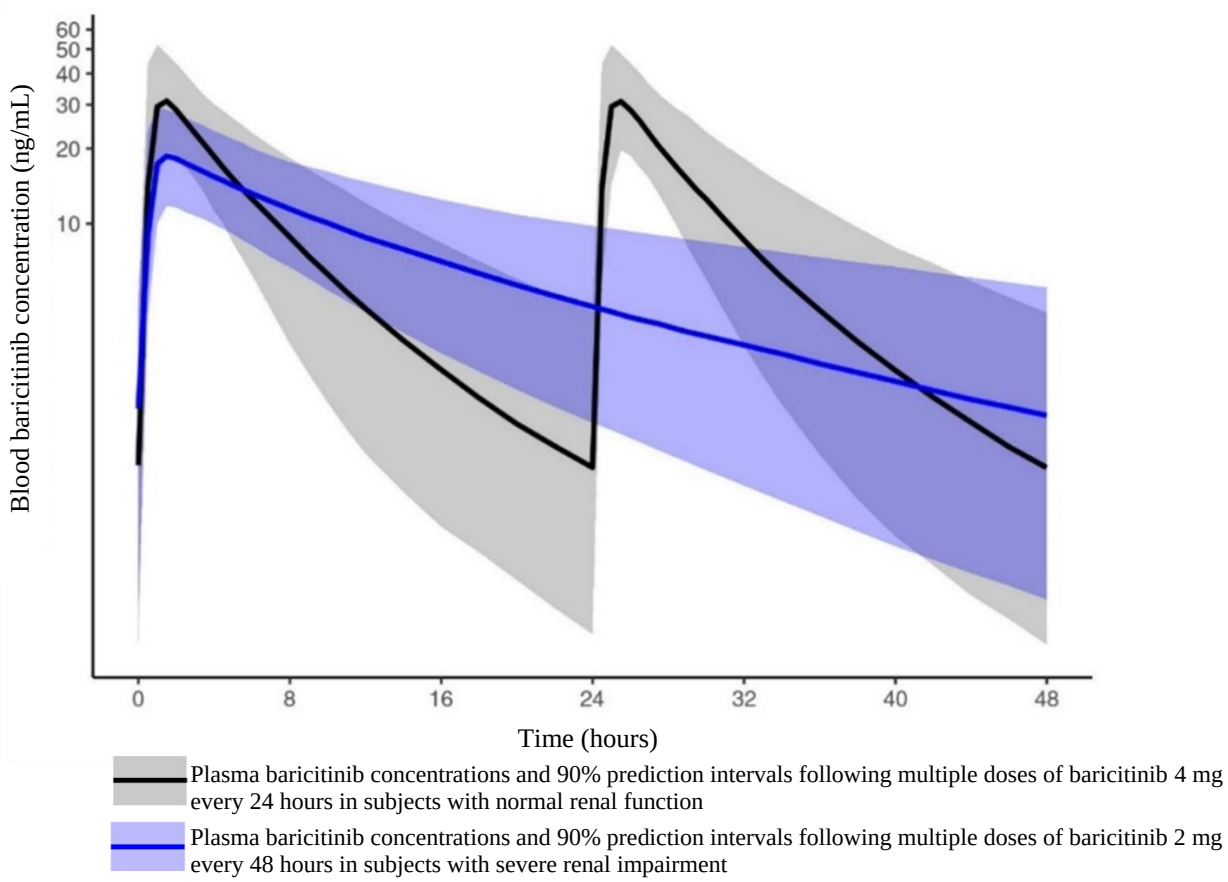


Figure 7. Mean (90% prediction interval) estimated baricitinib concentrations by renal function

PMDA's view:

A dose of 2 mg of baricitinib is appropriate in patients with moderate renal impairment (eGFR, 30 to 60 mL/min/1.73 m^2). In contrast, baricitinib is contraindicated in patients with severe renal impairment (eGFR, 15 to 30 mL/min/1.73 m^2) when used for the approved indications (rheumatoid arthritis and atopic dermatitis), and there is only limited experience with the use of baricitinib in patients with severe renal impairment, including those with COVID-19. Nevertheless, in view of the seriousness of COVID-19 and the short duration of baricitinib therapy for COVID-19 (≤14 days), and in consideration of the applicant's investigations regarding the pharmacokinetics of baricitinib, the use of baricitinib in patients with severe renal impairment may be allowable, if the potential benefits of baricitinib are considered to outweigh its potential risks. In this regard, the dosage regimen of baricitinib 2 mg every 48 hours for patients with severe renal impairment is acceptable. However, baricitinib should be administered carefully to this patient population, with close monitoring of the patient's condition. In addition, the applicant should actively collect information regarding the safety and other aspects of baricitinib used in patients with severe renal impairment in the post-marketing setting, and should appropriately communicate new findings to healthcare professionals if they become available.

7.R.5.3 Administration of baricitinib to patients who are not able to swallow whole tablets

The applicant's explanation about the administration of baricitinib to patients with COVID-19 who are not able to swallow whole tablets:

Assuming that baricitinib tablets dispersed in water would be administered orally or through a nasogastric tube, the stability of dispersed baricitinib, as well as its passage and compatibility with gastrostomy and the nasogastric/orogastric tubes were assessed.[27)] The key results are described below.

- One 1-mg tablet or three 2-mg tablets of baricitinib were dispersed in 10 mL of water. The recovery rates of baricitinib contained in the one 1-mg tablet dispersed in water (which includes 10 mL of water used for rinsing the container) were 99.7%, both immediately after dispersion and after 4 hours of storage at ambient temperature, while those of baricitinib contained in the three 2-mg tablets of baricitinib dispersed in water were 97.4%, both immediately after dispersion and after 4 hours of storage at ambient temperature. When one 2-mg tablet of baricitinib was crushed and dispersed in 10 mL of water, and stored at ambient temperature, the acceptance criteria for the strength specification were met for up to 48 hours.
- There were no problems with the compatibility (adsorption) of baricitinib with silicone, polyurethane, or polyvinyl chloride (PVC) tubes. The three 2-mg tablets of baricitinib dispersed in water were found to pass through a polyurethane nasogastric/orogastric tube (10 Fr) and a silicon gastrostomy tube (12 Fr), while the two 2-mg tablets of baricitinib dispersed in water were found to pass through a PVC nasogastric/orogastric tube (16 Fr). However, tube clogging occurred when the two 2-mg tablets of baricitinib dispersed in water were placed into a silicon or polyurethane nasogastric/orogastric tube (8 Fr).

The pharmacokinetics of baricitinib that has been dispersed in water and then administered orally or through a nasogastric tube have not been assessed. However, in view of the fact that the absolute bioavailability of baricitinib is 78.9% [see "Review Report for Olumiant Tablets 2 mg and Olumiant Tablets 4 mg, dated May 19, 2017"], and the fact that the dissolution rates of baricitinib were almost 100% in 5 minutes at pH 1.2 and ≥85% in 15 minutes at pH 4.5 and pH 6.8 in the dissolution tests, the absorption of baricitinib administered as a dispersion preparation by mouth or nasogastric tube is unlikely to differ largely from that of baricitinib tablets.

The protocol of the ACTT-2 study allowed the following alternate method of administration of baricitinib or placebo to patients who were unable to swallow whole tablets: administration of baricitinib tablets or matched placebo as a dispersion preparation by mouth or nasogastric tube. For the alternate administration method, a written manual containing the preparation procedure as well as precautions concerning preparation (the possibility of accidental exposure to baricitinib when crushing tablets, given its reproductive toxicity, etc.) was distributed to each study site. No information regarding the dosage forms or routes of administration of baricitinib or placebo was collected in the ACTT-2 study. However, the oral dosing of tablets is difficult, at least in patients categorized as NIAID-OS = 7 who require invasive mechanical ventilation or ECMO. Therefore, such patients were assumed to have received baricitinib or placebo as a dispersion preparation via

[27)] The formulations of baricitinib that are approved worldwide include 1-mg tablet (unapproved in Japan), 2-mg tablet, and 4-mg tablet. The 1-mg tablet (the lowest baricitinib strength) and 2-mg tablet were used in the assessment of the stability of dispersed baricitinib, and its passage and compatibility with gastrostomy and the nasogastric/orogastric tubes, because the 2-mg tablet contains a greater amount of excipients relative to the amount of the drug substance than the 4-mg tablet.

nasogastric tube. Administration errors of study drug were reported as protocol deviations in the study. The sole protocol deviation due to dosing tubes was a change of the dosing timing to avoid the placement of a nasogastric tube in a prone patient. Thus, the administration of baricitinib as a dispersion preparation by mouth or nasogastric tube to patients who are unable to swallow whole tablets is unlikely to cause problems, or affect the efficacy or safety of baricitinib. The alternate administration method used in the ACTT-2 study may be used in the post-marketing setting, as well.

PMDA's view:

The ACTT-2 study was conducted amid the COVID-19 pandemic, at a time when the rapid development of therapeutic drugs was required. It is therefore understandable, to some extent, that the study was planned so that the alternate administration of baricitinib would be allowed in patients who were unable to swallow whole tablets, based on the available findings such as the formulation properties. However, because the pharmacokinetics of baricitinib, administered as a dispersion preparation by mouth or nasogastric tube, had not been compared with those of baricitinib tablets administered orally, the applicant should have collected information regarding at least the dosage forms and routes of administration that were actually used in the study, so as to enable an assessment of whether the administration of dispersed baricitinib via nasogastric tube had caused any problems, and to enable an evaluation of the possible impacts of differences in dosage form or route of administration on the efficacy and safety of baricitinib. Nevertheless, the alternate method of administration of baricitinib (dispersion preparation given by mouth or nasogastric tube) to patients who are unable to swallow whole tablets is acceptable in the post-marketing setting, in view of the fact that more than a few patients who were unable to swallow whole tablets must have been enrolled in the ACTT-2 study because of the target patient population, and considering the protocol-specified administration method and the efficacy and safety results obtained by the study [see Section 7.R.4]. Further, as in the case of the ACTT-2 study, the applicant should appropriately provide healthcare professionals with the information necessary for administering baricitinib as a dispersion preparation by mouth or nasogastric tube, including precautionary advice for healthcare professionals to avoid being unintentionally exposed to baricitinib when preparing a dispersion, through written materials or by other means. In addition, the applicant should evaluate the effects of dosage forms and routes of administration on the safety and other aspects of baricitinib in the post-marketing setting, and appropriately communicate new findings to healthcare professionals if they become available.

7.R.5.4 Use in pediatric patients

The applicant provided the following explanation about the use of baricitinib in pediatric patients and the dosage regimen for children, though no clinical data are available from pediatric patients treated with baricitinib for COVID-19:

Based on the facts described below, the inclusion of pediatric patients in the intended patient population of baricitinib is acceptable.[28)] The proposed dosage and administration for pediatric patients are as follows, in agreement with the Emergency Use Authorization in the US: "Baricitinib 4 mg once daily orally in children aged ≥9 years, or baricitinib 2 mg once daily orally in children aged ≥2 to <9 years. Multisystem inflammatory

[28)] The applicant also explained that [redacted] had commented that [redacted] during a consultation.

syndrome in children (MIS-C) has been reported as a COVID-19 symptom that is unique to children. However, both the pathogenic mechanism and the clinical manifestations remain unclear, and baricitinib is unlikely to be indicated for the treatment of this symptom. The applicant is currently planning to conduct a clinical study in pediatric patients with COVID-19.

- The incidences of COVID-19 and severe COVID-19 tended to be lower in children than in adults, with more children experiencing gastrointestinal symptoms. On the other hand, there are reports that pediatric patients with COVID-19 presenting with severe respiratory symptoms suffered from acute respiratory distress syndrome, as in the case of adult patients (*Nature.* 2021;590:140-5, *Pediatric*s. 2020; 146:e2020009399, *Asian Pac J Allergy Imunol.* 2020;38:170-7). Thus, the pathophysiology of severe respiratory symptoms associated with SARS-CoV-2 infection does not largely differ between children and adults.
- Although there are no study results that can be used to make a comparison between adults and children, regarding the response to baricitinib or changes in the cytokine profiles associated with baricitinib therapy, improved clinical manifestations and decreased blood concentrations of pro-inflammatory cytokines (e.g., IL-6) following baricitinib therapy were reported in a clinical study of type-1 interferonopathies of childhood (*J Clin Invest.* 2018;128:3041-52).
- In clinical studies of baricitinib in children,[29)] no events requiring particular additional attention have been identified in children, as compared with adults.
- In the JAHV study in patients with juvenile idiopathic arthritis aged ≥6 to <18 years,[30)] changes in blood baricitinib concentrations [redacted] were [redacted] (Figure 8).

[29)] The submitted results from pediatric clinical studyof baricitinib included safety data (as of [redacted], 20[redacted]) from the JAHV study in pediatric patients with juvenile idiopathic arthritis, the JAIP study in pediatric patients with atopic dermatitis, and from the JAGA study in patients with type-1 interferonopathies.

[30)] The JAHV study was composed of [redacted]. In [redacted], [redacted] was orally administered to [redacted]. As of [redacted], 20[redacted], [redacted] pediatric patients with juvenile idiopathic arthritis ([redacted]) were enrolled in the study to obtain the pharmacokinetic data.

[31)] [redacted] [see "Review Report for Olumiant Tablets 2 mg and Olumiant Tablets 4 mg, dated May 19, 2017"] [redacted]

Figure 8. Changes in plasma baricitinib concentrations following oral doses of

- In the JAIP study in patients with atopic dermatitis in patients aged ≥ to <18 years,[32] changes in plasma baricitinib concentrations following were (Figure 9).

Figure 9. Changes in plasma baricitinib concentrations following oral doses of

- analysis using the pharmacokinetic data ( ) from the JAGA study in patients with type-1 interferonopathies[34] revealed that

[32] The JAIP study was composed of . In , was to be orally administered to . As of , 20 , pediatric patients with atopic dermatitis ( ) were enrolled in the study to obtain the pharmacokinetic data.

[33] [see "Review Report for Olumiant Tablets 2 mg and Olumiant Tablets 4 mg, dated November 25, 2020"].

[34] In the JAGA study, patients received .

[redacted]. Table 21 shows the estimated pharmacokinetic parameters of baricitinib [redacted].

Table 21. Pharmacokinetic parameters of baricitinib in patients with type-1 interferonopathies

Patient population	Dosage regimen	$C_{max,ss}$ (ng/mL)	$AUC_{0-24,ss}$ (ng·h/mL)	CL/F (L/h)	V/F (L)	$t_{1/2}$ (h)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Geometric mean (CV%)

PMDA's view:

The applicant's explanation is understandable to some extent. However, the determination of the dosage regimen for pediatric patients should await the results from the pediatric clinical study that is currently being planned, because evaluating the clinical benefits of baricitinib in Japanese pediatric patients with COVID-19 and choosing the dosage regimen for pediatric patients is currently difficult, in view of the following facts:

- There are no available data from any clinical study evaluating the use of baricitinib in pediatric patients with COVID-19.
- No safety information is available from children treated with baricitinib in combination with remdesivir.
- The efficacy and safety of baricitinib has not been established in children for any indication, including COVID-19. In addition, the clinical data that are currently available for the approved indications are not sufficient to evaluate the efficacy or safety of baricitinib in pediatric patients with COVID-19.
- There are no available clinical data from even Japanese adult patients with COVID-19 treated with baricitinib [see Section 7.R.1].

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

7.R.6 Post-marketing investigations and safety measures

The applicant is planning to conduct a post-marketing drug use-results survey, in addition to routine pharmacovigilance practices, to evaluate the safety and other aspects of baricitinib in clinical practice. The sample size of the survey will be [redacted] patients, and the observation period will be 1 month.

PMDA's view:

Since no clinical data are available from Japanese patients treated with baricitinib for pneumonia caused by SARS-CoV-2 infection (COVID-19), the applicant should conduct a use-results survey in the post-marketing setting to assess the safety and other aspects of baricitinib in clinical practice. In addition, in the light of the review presented in Section 7.R.5, the applicant should collect further information about the post-marketing safety and other aspects of baricitinib in patients with renal impairment or about those of baricitinib administered via the alternate method to patients who are unable to swallow whole tablets.

At the same time, the applicant should advise healthcare professionals to administer VTE prophylaxis to patients with pneumonia caused by SARS-CoV-2 infection (COVID-19) during treatment with baricitinib, whenever possible, and should also prepare and disseminate a written material containing information regarding the safety of baricitinib and procedures and requirements for administering baricitinib via the alternate method, so as to promote the proper use of baricitinib.

The above PMDA's conclusions and the necessity of additional safety measures 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, and 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, and 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 baricitinib, when administered in combination with remdesivir, has efficacy in the treatment of patients with pneumonia caused by SARS-CoV-2 infection (COVID-19) requiring supplemental oxygen and that baricitinib has acceptable safety in view of its benefits. Baricitinib has a certain level of clinical significance, because it offers a new treatment option for patients with pneumonia caused by SARS-CoV-2 infection (COVID-19) requiring supplemental oxygen. The safety and other aspects of baricitinib in Japanese patients with pneumonia caused by SARS-CoV-2 infection (COVID-19) in clinical practice should be further evaluated through post-marketing surveillance, etc.

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

Review Report (2)

April 12, 2021

Product Submitted for Approval

Brand Name	Olumiant Tablets 2 mg
	Olumiant Tablets 4 mg
Non-proprietary Name	Baricitinib
Applicant	Eli Lilly Japan K.K.
Date of Application	December 25, 2020

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy and safety

At the Expert Discussion, the expert advisors supported the PMDA's conclusions on the efficacy and safety of baricitinib presented in Review Report (1).

1.2 Clinical positioning and indication

At the Expert Discussion, the expert advisors supported the PMDA's conclusions on the clinical positioning and indication of baricitinib presented in Review Report (1), while raising the following comment:

- The intended population for baricitinib therapy should be clearly specified as hospitalized patients.

Based on the discussion at the Expert Discussion, PMDA has concluded that the following statements should be included in the "Indications" and the "Precautions Concerning Indications" sections.

Indication

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

Precautions Concerning Indications

Baricitinib should be administered to hospitalized patients who require supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

1.3 Dosage and administration

At the Expert Discussion, the expert advisors supported the PMDA's conclusion on the dosage and administration of baricitinib presented in the Review Report (1), while raising the following comments on the use of baricitinib in children:

- In view of the intended population of baricitinib therapy under the Emergency Use Authorization in the US, baricitinib may serve as a treatment option for pediatric patients with pneumonia caused by SARS-CoV-2 infection (COVID-19).
- Due to insufficient data supporting the inclusion of pediatric patients with pneumonia caused by SARS-CoV-2 infection (COVID-19) in the intended population of baricitinib, the use of baricitinib in pediatric patients should be evaluated based on the results from the pediatric clinical study that is currently being planned.

Based on the discussion at the Expert Discussion, PMDA has concluded that the dosage and administration of baricitinib should be set as presented below, and that an evaluation of the clinical benefits, etc. of baricitinib in pediatric patients with pneumonia caused by SARS-CoV-2 infection (COVID-19) should await the results from a clinical study involving such patients, as described in Section 7.R.5.4.

Dosage and Administration

The usual adult dosage is 4 mg of baricitinib administered orally once daily, in combination with remdesivir. The total duration of baricitinib therapy should be ≤14 days.

1.4 Post-marketing investigations and safety measures

At the Expert Discussion, the expert advisors supported the PMDA's conclusion on the post-marketing investigations and safety measures presented in the Review Report (1), while raising the following comment:

- Since no clinical study results are available from Japanese patients treated with baricitinib for pneumonia caused by SARS-COV-2 infection (COVID-19), both the efficacy and safety of baricitinib should be evaluated through post-marketing surveillance, etc.

PMDA instructed the applicant to advise healthcare professionals to administer VTE prophylaxis to patients with pneumonia caused by SARS-CoV-2 infection (COVID-19) during treatment with baricitinib, whenever possible, and to prepare and disseminate a written material containing information regarding the safety of baricitinib and procedures and requirements for administering baricitinib via the alternate method, so as to promote the proper use of baricitinib.

In view of the above discussion, PMDA has concluded that the risk management plan (draft) for baricitinib should include the safety specification presented in Table 22, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 23. Accordingly, PMDA instructed the applicant to conduct post-marketing surveillance, etc. which cover all of the issues.

Table 22. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Herpes zoster • Serious infections (e.g., tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, and opportunistic infection) • Gastrointestinal perforation • Hepatitis B virus reactivation • Interstitial pneumonia • Neutrophil count decreased, lymphocyte count decreased, haemoglobin decreased • Hepatic function disorder • Venous thromboembolism	• Rhabdomyolysis, myopathy • Malignant tumor • Cardiovascular events	None
Efficacy specification		
Efficacy in routine clinical settings (rheumatoid arthritis)		

(Unchanged)

Table 23. 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 (pneumonia caused by SARS-CoV-2 infection) • Specified use-results survey (rheumatoid arthritis) • Specified use-results survey (atopic dermatitis) • General use-results survey (pneumonia caused by SARS-CoV-2 infection) • Post-marketing database survey (serious infections) (rheumatoid arthritis) • Post-marketing database survey (malignant tumors) (rheumatoid arthritis) • Post-marketing clinical study (the JADY study) (rheumatoid arthritis) • Post-marketing clinical study (the JAHN study) (atopic dermatitis) • Post-marketing clinical study (the JAIN study) (atopic dermatitis)	• Specified use-results survey (rheumatoid arthritis)	• Prepare and disseminate written information for healthcare professionals (a proper use guide for healthcare professionals) • Prepare and disseminate written information for patients (a leaflet for patients) (rheumatoid arthritis, atopic dermatitis) • Ensure that information on proper use is provided before delivery (rheumatoid arthritis, atopic dermatitis) • Disseminate data gathered during early post-marketing phase vigilance (pneumonia caused by SARS-CoV-2 infection [COVID-19])

(Underline denotes additions for the present application.)

The applicant's explanation:

As presented in Table 24, a use-results survey will be conducted in patients with pneumonia caused by SARS-CoV-2 infection, to evaluate the safety and efficacy of baricitinib in clinical practice. The observation period will be ≤4 weeks and the planned sample size will be 250 patients evaluable for safety.

Table 24. Outline of use-results survey (draft)

Objective	To collect and evaluate information regarding the safety and efficacy of baricitinib in clinical practice
Survey method	Continuous registry
Population	Patients with pneumonia caused by SARS-CoV-2 infection (COVID-19) requiring supplemental oxygen
Observation period	≤4 weeks (or until hospital discharge, whichever occurs first)
Planned sample size	250 patients (for the safety analysis set)
Main survey items	• Safety specification: venous thromboembolism • Patient characteristics • Medical history/comorbidities • Exposure to baricitinib (route of administration, dosage form, etc.) • Concomitant drugs/therapies • Adverse events/clinical laboratory test results • Efficacy endpoints (time to recovery, National Institute of Allergy and Infectious Disease Ordinal Scale [NIAID-OS])

PMDA has accepted the above actions of the applicant. The gathered information should be appropriately and promptly communicated to healthcare professionals.

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, since the application documents had been generally collected and prepared in compliance with the standards for integrity of data submitted for product application. At the same time, the assessment revealed the following finding in CTD 5.3.5.1.1, despite its minor impact on the overall assessment of the study. The applicant was notified of the issue.

Finding requiring corrective action

Sponsor-investigator

- The change in the method of evaluating the primary endpoint and its results were not appropriately documented in the clinical study report.

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

The new drug application data (CTD 5.3.5.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of 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.

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 as shown below, with the following approval condition. Although the present partial change approval application is intended for the addition of a new indication, the remainder of the ongoing re-examination period is ≥4 years; therefore, the re-examination period for the present application should be the remainder of the ongoing re-examination period (until July 2, 2025).

Indications

The following diseases in patients who have had an inadequate response to conventional treatments:

Rheumatoid arthritis (including the prevention of structural joint damage)

Atopic dermatitis

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

(The underlined words are added to the proposed text. The strikethrough words are deleted from the proposed text. Double underline denotes additions made on December 25, 2020.)

Dosage and Administration

Rheumatoid arthritis, atopic dermatitis

The usual adult dosage is 4 mg of baricitinib administered orally once daily. The dose should be reduced to 2 mg according to the patient's condition.

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

The usual dosage for adult patients ~~and pediatric patients ≥9 years of age~~ is 4 mg of baricitinib administered orally once daily, in combination with remdesivir.

~~The usual dosage for pediatric patients ≥2 years to <9 years of age is 2 mg of baricitinib administered orally once daily, in combination with remdesivir. Baricitinib therapy may continue for ≤14 days or until hospital discharge, whichever occurs first.~~ The total duration of baricitinib therapy should be ≤14 days.

(The underlined words are added to the proposed text. The strikethrough words are deleted from the proposed text. Double underline denotes additions made on December 25, 2020.)

Approval Conditions

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

Appendix

List of Abbreviations

AAK1	AP2-assoiated protein kinase
ACE2	Angiotensin-converting enzyme 2
ACTT-2	I4V-MC-K001
AD	Atopic dermatitis
ALT	Alanine aminotransferase
AST	Asparate aminotransferase
AUC	Area under the plasma concentration-time curve
BCRP	Breast cancer resistance protein
BIKE	BMP2-inducible kinase
C_{max}	Maximum observed plasma drug concentration
CT	Computed tomography
CYP	Cytochrome P450
ECMO	Extracorporeal membrane oxygenation
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
GAK	Cyclin G-associated kinase
IFN	Interferon
IL	Interleukin
ITT	Intent to treat
JAK	Janus kinase
JIA	Juvenile idiopathic arthritis
KHAA	I4V-MC-KHAA
MATE	Multidrug and toxin extrusion
MIS-C	Multisystem Inflammatory Syndrome in Children
NAK	Numb-associated kinase
NIAID	National Institute of Allergy and Infectious Disease
NIAID-OS	National Institute of Allergy and Infectious Disease Ordinal Scale
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
PCR	Polymerase chain reaction
Peficitinib	Peficitinib hydrobromide
P-gp	P-glycoprotein
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
PVC	Polyvinyl chloride
RA	Rheumatoid arthritis
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
STAT	Signal transducer and activator of transcription
STK16	Serine/threonine kinase 16
SpO_2	Saturation pulse oxygen
TNF	Tumor necrosis factor
VTE	Venous thromboembolism