Report on the Deliberation Results

June 7, 2017
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	March 11, 2016

Results of Deliberation

In its meeting held on May 30, 2017, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. A post-marketing use-results survey must be conducted covering all patients treated with the product until data are gathered from a certain number of patients so that the safety and efficacy data of the product are available early. The applicant is required to take any necessary measures to ensure proper use of the product based on data obtained through the survey.

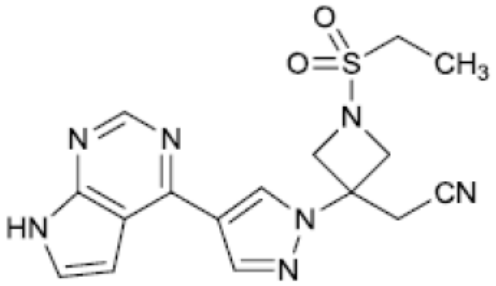
**Japanese Accepted Name (modified INN)*

Review Report

May 19, 2017
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Olumiant Tablets 2 mg Olumiant Tablets 4 mg
Non-proprietary Name	Baricitinib
Applicant	Eli Lilly Japan K.K.
Date of Application	March 11, 2016
Dosage Form/Strength	Each tablet contains 2 or 4 mg of baricitinib.
Application Classification	Prescription drug (1) Drug with a new active ingredient
Chemical Structure	



Molecular formula:	$C_{16}H_{17}N_7O_2S$
Molecular weight:	371.42
Chemical name:	{1-(Ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl} acetonitrile

Items Warranting Special Mention

Reviewing Office Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of rheumatoid arthritis in patients who have had an inadequate response to conventional therapies, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. Because of possible serious adverse reactions such as serious infection and malignant tumor, adequate safety measures should be taken in its clinical use, as practiced for existing Janus kinase (JAK) inhibitors and biologics for the treatment of rheumatoid arthritis. To early determine the safety profile of the product including the occurrence of unknown adverse events, a post-marketing use-results survey must be conducted covering all patients treated with the product until data are obtained from a specific number of patients. Another survey should also be conducted to trace serious infection and malignant tumor, etc. in prolonged use of the product.

Indication	Rheumatoid arthritis in patients who have had an inadequate response to conventional treatments (including the prevention of structural joint damage)
Dosage and Administration	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.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. A post-marketing use-results survey must be conducted covering all patients treated with the product until data are gathered from a certain number of patients so that the safety and efficacy data of the product are available early. The applicant is required to take any necessary measures to ensure proper use of the product based on data obtained through the survey.

Attachment

Review Report (1)

April 20, 2017

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

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	March 11, 2016
Dosage Form/Strength	Film-coated tablets; each containing 2 or 4 mg of baricitinib
Proposed Indication	Rheumatoid arthritis (including the prevention of structural joint damage)
Proposed Dosage and Administration	The usual adult dosage is 4 mg of baricitinib administered orally once daily. The dose may be reduced to 2 mg according to symptoms.

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List of Abbreviations

ACR	American college of rheumatology
ACR20, ACR50, or ACR70 responder index	Proportion of patients achieving American College of Rheumatology 20%, 50%, or 70% improvement
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration versus time curve
$AUC_{0\text{-}24}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, $AUC_{\tau,\ ss}$	area under the plasma concentration versus time curve from zero to 24 hours, from time zero to time t, where t is the last time point with a measurable concentration, from time zero to infinity, during one dosing interval at steady state
BCRP	breast cancer resistance protein
BID	twice daily
CDAI	clinical disease activity index
CRP	C-reactive protein
CL	clearance
CL/F	apparent total body clearance
CLnr/F	apparent non-renal clearance
CLr/F	apparent renal clearance
C_{max}	maximum observed plasma drug concentration
$C_{max,\ ss}$	maximum observed plasma drug concentration during a dosing interval at steady state
$C_{min,\ ss}$	minimum observed plasma drug concentration during a dosing interval at steady state
cDMARDs	conventional disease-modifying antirheumatic drug
CMV	cytomegalovirus
CPK	creatine phosphokinase
Cr	creatinine
CTCAE	common terminology criteria for adverse event ver.3.0
CYP	cytochrome P450
D_1	absorption duration
DAS28	disease activity score based on 28 joint counts
DAS28-hsCRP	disease activity score modified to include the 28 diarthrodial joint count and high-sensitivity C-reactive protein
EBV	epstein-barr virus
eGFR	estimated glomerular filtration rate
EULAR	European league against rheumatism
FAS	full analysis set
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
HAQ-DI	health assessment questionnaire-disability index
HBV	hepatitis B virus
HEK cell	human embryonic kidney cell
HEK-PEAK cell	Epstein-barr virus nuclear antigen 1-expressing human embryonic kidney cell
HPLC	high performance liquid chromatography
hsCRP	high-sensitivity C-reactive protein
IC_{50}	half maximal inhibitory concentration

IFN	interferon
IL	interleukin
IR	infrared absorption spectrum
JAK	janus kinase
LC/MS/MS	liquid chromatography with tandem mass spectrometry
LOCF	last observation carried forward
MACE	major adverse cardiovascular events
MATE	multidrug and toxin extrusion protein
mBOCF	modified baseline observation carried forward
MCP-1	monocyte chemotactic protein-1
MDCK cell	madin-darby canine kidney cell
MedDRA/J	medical dictionary for regulatory activities Japanese version
mITT	modified intent-to-treat
mTSS	modified total sharp score
MTX	methotrexate
NK cell	natural killer cell
NMR	nuclear magnetic resonance spectrum
NMSC	nonmelanoma skin cancer
NRI	non-responder imputation
NSAIDs	non-steroidal anti-inflammatory drugs
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OC	observed case
OCT	organic cation transporter
P-gp	p-glycoprotein
PK/PD	pharmacokinetics/pharmacodynamics
QTcP	population-corrected QT interval
QD	once daily
RA	rheumatoid arthritis
RH	relative humidity
SDAI	simplified disease activity index
SDC	smallest detectable change
SEER	surveillance epidemiology and end result
SIR	standardized incidence rate
STAT	signal transducer and activator of transcription
TYK	tyrosine kinase
t_{max}	time to reach maximum concentration
TNF	tumor necrosis factor
$t_{1/2}$	elimination half-life
Vz/F	apparent volume of distribution during the terminal phase
V_1/F	apparent central volume of distribution
V_2/F	apparent peripheral volume of distribution
PMDA	Pharmaceuticals and Medical Devices Agency
Olumiant	Olumiant Tablets 2 mg and 4 mg

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

Baricitinib was developed by Incyte Corporation in the US. The compound selectively inhibits Janus kinase (JAK) 1 and JAK2.

Conventional disease-modifying antirheumatic drugs (cDMARDs) such as methotrexate (MTX) are used as standard drug therapies for rheumatoid arthritis (RA) from its early stage for pathological control including the inhibition of the progression of joint destruction. For the treatment of RA in patients who have responded inadequately to cDMARDs, human tumor necrosis factor (TNF) inhibitors are used.

The JAK family of intracellular tyrosine kinases consists of JAK1, JAK2, JAK3, and tyrosine kinase (TYK) 2. The JAK family is involved in type I and type II cytokine receptor-mediated signal transduction. In response to ligand stimulation, each of 2 subunits constituting cytokine receptors forms a complex with a specific JAK. When intracellular adenosine triphosphate (ATP) binds to this complex, phosphorylates and activates the JAK, signal transducer and activator of transcription (STAT), a transcription factor, is phosphorylated and transduced into the nucleus. The activation of the JAK-STAT pathway affects the expression of genes contributing to cellular localization, cellular differentiation, and inhibition of cellular proliferation. Because JAK1 and JAK2 are involved in signal transduction mediated by various cytokine receptors, such as interleukin (IL)-6 receptors (JAK1/JAK2), granulocyte-macrophage colony-stimulating factor receptors (JAK2/JAK2), and interferon (IFN) receptors (JAK1/JAK2, JAK1/TYK2) and are suggested to be involved in autoimmune disease, the development of baricitinib was started for the treatment of RA, etc.

In Europe, baricitinib in 2- and 4-mg tablets were approved in February 2017 for the treatment of moderate to severe active rheumatoid arthritis in patients who have had an inadequate response to MTX or are intolerant to MTX. In the US, a new drug application was filed in January 2016 and is under review as of April 2017. In a meantime, Eli Lilly and Company (US) issued a press release on April 14, 2017 to the effect that the company had received a complete response letter to the new drug application for baricitinib from U.S. Food and Drug Administration (FDA) indicating that the FDA is unable to approve the use of Olumiant in the treatment of RA (http://lilly.mediaroom.com/index.php?s=9042&item=137646).

In Japan, the development of baricitinib started in November 2011. A marketing application has now been filed based mainly on the results of multi-regional Phase III studies conducted in various countries including Japan.

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

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white powder. Its description, solubility, thermal analysis, dissociation constant, polymorphism, and hygroscopicity were determined. While multiple crystalline forms were identified,

it was confirmed that only the [redacted], which is most thermodynamically stable, is produced by the commercial manufacturing process. In specifications, [redacted] is controlled.

The chemical structure of the drug substance was elucidated by hydrogen nuclear magnetic resonance spectrometry (^{1}H-NMR), carbon nuclear magnetic resonance spectrometry (^{13}C-NMR), mass spectrometry, infrared spectrophotometry (IR), Raman spectroscopy, ultraviolet spectroscopy, elemental analysis, and single-crystal X ray diffraction.

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted], [redacted], and [redacted] as starting materials.

Using a quality-by-design approach, quality control strategies were established through evaluation of the following quality elements:

- Identification of [redacted], [redacted], [redacted], and [redacted] as critical quality attributes
- Identification of critical process parameters based on quality risk assessment and experimental scheme
- Development of a design space

The synthetic steps of [redacted] and [redacted] have been defined as critical steps.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification ([redacted], [redacted]), purity (impurities [HPLC], residual solvents [gas chromatography], and [redacted] [[redacted]]), loss on drying, residue on ignition, [redacted], [redacted], and assay (HPLC).

2.1.4 Stability of drug substance

The main stability studies of the drug substance are shown in Table 1. Photostability testing demonstrated that the drug substance was photostable.

Table 1. Stability studies of the drug substance

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 production batches	25ºC	60%RH	[redacted]	[redacted] months
Accelerated	3 production batches	40ºC	75%RH		6 months

Based on the above, a retest period of [redacted] months was proposed for the drug substance when stored at room temperature in a polyethylene bag placed inside an aluminum bag.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a film-coated tablet. Each containing 2 or 4 mg of the drug substance. The drug product also contains D-mannitol, crystalline cellulose, croscarmellose sodium, magnesium stearate, and [redacted] (2 mg tablets, [redacted]; 4 mg tablets, [redacted]) as excipients.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprising [redacted], [redacted], [redacted], [redacted], coating, and packaging steps. [redacted] was defined as a critical step.

Using a quality-by-design approach, quality control strategies were established through evaluation of the following quality elements:

- Identification of [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] as critical quality attributes
- Identification of critical process parameters based on a quality risk assessment and experimental scheme

2.2.3 Control of drug product

The proposed specifications for the drug product consist of content, description, identification (IR), purity (related substances [HPLC]), uniformity of dosage units (content uniformity test [HPLC]), dissolution test (paddle method, HPLC), and assay (HPLC).

2.2.4 Stability of drug product

The main stability studies of the drug product are shown in Table 2. Photostability testing demonstrated that the drug substance was photostable.

Table 2. Stability studies of the drug product

Study	Formulation	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	2 mg tablets	3 production batches	30ºC	65%RH	PTP packaging	24 months
Accelerated			40ºC	75%RH		6 months
Long-term	4 mg tablets	3 production batches	30ºC	65%RH	PTP packaging	24 months
Accelerated			40ºC	75%RH		6 months

Based on the above, a shelf life of 24 months was proposed for the drug product when stored at room temperature in a push-through pack (PTP) ([redacted] and aluminum foil). The long-term stability study testing is planned to be continued for up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

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

As data on primary pharmacodynamics, the results from studies on the inhibitory activity of baricitinib against JAK family members and its effects on animal arthritis models were submitted. As data on secondary pharmacodynamics, the results from studies on the effects of baricitinib on various receptors, ion channels, enzymes, and transporters were submitted. As data on safety pharmacology, the results from studies on the effects of baricitinib on the central nervous, cardiovascular, and respiratory systems were submitted.

While baricitinib phosphate was used in these studies, doses are expressed as doses of baricitinib in this section unless otherwise noted. Pharmacokinetic parameters are expressed as mean values.

3.1 Primary pharmacodynamics

3.1.1 Inhibitory activity against JAK family members (CTD 4.2.1.1.1, 4.2.1.1.2)

The results of enzyme assays using recombinant human kinase domains of JAK1, JAK2, JAK3, and TYK2 showed that the IC_{50} values of baricitinib against JAK1, JAK2, JAK3, and TYK2 were 1.09. 0.31, 8.77, and 3.45 nmol/L, respectively, in the presence of ATP at concentrations corresponding to the Michaelis constant (K_m) values of the respective enzymes, and 5.9, 5.7, ≥400, and 53 nmol/L, respectively, in the presence of ATP at 1 mmol/L that was equivalent to its intracellular concentration.

3.1.2 Effects on IL-2-induced T-cell proliferation and signaling (CTD 4.2.1.1.3)

When phytohemagglutinin-treated T-cells derived from human peripheral blood mononuclear cells were stimulated with IL-2 (100 units/mL), baricitinib at a concentration of ≥3 nmol/L inhibited the phosphorylation of JAK2, STAT3, and STAT5 with IC_{50} values ranging from 3 to 30 nmol/L. The IC_{50} value of baricitinib against T-cell proliferation was 29 nmol/L.

3.1.3 Effects on IL-23-induced cytokine production and signaling (CTD 4.2.1.1.4)

When phytohemagglutinin-treated T-cells derived from human peripheral blood mononuclear cells were stimulated with IL-23 (100 ng/mL), baricitinib inhibited the production of IL-17 and IL-22 and the phosphorylation of STAT3 with IC_{50} values of 57, 41, and 20 nmol/L, respectively.

3.1.4 Effects on IL-12-induced interferon-gamma production and signaling (CTD 4.2.1.1.5)

When phytohemagglutinin-treated human T-cells were stimulated with IL-12 (10 or 20 ng/mL), baricitinib inhibited the production of interferon-gamma (IFNγ) and the phosphorylation of STAT3 with IC_{50} values of 5.8 μmol/L and 60 nmol/L, respectively.

3.1.5 Effects on IL-6-induced monocyte chemotactic protein-1 production and signaling (CTD 4.2.1.1.1, 4.2.1.1.6 to 4.2.1.1.8)

When human peripheral blood mononuclear cells were stimulated with IL-6 (10 ng/mL), baricitinib inhibited the production of monocyte chemotactic protein-1 (MCP-1) and the phosphorylation of STAT3 with IC_{50} values of 40 and 44 nmol/L, respectively.

When whole bloods of humans, dogs, and rats were stimulated with IL-6 (100 ng/mL), baricitinib inhibited the phosphorylation of STAT3 with IC_{50} values of 104, 49, and 128 nmol/L, respectively. In a 28-day repeated-dose toxicity study in dogs, when whole blood collected 1, 8, and 24 hours after administration of baricitinib (at 0.15, 0.45, or 3 mg/kg/day) on Day 7 was stimulated with IL-6 (100 ng/mL), baricitinib inhibited STAT3 phosphorylation dose-dependently. The shorter the time from administration was, the greater the inhibitory effect was.

3.1.6 Effects on signaling stimulated with various cytokines (CTD 4.2.1.1.10)

When differentiated human peripheral blood mononuclear cells were stimulated with various cytokines (30 ng/mL; 100 pg/mL for GM-CSF only), baricitinib and tofacitinib citrate inhibited the phosphorylation of STAT molecules with IC_{50} values presented in Table 3.

Table 3. Inhibitory effects of baricitinib and tofacitinib citrate on the phosphorylation of transcription factors

Cytokine	Trans-cription factor	B cells		CD4-positive T cells		CD8-positive T cells		NK cells		Monocytes	
		Baricitinib	Tofa	Baricitinib	Tofa	Baricitinib	Tofa	Baricitinib	Tofa	Baricitinib	Tofa
IL-2	STAT5			24	9	25	10	44	15		
IL-3	STAT5	112	645							170	243
IL-4	STAT5	29	12								
	STAT6	139	63	51	19	27	10	18	6	50	39
IL-6	STAT3			45	41					54	44
IL-10	STAT3	84	77	60	49	64	57	72	61	167	122
IL-15	STAT5			37	14	64	24	75	25		
IL-21	STAT3	88	29	63	22	66	23	62	21		
	STAT5			20	7						
IFNα	STAT1	246	195	78	60	119	92	138	110	143	101
	STAT3	27	19	25	19	27	20	25	18	18	13
	STAT5	26	18	21	15	27	19			13	9
IFNγ	STAT1	17	21							46	55
	STAT5									6	7
G-CSF	STAT3									73	111
GM-CSF	STAT5									122	173

Tofa, tofacitinib citrate
IC_{50}, nmol/L

3.1.7 Effects on animal arthritis models (CTD 4.2.1.1.1, 4.2.1.1.9)

3.1.7.1 Effects on collagen-induced arthritis mouse model

Arthritis was induced in male mice by inoculation of bovine type II collagen twice (Days 1 and 22). To these mice, baricitinib was administered orally twice daily for 15 days at 0 (vehicle), 1, 3, or 10 mg/kg. The severity of inflammation in the footpad decreased in the 3 and 10 mg/kg groups, and the histological

severity (arthritis, pannus formation, bone injury, and cartilage injury) in the 10 mg/kg group decreased as compared to the vehicle group.

3.1.7.2 Effects on anti-collagen antibody-induced arthritis mouse model

Arthritis was induced in female mice by administration of anti-type II collagen antibodies on Day 1 and lipopolysaccharide on Day 3. To these mice, baricitinib was administered orally twice daily for 12 days at 0 (vehicle), 1, or 10 mg/kg. In the 10 mg/kg group, the severity of inflammation in the footpad decreased, and the histological severity tended to decrease as compared to the vehicle group.

3.1.7.3 Effects on adjuvant-induced arthritis rat model

Following 14-day continuous subcutaneous infusion of baricitinib at 0 (vehicle) or 0.018 to 6.0 mg/kg/day in female rats with adjuvant-induced arthritis, the disease severity (severity as assessed based on pathological images of periarticular tissues in combination with the cross-sectional thickness of the flexion of the tarsal joint) decreased in a dose-dependent manner. Following a 14-day oral doses of baricitinib at 0 (vehicle) or 0.3 to 3 mg/kg twice daily or at 1 to 10 mg/kg once daily, the disease severity in these mice decreased in a dose-dependent manner.

In another study, following 14-day oral doses of baricitinib at 0 (vehicle), 1, 3, or 10 mg/kg once daily, inflammation score, footpad volume, arthritis, ankle joint width, and bone absorption decreased or were suppressed in a dose-dependent manner. The results of X-ray image analysis of joint samples collected from rats receiving baricitinib at 0 (vehicle) or 10 mg/kg showed that bone and joint destruction was inhibited in rats receiving baricitinib at 10 mg/kg.

In the above investigations, whole blood collected from rats after the final dose of baricitinib was stimulated with IL-6 (100 ng/mL). Baricitinib inhibited the phosphorylation of STAT3 dose-dependently, showing inhibition of 55% to 100% at 1 hour post-dose and 0% to 84% at 4 hours post-dose as compared to the vehicle group. The inhibitory effect of baricitinib was eliminated at 24 hours post-dose.

3.1.7.4 Effects on cytokine mRNA in adjuvant-induced arthritis rat model

Baricitinib was orally administered once daily for 14 days at 0 (vehicle) or 10 mg/kg to rats with adjuvant-induced arthritis. The mRNA expression levels of IL-12A, IL-17A, IL-21, IL-22, and IFNγ in groin lymph nodes in the baricitinib group decreased by 55% to 83% as compared to those in the vehicle group.

3.2 Secondary pharmacodynamics

3.2.1 Effects on receptors, ion channels, enzymes, and transporters (CTD 4.2.1.2.1 to 4.2.1.2.4)

Baricitinib inhibited calmodulin-dependent protein kinase (CaMK) 2d and 2g with IC_{50} values of 170 and 150 nmol/L, respectively. IC_{50} values of baricitinib against other CaMKs investigated were >500 nmol/L or >5 μmol/L.

3.3 Safety pharmacology

3.3.1 Effects on the central nervous system (CTD 4.2.1.3.3)

Rats received a single oral dose of baricitinib at 2, 10, or 100 mg/kg. Darkening of skin and mucosae, mild eyelid ptosis, loss of pupillary reflex, a trend towards decrease in body temperature, lacrimation, gasping respiration, and decreased locomotor activity were observed only in the 100 mg/kg group. The $AUC_{0\text{-}24}$ (2433 ng·h/mL) and C_{max} (826 ng/mL) in rats receiving a dose of 10 mg/kg were 5.0- and 15.2-fold (calculated taking into account the unbound fraction of baricitinib) the estimated $AUC_{0\text{-}24}$ and C_{max} in RA patients (477.6 ng·h/mL and 53.4 ng/mL, respectively) following once daily multiple doses of baricitinib at 4 mg.

3.3.2 Effects on the cardiovascular system (CTD 4.2.1.3.1, 4.2.1.3.2)

3.3.2.1 Effects on the human ether-a-go-go related gene (hERG) current

Using human embryonic kidney 293 cells transfected with the human ether-a-go-go related gene (hERG), effects of baricitinib on hERG current were investigated by the patch clamp method. Baricitinib exerted an inhibitory effect on hERG current in a concentration-dependent manner with an IC_{50} value of 161.5 μmol/L. This concentration was approximately 1400-fold (calculated taking into account the unbound fraction of baricitinib) the estimated C_{max} (53.4 ng/mL) in RA patients following once daily multiple doses of baricitinib at 4 mg.

3.3.2.2 Effects on the cardiovascular system

Dogs received a single oral dose of baricitinib at 0.15, 0.45, or 3 mg/kg. Mildly increased heart rate and decreased arterial pressure were observed only in the 3 mg/kg group. The $AUC_{0\text{-}24}$ (557 ng·h/mL) and C_{max} (134.5 ng/mL) in the 0.45 mg/kg group were 1.3- and 2.8-fold (calculated taking into account the unbound fraction of baricitinib) the estimated $AUC_{0\text{-}24}$ and C_{max} in RA patients (477.6 ng·h/mL and 53.4 ng/mL, respectively) following once daily multiple doses of baricitinib at 4 mg.

3.3.3 Effects on the respiratory system (CTD 4.2.1.3.4)

Following a single oral dose of baricitinib at 2, 10, or 100 mg/kg in male rats, no deaths or baricitinib-related clinical signs occurred in any dose groups. Decreases in respiratory rate and minute ventilation volume were observed in the 100 mg/kg group only.

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of baricitinib against rheumatoid arthritis

The applicant's explanation about the mechanism of action of baricitinib against RA:

Inflammatory cytokines, such as IL-6, GM-CSF, IFNγ, IFNα, IL-12, and IL-23, are involved in the onset of clinical symptoms of RA. Pharmacology studies demonstrated that baricitinib inhibits the signaling of inflammatory cytokines including IL-6, IFN, IL-12, and IL-23. Baricitinib is likely to inhibit inflammation and immune cell growth by binding to the adenosine triphosphate (ATP) binding site of the JAK and thereby inhibiting the JAK-STAT pathway.

The applicant's explanation about differences in the mechanism of action between baricitinib and its analogue, i.e., tofacitinib citrate, and the clinical impact of the differences:
Baricitinib inhibits the binding of ATP to JAK1, JAK2, JAK3, and TYK2 with IC_{50} values of 4.0, 6.6, 787, and 61.0 nmol/L, respectively. Tofacitinib citrate inhibits these JAK family members with IC_{50} values of 15.1, 77.4, 55.0, and 489 nmol/L, respectively (*J Med Chem*. 2014;57:5023-38), showing baricitinib's selectivity for JAK1 and JAK2. Baricitinib 4 mg (once daily) or tofacitinib citrate 5 mg (twice daily) was administered to RA patients to investigate time to blood concentration exceeding IC_{50} value against cytokine-induced signaling and the STAT phosphorylation inhibition rate per 24 hours of each drug. The results are tabulated in Table 4 and Table 5, respectively. As shown in the tables, the inhibitory effect of baricitinib on IL-6 and IFN signaling lasts for only a short time and is weak as compared to that of tofacitinib citrate ([Abstract THU0182]. *EULAR*. 2016).

Time to blood baricitinib concentration exceeding the IC_{50} values against the JAK1/JAK3-mediated signaling of cytokines (IL-2, IL-4, IL-15, and IL-21) was shorter than that of tofacitinib citrate (Table 4). IL-15 and IL-21 are known to be involved in the proliferation and functional expression of NK cells (*Semin Oncol*. 2015;42:539-48). These observations indicate that baricitinib may be slower in exerting an immunosuppressive effect compared to tofacitinib citrate. Concerning JAK2/JAK2-mediated erythropoietin, while a slight increase in mean hemoglobin level was observed in clinical studies of tofacitinib citrate, anemia and a dose-dependent decrease in hemoglobin were observed in clinical studies of baricitinib. These results may reflect the difference in action between these 2 agents.

PMDA concluded that the data submitted demonstrate the pharmacological effects of baricitinib and that baricitinib is expected to have efficacy in the treatment for RA.

The pharmacological actions of baricitinib indicate its effect on the hematopoietic system and the immune system. As shown in Table 5, baricitinib inhibits cytokine-induced signal transduction to some extent in a similar way as tofacitinib citrate does. Therefore, attention should be paid to the occurrence of serious infection or malignant tumor and the effect on the hematopoietic system [for the safety of baricitinib, see Section "7.R.2 Safety"].

Table 4. Time to IC_{50} of baricitinib or tofacitinib citrate

Cytokine	Trans-cription factor	B cells		CD4-positive T cells		CD8-positive T cells		NK cells		Monocytes	
		Baricitinib	Tofa	Baricitinib	Tofa	Baricitinib	Tofa	Baricitinib	Tofa	Baricitinib	Tofa
IL-6	STAT3			3.1	9.5					2.5	9.3
IFNγ	STAT1	13.5	22.3							4.1	7.7
IFNα	STAT1	0	0	0	9.9	0	4.3	0	1.2	0	2.2
	STAT3	8.1	17.8	9.6	19.2	8.8	17.7	10.4	17.8	14.9	21.7
	STAT5	9.1	19.8	12	20.8	10.6	21.3			18	24
IL-2	STAT5			20.5	24	11.4	24	4.6	20.6		
IL-4	STAT6	0	5.6	2.7	17.9	9.8	24	16.9	24	2.8	10.2
IL-15	STAT5			5.8	21.1	0	15.5	0	15.3		
IL-21	STAT3	0	13.9	0	16.2	0	16.2	0	16.5		

Tofa, tofacitinib citrate
Time to IC_{50}, hours

Table 5. Transcription factor phosphorylation inhibition rate by baricitinib or tofacitinib citrate per 24 hours

Cytokine	Trans-cription factor	B cells		CD4-positive T cells		CD8-positive T cells		NK cells		Monocytes	
		Baricitinib	Tofa	Baricitinib	Tofa	Baricitinib	Tofa	Baricitinib	Tofa	Baricitinib	Tofa
IL-6	STAT3			31	45					30	44
IFNγ	STAT1	55	68							33	41
IFNα	STAT1	10	20	32	48	23	37	16	29	24	35
	STAT3	43	65	46	66	45	63	50	65	57	73
	STAT5	45	67	51	71	49	69			63	79
IL-2	STAT5			56	82	50	81	34	71		
IL-4	STAT6	9	34	26	66	45	79	59	85	26	44
IL-15	STAT5			36	73	24	59	21	58		
IL-21	STAT3	22	54	25	60	25	60	27	61		

Tofa, tofacitinib citrate
Inhibition rate, %

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

As data on the absorption, distribution, metabolism, and excretion of baricitinib, the study results on oral or intravenous baricitinib in mice, rats, rabbits, and dogs were submitted. Plasma concentrations of baricitinib were determined by the liquid chromatography with tandem mass spectrometry (LC/MS/MS) method (lower limit of quantitation, 0.002 to 9.2855 ng/mL), and radioactivity levels in samples were determined using a liquid scintillation counter (lower limit of quantitation, 2-fold the background value).

While baricitinib phosphate was used in these studies, unless otherwise noted, doses are expressed as doses of baricitinib in this section. Pharmacokinetic parameters are expressed as mean values or mean ± standard deviation (SD).

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2.1, 4.2.2.2.2, 4.2.2.2.7, 4.2.2.5.1)

Table 6 and Table 7 show the pharmacokinetic parameters following a single oral dose of ^{14}C-baricitinib in male and female mice and rats and male dogs.

When male rats received an oral dose of baricitinib (free base) at 2 mg/kg while receiving a continuous intravenous infusion of ^{13}C-baricitinib at 2.26 μg/kg over 30 minutes, the absolute bioavailability was 53.8%.

Table 6. Pharmacokinetic parameters following a single oral dose of ^{14}C-baricitinib

Animal species	Sex	N	C_{max} (ng eq/g)		AUC_{0-24} (ng eq·h/g)		t_{max} (h)		$t_{1/2}$ (h)	
			Plasma	Blood	Plasma	Blood	Plasma	Blood	Plasma	Blood
Mouse	Male	3	11.9 ± 2.76	9.78 ± 2.41	32.4	NA	1	1	1.1	NA
	Female	3	8.87 ± 2.12	7.53 ± 2.02	35.7	NA	1	1	1.2	NA
Rat	Male	3	3890 ± 650	3470 ± 420	11,700	10,575	1	1	8.23	9.5
	Female	3	5410 ± 870	5210 ± 820	15,239	15,017	1	1	5.15	6.42

Mean ± standard deviation; t_{max} and $t_{1/2}$, mean values; NA, not applicable
Dose, 50 mg/kg for mice and 25 mg/kg for rats

Table 7. Pharmacokinetic parameters following a single oral dose in dogs

	C_{max} (ng eq/g or ng/mL)	$AUC_{0-\infty}$ (ng eq·h/g or ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)
Plasma (^{14}C)	218, 264	1200, 1580	0.50, 1.0	4.89, 11.4
Blood (^{14}C)	218, 280	1240, 1750	0.50, 1.0	5.17, 10.6
Plasma (baricitinib)	193, 195	968, 1090	0.50, 1.0	3.69, 3.24

N = 2
Dose, 0.5 mg/kg

4.1.2 Comparison of the free base form and the phosphate form of baricitinib (CTD 4.2.2.2.3, 4.2.2.2.4)

Male and female mice and rats received repeated oral doses of baricitinib free base or baricitinib phosphate once daily, and the pharmacokinetics of baricitinib were evaluated. The ratios of exposure to baricitinib free base to baricitinib phosphate are shown in Table 8. Baricitinib exposures tended to be low following the free base doses.

Table 8. Ratio of exposure to baricitinib free base to baricitinib phosphate following repeated doses of baricitinib free base or baricitinib phosphate

Animal species	Sex	N	Dose[a)]	Day 1		Day 7	
				C_{max}	AUC[b)]	C_{max}	AUC[b)]
Mouse	Male	4	75 mg/kg	1.02	0.77	0.83	0.63
		4	300 mg/kg	0.95	1.34	0.94	0.92
	Female	4	25 mg/kg	0.68	0.90	0.69	0.81
		4	150 mg/kg	0.96	1.28	0.89	1.09
Rat	Male	4	1 mg/kg	1.07	1.05	1.00	1.10
		4	8 mg/kg	0.62	0.80	0.73	0.95
	Female	4	3 mg/kg	0.56	0.88	0.60	0.93
		4	25 mg/kg	0.72	0.78	0.88	0.92

[a)] Doses of baricitinib phosphate were corrected based on molecular weight so that it became free base equivalent.
[b)] $AUC_{0-\infty}$ for mice and AUC_{0-24} for rats

4.1.3 Repeated-dose studies (toxicokinetics) (CTD 4.2.3.4.2.1, 4.2.3.2.10, 4.2.3.2.11, 4.2.3.2.4, 4.2.3.2.6, 4.2.3.2.7, 4.2.3.5.1.1, 4.2.3.5.2.1, 4.2.3.5.3.1, 4.2.3.4.1.1, 4.2.3.5.2.3, 4.2.3.2.9)

Toxicokinetics of baricitinib were investigated in repeated toxicity studies in mice, rats, rabbits, and dogs. Baricitinib free base was used in mouse studies and rat studies on pre- and postnatal development. Baricitinib phosphate was used in the other rat studies and all the studies in rabbits or dogs. The

pharmacokinetic parameters of baricitinib in the main studies are shown in Table 9. In pregnant rabbits, baricitinib tended to accumulate after repeated doses.

Table 9. Pharmacokinetic parameters following repeated doses of baricitinib free base or baricitinib phosphate

Animal species	Duration	Dose (mg/kg)	Time point	N	Male			Female		
					C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	t_{max} (h)
Mouse	1 month	75	Day 1	3	2553 ± 2177	8482 ± 1891[a)]	1.0	8673 ± 1152	15,951 ± 2302[a)]	0.5
			Day 28	3	4857 ± 1855	14,765 ± 1258[a)]	0.5	11,300 ± 1664	21,755 ± 2442[a)]	0.5
		150	Day 1	3	5053 ± 2964	17,846 ± 2092[a)]	1.0	8727 ± 2352	18,764 ± 1900[a)]	1.0
			Day 28	3	8483 ± 1800	21,793 ± 2477[a)]	1.0	13,187 ± 5574	22,664 ± 2821[a)]	0.5
		300	Day 1	3	7620 ± 2018	28,831 ± 5630[a)]	1.0	10,080 ± 3115	80,700 ± 7943[a)]	1.0
			Day 28	3	9323 ± 3590	24,030 ± 2579[a)]	0.5	12,543 ± 2785	31,271 ± 2872[a)]	0.5
Rat	28 days	2	Day 1	9[b)]	120	354	1.0	103	435	1.0
			Day 28	9[b)]	148	461	1.0	129	498	1.0
		10	Day 1	9[b)]	839	2177	1.0	813	2689	1.0
			Day 28	9[b)]	1033	2737	1.0	906	2867	1.0
		40	Day 1	9[b)]	3673	10,363	1.0	4828	13,445	1.0
			Day 28	9[b)]	4123	12,814	1.0	6834	17,754	1.0
Rabbit		3	Gestational day 7	4				146 ± 52	383 ± 85	1.0
			Gestational day 20	4				297 ± 48	1096 ± 446	0.8
		10	Gestational day 7	4				594 ± 182	1790 ± 152	0.5
			Gestational day 20	4				1125 ± 208	3027 ± 1226	0.5
		30	Gestational day 7	4				3272 ± 557	9991 ± 1523	0.8
			Gestational day 20	4				6388 ± 2,080	20,094 ± 3714	0.5
Dog	1 month	0.15	Day 1	6	46.8 ± 8.2	202 ± 52.0	1.0	45.3 ± 6.3	209 ± 48.3	1.0
			Day 27	6	32.6 ± 6.7	153 ± 48.3	1.0	37.5 ± 5.9	147 ± 33.4	1.0
		0.45	Day 1	6	138 ± 16.7	557 ± 96.6	1.0	131 ± 25.3	557 ± 111	1.0
			Day 27	6	118 ± 32.7	542 ± 219	1.0	131 ± 26.0	553 ± 137	1.0
		3	Day 1	6	1010 ± 186	4606 ± 1337	1.0	1029 ± 297	5014 ± 1746	1.5
			Day 27	6	858 ± 297	3974 ± 1449	1.5	947 ± 409	4754 ± 1709	1.0

Mean ± standard deviation; t_{max}, median
[a)] Mean ± standard error, [b)] N = 3 per time point

4.1.4 Membrane permeability (CTD 5.3.2.2.7, 5.3.2.2.14)

The membrane permeation coefficient of baricitinib was 2.41×10^{-6} cm/s in Caco-2 cells. In *MDR1*-transfected madin-darby canine kidney (MDCK) cells, the membrane permeation coefficient was 0.9 to 1.82×10^{-6} cm/s, which increased to 3.65 to 6.69×10^{-6} cm/s in the presence of a compound with an inhibitory effect on p-glycoprotein (P-gp) (LSN335984, verapamil, or quinidine).

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.3.1)

Following a single oral dose of ^{14}C-baricitinib at 25 mg/kg to male and female pigmented rats (N = 28) and male albino rats (N = 10), radioactivity was extensively distributed in tissues. A high level of radioactivity was detected particularly in gastrointestinal contents, bile, urine, kidney cortex, liver, skin, cecum, aortae, and bladder. In pigmented rats, radioactivity was distributed in the uvea, suggesting the binding of baricitinib to melanin-containing tissues. While the radioactivity level was below the lower limit of quantitation in most tissues by 168 hours post-dose in albino rats and by 672 hours post-dose in pigmented rats, a low level of radioactivity was detected in the dorsal caudal nerve, aorta, and uvea of pigmented rats at 672 hours post-dose.

4.2.2 Protein binding (CTD 4.2.2.3.2, 4.2.2.3.3)

The *in vitro* protein-unbound fraction of baricitinib (1 to 10 μmol/L) was 44.1% to 55.0% in mouse, rat, dog, and rabbit plasma; 40.0% to 56.0% in rat and dog serum; and 50.0% in human plasma and 45.0% in human serum. The *ex vivo* protein-unbound fraction in plasma samples obtained in repeated-dose toxicity studies in mice, rats, dogs, and rabbits (Studies P08-06-01, P07-11-01, T08-05-03, T07-08-03, and T07-07-09) was 41.0% to 61.0%, showing no marked difference by species.

4.2.3 Distribution in blood cells (CTD 4.2.2.5.1, 4.2.2.2.1, 4.2.2.2.2)

Following a single oral dose of ^{14}C-baricitinib at 50 mg/kg to male and female mice, 25 mg/kg to male and female rats, and 0.5 mg/kg to male dogs, the mean blood/plasma distribution ratio in these animals was 0.671 to 0.844, 0.898 to 1.16, and 0.968 to 1.14, respectively.

4.2.4 Placental transfer (CTD 4.2.2.3.4)

Following a single oral dose of ^{14}C-baricitinib at 25 mg/kg to pregnant rats, the radioactivity level at 0.5 hours post-dose was 4780 and 6140 ng eq./g in maternal blood and plasma, respectively, and 2200 ng eq./g in fetal blood. The radioactivity level in fetal tissue reached a peak at 0.5 hours post-dose (the maximum radioactivity level was 5080 ng eq./g in the adrenal gland) and decreased to below the lower limit of quantitation by 24 hours post-dose.

4.3 Metabolism

4.3.1 *In vitro* (CTD 4.2.2.4.1)

In rat, dog, monkey, and human liver microsomes and S9 fractions, 10 μmol/L baricitinib was metabolized by oxidation. A total of 4 metabolites (M1, M3, M4, and M10) were identified. The rate of formation of each metabolite in any sample was <5% of the unchanged parent compound.

4.3.2 *In vivo* (CTD 4.2.2.4.2 to 4.2.2.4.5)

Following a single oral dose of ^{14}C-baricitinib at 50 mg/kg to male and female mice, unchanged parent compound was mainly detected in plasma with metabolites, namely, M3, M6, M9, M10, M22, M23, and unknown metabolites, by 8 hours post-dose. In urine, unchanged parent compound and 4 metabolites

(M3, M6, M10, and M22) were detected by 24 hours post-dose. In feces, mainly unchanged parent compound was detected with 12 minor metabolites.

Following a single oral dose of ^{14}C-baricitinib at 25 mg/kg to male and female rats, mainly unchanged parent compound was detected in plasma with metabolites M13 and M22. In urine, mainly unchanged parent compound was detected with M3, M10, M13, and M22 by 48 hours post-dose. In feces, mainly unchanged parent compound was detected with 8 metabolites (predominantly M10 and M27) by 48 hours post-dose.

Following repeated once-daily oral doses of baricitinib at 30 mg/kg to female rabbits, unchanged parent compound was mainly detected in plasma collected on Day 20 with M7, M17, and an unidentified metabolite.

Following a single oral dose of ^{14}C-baricitinib at 0.5 mg/kg to male and female dogs, mainly unchanged parent compound was detected in plasma with M2. In urine and feces, mainly unchanged parent compound was detected by 48 hours post-dose. Detected metabolites were M2, M4, and M10 in urine and M2, M3, M4, and M13 in feces.

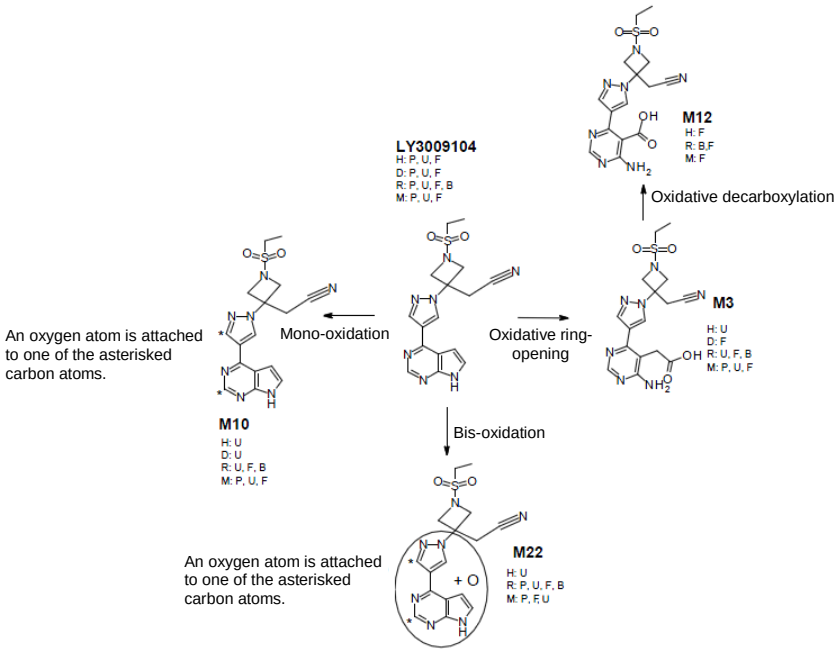

Figure 1. Postulated metabolic pathway for baricitinib in humans (source, Figure 2.6.4-2 in CTD 2.6.4)

4.3.3 Identification of cytochromes P450 (CYPs) involved in the metabolism of baricitinib (CTD 5.3.2.2.6)

When 1 µmol/L baricitinib was incubated with human recombinant cytochrome P450 (CYP) microsomes, baricitinib was metabolized by CYP3A4 but not by CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6.

4.4 Excretion

4.4.1 Fecal, urinary, and biliary excretion (CTD 4.2.2.2.1, 4.2.2.2.2, 4.2.2.2.5, 4.2.2.2.6, 4.2.2.5.1, 4.2.2.5.2)

Male and female mice received a single oral dose of ^{14}C-baricitinib at 50 mg/kg. The cumulative excretion of radioactivity into urine and feces up to 48 hours post-dose was 18% and 70%, respectively, in male mice and 29% and 52%, respectively, in female mice.

Male bile-duct cannulated rats received ^{14}C-baricitinib orally at 25 mg/kg or intravenously at 5 mg/kg. The cumulative excretion of radioactivity into feces, urine, and bile up to 96 hours post-dose was 40%, 30%, and 17%, respectively, of the dose administered to rats receiving an oral dose and 12%, 50%, and 21%, respectively, of the dose administered to rats receiving an intravenous dose.

Male and female dogs received a single oral dose of ^{14}C-baricitinib at 0.5 mg/kg. The cumulative excretion of radioactivity into feces and urine, respectively, up to 120 hours post-dose was 47% and 39% in male dogs and 41% and 40% in female dogs.

4.4.2 Excretion into milk (CTD 4.2.2.3.4)

Following a single oral dose of ^{14}C-baricitinib to lactating rats, the radioactivity level in plasma reached a peak (1900 ng eq./g) at 1 hour post-dose. The radioactivity level in milk reached a peak (33,600 ng eq./g) at 4 hours post-dose and decreased to 230 ng eq./g at 24 hours post-dose. The $AUC_{0-\infty}$ of radioactivity in milk and plasma was 352,000 and 8980 ng eq·h/g, respectively. The milk to plasma ratio of radioactivity, $AUC_{0-\infty}$, and C_{max} was 37-, 39-, and 18-fold, respectively, at 4 hours post-dose.

4.5 Pharmacokinetic drug interactions

4.5.1 Identification of transporters involved in the transport of baricitinib (CTD 5.3.2.2.7, 5.3.2.2.10 to 5.3.2.2.13)

Studies using P-gp- or breast cancer resistance protein (BCRP)-expressing MDCK cells demonstrated that 5 μmol/L baricitinib is the substrate of P-gp and BCRP. Studies using various transporter-expressing human embryonic kidney (HEK)-PEAK cells demonstrated that 5 or 10 μmol/L baricitinib (0 to 100 μmol/L baricitinib for organic anion transporting polypeptide [OATP] 1B3 only) is the substrate of organic anion transporter (OAT) 3 but not the substrate of OAT1, organic cation transporter (OCT) 1, OCT2, OATP1B1, or OATP1B3. Studies using multidrug and toxin extrusion protein (MATE) 1- or MATE2-K-expressing HEK cells demonstrated that 0.25 μmol/L baricitinib is the substrate of MATE2-K but not of MATE1.

4.5.2 Effects of baricitinib on the pharmacokinetics of concomitant drugs (CTD 5.3.2.2.2 to 5.3.2.2.4, 5.3.2.2.7 to 5.3.2.2.9, 5.3.2.2.12, 5.3.2.2.13)

4.5.2.1 Inhibitory effect on metabolic enzymes

Baricitinib 0.02 to 20 μmol/L did not inhibit activity of CYP3A4, CYP2D6, CYP2C19, CYP2C8, CYP2C9, CYP2B6, or CYP1A2 in human liver microsomes.

4.5.2.2 Inductive effect on metabolic enzymes

Baricitinib 0.05 to 50 μmol/L did not increase CYP1A2, CYP2B6, or CYP3A activity in human primary-cultured hepatocytes. While baricitinib 50 μmol/L inhibited CYP3A activity, the applicant explained that this concentration was approximately 1000-fold the C_{max} (53.4 ng/mL) following a once daily dose of baricitinib 4 mg, based on an estimation from the population pharmacokinetic model [see Section "6.2.3.1 Pharmacokinetics in patients"] and that baricitinib is therefore unlikely to cause clinically significant drug interactions.

4.5.2.3 Inhibitory effect on transporters

The inhibitory effect of baricitinib was investigated using inverted membrane vesicles prepared from *MDR1*-transfected HEK cells, inverted membrane vesicles prepared from *hBCRP*-transfected Sf9 insect cells, *OATP1B1*-, *OCT1*-, *OCT2*-, *OAT1*-, *OAT3*-, or *OATP1B3*-transfected HEK-PEAK cells, and *MATE1*- or *MATE2-K*-transfected HEK cells. IC_{50} values of transporters and the ratios of plasma concentrations of baricitinib after a dose of 4 mg, which were estimated from the population pharmacokinetic model at the clinical dose [see Section "6.2.3.1 Pharmacokinetics in patients"], relative to IC_{50} values are presented in Table 10. Based on the results shown, the applicant explained that baricitinib is unlikely to exert an inhibitory effect of clinical concern on the transporters.

Table 10. Inhibitory effect of baricitinib on transporters

	Dose (μmol/L)	IC_{50} (μmol/L)	Ratio of plasma concentration of baricitinib at the clinical dose to IC_{50} value
P-gp	0-50	No inhibition	NC
BCRP	0-100	50.3	0.003[a)]
OATP1B1	0-100	No inhibition	NC
OATP1B3	0-100	49.4	0.003[a)]
OAT1	0-100	> 100	< 0.0007[b)]
OAT3	0-100	8.4	0.009[b)]
OCT1	0-50	6.9	0.02[a)]
OCT2	0-50	11.6	0.006[b)]
MATE1	0-100	76.7	0.0009[b)]
MATE2-K	0-100	13.7	0.005[b)]

a) Ratio of total C_{max} (53.4 ng/mL) after the administration of baricitinib 4 mg based on an estimation from the population pharmacokinetic model [see Section "6.2.3.1 Pharmacokinetics in patients"] to IC_{50} value

b) Ratio to C_{max} of baricitinib free base (26.7 ng/mL as calculated based on the total C_{max} assuming that the protein binding ratio was 50%)

4.R Outline of the review conducted by PMDA

Based on the submitted results from nonclinical pharmacokinetic studies, PMDA concluded that the *in vivo* kinetics of baricitinib have been elucidated to some extent.

5. Toxicity and Outline of the Review Conducted by PMDA

The results from the following toxicity studies were submitted as toxicity data: single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, and other toxicity studies (a phototoxicity study, an eye irritation study, and a skin irritation study).

While baricitinib phosphate was used in these studies, unless otherwise noted, doses are expressed as doses of baricitinib in this section. In *in vivo* studies, 0.5% methylcellulose aqueous solution was used as a vehicle.

5.1 Single-dose toxicity (reference data, CTD 4.2.3.1.1, 4.2.3.1.3, 4.2.3.1.5)

Male and female CD-1 mice received a single oral dose of baricitinib at 0 (vehicle), 600, 900, or 1200 mg/kg. No baricitinib-related deaths or sacrifices in extremis occurred; therefore, the approximate lethal dose was determined to be >1200 mg/kg.

Male and female rats received a single oral dose of baricitinib at 0 (vehicle), 200, or 600 mg/kg. No baricitinib-related deaths or moribund sacrifices occurred. The approximate lethal dose was determined to be >600 mg/kg.

Beagle dogs received a single oral dose of baricitinib at 5, 10, 20, or 40 mg/kg. No baricitinib-related deaths or moribund sacrifices occurred. Ataxia and tremor were observed in the 40 mg/kg group. Based on these results, the approximate lethal dose was determined to be >40 mg/kg.

5.2 Repeated-dose toxicity

As repeated-dose toxicity studies, oral dose toxicity studies were conducted in mice (28-day and 3-month studies), rats (28-day and 6-month studies), and dogs (28-day, 6-month, and 9-month studies). In the rat 6-month and dog 9-month repeated oral dose toxicity studies, the no-observed-adverse-effect level (NOAEL) was determined to be 5 and 0.5 mg/kg, respectively. The $AUC_{0\text{-}24}$ at the NOAEL (1616 and 447.5 ng·h/mL, respectively) was 3.4- and 0.9-fold, respectively, as compared with $AUC_{0\text{-}24}$ (477.6 ng·h/mL)[1)] following multiple oral doses of baricitinib at 4 mg to RA patients.

Major toxic changes caused by baricitinib observed in mice, rats, and dogs were immunosuppression, lymphocyte depletion, and decreased bone marrow cellularity, which were attributed to decreased lymphocyte and eosinophil counts. The applicant explained that these changes were anticipated because of the pharmacological action of baricitinib [see Section “3.R.1 Mechanism of action of baricitinib against rheumatoid arthritis”].

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1 $AUC_{0\text{-}24}$ (477.6 ng·h/mL) and C_{max} (53.4 ng/mL) in RA patients following once daily repeated doses of baricitinib 4 mg, based on an estimation from the population pharmacokinetic model established based on the results from Phase II and III studies [see Section “6.2.3.1 Pharmacokinetics in patients”]

5.2.1 Twenty-eight-day repeated oral dose toxicity study in mice (CTD 4.2.3.2.1)

Baricitinib was administered orally to male and female CD-1 mice for 28 days at 0 (vehicle), 10, 75, 250, or 500 mg/kg. Deaths or moribund sacrifices occurred in 5 of 20 mice in the 500 mg/kg group. The dead animals exhibited incomplete eyelid opening, emaciation, decreased fecal excretion, decreased skin elasticity, cold feeling, labored respiration, intermittent tremor, handling-induced convulsion, yellowing of the body surface, renal pallor, and reddened cortico-medullary junction. Changes observed in the ≥250 mg/kg groups were suppressed body weight gain, decreased erythrocyte, reticulocyte, leukocyte, and lymphocyte counts, renal pallor, and shrunken kidney. In the 500 mg/kg group, increased platelet count, increased red cell distribution width, increased mean corpuscular hemoglobin, and increased serum urea nitrogen were observed.

Based on the above, the NOAEL was determined to be 75 mg/kg.

5.2.2 Three-month repeated oral dose toxicity study in mice (CTD 4.2.3.2.3)

Baricitinib was administered orally to male and female CD-1 mice for 3 months at 0 (vehicle), 10, 75, or 150 mg/kg. Deaths occurred in 2 of 20 mice in the 150 mg/kg group. The dead animals exhibited decreased activity, decreased skin elasticity, labored respiration, cold feeling, handling-induced convulsion, decreased femoral bone marrow cell count, and lymphocyte depletion in the spleen, thymic gland, and lymph nodes. Changes observed in animals receiving ≥75 mg/kg were decreased skin elasticity, increased platelet count, increased red cell distribution width and mean corpuscular hemoglobin, decreased erythrocyte, leukocyte, and lymphocyte counts, decreased lymphocyte ratio, decreased weights of the spleen, thymic gland, and adrenal gland, and decreased mononuclear cell infiltration in the liver and lymphocytic infiltration in the exorbital lacrimal gland. In the 150 mg/kg group, decreased femoral bone marrow cell count was observed.

Based on the above, the NOAEL was determined to be 10 mg/kg.

5.2.3 Twenty-eight-day repeated oral dose toxicity study in rats with a 4-week recovery period (CTD 4.2.3.2.4)

Baricitinib was administered orally to male and female SD rats for 28 days at 0 (vehicle), 2, 10, or 40 mg/kg in this study (including reversibility assessment after a 4-week recovery period). No baricitinib-related deaths or moribund sacrifices occurred. Decreased leukocyte count and decreased leukocyte subtypes were observed in groups receiving ≥2 mg/kg, and decreased eosinophil count and decreased bone marrow cellularity were observed in groups receiving ≥10 mg/kg. Changes observed in the 40 mg/kg group were suppressed body weight gain, decreased reticulocyte and neutrophil counts, decreased weights of the spleen and thymic gland, increased histiocytes accompanied with finely vacuolated (foamy) cytoplasm in the lymph node paracortical area, and lymphocyte depletion in the spleen and thymic gland.

The decreased leukocyte and lymphocyte counts observed in the 2 and 10 mg/kg groups were mild in severity with no effects on clinical signs. The applicant therefore explained that these findings are of little clinical significance. After a 4-week recovery period, although decreased thymic gland weight was detected, all other changes reversed.

Based on the above, the NOAEL was determined to be 10 mg/kg.

5.2.4 Six-month repeated oral dose toxicity study in rats with a 6-week recovery period (CTD 4.2.3.2.6)

Baricitinib was administered orally to male and female SD rats for 6 months at 0 (vehicle), 0.5, 5, 25, or 100/60 mg/kg in this study (including reversibility assessment after a 6-week recovery period). In the 100/60 mg/kg group, while male animals received baricitinib at 100 mg/kg for 6 months, and female animals first received baricitinib at 100 mg/kg for 22 days, then, after a 4-day recovery period, the treatment resumed at 60 mg/kg.[2)]

Deaths or moribund sacrifices occurred in 2 of 46 rats in the 25 mg/kg group and 7 of 46 rats in the 100/60 mg/kg group. The causes of the deaths in the 25 mg/kg group could not be ascertained. Cardiomyopathy, hepatitis, and hepatocellular necrosis were identified in the dead animals in the 100/60 mg/kg group.

Decreased lymphocyte count, decreased femoral bone marrow cell count, and decreased spleen weight were observed at ≥5 mg/kg, and suppressed body weight gain, decreased food intake, increased alkaline phosphatase, and lymphocyte depletion in the spleen, Peyer's patch, mesenteric lymph node, and thymic gland were observed at ≥25 mg/kg. Changes observed at 100/60 mg/kg were increased serum urea nitrogen, albumin, potassium, and chlorine, aggravated cardiomyopathy, kidney crystallization, renal tubular degeneration, renal tubular dilation, pyelitis, and transitional epithelial hyperplasia.

The applicant considers that cardiomyopathy in rats has little toxicological significance for the following reasons and is unlikely to pose concerns in clinical use of baricitinib:

- Cardiomyopathy is a known male rat-specific change with aging (*Aging Clin Exp Res*. 2004;16:68-78), and it does not suggest that baricitinib may cause cardiomyopathy in other animal species including humans (*Toxicol Pathol*. 2013;41:1126-36, *Toxicol Pathol*. 2011;39:850-60).
- None of 168 cases of increased creatine phosphokinase (CPK) in 142 subjects in clinical studies met the criteria for major adverse cardiovascular events (MACE). All the cases were therefore considered unrelated to cardiovascular adverse events.
- The plasma exposure ($AUC_{0\text{-}24}$ [10,363 ng·h/mL]) following the administration of baricitinib, at a dose which did not cause aggravated cardiomyopathy in rats, was 21.7-fold the plasma exposure after the administration at the human clinical dose of 4 mg ($AUC_{0\text{-}24}$ [477.6 ng·h/mL]). This indicates a wide safety margin of baricitinib.

[2] The dose was changed because 5 of the 15 rats in the group died during the first 3 weeks of administration.

The decreases in lymphocyte and femoral bone marrow cell counts in the 5 mg/kg group were mild in severity with no effect on clinical signs in rats. The applicant therefore explained that these changes have little clinical significance. After a 6-week recovery period, all changes reversed except increased thymic gland weight.

Based on the above, the NOAEL was determined to be 5 mg/kg.

5.2.5 Twenty-eight-day repeated oral dose toxicity study in dogs with a 4-week recovery period (CTD 4.2.3.2.7)

Baricitinib was administered orally to male and female beagle dogs for 28 days at 0 (vehicle), 0.15, 0.45, or 3 mg/kg in this study (including reversibility assessment after a 4-week recovery period). No baricitinib-related deaths or moribund sacrifices occurred. Changes observed in the 3 mg/kg group were lacrimation, scleral hyperemia, yellow nasal discharge, decreased erythrocyte count, decreased reticulocyte count, decreased hemoglobin, decreased hematocrit, lymphocyte depletion in the lymph nodes, spleen, Peyer's patch, and thymic gland, decreased costal and sternal bone marrow cell counts, necrotic inflammation focus in the ileac Peyer's patches, and multifocal or confluent necrotic inflammation in the intestinal membrane lymph nodes.

After a 4-week recovery period, all these changes reversed.

Based on the above, the NOAEL was determined to be 0.45 mg/kg.

5.2.6 Six-month repeated oral dose toxicity study in dogs with a 6-week recovery period (CTD 4.2.3.2.9)

Baricitinib was administered orally to male and female beagle dogs for 6 months at 0 (vehicle), 0.25, 1/0.75, 5/2.5, or 20/15/5 mg/kg in this study (including reversibility assessment after a 6-week recovery period). In the 1/0.75 group, baricitinib was administered at 1 mg/kg for 16 days and at 0.75 mg/kg from Day 17 onward. In the 5/2.5 mg/kg group, animals received 5 mg/kg for 16 days and or 2.5 mg/kg from Day 17 onward.[3)] In the 20/15/5 mg/kg group, baricitinib was administered at 20 mg/kg for 3 days, and after a 3-day recovery period, at 15 mg/kg for 5 days, and after a 10-day recovery period, the treatment was resumed at 5 mg/kg.[3)] The treatment in the 5/2.5 and 20/15/5 mg/kg groups was discontinued on Day 154.

Baricitinib-related moribund sacrifices occurred in 1 of 14 animals in the 1/0.75 mg/kg group, 10 of 14 animals in the 5/2.5 mg/kg group, and 10 of 14 animals in the 20/15/5 mg/kg group. Worsened clinical signs and systemic inflammation associated with demodectic mange were observed in these sacrificed animals. Cold feeling, reddening of the skin, tubercles were observed at ≥0.25 mg/kg, and reddish feces,

[3] The dose was changed because dogs in these groups exhibited worsened clinical signs, which was probably attributable to baricitinib, 3 weeks after the start of administration.

crusts, scleral hyperemia, coarse hair, demodectic mange, and lymphocytic depletion in the thymic gland were observed at ≥1/0.75 mg/kg. Changes observed at ≥5/2.5 mg/kg were vomiting, soft stool, swelling (legs, paws, lips, etc.), protrusion of the nictitating membrane, interdigital cysts, decreased body weight and food consumption, increased serum urea nitrogen and chlorine, decreased serum albumin and calcium, and inflammatory changes in organs (lungs, gastric fundus, pylorus of stomach, liver, large intestine, and lymph nodes). Changes observed at 20/15/5 mg/kg were thickened leathery skin, renal inflammation, and lymphocytic depletion in the spleen and lymph nodes.

The changes in clinical signs observed at 0.25 mg/kg were similar to those in the control group in severity with no effect on the systemic condition. The applicant therefore explained that these changes had little toxicological significance. The changes reversed after a 6-week recovery period.

Based on the above, the NOAEL was determined to be 0.25 mg/kg.

5.2.7 Nine-month repeated oral dose toxicity study in dogs with a 6-week recovery period (CTD 4.2.3.2.10)

Baricitinib was administered orally to male and female beagle dogs for 39 weeks (including reversibility assessment after a 6-week recovery period) at 0 (vehicle), 0.25, 0.5, 3, or 9/6 mg/kg. In the 9/6 mg/kg group, baricitinib was administered at 9 mg/kg for 50 days before a 7-day recovery period, and was resumed at 6 mg/kg.[4)] In groups receiving ≥3 mg/kg, baricitinib was suspended from Day 193 to Day 214.[5)] In the 3 and 9/6 mg/kg groups, baricitinib was discontinued on Day 231, when 8 of 14 dogs in each group were sacrificed moribund.[6)] Reddening of the skin, dry skin, crust formation, and decreased eosinophil and lymphocyte counts were observed at ≥0.25 mg/kg, and hair loss at ≥0.5 mg/kg. Changes observed at ≥3 mg/kg were decreased activity, decreased food consumption, conjunctivitis, eye discharge, pyrexia, sores from rubbing against the cage, decreased body weight, decreases in erythrocyte count, decreased hemoglobin, hematocrit, and mean corpuscular hemoglobin, increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyltransferase, and globulin, decreased serum albumin, demodectic mange, cellular infiltration with neutrophils consisting mainly of mononuclear cells and macrophages in the airway of the lung or around pulmonary blood vessels, fungus infection of the lung, lobar discoloration, cellular infiltration and inflammation in the hepatic portal region, and biliary hyperplasia. In the 9/6 mg/kg group, multiple inflammation characterized by mononuclear cells around blood vessels and muscle layers on the gastric and jejunal serosae and increased mononuclear cell infiltration in the cecum and colon were observed. Changes related to demodectic mange were suppurative granulomatous inflammation, follicular dilation and thickening, ulcer, Demodex canis in or outside the follicle, crust formation, discoloration, scaly skin, exfoliation of skin and subcutaneous tissue, inflammation of mandibular lymph nodes, lymphoid

4 The dose was changed because a considerable number of animals discontinued baricitinib during the first 7 weeks of administration.

5 The administration of baricitinib was discontinued because of severe clinical signs associated with demodectic mange.

6 Despite treatment by the veterinarian, the progression of demodectic mange could not be controlled. Therefore, it was decided to discontinue the administration of baricitinib. Reversibility was assessed after a 6-week recovery period in 6 of 14 animals each in the 3 and 9/6 mg/kg groups.

follicular hyperplasia, increased lymphoblasts in the paracortical area and increased macrophages in the medullary sinuses, decreased follicle counts in the spleen, and lymphocytic depletion characterized by shrinkage of the embryonic follicles.

According to the applicant, the following observations suggest that the biliary hyperplasia observed in groups receiving ≥3 mg/kg may not have been attributable to direct toxicity of baricitinib or its metabolites:

- Neither biliary hyperplasia nor changes in hepatic enzyme levels suggesting hepatic dysfunction occurred in the 7-day, 28-day, or 6-month repeated-dose toxicity study.
- For the treatment or prevention of demodectic mange or opportunistic infection caused by the immunosuppressive effect of baricitinib, various types of therapeutic drugs including those excreted via the bile duct were often used.
- The immunosuppressive effect of baricitinib may have caused inflammation of the portal and surrounding area of the liver. As secondary changes of such inflammation, the occurrence of reactive changes in the bile duct was reported (*Hepatology*. 2011;54:1853-63). The immunosuppressive effect of baricitinib, chronic inflammation in the portal area, and the effects of drugs used to treat demodectic mange and its symptoms may have been involved in the onset of biliary hyperplasia in a complex manner.

Clinical signs observed at ≤0.5 mg/kg were mild in severity with minimal to mild histopathological changes. These signs and changes resolved or tended to resolve after a 6-week recovery period. Therefore, the applicant considers the changes are of toxicologically insignificant.

Based on the above, the NOAEL was determined to be 0.5 mg/kg.

5.3 Genotoxicity (CTD 4.2.3.3.1.1, 4.2.3.3.1.2, 4.2.3.3.2.1)

A bacterial reverse mutation assay (CTD 4.2.3.3.1.1) and a chromosomal aberration assay in human peripheral blood lymphocytes (CTD 4.2.3.3.1.2) were conducted. The results were negative. In a rat micronucleus assay (CTD 4.2.3.3.2.1), an increase in micronucleus frequency was observed in the 800 mg/kg group.

The applicant explained that the increase in micronucleus frequency observed in the 800 mg/kg group is considered a secondary change associated with decreased body temperature for the following reasons:

- Rodents are known to have micronuclei induced by decreased body temperature (*Mutat Res*. 1997;393:91-8, *Mutat Res*. 2000;471:81-6).
- In a safety pharmacological study, decreased body temperature was observed in rats after receiving a single oral dose of baricitinib at 100 mg/kg [see Section “3.3.1 Effects on the central nervous system”]. Although body temperature was not measured in the rat micronucleus assay, piloerection was observed in the 800 mg/kg group. This change is considered a compensatory physiological reaction to decreased body temperature.

It is difficult to extrapolate the above-mentioned mechanism of action to humans (*Mutat Res*. 2007;627:78-91). The $AUC_{0\text{-}24}$ (81,708 ng·h/mL) and C_{max} (8337.9 ng/mL), respectively, of plasma baricitinib in rats at the dose of 400 mg/kg, which caused no significant difference in micronucleus frequency, was 171- and 156-fold the plasma baricitinib[1)] in RA patients receiving multiple oral doses of baricitinib 4 mg. The applicant, therefore, explained that a genotoxic risk of baricitinib in its clinical use would be low.

5.4 Carcinogenicity

Carcinogenicity was evaluated in oral dose studies in mice and rats. There was no baricitinib-related increase in the incidence of tumors, and the non-carcinogenic dose was determined to be 150 and 300 mg/kg in female and male mice, respectively, and 25 and 8 mg/kg in female and male rats, respectively. The plasma exposure ($AUC_{0\text{-}24}$) at the non-carcinogenic dose was 37,200 and 26,400 ng·h/mL in female and male mice, respectively, and 12,964 and 2874 ng·h/mL in female and male rats, respectively, which was 78- and 55-fold in female and male mice and 27- and 6-fold in female and male rats as compared with the $AUC_{0\text{-}24}$ (477.6 ng·h/mL)[1)] in RA patients receiving multiple doses of oral baricitinib 4 mg.

5.4.1 Twenty-eight-day repeated oral dose toxicity study in mice (CTD 4.2.3.2.11)

Baricitinib (free base) 0 (vehicle), 75, 150, or 300 mg/kg was administered orally to male and female rasH2 wild-type mice for 28 days. No baricitinib-related deaths or moribund sacrifices occurred. Changes observed at ≥75 mg/kg were decreased erythrocyte, reticulocyte, and lymphocyte counts, decreased weights of the thymic gland and spleen, decreased lymphocytes in the spleen and thymic gland, cellular debris in the epididymis, and decreased luteal maturation or involution at ≥75 mg/kg. At ≥150 mg/kg, decreases in hemoglobin and hematocrit and decreased neutrophil and eosinophil counts were observed. Changes observed at 300 mg/kg were increased platelet count, increased serum urea nitrogen, decreased weights of the testis, epididymis, ovary, and uterus, seminiferous tubular atrophy, uterine atrophy, renal tubular changes (degeneration, necrosis, dilation, mineral deposition, and regeneration), decreased lymphocytes in mesenteric lymph nodes, and decreased bone marrow cellularity.

According to the applicant, the changes in the reproductive organ in female animals in the 300 mg/kg group were attributable to reproductive cycle abnormality associated with suppressed body weight gain and decreased food consumption, and were, therefore, toxicologically insignificant.

Accordingly, the maximal tolerated dose in the 28-day repeated oral dose toxicity study was determined to be 150 mg/kg for female animals and 300 mg/kg for male animals.

5.4.2 Six-month carcinogenicity study in mice (CTD 4.2.3.4.2.1)

Baricitinib (free base) was administered orally to male and female rasH2 mice for 6 months at 0 (vehicle), 15, 40, or 300 mg/kg for male mice and at 0 (vehicle), 10, 30, or 150 mg/kg for female mice.

Changes such as decreased lymphocyte count in groups receiving ≥10 mg/kg and decreased bone marrow cellularity in groups receiving ≥150 mg/kg were observed. However, there was no baricitinib-related increase in the incidence of tumors.

5.4.3 Two-year carcinogenicity study in rats (CTD 4.2.3.4.1.1)

Baricitinib (free base) was administered orally to SD rats for 2 years at 0 (vehicle), 1, 3, or 8 mg/kg for male rats and at 0 (vehicle), 3, 8, or 25 mg/kg for female rats.

Changes observed were suppressed body weight gain in groups receiving ≥1 mg/kg; increased clear cell nests in the liver and increased lipoproteins in the alveolus in females in groups receiving ≥8 mg/kg; and decreased lymphocytes in the spleen, intestine-associated lymphoid tissue, and Peyer's patch and decreased splenic extramedullary hematopoiesis in the 25 mg/kg group. However, there was no baricitinib-related increase in the incidence of tumors.

The applicant explained that a decrease in the incidence of neoplastic lesions or hyperplasia in the mammary gland and liver may have been associated with the inhibitory effect of baricitinib on the JAK-STAT pathway for the following reasons:

- This phenomenon may be attributable to the pharmacological action of baricitinib. Tofacitinib, an analog that inhibits the JAK-STAT pathway was also reported to have reduced the incidences of mammary ductal ectasia, galactocele, mammary fibroadenoma, and mammary gland cancer and a decrease in the incidence of biliary hyperplasia (U.S. Food and Drug Administration. *XELJANZ (TOFACITINIB CITRATE) Pharmacology Review(s)*. 2012. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203214Orig1s000PharmR.pdf).
- In mammary gland cancer in rodents, JAK2 is involved in the differentiation and proliferation of the mature mammary gland (*Endocr Rev*. 2003;24:1-27) and malignancy of the mammary gland epithelium is induced by the activation of JAK2 (*Stem Cells*. 2010;28:928-38).
- Inhibition of the JAK-STAT pathway suppresses cytokine-induced cellular proliferation or tumor angiogenesis (*Oncogene*. 2016;35:939-51).

5.5 Reproductive and developmental toxicity

The following reproductive and developmental toxicity studies were conducted: a study on fertility and early embryonic development to implantation in male and female rats, studies on the effects on embryo-fetal development in rats and rabbits, and a study on the effects on pre- and postnatal development, including maternal function, in rats. When baricitinib was administered to the animals at the NOAEL for embryo-fetal development (2 mg/kg in rats and 10 mg/kg in rabbits), the $AUC_{0\text{-}24}$ (1092 and

3027 ng·h/mL, respectively) and C_{max} (222 and 1125 ng/mL, respectively)[7] were 2.3-fold (rats) and 6.3-fold (rabbits) for AUC and 4.2-fold (rats) and 21.1-fold (rabbits) for C_{max} as compared with the AUC_{0-24} (477.6 ng·h/mL) and C_{max} (53.4 ng/m)[1] in RA patients receiving multiple oral doses of baricitinib at 4 mg. Placental transfer and excretion into milk were confirmed in rats [see Sections "4.2.4 Placental transfer" and "4.4.2 Excretion into milk"].

5.5.1 Fertility and early embryonic development to implantation in male and female rats (CTD 4.2.3.5.1.1)

Baricitinib was administered orally to male SD rats from 4 weeks before mating to the day of necropsy at 0 (vehicle), 5, 15, or 50 mg/kg and to female SD rats from 2 weeks before mating to gestation day 6 at 0 (vehicle), 5, 25, or 100 mg/kg. In the female 100 mg/kg group, 1 of 20 rats died. General toxic effects observed were decreased body weight in male rats in groups receiving ≥5 mg/kg; decreased epididymal weight in groups receiving ≥15 mg/kg; decreased food consumption and decreased prostate weight in male rats in the 50 mg/kg group; reddening of forelimbs, hindlimbs, and ears in rats of both sexes in groups receiving ≥50 mg/kg; and suppressed body weight gain, lacrimation, and eyelid ptosis in the 100 mg/kg group. Effects on fertility and early embryonic development to implantation were increased post-implantation embryonic mortality in female rats in groups receiving ≥25 mg/kg; decreased fertility and conception rate in rats of both sexes in groups receiving ≥50 mg/kg; and decreased corpus luteum count and implantation counts in the 100 mg/kg group.

Based on the following observations, the applicant explained that the decreases in fertility and conception rates were probably attributable to the effect of baricitinib on the female reproductive process:

- In female animals, in addition to decreased fertility and conception rate, decreased corpus luteum count and increased post-implantation embryonic mortality were observed.
- Decreased male reproductive organ weight was not associated with histopathological changes, or effects on the ability to move, concentration, or shape of the sperm.
- The mating rate was 100% in the high-dose groups with no effects on the mean time (days) to mating. Therefore, baricitinib was unlikely to affect male mating performance.

Based on the above, the NOAEL was determined to be 25 mg/kg in females and <5 mg/kg in males for general toxicity, and 5 mg/kg in females and 15 mg/kg in males for fertility and early embryonic development to implantation.

5.5.2 Embryo-fetal development

5.5.2.1 Embryo-fetal development study in rats (CTD 4.2.3.5.2.1)

Baricitinib 0 (vehicle), 2, 10, or 40 mg/kg was administered orally to pregnant SD rats consecutively from gestation days 6 to 17. No deaths or moribund sacrifices occurred. In maternal animals, reddening was observed at ≥10 mg/kg and lacrimation and decreased body weight at 40 mg/kg. In embryos and

[7] Plasma exposures in rats on gestation day 17 and in rabbits on gestation day 20

fetuses, increased incidence of limb bone curvature and costal abnormalities were observed at ≥10 mg/kg, and decreased fetal weight and increased incidence of costal curvature and seventh cervical rib were observed at 40 mg/kg.

The reddening observed at 10 mg/kg was transient and had no effects on clinical signs. Therefore, the applicant explained that this change was toxicologically insignificant.

Based on the above, the NOAEL was determined to be 10 mg/kg for maternal general toxicity and 2 mg/kg for embryo-fetal development.

5.5.2.2 Pilot study on embryo-fetal development in rabbits (CTD 4.2.3.5.2.5)

Baricitinib 0 (vehicle), 20, 40, 60, or 80 mg/kg was administered orally to pregnant New Zealand White rabbits consecutively from gestation days 7. Baricitinib-related deaths or moribund sacrifices occurred in 1 of 6 animals each in the 20 and 40 mg/kg groups and 6 of 6 animals each in the 60 and 80 mg/kg groups. Changes observed in the dead or sacrificed animals in the 60 and 80 mg/kg groups were decreased body weight, decreased food consumption, decreased physical activity, gasping, prone position, labored respiration, and decreased stool output. In maternal animals receiving ≥40 mg/kg, decreased body weight, decreased food consumption, and decreased pregnant uterine weight were observed. In embryos and fetuses in the 40 mg/kg group, increased post-implantation embryo absorption rate, decreased number of live fetuses and litter ratio, and decreased fetal weight were observed.

Accordingly, the dose for embryo-fetal development studies in rabbits was determined to be 3, 10, or 30 mg/kg.

5.5.2.3 Embryo-fetal development study in rabbits (CTD 4.2.3.5.2.3)

Baricitinib 0 (vehicle), 3, 10, or 30 mg/kg was administered orally to pregnant New Zealand White rabbits consecutively from gestation days 7 to 20 at. Baricitinib-related deaths occurred in 2 of 23 animals in the 30 mg/kg group. While decreased body weight and decreased food consumption were observed in these dead animals, the causes of deaths could not be ascertained. In the 30 mg/kg group, decreased pregnant uterine weight was observed in maternal animals, and increased post-implantation embryonic mortality, decreases in live fetus ratio, litter ratio, and fetal weight, and costal and vertebral abnormalities were observed in embryos and fetuses.

Based on the above, the NOAEL was determined to be 10 mg/kg for both maternal general toxicity and embryo-fetal development.

5.5.3 Effects on pre- and postnatal development, including maternal function, in rats (CTD 4.2.3.5.3.1)

Baricitinib 0 (vehicle), 2, 5, or 25 mg/kg was administered orally to pregnant SD rats consecutively from gestation day 6 to postpartum day 20. F_1-offspring were evaluated by a peripheral blood lymphocyte

subset analysis and immunohistochemical tests, etc. Baricitinib-related deaths or moribund sacrifices occurred in 1 of 30 animals in the 5 mg/kg group and 2 of 30 animals in the 25 mg/kg group. The cause of the death in the 5 mg/kg group could not be ascertained but was considered unrelated to baricitinib because of no toxic changes. In maternal animals, decreased food consumption was observed at 25 mg/kg. Changes observed in F_1 offspring were decreased preweaning body weight, decreased grip strength of the fore- and hind-limbs, and decreased maximal and mean amplitudes of response in an auditory startle reaction test conducted at 22 days after birth at ≥5 mg/kg; and decreased postnatal survival, suppressed pre- and post-weaning body weight gains, downsizing, abnormal forelimb rotation, delayed balano-preputial separation and vagina opening at 25 mg/kg. In F_2 offspring, no baricitinib-related toxic changes were detected.

The applicant viewed the decreased food consumption observed at 25 mg/kg as toxicologically insignificant because it did not affect clinical signs.

Based on the above, the NOAEL was determined to be 25 mg/kg for maternal general toxicity, 2 mg/kg for the development of F_1 offspring, and 25 mg/kg for reproductive toxicity of F_1 offspring and neonatal toxicity of F_2 offspring.

5.6 Other toxicity studies

5.6.1 Phototoxicity (CTD 4.2.3.7.7.1)

Baricitinib has an optical absorption band at [redacted] nm, which is within the solar wavelength (290-700 nm), and the molar absorbance coefficient at the absorption band is [redacted] $Lmol^{-1}cm^{-1}$. Baricitinib was distributed in the uvea of pigmented rats [see Section “4.2.1 Tissue distribution”]. Therefore, an *in vitro* study was conducted to evaluate the survival ratio of Balb/c 3T3 mouse fibroblasts using the neutral red uptake method. The results demonstrated that baricitinib is not phototoxic.

5.6.2 Eye irritation study (CTD 4.2.3.7.7.2)

An *in vitro* eye irritation study was conducted using isolated bovine corneas to evaluate the opacity of the cornea and fluorescein permeability. The results demonstrated that baricitinib has no ocular irritation potential.

5.6.3 Skin irritation study (CTD 4.2.3.7.7.3)

A single transdermal patch of baricitinib (free base) was applied at 1000 mg/kg for 24 hours to male and female New Zealand White rabbits, which were observed during the subsequent 14 days. Skin reaction was evaluated based on the Draize criteria. No changes were observed at any baricitinib application site, demonstrating that baricitinib has no skin irritation potential.

5.R Outline of the review conducted by PMDA

5.R.1 Administration to pregnant or possibly pregnant women

A total of 19 women receiving baricitinib in the clinical studies became accidentally pregnant during study period. Follow-up of these 19 subjects detected no teratogenicity or other adverse events in the subjects or their neonates as of February 20, 2017. However, because of the following observations, PMDA concluded that baricitinib should be contraindicated in pregnant or possibly pregnant women and asked the applicant to give cautionary advice on the matter in the package insert.

- Baricitinib caused skeletal malformation in rats even at a low dose with no obvious maternal toxicity [see Section "5.5.2.1 Embryo-fetal development study in rats"]. The plasma baricitinib in rats at a dose posing no skeletal malformation was 2.3-fold that in humans receiving baricitinib at a clinical dose of 4 mg. These facts do not eliminate the possibility that the clinical use of baricitinib may induce developmental toxicity including teratogenicity.
- Abnormal forelimb rotation [see Section "5.5.3 Effects on pre- and postnatal development, including maternal function, in rats"] observed in fetuses in the rat study on effects on pre- and postnatal development including maternal function was a similar morphological change to the limb bone curvature [see Section "5.5.2.1 Embryo-fetal development study in rats"] observed in the embryo-fetal development study in rats, suggesting that skeletal malformation caused by baricitinib given at the stage of organogenesis may be irreversible.
- The JAK-STAT pathway is involved in early embryogenesis (*Science*. 2002;296:1653-5). Also in studies of a similar JAK-STAT pathway inhibitor, teratogenicity was observed in several animal species and considered associated with the pharmacological action of the drug (Review Report of Xeljanz Tablets 5 mg dated February 28, 2013).

The applicant commented that baricitinib will be contraindicated in pregnant or possibly pregnant women. The applicant will also advise in the package insert women of childbearing potential to use effective contraception during treatment and for a certain period after treatment with baricitinib.

PMDA accepted the applicant's comments.

5.R.2 Administration to nursing mothers

Because baricitinib is excreted in milk, and neonatal developmental toxicity was observed in association with baricitinib, PMDA asked the applicant whether breastfeeding should be allowed during treatment with baricitinib.

The applicant's explanation:

The following observations do not eliminate the possibility that baricitinib may affect the development of nursing infants who are exposed to baricitinib via milk. Therefore, nursing mothers will be advised to discontinue breastfeeding during treatment in the package insert.

- Given that the absorption process of breast milk, its composition and active transport mechanism for absorption differ among species, it is difficult to accurately estimate drug exposure of infants

via milk based on data on milk excretion from animal studies (*Clin Pharmacol Ther*. 2016;100:42-52). However, excretion of baricitinib in milk was detected in nursing rats receiving oral baricitinib, and AUC of baricitinib in milk was 39-fold and C_{max} 18-fold as compared with the plasma concentration of baricitinib in maternal animals [see Section "4.4.2 Excretion into milk"].

- The effects of baricitinib on the development of F_1 offspring observed in the rat study on the effects on pre- and postnatal development including maternal function [see Section "5.5.3 Effects on pre- and postnatal development, including maternal function, in rats] were consistent with the findings in offspring in the embryo-fetal development study in rats exposed to baricitinib during the fetal period [see Section "5.5.2.1 Embryo-fetal development study in rats]. This may have been attributable to baricitinib exposure during the fetal stage. However, because F_1 offspring were exposed to baricitinib during the fetal and suckling periods in the rat study on the effects on pre- and postnatal development including maternal function, it is difficult to ascertain which period was involved in these changes, and it is suggested that these changes could have been caused by exposure via milk.

PMDA accepted the applicant's explanation.

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

As evaluation data, results from a relative bioavailability and food effect study in healthy Japanese adult subjects (CTD 5.3.1.2.1) were submitted. As reference data, results from a relative bioavailability study (CTD 5.3.1.1.1) and an absolute bioavailability study (CTD 5.3.1.1.2) in non-Japanese healthy adult subjects were submitted.

Concentrations of baricitinib in plasma and urine were determined using the LC/MS/MS method (lower limit of quantitation, 0.186-0.200 ng/mL for plasma concentration and 9.29-10.0 ng/mL for urinary concentration).

In this section, doses are expressed as doses of baricitinib and pharmacokinetic parameters are expressed as mean values or mean ± standard deviation unless otherwise noted.

6.1.1 Absolute bioavailability (CTD 5.3.1.1.2, JAGM study [January to February 2015])

A single oral dose of 4 mg of baricitinib or a single intravenous dose of 4 μg of ^{13}C-baricitinib was administered to 8 non-Japanese healthy adults. The pharmacokinetic parameters are shown in Table 11. The absolute bioavailability of baricitinib [90% confidence interval (CI)] was 78.9% [76.9%, 81.0%].

Table 11. Pharmacokinetic parameters following a single dose of baricitinib or ^{13}C-baricitinib

Dose	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL/mg)	$t_{1/2}$ (h)	t_{max} (h)	F (%)
Baricitinib 4 mg	35.2 ± 7.7	55.7 ± 13.7	8.6	1.0 [0.5, 2.0]	78.9
^{13}C-baricitinib 4 μg	0.061 ± 0.0087	70.9 ± 18.6	4.1	1.5 [1.3, 1.5]	NA

Mean ± standard deviation; $t_{1/2}$, geometric mean; t_{max}, median [range]; NA, not applicable

6.1.2 Relative bioavailability and food effect

6.1.2.1 Relative bioavailability of the formulation used in Phase II studies[8] and late phase II studies[9] and food effects on the formulation used in Phase II studies (CTD 5.3.1.1.1, JADH study [July to September 2011])

In a 4-period crossover study, 15 non-Japanese healthy adults received a single oral dose of baricitinib phosphate capsules used in late Phase II studies (4-mg capsule × 2), a baricitinib free base (particle size of [redacted] μm) 8-mg tablet used in Phase II studies, or a baricitinib free base (particle size of [redacted] μm) 8-mg tablet used in Phase II studies in the fasted or fed state. The pharmacokinetic parameters after each treatment are presented in Table 12, showing no marked difference among tablets with 2 different particle sizes and capsules. The C_{max} and t_{max} (median) following administration in the fed state was lower by 18% and longer by 0.5 hours, respectively, than the C_{max} and t_{max} following administration in the fasted state; however, no obvious effects of food were detected on the pharmacokinetics following administration of a baricitinib free base (particle size of [redacted] μm) 8- mg tablet used in Phase II studies.

Table 12. Pharmacokinetic parameters following a single dose of capsules used in late Phase II studies or an 8-mg tablet used in Phase II studies

Formulation		C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	t_{max} (h)
Capsules used in late Phase II studies	Mean ± SD	99.2 ± 25.2	650 ± 200	1.00 [0.50, 3.00]
Tablet used in Phase II studies (particle size of [redacted] μm)	Mean ± SD	95.5 ± 19.4	661 ± 183	1.00 [0.50, 3.00]
	Geometric least square mean ratio to the capsule [90% CI]	0.979 [0.868, 1.10]	1.02 [0.951, 1.10]	NA
Tablet used in Phase II studies (particle size of [redacted] μm) (fasted state)	Mean ± SD	96.9 ± 28.6	661 ± 194	1.00 [0.50, 2.00]
	Geometric least square mean ratio to the capsule [90% CI]	0.962 [0.852, 1.08]	1.02 [0.947, 1.09]	NA
Tablet used in Phase II studies (particle size of [redacted] μm) (after a high-fat meal)	Mean ± SD	78.7 ± 24.6	591 ± 185	2.00 [1.00, 4.00]
	Geometric least square mean ratio to the fasted state [90% CI]	0.820 [0.727, 0.925]	0.888 [0.827, 0.953]	NA

t_{max}, median [range]; NA, not applicable

6.1.2.2 Relative bioavailability of the formulation used in Phase II studies and the proposed formulation for marketing[10] and food effects on the proposed formulation for marketing (CTD 5.3.1.2.1, JAGO study [November 2014 to January 2015])

In a 5-period crossover study, 16 Japanese healthy adult subjects received a single oral dose of one 4-mg tablet proposed for marketing (4 mg), two 4-mg tablets (8 mg), or each one of 4-mg and 8-mg tablets

8 Used in Phase I studies (the JADH, JADO, and JAGO studies) and Phase II studies (the JADA and JADN studies).
9 Used in Phase I studies (the JADH and JADM studies) and Phase II studies (the JADA and JADN studies).
10 Used in Phase I studies (including the JAGC, JAGM, and JAGO studies) and Phase III studies (the JADV, JADW, JADX, JADY, and JADZ studies).

used in Phase II studies. The pharmacokinetic parameters after each regimen are presented in Table 13, showing no marked difference between two 4-mg tablets for marketing and one 8-mg tablet used in Phase II studies or between one 4-mg tablet for marketing and one 4-mg tablet used in Phase II studies.

The pharmacokinetic parameters following administration of one 4-mg tablet for marketing in the fed state are also presented in Table 13. The t_{max} (median) after the fed dose was extended by 0.13 hours as compared with that in the fasted dose. There was no obvious food effect on the pharmacokinetics of tablets for marketing.

Table 13. Pharmacokinetic parameters following a single dose of the proposed formulation for marketing or the formulation used in Phase II studies

Dose	Formulation		C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	t_{max} (h)
4 mg	Formulation used in Phase II studies	Mean ± SD	54.0 ± 9.8	305 ± 51.3	0.75 [0.50, 2.00]
	Proposed formulation for marketing (fasted state)	Mean ± SD	52.0 ± 11.5	301 ± 51.8	0.88 [0.50, 2.00]
		Geometric least square mean ratio to the formulation used in Phase II studies [90% CI]	0.955 [0.876, 1.04]	0.986 [0.950, 1.02]	NA
	Proposed formulation for marketing (after a low-fat meal)	Mean ± SD	47.0 ± 13.3	257 ± 35.2	1.00 [0.50, 3.0]
		Geometric least square mean ratio to the fasted state [90% CI]	0.889 [0.816, 0.969]	0.856 [0.825, 0.889]	NA
8 mg	Formulation used in Phase II studies	Mean ± SD	106 ± 25.3	595 ± 115	0.75 [0.50, 3.00]
	Proposed formulation for marketing	Mean ± SD	111 ± 28.6	636 ± 117	0.88 [0.50, 2.00]
		Geometric least square mean ratio to the formulation used in Phase II studies [90% CI]	1.04 [0.954, 1.13]	1.07 [1.03, 1.11]	NA

t_{max}, median [range]; NA, not applicable

6.2 Clinical pharmacology

The evaluation data submitted were results from Phase I studies in healthy subjects (CTD 5.3.3.1.3, 5.3.3.1.1, and 5.3.3.1.2), population pharmacokinetic analysis (CTD 5.3.3.5.1 and 5.3.3.5.2), and a pharmacodynamic study (CTD 5.3.4.1.1). The reference data submitted included results from a Phase I study in healthy subjects (CTD 5.3.3.1.4), studies on the effects of renal or hepatic impairment on the pharmacokinetics (CTD 5.3.3.3.1 and 5.3.3.3.2), and drug interaction studies (CTD 5.3.3.4.1 to 5.3.3.4.9).

In this section, doses are expressed as doses of baricitinib and pharmacokinetic parameters are expressed as mean values or mean ± standard deviation, unless otherwise noted.

6.2.1 Studies in healthy adults

6.2.1.1 Japanese Phase I study (CTD 5.3.3.1.3, JADM study [November 2010 to April 2011])

Japanese healthy adult subjects received a single oral dose of baricitinib (phosphate) at 2, 5, 10, or 14 mg or multiple oral doses of baricitinib at 10 or 14 mg for 10 days. The pharmacokinetic parameters after

treatment are presented in Tables 14 and 15. The accumulation indices after multiple doses were 1.11 to 1.16.

Table 14. Pharmacokinetic parameters in Japanese healthy adults following a single dose of baricitinib

	$AUC_{0-\infty}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
2 mg (N = 6)	157 ± 18.0	29.2 ± 7.9	1.0 [0.5, 2.0]	5.3 ± 1.0	12.9 ± 1.4	97.6 ± 18.1
5 mg (N = 6)	505 ± 106	86.2 ± 32.0	1.0 [0.5, 1.0]	6.9 ± 0.9	10.3 ± 2.3	103 ± 31.5
10 mg (N = 6)	687 ± 139	130 ± 48.7	1.3 [0.5, 2.0]	6.7 ± 2.0	15.1 ± 3.0	147 ± 57.1
14 mg (N = 7)	1159 ± 192	155 ± 31.1	1.0 [0.5, 2.1]	8.6 ± 1.6	12.4 ± 2.0	152 ± 30.3

Mean ± standard deviation; t_{max}, median [range]

Table 15. Pharmacokinetic parameters in Japanese healthy adults following 10-day multiple doses of baricitinib

	AUC_{τ} (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
10 mg (N = 5)	743 ± 133	123 ± 33.7	1.0 [0.5, 2.0]	8.6 ± 0.7	13.8 ± 2.5	173 ± 37.3
14 mg (N = 6)	1151 ± 189	163 ± 14.0	1.0 [1.0, 1.0]	9.6 ± 2.3	12.5 ± 2.3	171 ± 38.3

Mean ± standard deviation; t_{max}, median [range]

6.2.1.2 Foreign Phase I studies

6.2.1.2.1 Single dose study (CTD 5.3.3.1.1, JADF study [[redacted] 20[redacted] to [redacted] 20[redacted]])

Non-Japanese healthy adult subjects received a single oral dose of baricitinib (phosphate) at 1, 2, 5, or 10 mg. The pharmacokinetic parameters following administration are presented in Table 16. Baricitinib exposure increased dose-proportionally.

Table 16. Pharmacokinetic parameters in non-Japanese healthy adults following a single dose of baricitinib

Dose	$AUC_{0-\infty}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
1 mg (N = 8)	66.1 ± 13.7	10.0 ± 2.1	1.0 [1.0,1.5]	6.0 ± 1.9	16.1 ± 5.5	132 ± 37.7
2 mg (N = 9)	130 ± 36.7	21.5 ± 8.1	1.0 [1.0, 3.0]	7.2 ± 2.2	16.3 ± 3.73	164 ± 44.3
5 mg (N = 8)	359 ± 62.0	52.0 ± 14.8	1.3 [1.0, 2.0]	8.4 ± 1.3	14.4 ± 3.22	174 ± 40.4
10 mg (N = 16)	643 ± 147	99.9 ± 26.4	1.3 [1.0, 4.0]	7.2 ± 1.2	16.4 ± 4.01	166 ± 34.5

Mean ± standard deviation; t_{max}, median [range]

6.2.1.2.2 Multiple dose study (CTD 5.3.3.1.2, JADE study [[redacted] 20[redacted] to [redacted] 20[redacted]])

Baricitinib (phosphate) was administered orally to non-Japanese healthy adults at 2, 5, 10, or 20 mg once daily or 5 mg twice daily. The pharmacokinetic parameters following multiple administration are presented in Table 17. Baricitinib exposure increased dose-proportionally.

Table 17. Pharmacokinetic parameters in non-Japanese healthy adults following multiple doses of baricitinib

Dosage regimen	$AUC_{0-\tau}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
2 mg QD (N = 8)	118 ± 23.0	17.2 ± 2.9	1.5 [1.0, 2.0]	8.5 ± 1.8	17.6 ± 3.8	216 ± 67.3
5 mg QD (N = 8)	313 ± 54.2	52.4 ± 14.2	1.2 [0.5, 2.0]	7.4 ± 1.3	16.4 ± 3.0	175 ± 36.3
10 mg QD (N = 8)	549 ± 96.2	80.6 ± 24.6	1.0 [0.5, 4.0]	9.3 ± 2.4	18.6 ± 2.65	249 ± 67.1
20 mg QD (N = 8)	947 ± 220	157 ± 34.8	1.2 [0.5, 2.0]	6.8 ± 1.3	22.1 ± 4.85	221 ± 82.8
5 mg BID (N = 8)	327 ± 57.6	55.0 ± 9.0	1.5 [0.5, 3.0]	11 ± 2.9	15.7 ± 2.86	245 ± 75.4

Mean ± standard deviation; t_{max}, median [range]

6.2.1.2.3 Mass balance (CTD 5.3.3.1.4, JADG study [February to March 2011])

Non-Japanese healthy adults received a single oral dose of ^{14}C-baricitinib at 10 mg. The pharmacokinetic parameters following the dose are presented in Table 18. The geometric least square mean ratio of AUC_{0-12} and C_{max} of total radioactivity in whole blood to plasma was 1.14. The cumulative excretion of radioactivity into urine and feces, respectively, up to 120 hours post-dose was 75.2% and 19.9% of the dose administered. In urine, unchanged parent compound (69% of the dose administered), M22, M3, and M10 were detected from 0 to 48 hours post-dose. In feces, unchanged parent compound (15% of the dose administered) and M12 were detected from 0 to 72 hours post-dose.

Table 18. Pharmacokinetic parameters in plasma in non-Japanese healthy adults following a single dose of ^{14}C-baricitinib

N	C_{max} (ng/mL)	AUC_{0-12h} (ng·h/mL)	$t_{1/2}$ (h)	t_{max} (h)
6	88.4 ± 31.3	483 ± 142	6.9 (20)	1.0 [1.0, 2.0]

Mean ± standard deviation; t_{max}, median [range]; $t_{1/2}$, geometric mean (CV%)
Dose, 10 mg

6.2.2 Assessment of intrinsic factors

6.2.2.1 Pharmacokinetics in subjects with renal impairment (CTD 5.3.3.3.1, JADL study [[redacted] 20[redacted] to [redacted] 20[redacted]])

This study was conducted in non-Japanese subjects with normal renal function and those with renal impairment. A single oral dose of baricitinib 10 mg was administered to subjects with normal renal function and those with mild to moderate renal impairment and 5 mg to subjects with severe renal impairment. The pharmacokinetic parameters following the dose are presented in Table 19. C_{max} and AUC tended to increase with the increase in severity of renal impairment. Table 19 also includes the pharmacokinetic parameters of subjects on hemodialysis following a single oral dose of baricitinib 5 mg administered to 3 hours before or after hemodialysis. Approximately 17% of the dose administered was removed by 4-hour hemodialysis.

Table 19. Pharmacokinetic parameters in subjects with renal impairment following a single dose of baricitinib

Renal function[a)]	N	Dose (mg)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	CL/F (L/h)	Vz/F (L)
Normal	10	10	85.8 ± 20.2	1.0 [1.0, 3.0]	8.4 ± 2.4	579 ± 121	18.0 ± 3.69	215 ± 64.4
Mild impairment	10	10	102 ± 39.4	1.5 [1.0, 4.0]	10 ± 3.5	828 ± 208	12.8 ± 3.45	197 ± 124
Moderate impairment	10	10	123 ± 21.6	1.3 [1.0, 1.5]	12 ± 3.7	1330 ± 472	8.35 ± 2.79	129 ± 24.3
Severe impairment	8	5	60.9 ± 18.8	1.5 [1.0, 2.0]	19 ± 4.6	1170 ± 241	4.43 ± 0.88	116 ± 26.6
Before hemodialysis	8	5	39.0 ± 14.5	2.0 [1.0, 3.0]	19 ± 4.6	713 ± 212	7.67 ± 2.63	199 ± 55.9
After hemodialysis	8	5	46.4 ± 10.8	1.8 [1.0, 4.0]	18 ± 6.7	936 ± 271	5.75 ± 1.65	150 ± 58.7

Mean ± standard deviation; t_{max}, median [range]

a) Based on eGFR (mL/min/1.73m^2), each renal status was defined as follows: normal, ≥90; mild renal impairment, ≥60 to <90; moderate renal impairment, ≥30 to <60; and severe renal impairment, ≥15 to <30.

6.2.2.2 Pharmacokinetics in subjects with hepatic impairment (CTD 5.3.3.3.2, JAGC study [June to July 2013])

A single oral dose of 4 mg of baricitinib was administered to non-Japanese subjects with normal hepatic function and those with moderate hepatic impairment (Child-Pugh Class B). The pharmacokinetic parameters following the dose are presented in Table 20. The geometric least square mean ratio of

$AUC_{0-\infty}$ [90% CI] adjusted according to the hepatic functions of individual subjects was 0.981 [0.831, 1.16].

Table 20. Pharmacokinetic parameters in subjects with hepatic impairment following a single dose of baricitinib

	N	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_{0-t} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	CL/F (L/h)	Vz/F (L)
Normal	8	36.2 ± 8.48	0.75 [0.5, 3.0]	9.07 ± 0.93	298 ± 80.0	303 ± 80.2	13.9 ± 3.23	184 ± 49.1
Moderate impairment	8	39.1 ± 8.82	1.25 [0.5, 3.0]	8.39 ± 1.52	353 ± 85.6	361 ± 88.6	11.8 ± 3.46	139 ± 28.5

Mean ± standard deviation; t_{max}, median [range]
Dose, 4 mg

6.2.3 Population pharmacokinetic analysis (CTD 5.3.3.5.1, 5.3.3.5.2)

6.2.3.1 Pharmacokinetics in patients

A population pharmacokinetic analysis (NONMEM Version 7.3; Phase 2/3 PopPK) was conducted using blood samples collected from 2403 subjects at 14,034 time points in the Phase II and III studies in Japanese and non-Japanese patients with RA (the JADA, JADC, JADN, JADV, JADW, JADX, and JADZ studies). The final model was a two-compartment model with zero-order absorption and first-order elimination. Body weight, renal function, and erythrocyte sedimentation rate were selected as covariates for apparent renal clearance (CLr/F), and body weight and sex as covariates for apparent central volume of distribution (V1/F).

The pharmacokinetic parameters (inter-individual variation, %CV) estimated from the final model were as follows: CLr/F, 6.54 L/h (36.2%); apparent non-renal clearance (CLnr/F), 2.39 L/h (43.6%); V1/F, 95.1 L (14.4%); and apparent peripheral volume of distribution (V2/F), 23.3 L (37.6%). The estimated values (%CV) of $AUC_{\tau,ss}$, $C_{max,ss}$, and $C_{min,ss}$ following a once-daily multiple doses of baricitinib 4 mg in RA patients were 477.6 ng·h/mL (40.7%), 53.4 ng/mL (21.8%), and 6.91 ng/mL (91.8%), respectively.

6.2.3.2 Comparison of pharmacokinetics between healthy subjects and RA patients

A population pharmacokinetic analysis (NONMEM Version 7.2; Phase 1/2a PopPK) was conducted using blood samples collected from 335 subjects at 5828 time points in Phase I and II studies in non-Japanese patients (the JADE, JADF, JADL, JADB, and JADC studies). A two-compartment model with lag time and zero-order absorption was chosen as the final model with covariates of food for absorption duration (D_1) and lag time, glomerular filtration rate modification of diet in renal disease (GFR_{MDRD}) and the presence or absence of RA for CLr/F, body weight and sex for V1/F, and the JADC study for residual error.

The pharmacokinetic parameters estimated from the final models of Phase1/2a PopPK and Phase2/3 PopPK are presented in Table 21. As compared with healthy subjects, RA patients tended to have low CLr/F. The applicant explained that CLr/F in RA patients may have been affected by inflammatory responses and reduced renal function caused by the use of non-steroidal anti-inflammatory drugs (NSAIDs) and cDMARDs.

Table 21. Comparison of pharmacokinetics between healthy adults and RA patients estimated from the population pharmacokinetic models

	CL/F (L/h)	Vss/F (L)	$t_{1/2}$ (h)	$AUC_{\tau,ss}$ (ng·h/mL)	$C_{max,ss}$ (ng/mL)
Healthy subjects (Phase1/2a PopPK)	17.3 (24)	148 (24.8)	10.0 (18.9)	245 (25.3)[a)]	36.5 (24.3)[a)]
RA patients (Phase2/3 PopPK)	9.4 (34.3)	108 (19.3)	12.5 (27.4)	478 (40.7)[b)]	53.4 (21.8)[b)]

Mean (CV%)
[a)] Corrected based on the dose of 4 mg; [b)] Based on values in subjects receiving 4 mg of baricitinib in Phase III studies

6.2.4 Drug interactions (CTD 5.3.3.4.1 to 5.3.3.4.9)

Interactions between baricitinib and other drugs were evaluated in 9 studies. The pharmacokinetic parameters of baricitinib and other drugs in plasma are presented in Table 22 and Table 23. When baricitinib was used in combination with rifampicin, which induces CYP3A, CYP2B6, CYP2C8, CYP2C9, and CYP2C19, the $AUC_{0-\infty}$ of baricitinib was reduced by approximately 34%. When baricitinib was used in combination with probenecid, which inhibits OAT3, the CL_r and CL/F of baricitinib were reduced by 69% and 51%, respectively, while the AUC of baricitinib was nearly doubled.

Table 22. Effects of concomitant drugs on the pharmacokinetics of baricitinib

Concomitant drug (dosing regimen)	Dosing regimen of baricitinib	N	Baricitinib alone or in combination	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	Geometric least square mean ratio [90% CI] (combination/baricitinib alone)	
						C_{max}	AUC
Ketoconazole 400 mg QD for 6 days	Single dose of 10 mg	18	Alone	110 ± 27.7	737 ± 157	1.08 [1.01, 1.17]	1.21 [1.17, 1.24]
		17	Combination	120 ± 33.8	890 ± 206		
Fluconazole Single dose of 400 mg + 200 mg QD for 6 days	Single dose of 10 mg	18	Alone	109 ± 36.0	716 ± 161	1.05 [0.95, 1.15]	1.23 [1.18, 1.29]
		17	Combination	114 ± 41.4	873 ± 209		
Rifampicin 600 mg QD for 9 days	Single dose of 10 mg	18	Alone	98.3 ± 20.7	645 ± 121	1.05 [0.95, 1.16]	0.66 [0.62, 0.69]
		18	Combination	104 ± 27.2	423 ± 84.5		
Cyclosporine Single dose of 600 mg	Single dose of 4 mg	18	Alone	37.1 ± 8.5	247 ± 55.5	0.99 [0.91, 1.07]	1.29 [1.23, 1.36]
		18	Combination	36.6 ± 8.3	320 ± 78.7		
Probenecid 1000 mg BID for 5 days	Single dose of 4 mg	18	Alone	37.0 ± 7.9	242 ± 50.3	1.03 [0.94, 1.13]	2.03 [1.91, 2.16]
		18	Combination	38.0 ± 7.3	485 ± 69.8		
Omeprazole 40 mg QD for 8 days	Single dose of 10 mg	30	Alone	104 ± 29.8	679 ± 154	0.77 [0.72, 0.83]	1.07 [1.05, 1.10]
		30	Combination	79.0 ± 19.5	731 ± 168		
MTX Single dose	10 mg QD for 26 days	18	Alone	134.8 ± 36.8	997 ± 289[a)]	1.01 [0.92, 1.11]	0.98 [0.93, 1.03]
		18	Combination	135.9 ± 36.0	973 ± 276[a)]		

Mean ± standard deviation
[a)] AUC_{0-t}

Table 23. Effects of baricitinib on the pharmacokinetics of concomitant drugs

Concomitant drug (dosing regimen)	Dosing regimen of baricitinib	N	Drug investigated	Alone or in combination	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	Geometric least square mean ratio (%) [90% CI] (combination/concomitant drug alone)	
							C_{max}	AUC
Simvastatin Single dose of 40 mg	10 mg QD for 5 days	40	Simvastatin	Simvastatin alone	8.8 ± 8.0	52.3 ± 36.5[a)]	0.71 [0.63, 0.80]	0.85 [0.76, 0.96]
		38		Combination	5.3 ± 2.7	41.7 ± 28.6[b)]		
		40	Simvastatin acid	Simvastatin alone	2.5 ± 2.6	36.1 ± 40.4[c)]	0.88 [0.79, 0.98]	0.84 [0.75, 0.94]
		38		Combination	1.8 ± 1.3	26.0 ± 23.6[d)]		
Oral contraceptive (ethinyl estradiol 30 µg and levonorgestrel 150 µg) Single dose	10 mg QD for 8 days	20	Ethinyl estradiol	Oral contraceptive alone	65.3 ± 14.4[e)]	712 ± 168[f)]	0.94 [0.89, 0.99]	1.0 [0.96, 1.04]
		18		Combination	61.3 ± 14.3[e)]	718 ± 186[f)]		
		20	Levon-orgestrel	Oral contraceptive alone	3.6 ± 1.2	56.4 ± 39.5	1.0 [0.91, 1.09]	0.87 [0.77, 0.98]
		18		Combination	3.5 ± 0.9	46.6 ± 22.7		
Digoxin Single dose of 0.5 mg + 0.25 mg QD for 15 days	10 mg QD for 9 days	28	Digoxin	Digoxin alone	2.09 ± 0.46	19.0 ± 3.4[g)]	0.88 [0.82, 0.95]	0.90 [0.87, 0.94]
		28		Combination	1.83 ± 0.34	17.1 ± 3.3[g)]		
MTX Single dose	10 mg QD for 26 days	18	MTX	MTX alone	275 ± 77.4	1089 ± 286	0.95 [0.86, 1.05]	1.03 [0.94, 1.13]
		18		Combination	265 ± 83.0	1135 ± 352		
		18	7-OH-MTX	MTX alone	36.7 ± 16.6	868 ± 612	1.05 [0.93, 1.19]	1.16 [1.02, 1.33]
		18		Combination	38.7 ± 18.6	991 ± 717		

Mean ± standard deviation; [a)] N = 39, [b)] N = 36, [c)] N = 33, [d)] N = 32, [e)] pg/mL, [f)] pg·h/mL, [g)] AUC_{τ}

6.2.5 Pharmacodynamic studies

6.2.5.1 Effects on QT/QTc interval (CTD 5.3.4.1.1, JADO study Part B [February 2012 to May 2013])

Effects of baricitinib on QTc interval were evaluated in non-Japanese healthy adults. Subjects received a single oral dose of 40 mg of baricitinib, 400 mg of moxifloxacin, or placebo. The difference [90% CI] in change from baseline in QTcP interval between the baricitinib group and the placebo group was up to 1.81 ms [−0.079, 3.69], and the upper bound of the two-sided 90% confidence interval at any time point was <10 ms. In the moxifloxacin (positive control) group, the difference [90% CI] in change from baseline in QTcP interval between moxifloxacin and placebo was up to 12.3 ms [10.0, 14.5]. The lower bound of the two-sided 90% confidence interval was ≥5 ms.

6.2.6 Exposure-response relationship

6.2.6.1 Efficacy-related exposure-response relationship

A population pharmacokinetic/pharmacodynamic analysis was conducted using plasma baricitinib concentrations and percentages of American College of Rheumatology (ACR) responders obtained from Phase II and III studies in Japanese and non-Japanese patients with RA (the JADA, JADC, JADN, JADV, JADW, JADX, and JADZ studies[11)]). The final model established in Section "6.2.3.1 Pharmacokinetics in patients" was used for the population pharmacokinetic analysis and an indirect response model was used for the pharmacodynamic analysis. Body weight was selected as a covariate. The dose/exposure-response curves estimated from the models are presented in Figure 2. The model-estimated percentage of subjects achieving ACR 20%, 50%, or 70% improvement (ACR20, ACR50, or ACR70 responders)

[11] The JADC study was excluded from the ACR model.

after administration of 4 mg of baricitinib was higher by approximately 5% as compared with that after administration of 2 mg of baricitinib.

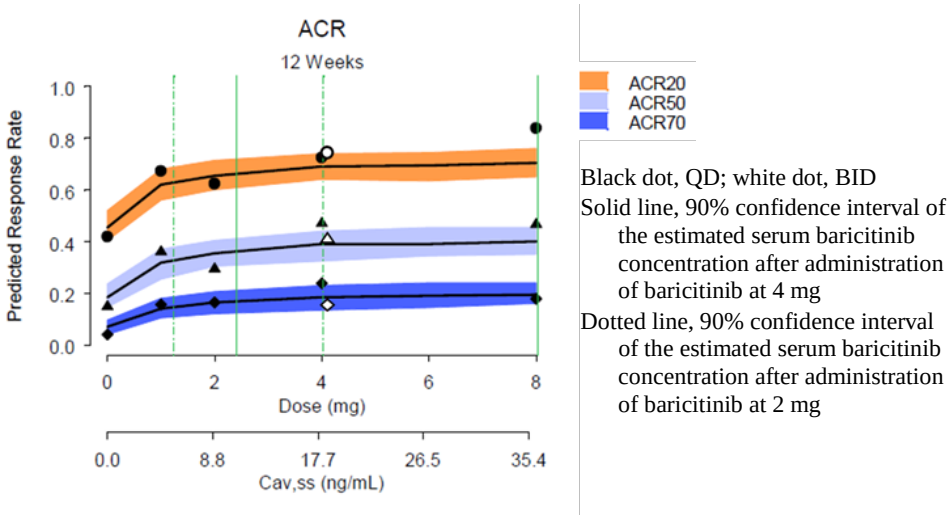


Figure 2. Dose/exposure-response curves for percentages of ACR responders at Week 12

6.R Outline of the review conducted by PMDA

6.R.1 Ethnic differences in pharmacokinetics of baricitinib

The applicant's explanation about the effects of ethnic factors on the pharmacokinetics of baricitinib:

In the JADM and JADF studies in Japanese and non-Japanese healthy subjects, the C_{max} and $AUC_{0-\infty}$ (mean ± standard deviation) after a single dose of baricitinib at 5 mg were 86.2 ± 32.0 ng/mL and 505 ± 106 ng·h/mL, respectively, in Japanese subjects and 52.0 ± 14.8 ng/mL and 359 ± 62.0 ng·h/mL, respectively, in non-Japanese subjects, tending to be high in Japanese subjects as compared with non-Japanese subjects [see Section "6.2.1 Studies in healthy adults"]. The results were likely to be associated with difference in body weight, based on the body weight-adjusted CL/F and Vz/F (median [25 and 75 percentiles]) of 0.21 [0.18, 0.25] L/h/kg and 1.9 [1.6, 2.5] L/kg, respectively, in Japanese subjects and 0.21 [0.18, 0.25] L/h/kg and 2.1 [1.9, 2.6] L/kg, respectively, in non-Japanese subjects, showing similarity between the 2 patient populations.

Meanwhile, the steady-state C_{max} and AUC_{τ} (mean [CV%]) in RA patients estimated from the population pharmacokinetic model [see Section "6.2.3.1 Pharmacokinetics in patients"] after administration of baricitinib 4 mg were 59.1 (19.4) ng/mL and 431 (32.2) ng·h/mL, respectively, in Japanese patients and 52.5 (22.4) ng/mL and 492 (41.5) ng·h/mL, respectively, in non-Japanese patients, showing no marked difference between the 2 patient populations.

PMDA's view:

In the population pharmacokinetic analysis in RA patients, C_{max} tended to be high and AUC tended to be low in the Japanese as compared with the non-Japanese, in contrast to the results of Phase I studies in healthy Japanese and non-Japanese adults. The results indicate that the possibility the pharmacokinetics of baricitinib was affected by a factor other than body weight. However, PMDA

concluded that there are no apparent ethnic differences between Japanese and non-Japanese in healthy adults as well as in patients with RA in the pharmacokinetics of baricitinib which may affect its efficacy and safety.

6.R.2 Drug interactions

The applicant explained about the combination use of baricitinib with other OAT3 inhibitors:

When baricitinib was administered in combination with probenecid, an OAT3 inhibitor, the C_{max} of baricitinib did not increase while $AUC_{0-\infty}$ nearly doubled. In a foreign late Phase II study (the JADA study), the ACR20 responder rates following treatment with baricitinib once daily at 4 mg and twice daily at 2 mg was 76% and 78%, respectively, being similar. From the population pharmacokinetic model [see Section "6.2.3.1 Pharmacokinetics in patients"], AUC was estimated to be similar and C_{max} was estimated to decrease in the 2 mg group. The above results suggested that the efficacy of baricitinib was associated with AUC not C_{max}. Relationships between baricitinib exposure and a decrease in hemoglobin and neutrophils were investigated based on the results from the late Phase II study in non-Japanese patients with RA (the JADA study in which baricitinib was administered at 1 to 8 mg). The results showed that baricitinib exposure increased dose-proportionally while hemoglobin and neutrophils tended to decrease. By reducing the dose of baricitinib to 2 mg when administered in combination with probenecid, the C_{max} of baricitinib is expected to decrease while its AUC remains similar. Therefore, the dose of baricitinib should be reduced to 2 mg when used in combination with an OAT3 inhibitor, and this should be communicated to healthcare professionals.

PMDA's view:

The combination of baricitinib with probenecid nearly doubled the AUC of baricitinib suggesting increased risks associated with an increase in baricitinib exposure. As shown in Section "6.R.2 Drug interactions," the efficacy of baricitinib 2 mg in RA patients with moderate renal impairment is expected to be equivalent to that of baricitinib 4 mg in RA patients with normal renal function or mild renal impairment [see Section "7.R.5.2 Pharmacokinetics of baricitinib in patients with renal impairment"], the applicant's view on the need of dose adjustment of baricitinib when used in combination with probenecid or any other OAT3 inhibitors is reasonable. The package insert should highlight that baricitinib exposure may increase in its combination use with an OAT3 inhibitor such as probenecid. Because only limited efficacy and safety data of baricitinib used in combination with any OAT3 inhibitor other than probenecid or any other drug, relevant data should be further collected via post-marketing surveillance.

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

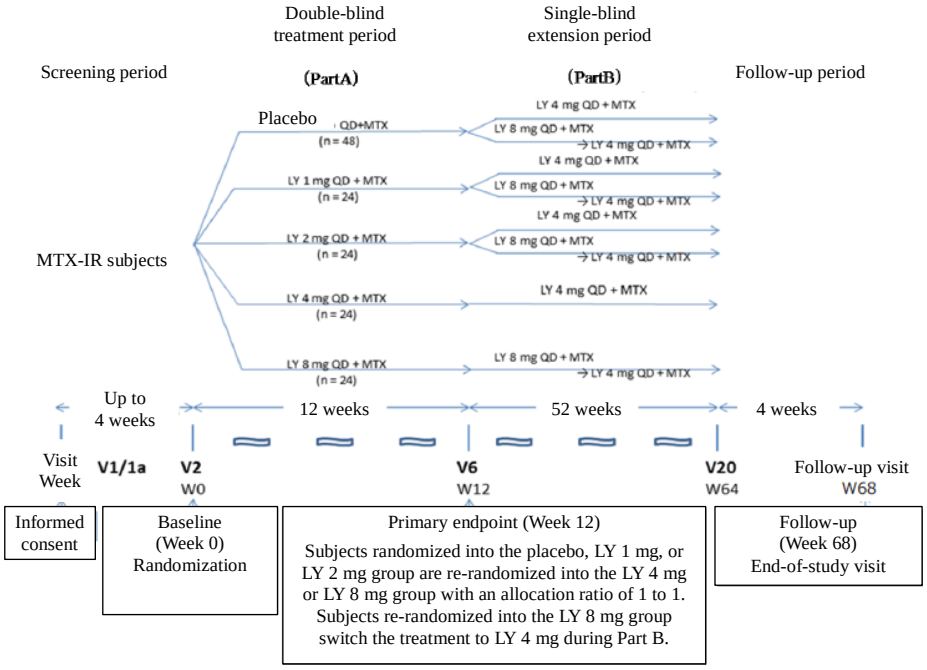
The efficacy and safety evaluation data submitted consisted of results from Phase II studies in RA patients (Studies I4V-JE-JADN [CTD 5.3.5.1.1] and I4V-MC-JADA [CTD 5.3.5.1.2]), multi-regional (Japan included) Phase III studies (Studies I4V-MC-JADW [CTD 5.3.5.1.4], I4V-MC-JADX [CTD 5.3.5.1.5], I4V-MC-JADV [CTD 5.3.5.1.6], and I4V-MC-JADZ [CTD 5.3.5.1.7]), and a long-term treatment study (Study I4V-MC-JADY [CTD 5.3.5.2.1]).

7.1 Phase II studies

7.1.1 Japanese study in RA patients with an inadequate response to MTX (Study 14V-JE-JADN [November 2011 to December 2013])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in RA patients with an inadequate response to MTX[12] (target sample size, 144 subjects [24 for each baricitinib group and 48 for the placebo group]) to evaluate the efficacy and safety of baricitinib.

This study consisted of 2 parts (up to Week 12, a double-blind part [Part A]; Week 12 and subsequent weeks, a single-blind part [Part B]) as shown in Figure 3. In combination with a fixed dose of MTX,[13] placebo or baricitinib at 1, 2, 4, or 8 mg was administered orally once daily for 64 weeks. Subjects randomized into the baricitinib 1 mg (hereinafter, 1-mg) group, 2-mg group, or the placebo group in Part A were re-randomized into the 4-mg or 8-mg group in Part B. During the treatment period in Part B, the regimen for subjects in the 8-mg group was changed to 4 mg of baricitinib given once daily from [redacted], 20[redacted].



MTX-IR subjects, MTX-irresponsive subjects

Figure 3. JADN study design

All 145 randomized subjects (24 each in the 1-, 2-, 4-, and 8-mg groups and 49 in the placebo group) were included in the safety analysis set and the full analysis set (FAS). The FAS also served as the efficacy analysis set. In Part A, subjects who discontinued study treatment accounted for 4.2% (1 of 24

[12] Main inclusion criteria: Patients who have active RA who meet all of the following criteria: (a) ≥6 swollen joints and ≥6 tender joints, (b) CRP of >0.5 mg/dL or erythrocyte sedimentation rate (ESR) of >28 mm/hour, (c) ACR functional class I, II, or III, and (d) use of MTX for ≥12 weeks including ≥8 consecutive weeks with a fixed dose of 6 to 16 mg/week (administered 2 or 3 times per week).

[13] Dose adjustment was allowed for safety reasons.

subjects) each in the 1- and 4-mg groups and 2.0% (1 of 49 subjects) in the placebo group. The major reason for discontinuation was adverse events (1 each in the 1-mg group and the placebo group). In Part B, subjects who discontinued study treatment accounted for 22.5% (16 of 71 subjects) in the 4-mg group[14)] and 22.9% (16 of 70 subjects) in the 8-mg group.[15)] The major reason for discontinuation was adverse events (21.1% [15 of 71 subjects] in the 4-mg group and 17.1% [12 of 70 subjects] in the 8-mg group).

The primary efficacy endpoint was the ACR20 responder rates at Week 12. As shown in Table 24, the results demonstrated a statistically significant difference between the combined 4 + 8-mg group and the placebo group (one-sided significance level of 0.05). The secondary efficacy endpoints were the ACR50 and ACR70 responder rates at Week 12 and are also shown in Table 24.

Table 24. ACR responder rates at Week 12 (FAS, NRI)

	1 mg	2 mg	4 mg	8 mg	Placebo
ACR20 responders	66.7 (16/24)	83.3 (20/24)	66.7 (16/24)	87.5 (21/24)	30.6 (15/49)
Difference from placebo [95% CI][a)]	36.1 [13.2, 58.9]	52.7 [33.0, 72.4]	36.1 [13.2, 58.9]	56.9 [38.4, 75.4]	–
Difference from placebo [95% CI][a)] *P* value[b)]	–	–	46.5 [28.9, 64.0] *P* < 0.001		–
ACR50 responders	33.3 (8/24)	45.8 (11/24)	54.2 (13/24)	54.2 (13/24)	8.2 (4/49)
Difference from placebo [95% CI][a)]	25.2 [4.8, 45.5]	37.7 [16.3, 59.0]	46.0 [24.6, 67.4]	46.0 [24.6, 67.4]	–
ACR70 responders	12.5 (3/24)	29.2 (7/24)	29.2 (7/24)	20.8 (5/24)	0 (0/49)
Difference from placebo [95% CI][a)]	12.5 [-0.7, 25.7]	29.2 [11.0, 47.4]	29.2 [11.0, 47.4]	20.8 [4.6, 37.1]	–

% (number of subjects)

a) Newcombe-Wilson method (without continuity correction)

b) Comparison between the combined 4 + 8-mg group and the placebo group based on a logistic regression model with baseline DAS28-hsCRP and treatment group as explanatory variables (one-sided significance level of 0.05)

In Part A, the incidence of adverse events was 45.8% (11 of 24 subjects) in the 1-mg group, 50.0% (12 of 24 subjects) in the 2-mg group, 54.2% (13 of 24 subjects) in the 4-mg group, 75.0% (18 of 24 subjects) in the 8-mg group, and 53.1% (26 of 49 subjects) in the placebo group. The major adverse events observed are shown in Table 25.

No deaths occurred. The incidence of serious adverse events was 4.2% (1 of 24 subjects; pancreatitis acute) in the 2-mg group, 4.2% (1 of 24 subjects; cataract) in the 8-mg group, and 2.0% (1 of 49 subjects; cholecystitis) in the placebo group. A causal relationship with the study drug was ruled out for all these serious adverse events excluding cholecystitis in the placebo group. The incidence of adverse events leading to treatment discontinuation was 4.2% (1 of 24 subjects; herpes simplex) in the 1-mg group and 2.0% (1 of 49 subjects; pollakiuria) in the placebo group.

14 The combined group of the placebo→4-mg group, 1-mg→4-mg group, 2-mg→4-mg group, and 4-mg→4-mg group

15 The combined group of the placebo→8-mg group, 1-mg→8-mg group, 2-mg→8-mg group, and 8-mg→8-mg group

The incidence of adverse drug reactions was 29.2% (7 of 24 subjects) in the 1-mg group, 20.8% (5 of 24 subjects) in the 2-mg group, 54.2% (13 of 24 subjects) in the 4-mg group, 62.5% (15 of 24 subjects) in the 8-mg group, and 26.5% (13 of 49 subjects) in the placebo group.

Table 25. Adverse events that occurred in ≥2 subjects in any group (Part A [up to Week 12], safety analysis set)

Adverse event	1 mg (N = 24)	2 mg (N = 24)	4 mg (N = 24)	8 mg (N = 24)	Placebo (N = 49)
Nasopharyngitis	2 (8.3)	2 (8.3)	2 (8.3)	2 (8.3)	6 (12.2)
Pharyngitis	1 (4.2)	1 (4.2)	0	2 (8.3)	1 (2.0)
Liver function test abnormal	1 (4.2)	0	2 (8.3)	2 (8.3)	0
Pyrexia	1 (4.2)	0	0	0	2 (4.1)
Hepatic function abnormal	0	3 (12.5)	0	3 (12.5)	0
Cystitis	0	1 (4.2)	0	0	2 (4.1)
Blood creatine phosphokinase increased	0	0	2 (8.3)	3 (12.5)	2 (4.1)
Nausea	0	0	2 (8.3)	0	0
Pertussis	0	0	2 (8.3)	0	0
Hypercholesterolaemia	0	0	1 (4.2)	3 (12.5)	0
Leukopenia	0	0	0	2 (8.3)	0
Cell marker increased	0	0	0	2 (8.3)	0

Number of subjects (%)

In Part B, the incidence of adverse events was 91.5% (65 of 71 subjects) in the 4-mg group and 98.6% (69 of 70 subjects) in the 8-mg group. The major adverse events observed are shown in Table 26.

No deaths occurred. The incidence of serious adverse events was 11.3% (8 of 71 subjects; pneumocystis jirovecii pneumonia, pneumonia, large intestine polyp, herpes zoster, pancreatitis acute/clavicle fracture/fall, gastroenteritis, rectal cancer, and deep vein thrombosis in 1 subject each) in the 4-mg group and 17.1% (12 of 70 subjects; cataract in 2 subjects, Meniere's disease, fall/forearm fracture, herpes zoster, fall/ulna fracture/blood creatine phosphokinase increased/cerebral haemorrhage, pneumocystis jirovecii pneumonia, angina pectoris, myocardial infarction, large intestine polyp, herpes zoster/ VIIth nerve paralysis, and interstitial lung disease in 1 subject each) in the 8-mg group. A causal relationship with the study drug could not be ruled out for herpes zoster, pneumonia, pneumocystis jirovecii pneumonia, and deep vein thrombosis in 1 subject each in the 4-mg group and herpes zoster in 2 subjects and pneumocystis jirovecii pneumonia, interstitial lung disease, angina pectoris, myocardial infarction, and VIIth nerve paralysis in 1 subject each in the 8-mg group.

The incidence of adverse events leading to treatment discontinuation was 21.1% (15 of 71 subjects; herpes zoster in 5 subjects, oral herpes and lymphopenia in 2 subjects each, abdominal pain, pneumocystis jirovecii pneumonia, herpes virus infection, oral herpes, rectal cancer, and deep vein thrombosis in 1 subject each) in the 4-mg group and 17.1% (12 of 70 subjects; herpes zoster in 6 subjects, lymphopenia, oral herpes, pneumocystis jirovecii pneumonia, hepatic function abnormal, genital herpes, and interstitial lung disease in 1 subject each) in the 8-mg group.

The incidence of adverse drug reactions was 70.4% (50 of 71 subjects) in the 4-mg group and 82.9% (58 of 70 subjects) in the 8-mg group.

Table 26. Adverse events occurring in ≥2 subjects in any group (Part B [Weeks 12 to 64], safety analysis set)

Adverse event	4 mg				8 mg			
	Placebo → 4-mg (N = 24)	1-mg → 4-mg (N = 12)	2-mg → 4-mg (N = 12)	4-mg → 4-mg (N = 23)	Placebo → 8-mg (N = 23)	1-mg → 8-mg (N = 11)	2-mg → 8-mg (N = 12)	8-mg → 8-mg (N= 24)
Nasopharyngitis	4 (16.7)	5 (41.7)	6 (50.0)	7 (30.4)	9 (39.1)	1 (9.1)	1 (8.3)	5 (20.8)
Blood creatine phosphokinase increased	4 (16.7)	1 (8.3)	0	3 (13.0)	4 (17.4)	3 (27.3)	2 (16.7)	2 (8.3)
Insomnia	3 (12.5)	0	1 (8.3)	0	0	0	0	0
Stomatitis	3 (12.5)	0	0	0	1 (4.3)	0	0	2 (8.3)
Constipation	2 (8.3)	2 (16.7)	1 (8.3)	0	2 (8.7)	1 (9.1)	1 (8.3)	1 (4.2)
Headache	2 (8.3)	1 (8.3)	1 (8.3)	1 (4.3)	1 (4.3)	1 (9.1)	0	1 (4.2)
Pharyngitis	2 (8.3)	0	0	1 (4.3)	0	0	1 (8.3)	2 (8.3)
Dry eye	2 (8.3)	0	0	0	1 (4.3)	0	0	0
Spinal osteoarthritis	2 (8.3)	0	0	0	1 (4.3)	0	0	0
Hepatic function abnormal	1 (4.2)	2 (16.7)	1 (8.3)	3 (13.0)	0	0	0	2 (8.3)
Lymphopenia	1 (4.2)	1 (8.3)	0	3 (13.0)	3 (13.0)	1 (9.1)	1 (8.3)	0
Hyperlipidaemia	1 (4.2)	1 (8.3)	0	1 (4.3)	3 (13.0)	2 (18.2)	1 (8.3)	3 (12.5)
Cough	1 (4.2)	1 (8.3)	0	1 (4.3)	2 (8.7)	0	1 (8.3)	0
Hypercholesterolaemia	1 (4.2)	0	1 (8.3)	3 (13.0)	2 (8.7)	1 (9.1)	0	3 (12.5)
Upper respiratory tract infection	1 (4.2)	0	0	2 (8.7)	1 (4.3)	1 (9.1)	0	1 (4.2)
Paronychia	1 (4.2)	0	0	0	2 (8.7)	0	0	0
Nausea	1 (4.2)	0	0	0	0	1 (9.1)	2 (16.7)	0
Herpes zoster	0	1 (8.3)	3 (25.0)	1 (4.3)	1 (4.3)	2 (18.2)	0	3 (12.5)
Tonsillitis	0	1 (8.3)	0	2 (8.7)	0	0	0	0
Alanine aminotransferase increased	0	1 (8.3)	0	1 (4.3)	2 (8.7)	0	0	1 (4.2)
Aspartate aminotransferase increased	0	1 (8.3)	0	1 (4.3)	2 (8.7)	0	0	1 (4.2)
Upper respiratory tract inflammation	0	1 (8.3)	0	1 (4.3)	1 (4.3)	2 (18.2)	1 (8.3)	0
Contusion	0	1 (8.3)	0	0	1 (4.3)	0	0	2 (8.3)
Laceration	0	0	2 (16.7)	0	0	0	0	0
Gastroenteritis	0	0	0	2 (8.7)	1 (4.3)	0	1 (8.3)	1 (4.2)
Diarrhoea	0	0	0	2 (8.7)	1 (4.3)	0	1 (8.3)	0
Tooth extraction	0	0	0	2 (8.7)	0	0	0	0
Cystitis	0	0	0	1 (4.3)	1 (4.3)	1 (9.1)	1 (8.3)	2 (8.3)
Dental caries	0	0	0	1 (4.3)	0	2 (18.2)	0	0
Gastritis	0	0	0	0	3 (13.0)	0	0	1 (4.2)
Leukopenia	0	0	0	0	3 (13.0)	0	0	1 (4.2)
Interstitial lung disease	0	0	0	0	0	0	0	2 (8.3)

Number of subjects (%)

7.1.2 Foreign study in RA patients with an inadequate response to MTX (Study 14V-MC-JADA [November 2010 to March 2014])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in RA patients with an inadequate response to MTX[16)] (target sample size, 270 subjects [45 for each of the baricitinib groups and 90 for the placebo group]) to evaluate the efficacy and safety of baricitinib.

[16] Main inclusion criteria: Patients who have active RA and who meet all of the following criteria: (1) ≥8 swollen joints and ≥8 tender joints, (2) CRP of >1.2-fold the upper limit of normal (ULN; 0.3 mg/dL) or erythrocyte sedimentation rate (ESR) of >28 mm/hour, (3) ACR functional class I, II, or III, and (4) use of MTX for ≥12 weeks including ≥8 consecutive weeks at a fixed dose of 10 to 25 mg/week.

This study consisted of 4 parts (up to Week 12, double-blind placebo-controlled part [Part A]; up to Week 24, double-blind extension part [Part B]; up to Week 76, open-label extension part [Part C]; and Week 76 and subsequent weeks, open-label additional extension part [Part D]) as shown in Figure 4. In Part A, in combination with a fixed dose of MTX,[17] placebo or baricitinib at 1, 2, 4, or 8 mg was administered orally once daily (QD) for 12 weeks. Subjects randomized to the baricitinib 1 mg QD group (1-mg QD group) or the placebo group in Part A were re-randomized to the baricitinib 2 mg twice daily (BID) group (2-mg BID group) or 4-mg QD group in Part B. Subjects randomized to the 2-mg QD group or 2-mg BID group in Part B were re-assigned to the 4-mg QD group in Part C. Of subjects in the 4-mg QD group in Part C, those who met the dose-increase criteria[18] at Week 28 or 32 may have changed their treatment regimen to 8 mg QD. In Part D, subjects received baricitinib at 4 mg QD regardless of the dose in Part B or C.

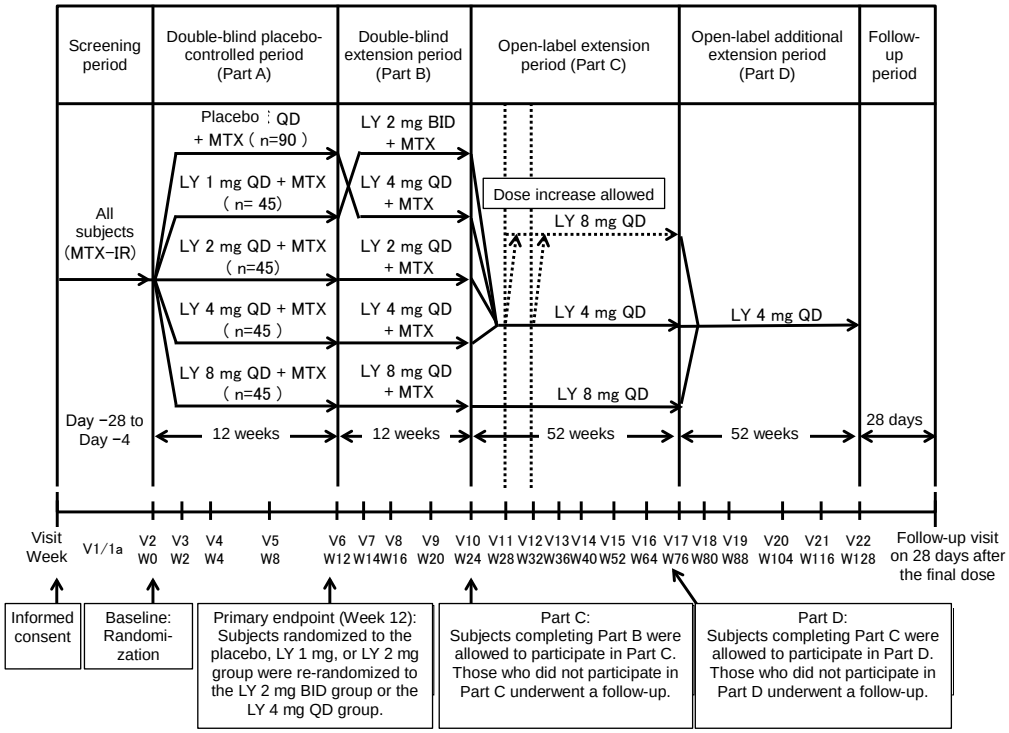


Figure 4. JADA study design

In Part A, all 301 randomized subjects (49 in the 1-mg group, 52 in the 2-mg group, 52 in the 4-mg group, 50 in the 8-mg group, and 98 in the placebo group) were included in the safety analysis set and the FAS. The FAS also served as the efficacy analysis set. Subjects who discontinued study treatment by Week 12 accounted for 10.2% (5 of 49) of subjects in the 1-mg group, 1.9% (1 of 52) of subjects in the 2-mg group, 3.8% (2 of 52) of subjects in the 4-mg group, 2.0% (1 of 50) of subjects in the 8-mg group, and 16.3% (16 of 98) of subjects in the placebo group. The major reason for discontinuation was adverse events (2.0% [1 of 49] of subjects in the 1-mg group, 1.9% [1 of 52] of subjects in the 2-mg group, 1.9% [1 of 52] of subjects in the 4-mg group, 2.0% [1 of 50] of subjects in the 8-mg group, and

[17] Dose adjustment was allowed for safety reasons.
[18] ≥6 tender joints and ≥6 swollen joints out of 28 joints, and clinical assessment and the investigator's opinion.

5.1% [5 of 98] of subjects in the placebo group). In Part B, 272 subjects (51 subjects in the 2-mg QD group, 50 subjects in the 4-mg QD group, 49 subjects in the 8-mg QD group, 39 subjects in the placebo → 2-mg BID group, 22 subjects in the 1-mg QD → 2-mg BID group, 39 subjects in the placebo → 4-mg QD group, and 22 subjects in the 1-mg QD → 4-mg QD group) were included in the FAS, excluding 4 subjects who discontinued the study drug before the start of Part B. In Parts C and D, 201 treated subjects (108 subjects in the 4/4-mg group,[19] 61 subjects in the 4:8/4-mg group,[20] and 32 subjects in the 8/4-mg group[21]) and 144 treated subjects (79 subjects in the 4/4-mg group, 47 subjects in the 4:8/4-mg group, and 18 subjects in the 8/4-mg group) were respectively included in the FAS.

The efficacy primary endpoint, the ACR20 responder rates at Week 12, are presented in Table 27, showing a statistically significant difference between the combined 4/8 mg group and the placebo group (one-sided significance level of 0.10). The ACR50 and ACR70 responder rates at Week 12, the secondary endpoints, are also shown in Table 27.

Table 27. ACR responder rates at Week 12 (FAS, NRI)

	1 mg	2 mg	4 mg	8 mg	Placebo
ACR20 responders	57.1 (28/49)	53.8 (28/52)	75.0 (39/52)	78.0 (39/50)	40.8 (40/98)
Difference from placebo [95% CI][a)]	16.3 [-0.6, 33.3]	13.0 [-3.7, 29.7]	34.2 [18.9, 49.5]	37.2 [22.1, 52.2]	–
Difference from placebo [95% CI][a)] *P* value[b)]	–	–	35.7 [22.9, 48.4] *P* < 0.001		
ACR50 responders	30.6 (15/49)	17.3 (9/52)	34.6 (18/52)	40.0 (20/50)	10.2 (10/98)
Difference from placebo [95% CI][a)]	20.4 [6.2, 34.6]	7.1 [-4.8, 19.0]	24.4 [10.2, 38.7]	29.8 [15.0, 44.6]	–
ACR70 responders	12.2 (6/49)	7.7 (4/52)	23.1 (12/52)	20.0 (10/50)	2.0 (2/98)
Difference from placebo [95% CI][a)]	10.2 [0.6, 19.8]	5.7 [-2.1, 13.4]	21.0 [9.2, 32.8]	18.0 [6.5, 29.4]	–

% (number of subjects)

a) Newcombe-Wilson method (without continuity correction)

b) Comparison between the combined baricitinib 4/8 mg group and the placebo group based on a logistic regression model with baseline DAS28-hsCRP and treatment group as explanatory variables (one-sided significance of 0.10)

In Part A (up to Week 12), the incidence of adverse events was 40.8% (20 of 49 subjects) in the 1-mg group, 46.2% (24 of 52 subjects) in the 2-mg group, 42.3% (22 of 52 subjects) in the 4-mg group, 52.0% (26 of 50 subjects) in the 8-mg group, and 45.9% (45 of 98 subjects) in the placebo group. The major adverse events observed are shown in Table 28.

19 The group treated with baricitinib 4 mg in Part C

20 The group treated with baricitinib increased from 4 mg to 8 mg in Part C

21 The group treated with baricitinib 8 mg in part C

Table 28. Adverse events that occurred in ≥2 subjects in any group (Part A [up to Week 12], safety analysis set)

Adverse event	1 mg (N = 49)	2 mg (N = 52)	4 mg (N = 52)	8 mg (N = 50)	Placebo (N = 98)
Urinary tract infection	2 (4.1)	2 (3.8)	2 (3.8)	2 (4.0)	3 (3.1)
Hypercholesterolaemia	2 (4.1)	2 (3.8)	0	2 (4.0)	2 (2.0)
Blood cholesterol increased	2 (4.1)	1 (1.9)	2 (3.8)	2 (4.0)	2 (2.0)
Headache	2 (4.1)	1 (1.9)	1 (1.9)	2 (4.0)	2 (2.0)
Oedema peripheral	2 (4.1)	1 (1.9)	0	0	0
Blood creatine phosphokinase increased	2 (4.1)	0	2 (3.8)	1 (2.0)	1 (1.0)
Dyspepsia	2 (4.1)	0	0	0	0
Bronchitis	1 (2.0)	2 (3.8)	2 (3.8)	1 (2.0)	3 (3.1)
Pharyngitis	1 (2.0)	1 (1.9)	3 (5.8)	0	0
Viral infection	0	2 (3.8)	1 (1.9)	0	0
Cataract	0	2 (3.8)	0	0	0
Arthralgia	0	1 (1.9)	2 (3.8)	0	0
Upper respiratory tract infection	0	1 (1.9)	1 (1.9)	1 (2.0)	2 (2.0)
Haemoglobin decreased	0	1 (1.9)	1 (1.9)	1 (2.0)	2 (2.0)
Alanine aminotransferase increased	0	1 (1.9)	0	1 (2.0)	3 (3.1)
Nasopharyngitis	0	0	2 (3.8)	1 (2.0)	2 (2.0)
Glomerular filtration rate decreased	0	0	2 (3.8)	1 (2.0)	1 (1.0)
Anaemia	0	0	2 (3.8)	0	1 (1.0)
Low density lipoprotein increased	0	0	1 (1.9)	1 (2.0)	2 (2.0)
White blood cell count decreased	0	0	1 (1.9)	0	3 (3.1)
Hyperlipidaemia	0	0	0	2 (4.0)	2 (2.0)
Leukopenia	0	0	0	2 (4.0)	0
Aspartate aminotransferase increased	0	0	0	1 (2.0)	3 (3.1)
Blood urea increased	0	0	0	1 (2.0)	2 (2.0)
Hypothyroidism	0	0	0	0	2 (2.0)
Contusion	0	0	0	0	2 (2.0)
Fall	0	0	0	0	2 (2.0)
Foot fracture	0	0	0	0	2 (2.0)

Number of subjects (%)

The incidence of adverse events observed during Parts A and B in subjects assigned to the 2-, 4-, or 8-mg group in Part A was 59.6% (31 of 52 subjects) in the 2-mg group, 61.5% (32 of 52 subjects) in the 4-mg group, and 72.0% (36 of 50 subjects) in the 8-mg group. In subjects who were re-randomized at Week 12, the incidence of adverse events in Part B (Weeks 12 through 24) was 41.0% (16 of 39 subjects) in the placebo → 2-mg BID group, 59.1% (13 of 22 subjects) in the 1-mg QD → 2-mg BID group, 38.5% (15 of 39 subjects) in the placebo → 4-mg QD group, and 54.5% (12 of 22 subjects) in the 1-mg QD → 4-mg QD group. In Part C, the incidence of adverse events was 63.0% (68 of 108 subjects) in the 4/4-mg group, 23.0% (14 of 61 subjects) in the 4:8/4-mg group (before the regimen was changed to 8 mg QD), 68.9% (42 of 61 subjects) in the 4:8/4-mg group (after the regimen was changed to 8 mg QD), and 62.5% (20 of 32 subjects) in the 8/4-mg group. In Part D, the incidence of adverse events was 51.9% (41 of 79 subjects) in the 4/4-mg group, 53.2% (25 of 47 subjects) in the 4:8/4-mg group, and 55.6% (10 of 18 subjects) in the 8/4-mg group.

One subject died (1 of 32 subjects [3.1%]; myocardial infarction) in the 8/4-mg group. However, a causal relationship with the study drug was ruled out for the death. In Part A, the incidence of serious adverse events was 5.8% (3 of 52 subjects; pneumonia, laceration, and asthma/bronchitis in 1 subject each) in

the 2-mg group, 2.0% (1 of 50 subjects; pancytopenia) in the 8-mg group, and 3.1% (3 of 98 subjects; anaemia, hyperglycaemia, and haematuria in 1 subject each) in the placebo group. For pancytopenia in the 8-mg group, a causal relationship with the study drug could not be ruled out. In subjects randomized to the 2-, 4-, or 8-mg group in Part A, the incidence of serious adverse events in Part B was 6.0% (3 of 50 subjects; anaemia/gastritis, pneumonia bacterial, and renal failure in 1 subject each) in the 8-mg group. In subjects re-assigned at Week 12, the incidence of serious adverse events was 2.6% (1 of 39 subjects; hyperglycaemia) in the placebo → 2-mg BID group, 9.1% (2 of 22 subjects; pyrexia and cholecystitis in 1 subject each) in the 1-mg QD → 2-mg BID group, and 2.6% (1 of 39 subjects; haematuria) in the placebo → 4-mg QD group. A causal relationship with the study drug could not be ruled out for renal failure in the 8-mg group. In Part C, the incidence of serious adverse events was 15.7% (17 of 108 subjects; herpes zoster in 4 subjects, cataract and alanine aminotransferase increased in 2 subjects each, and anaemia, gastroenteritis, head injury, road traffic accident, scar, aspartate aminotransferase increased, blood creatine phosphokinase increased, transaminases increased, dehydration, arthritis, neck pain, carotid artery stenosis, and angioedema in 1 subject each) in the 4/4-mg group, 1.6% (1 of 61 subjects; gastroenteritis viral) in the baricitinib 4:8/4-mg group (before change to 8 mg QD), 9.8% (6 of 61 subjects; normochromic normocytic anaemia, colitis, gastritis, herpes simplex, fall, rib fracture, intervertebral disc protrusion, pregnancy, and pneumothorax in 1 subject each) in the 4:8/4-mg group (after the change in regimen to 8 mg QD), and 18.8% (6 of 32 subjects; myocardial infarction, ulcerative keratitis, colitis, herpes zoster, acute hepatitis B, dehydration/presyncope in 1 subject each) in the 8/4-mg group.

In Part A, the incidence of adverse events leading to treatment discontinuation was 1.9% (1 of 52 subjects; rhinitis allergic) in the 2-mg group, 1.9% (1 of 52 subjects; glomerular filtration rate decreased) in the 4-mg group, 2.0% (1 of 50 subjects; pancytopenia) in the 8-mg group, and 2.0% (2 of 98 subjects; episcleritis and myalgia in 1 subject each) in the placebo group. In Part B, there were no adverse events leading to treatment discontinuation. In Part C, the incidence of adverse events leading to treatment discontinuation was 7.4% (8 of 108 subjects; herpes zoster in 4 subjects, and anaemia, aspartate aminotransferase increased, blood creatine phosphokinase increased, and transaminases increased in 1 subject each) in the 4/4-mg group, 1.6% (1 of 61 subjects; basal cell carcinoma) in the 4:8/4-mg group (before change to 8 mg QD), 1.6% (1 of 61 subjects; herpes simplex) in the 4:8/4-mg group (after the change in regimen to 8 mg QD), and 9.4% (3 of 32 subjects; myocardial infarction, colitis, and acute hepatitis B in 1 subject each) in the 8/4-mg group. In Part D, there were no adverse events leading to treatment discontinuation.

In Part A, the incidence of adverse drug reactions was 16.3% (8 of 49 subjects) in the 1-mg group, 13.5% (7 of 52 subjects) in the 2-mg group, 21.2% (11 of 52 subjects) in the 4-mg group, 20.0% (10 of 50 subjects) in the 8-mg group, and 17.3% (17 of 98 subjects) in the placebo group. In subjects randomized into the 2-, 4-, or 8-mg group in Part A, the incidence of adverse drug reactions in Part A through B was 19.2% (10 of 52 subjects) in the 2-mg group, 30.8% (16 of 52 subjects) in the 4-mg group, and 30.0% (15 of 50 subjects) in the 8-mg group. In subjects who were re-randomized at Week 12, the incidence of

adverse drug reactions in Part B (Weeks 12 through 24) was 17.9% (7 of 39 subjects) in the placebo → 2-mg BID group, 36.4% (8 of 22 subjects) in the 1-mg QD → 2-mg BID group, 12.8% (5 of 39 subjects) in the placebo → 4-mg QD group, and 9.1% (2 of 22 subjects) in the 1-mg QD → 4-mg QD group. In Part C, the incidence of adverse drug reactions was 22.2% (24 of 108 subjects) in the 4/4-mg group, 1.6% (1 of 61 subjects) in the 4:8/4-mg group (before the regimen was changed to 8 mg QD), 9.8% (6 of 61 subjects) in the 4:8/4-mg (after the regimen was changed to 8 mg QD), and 18.8% (6 of 32 subjects) in the 8/4-mg group. In Part D, the incidence of adverse drug reactions was 5.1% (4 of 79 subjects) in the 4/4-mg group, 6.4% (3 of 47 subjects) in the 4:8/4-mg group, and 11.1% (2 of 18 subjects) in the 8/4-mg group.

7.2 Phase III studies

7.2.1 Multi-regional study in RA patients with an inadequate response to TNF inhibitors (Study 14V-MC-JADW [January 2013 to September 2014])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in RA patients with an inadequate response to TNF inhibitors[22)] (target sample size, 525 subjects [175/group]) in 21 countries including Japan, the US, and South Korea to evaluate the efficacy and safety of baricitinib.

In combination with a fixed dose of cDMARDs, baricitinib at 2 or 4 mg[23)] or placebo was administered orally once daily for 24 weeks. Subjects who were assessed as non-responder[24)] at Week 16 or those who were assessed by the investigator as needing a dose increase at Week 20 had a change in regimen to baricitinib 4 mg in a blinded manner (Figure 5). The change to baricitinib 4 mg was allowed only once, and subjects who had underwent the change at Week 16 would discontinue the study drug if they still met the non-responder criteria at Week 20. Subjects were allowed to move onto a long-term study (Study 14V-MC-JADY) after completing the Week-24 visit.

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22 Main inclusion criteria: Patients who have active RA and who meet all of the following criteria: (1) ≥6 swollen joints and ≥6 tender joints, (2) CRP (or hsCRP) of ≥1-fold the ULN, (3) inadequate response or intolerance to treatment with ≥1 type of TNF inhibitor administered for ≥3 months at an approved dose in each country, and (4) use of a cDMARD for ≥12 weeks before participating in the study.

23 Of those assigned to the 4-mg group, subjects with eGFR of ≥40 mL/min/1.73 mm^2 to <60 mL/min/1.73 mm^2 received baricitinib 2 mg orally once daily.

24 Subjects who failed to achieve improvement from baseline by ≥20% in the number of swollen or tender joints at Week 14 and Week 16.

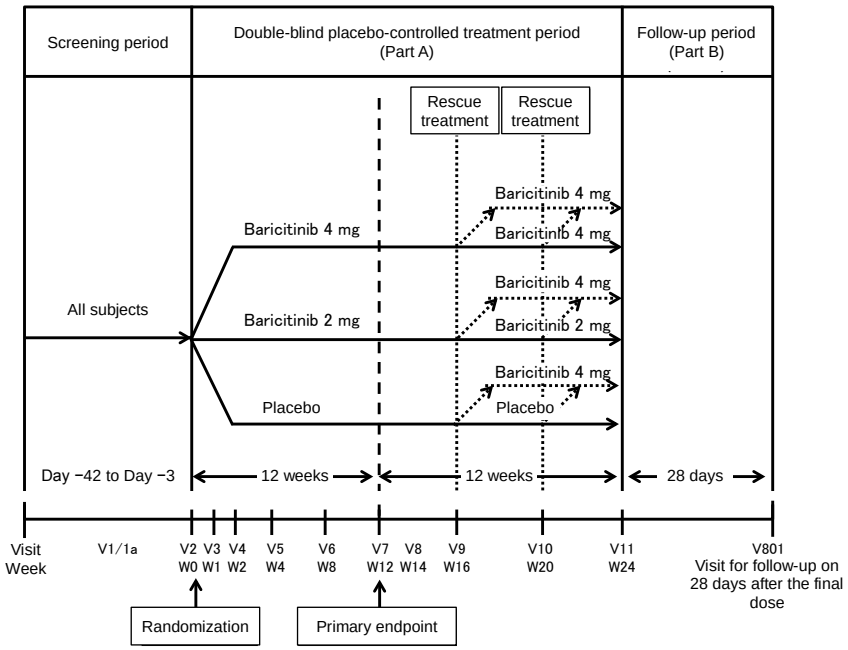

Figure 5. JADW study design

All of 527 randomized subjects (174 in the baricitinib 2 mg [2-mg] group, 177 in the baricitinib 4 mg [4-mg] group, and 176 in the placebo group) were included in the safety analysis set and the modified intent-to-treat (mITT) population. The mITT population also served as the efficacy analysis set. Subjects who discontinued study treatment by Week 24 accounted for 12.5% (17 of 174) of subjects in the 2-mg group, 12.5% (18 of 177) of subjects in the 4-mg group, and 25.8% (31 of 176) of subjects in the placebo group. The major reasons for discontinuation were adverse events (5.1% [7 of 174] of subjects in the 2-mg group, 6.9% [10 of 177] of subjects in the 4-mg group, and 5.8% [7 of 176] of subjects in the placebo group) and a lack of efficacy (2.9% [4 of 174] of subjects in the 2-mg group, 2.1% [3 of 177] of subjects in the 4-mg group, and 12.5% [15 of 176] of subjects in the placebo group). Subjects who experienced the change in regimen to baricitinib 4 mg at or after Week 16 because of poor response accounted for 21.8% (38 of 174) of subjects in the 2-mg group, 18.6% (33 of 177) of subjects in the 4-mg group, and 31.8% (56 of 176) of subjects in the placebo group.

The mITT population included 20 Japanese subjects (6 in the 2-mg group, 8 in the 4-mg group, and 6 in the placebo group). Japanese subjects who discontinued study treatment by Week 24 accounted for 33.3% (2 of 6) of subjects in the 2-mg group, 25.0% (2 of 8) of subjects in the 4-mg group, and 16.7% (1 of 6) of subjects in the placebo group. The major reason for discontinuation was lack of efficacy (2 subjects in the 2-mg group). Subjects who experienced the change in regimen to baricitinib 4 mg at or after Week 16 because of inadequate response accounted for 16.7% (1 of 6) of subjects in the 2-mg group and 33.3% (2 of 6) of subjects in the placebo group.

The primary efficacy endpoint of ACR20 responder rates at Week 12 [for the definitions of the respective endpoints, see Section “10. Other”] are shown in Table 29. The statistically significant difference

between the 4-mg group and the placebo group[25)] demonstrated the superiority of baricitinib 4 mg over placebo. The efficacy secondary endpoints were changes from baseline in HAQ-DI and disease activity score modified to include the 28 diarthrodial joint count and high-sensitivity C-reactive protein (DAS28-hsCRP) at Week 12 and simplified disease activity index (SDAI)-based remission rates (SDAI score ≤3.3) at Week 12, and are also shown in Table 29.

The results in the Japanese subgroup are shown in Table 30.

Table 29. ACR20 responder rates and other endpoints at Week 12 (mITT population)

	2 mg	4 mg	Placebo
ACR20 responders[a)]	48.9 (85/174)	55.4 (98/177)	27.3 (48/176)
Difference from placebo [95% CI][b)] *P* value[c),f)]	21.6 [11.7, 31.5] –	28.1 [18.2, 37.9] *P* = 0.001	–
Change in HAQ-DI[d)]	-0.38 ± 0.51 (174)	-0.42 ± 0.49 (177)	-0.20 ± 0.50 (176)
Difference from placebo [95% CI][e)] *P* value[e),f)]	-0.20 [-0.30, -0.10] –	-0.23 [-0.33, -0.13] *P* = 0.001	–
Change in DAS28-hsCRP[d)]	-1.53 ± 1.34 (174)	-1.81 ± 1.43 (177)	-0.85 ± 1.19 (176)
Difference from placebo [95% CI][e)] *P* value[e),f)]	-0.66 [-0.93, -0.39] –	-0.95 [-1.22, -0.69] *P* = 0.001	–
SDAI-based remission rate (SDAI ≤3.3)[a)]	2.3 (4/174)	5.1 (9/177)	1.7 (3/176)
Difference from placebo [95% CI][b)] *P* value[c),f)]	0.6 [-2.3, 3.5] –	3.4 [-0.4, 7.1] *P* = 0.140	–

% (number of subjects) or mean ± standard deviation (N)

a) NRI

b) Newcombe-Wilson method (without continuity correction)

c) Logistic regression model with region, previous use of biological products (<3, ≥3), and treatment group as explanatory variables

d) mBOCF

e) Analysis of covariance model with baseline value, region, previous use of biological products (<3, ≥3), and treatment group as explanatory variables

f) Multiplicity was adjusted by the gatekeeping method with ranks set in the order of a comparison of the 4-mg group with the placebo group in the ACR20 responder rate, changes in HAQ-DI and DAS28-hsCRP, and SDA-based remission rate and a comparison between the 2-mg group and the placebo group in the ACR20 responder rate, changes in HAQ-DI and DAS28-hsCRP, and SDA-based remission rate.

Table 30. ACR20 responder rates and other endpoints at Week 12 (Japanese subgroup)

	2 mg	4 mg	Placebo
ACR20 responders[a)]	50.0 (3/6)	75.0 (6/8)	50.0 (3/6)
Difference from placebo [95% CI][b)]	0.0 [-56.6, 56.6]	25.0 [-25.0, 75.0]	–
Change in HAQ-DI[c)]	-0.31 ± 0.50 (6)	-0.44 ± 0.53 (8)	-0.25 ± 0.54 (6)
Difference from placebo [95% CI][d)]	-0.01 [-0.73, 0.71]	-0.15 [-0.78, 0.48]	–
Change in DAS28-hsCRP[c)]	-1.06 ± 1.88 (6)	-1.73 ± 1.32 (8)	-1.01 ± 1.24 (6)
Difference from placebo [95% CI][d)]	-0.44 [-2.58, 1.70]	-0.77 [-2.58, 1.03]	–
SDAI-based remission rate (SDAI ≤3.3)[a)]	0 (0/6)	12.5 (1/8)	0 (0/6)
Difference from placebo [95% CI][b)]	0	12.5 [-10.4, 35.4]	–

% (number of subjects) or mean ± standard deviation (number of subjects)

a) NRI

b) Newcombe-Wilson method (without continuity correction)

c) mBOCF

d) Analysis of covariance model with baseline value, previous use of biological products (<3, ≥3), and treatment group as explanatory variables

25 In this study, the primary analysis was a comparison between the 4-mg group and the placebo group, and a comparison between the 2-mg group and the placebo group was conducted as a secondary analysis.

The incidence of adverse events at Week 24 or before change to baricitinib 4 mg was 70.7% (123 of 174 subjects) in the 2 mg group, 77.4% (137 of 177 subjects) in the 4 mg group, and 63.6% (112 of 176 subjects) in the placebo group. The major adverse events are shown in Table 31.

Table 31. Adverse events that occurred at an incidence of ≥3% in any group (by Week 24 or before change to baricitinib 4 mg, safety analysis set)

Adverse event	2 mg (N = 174)	4 mg (N = 177)	Placebo (N = 176)
Headache	17 (9.8)	13 (7.3)	11 (6.3)
Upper respiratory tract infection	16 (9.2)	10 (5.6)	8 (4.5)
Nasopharyngitis	12 (6.9)	9 (5.1)	7 (4.0)
Diarrhoea	10 (5.7)	7 (4.0)	12 (6.8)
Back pain	8 (4.6)	6 (3.4)	6 (3.4)
Sinusitis	8 (4.6)	4 (2.3)	1 (0.6)
Urinary tract infection	7 (4.0)	10 (5.6)	6 (3.4)
Nausea	7 (4.0)	10 (5.6)	5 (2.8)
Hypertension	7 (4.0)	9 (5.1)	6 (3.4)
Abdominal pain upper	7 (4.0)	4 (2.3)	1 (0.6)
Pyrexia	7 (4.0)	3 (1.7)	1 (0.6)
Bronchitis	6 (3.4)	10 (5.6)	6 (3.4)
Fatigue	6 (3.4)	3 (1.7)	5 (2.8)
Rheumatoid arthritis	5 (2.9)	9 (5.1)	10 (5.7)
Influenza	4 (2.3)	8 (4.5)	2 (1.1)
Gastroenteritis	4 (2.3)	7 (4.0)	3 (1.7)
Blood creatine phosphokinase increased	4 (2.3)	6 (3.4)	1 (0.6)
Arthralgia	3 (1.7)	5 (2.8)	8 (4.5)
Herpes zoster	2 (1.1)	7 (4.0)	2 (1.1)
Cough	2 (1.1)	5 (2.8)	6 (3.4)
Hypercholesterolaemia	1 (0.6)	7 (4.0)	2 (1.1)

Number of subjects (%)

One subject in the 4-mg group died (basilar artery thrombosis). The death was assessed as not related to the study drug. The incidence of serious adverse event was 4.0% (7 of 174 subjects) in the 2 mg group, 10.2% (18 of 177 subjects) in the 4 mg group, and 7.4% (13 of 176 subjects) in the placebo group. The major serious adverse events observed are shown in Table 32.

The incidence of adverse events leading to treatment discontinuation was 5.2% (9 of 174 subjects) in the 2-mg group, 8.5% (15 of 177 subjects) in the 4-mg group, and 4.5% (8 of 176 subjects) in the placebo group.

The incidence of adverse drug reactions was 35.6% (62 of 174 subjects) in the 2-mg group, 36.7% (65 of 177 subjects) in the 4-mg group, and 23.9% (42 of 176 subjects) in the placebo group.

Table 32. Serious adverse events that occurred in ≥2 subjects in any group
(by Week 24 or before change to baricitinib 4 mg, safety analysis set)

Adverse event	2 mg (N = 174)	4 mg (N = 177)	Placebo (N = 176)
Rheumatoid arthritis	0	2 (1.1)	3 (1.7)
Coronary artery disease	0	2 (1.1)	0
Urinary tract infection	0	2 (1.1)	0
Cellulitis	0	0	2 (1.1)
Hypertension	0	0	2 (1.1)

Number of subjects (%)

The incidence of adverse events that occurred in the Japanese subgroup by Week 24 or before change to baricitinib 4 mg was 66.7% (4 of 6 subjects) in the 2-mg group, 75.0% (6 of 8 subjects) in the 4-mg group, and 83.3% (5 of 6 subjects) in the placebo group. The events that occurred in ≥2 subjects in any group were hyperlipidaemia and upper respiratory tract inflammation (2 subjects each in the 4-mg group).

Neither deaths nor serious adverse events occurred. The incidence of adverse events leading to treatment discontinuation was 16.7% (1 of 6 subjects; chronic tonsillitis/folliculitis) in the 2-mg group and 12.5% (1 of 8 subjects; upper respiratory tract inflammation) in the 4-mg group.

The incidence of adverse drug reactions was 33.3% (2 of 6 subjects) in the 2-mg group, 50.0% (4 of 8 subjects) in the 4-mg group, and 50.0% (3 of 6 subjects) in the placebo group.

7.2.2 Multi-regional study in RA patients with an inadequate response to cDMARDs (Study 14V-MC-JADX [January 2013 to December 2014])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in RA patients with an inadequate response to cDMARDs[26)] (target sample size, 660 subjects [220 per group]) in 22 countries including Japan, the US, and South Korea to evaluate the efficacy and safety of baricitinib.

In combination with a fixed dose of cDMARDs,[27)] baricitinib at 2 or 4 mg[28)] or placebo was administered orally once daily for 24 weeks. Subjects who were assessed as non-responder[29)] at Week 16 or those who were assessed to need a dose increase at Week 20 by the investigator had a change in regimen to baricitinib 4 mg in a blinded manner (Figure 6). The change to baricitinib 4 mg was allowed only once, and subjects who had experienced the change in regimen at Week 16 would discontinue the study treatment if they still met the non-responder criteria at Week 20. Subjects were allowed to move onto a long-term treatment study (Study 14V-MC-JADY) after completing the Week-24 visit.

26 Main inclusion criteria: Patients who have active RA and who meet all of the following criteria: (1) ≥6 swollen joints and ≥6 tender joints, (2) CRP (or hsCRP) of ≥1.2-fold the ULN, (3) having used at least one type of cDMARDs for ≥12 weeks before participating in the study and at a fixed dose for ≥8 consecutive weeks before study participation; or having responded inadequately to or being intolerant to cDMARDs, which was administered ≥4 weeks before study participation, if not using cDMARDs at study participation, and (4) no previous use of biological drugs.

27 Dose adjustment for safety reasons was allowed.

28 Of those assigned to the 4 mg group, subjects with eGFR of ≥40 mL/min/1.73 mm^2 to <60 mL/min/1.73 mm^2 received 2 mg of baricitinib orally once daily.

29 Subjects who failed to achieve improvement from baseline by ≥20% in the number of swollen or tender joints at Week 14 and Week 16.

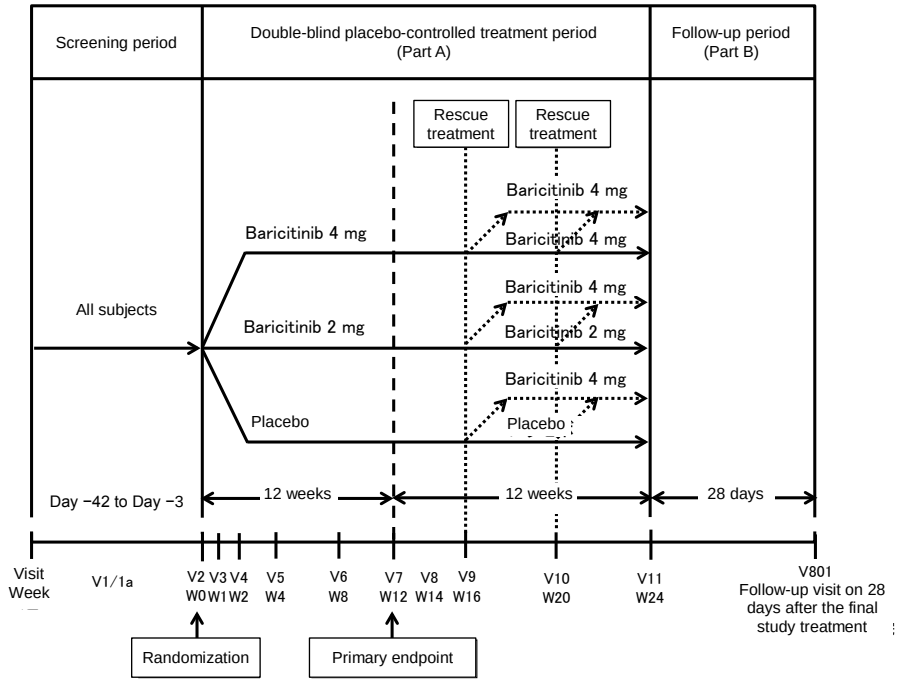

Figure 6. JADX study design

All of 684 randomized subjects (229 in the baricitinib 2 mg group, 227 in the baricitinib 4 mg group, and 228 in the placebo group) were included in the safety analysis set and the mITT population. The mITT population also served as the efficacy analysis set. Subjects who discontinued study treatment by Week 24 accounted for 9.1% (19 of 229) of subjects in the 2-mg group, 10.8% (23 of 227) of subjects in the 4-mg group, and 16.2% (28 of 228) of subjects in the placebo group. The major reason for discontinuation was adverse events (4.8% [10 of 229 subjects] in the 2-mg group, 5.7% [12 of 227 subjects] in the 4-mg group, and 4.0% [7 of 228 subjects] in the placebo group). Subjects who experienced the change in regimen to baricitinib 4 mg at or after Week 16 because of inadequate efficacy accounted for 9.2% (21 of 229) of subjects in the 2-mg group, 6.6% (15 of 227) of subjects in the 4-mg group, and 24.1% (55 of 228) of subjects in the placebo group.

The mITT population included 21 Japanese subjects (6 in the 2-mg group, 7 in the 4-mg group, and 8 in the placebo group). Japanese subjects who discontinued study treatment by Week 24 accounted for 33.3% (2 of 6) of subjects in the 2-mg group and 14.3% (1 of 7) of subjects) in the 4-mg group. The major reason for discontinuation was adverse events (1 subject each in the 2-mg and 4-mg groups). Subjects who experienced the change in regimen to baricitinib 4 mg at or after Week 16 because of inadequate efficacy accounted for 37.5% (3 of 8) of subjects in the placebo group.

The primary efficacy endpoint of ACR20 responder rates at Week 12 [for the definitions of the respective endpoints, see Section “10. Other”] are shown in Table 33. A statistically significant difference between

4 or 2 mg and the placebo[30)] was observed and the superiority of baricitinib 4 mg over placebo was demonstrated. The secondary efficacy endpoints of changes from baseline in HAQ-DI and in DAS28-hsCRP at Week 12 and SDAI-based remission rates (SDAI score ≤3.3) at Week 12 are also shown in Table 33.

The results in the Japanese subgroup are shown in Table 34.

Table 33. ACR20 responder rates and other endpoints at Week 12 (mITT population)

	2 mg	4 mg	Placebo
ACR20 responders[a)]	65.9 (151/229)	61.7 (140/227)	39.5 (90/228)
Difference from placebo [95% CI][b)] *P* value[c),f)]	26.5 [17.6, 35.3] *P* = 0.001	22.2 [13.2, 31.2] *P* = 0.001	–
Change in HAQ-DI[d)]	-0.52 ± 0.59 (229)	-0.52 ± 0.60 (227)	-0.30 ± 0.45 (228)
Difference from placebo [95% CI][e)] *P* value[e),f)]	-0.21 [-0.30, -0.11] *P* = 0.001	-0.20 [-0.30, -0.10] *P* = 0.001	–
Change in DAS28-hsCRP[d)]	-1.83 ± 1.22 (229)	-1.92 ± 1.21 (227)	-1.05 ± 1.23 (228)
Difference from placebo [95% CI][e)] *P* value[e),f)]	-0.75 [-0.97, -0.53] *P* = 0.001	-0.84 [-1.07, -0.62] *P* = 0.001	–
SDAI-based remission rate (SDAI ≤3.3)[a)]	9.2 (21/229)	8.8 (20/227)	0.9 (2/228)
Difference from placebo [95% CI][b)] *P* value[c),f)]	8.3 [4.4, 12.2] *P* = 0.001	7.9 [4.1, 11.8] *P* = 0.001	–

% (number of subjects) or mean ± standard deviation (N)

a) NRI

b) Newcombe-Wilson method (without continuity correction)

c) Logistic regression model with region, baseline status of bone erosion, and treatment group as explanatory variables

d) mBOCF

e) Analysis of covariance model with baseline value, region, baseline status of bone erosion, and treatment group as explanatory variables

f) Multiplicity was adjusted by the gatekeeping method with ranks set in the order of (1) ACR20 responder rate, (2) comparison between the 4 mg group and the placebo group in changes in HAQ-DI and DAS28-hsCRP, (3)-a. comparison between the 4 mg group and the placebo group in SDA-based remission rate, (3)-b. comparison between the 2 mg group and the placebo group in percentage ACR20 responders and changes in HAQ-DI and DAS28-hsCRP, and (4) comparison between the 4 mg group and the placebo group in SDAI-based remission rate

Table 34. ACR20 responder rates and other endpoints at Week 12 (Japanese subgroup; mITT population)

	2 mg	4 mg	Placebo
ACR20 responders[a)]	83.3 (5/6)	100.0 (7/7)	50.0 (4/8)
Difference from placebo [95% CI][b)]	33.3 [-12.4, 79.0]	50.0 [15.4, 84.6]	–
Change in HAQ-DI[c)]	-0.81 ± 0.73 (6)	-0.89 ± 0.50 (7)	-0.28 ± 0.33 (8)
Difference from placebo [95% CI][d)]	-0.74 [-1.57, -0.10]	-0.68 [-1.26, -0.10]	–
Change in DAS28-hsCRP[c)]	-2.53 ± 1.27 (6)	-2.91 ± 0.83 (7)	-1.11 ± 0.97 (8)
Difference from placebo [95% CI][d)]	-1.15 [-2.60, 0.31]	-1.71 [-2.87, -0.54]	–
SDAI-based remission rate (SDAI ≤3.3)[a)]	0 (0/6)	28.6 (2/7)	0 (0/8)
Difference from placebo [95% CI][b)]	0	28.6 [-4.9, 62.0]	

% (number of subjects) or mean ± standard deviation (N)

a) NRI

b) Newcombe-Wilson method (without continuity correction)

c) mBOCF

d) Analysis of covariance model with baseline value, baseline status of bone erosion, and treatment group as explanatory variables

30 In this study, the primary analysis was a comparison between the 4 mg group and the placebo group, and a comparison between the 2 mg group and the placebo group was conducted as a secondary analysis.

The incidence of adverse events at Week 24 or before the change of treatment to baricitinib 4 mg was 67.2% (154 of 229 subjects) in the 2 mg group, 71.4% (162 of 227 subjects) in the 4 mg group, and 70.6% (161 of 228 subjects) in the placebo group. The major adverse events observed are shown in Table 35.

Two subjects in the placebo group died (subarachnoid haemorrhage, pneumonia/renal failure/subcutaneous emphysema in 1 subject each). A causal relationship with the study drug could not be ruled out for subarachnoid haemorrhage.

The incidence of serious adverse events was 2.6% (6 of 229 subjects; atrial fibrillation, gastroenteritis, migraine, post-traumatic stress disorder, acute respiratory distress syndrome/acute respiratory failure/pneumonia, and psoriasis in 1 subject each) in the 2 mg group, 5.3% (12 of 227 subjects; angina pectoris, cholecystitis acute/sepsis, disseminated tuberculosis/dyspepsia, viral infection/lower respiratory tract infection/bacterial infection, animal bite, tibia fracture, muscular weakness/myalgia/myositis, allergic bronchitis, interstitial lung disease, pleural effusion/pneumonia, pulmonary embolism/spinal pain, and rash pruritic in 1 subject each) in the 4 mg group, and 4.8% (11 of 228 subjects; myocardial infarction, anaemia/diverticulum intestinal/gastrointestinal haemorrhage, bronchitis, urinary tract infection, wound infection staphylococcal/fall/patella fracture, ventricular tachycardia/upper limb fracture/fall, back pain, synovial cyst, subarachnoid haemorrhage, depression/suicidal ideation, and pneumonia/renal failure/subcutaneous emphysema in 1 subject each) in the placebo group.

The incidence of adverse events leading to treatment discontinuation was 5.2% (12 of 229 subjects) in the 2 mg group, 6.2% (14 of 227 subjects) in the 4 mg group, and 3.9% (9 of 228 subjects) in the placebo group.

The incidence of adverse drug reactions was 24.9% (57 of 229 subjects) in the 2 mg group, 30.4% (69 of 227subjects) in the 4 mg group, and 23.7% (54 of 228 subjects) in the placebo group.

Table 35. Adverse events that occurred at an incidence of ≥3% in any group
(by Week 24 or before change to baricitinib 4 mg, safety analysis set)

Adverse event	2 mg (N = 229)	4 mg (N = 227)	Placebo (N = 228)
Headache	15 (6.6)	9 (4.0)	8 (3.5)
Upper respiratory tract infection	14 (6.1)	24 (10.6)	18 (7.9)
Urinary tract infection	12 (5.2)	9 (4.0)	5 (2.2)
Nasopharyngitis	10 (4.4)	18 (7.9)	18 (7.9)
Hypertension	10 (4.4)	6 (2.6)	2 (0.9)
Diarrhoea	10 (4.4)	4 (1.8)	10 (4.4)
Cough	9 (3.9)	9 (4.0)	3 (1.3)
Back pain	9 (3.9)	5 (2.2)	11 (4.8)
Blood creatine phosphokinase increased	8 (3.5)	15 (6.6)	0
Nausea	7 (3.1)	5 (2.2)	8 (3.5)
Constipation	7 (3.1)	5 (2.2)	3 (1.3)
Vomiting	7 (3.1)	4 (1.8)	4 (1.8)
Pharyngitis	6 (2.6)	8 (3.5)	3 (1.3)
Bronchitis	6 (2.6)	7 (3.1)	12 (5.3)
Anaemia	6 (2.6)	4 (1.8)	7 (3.1)
Hypercholesterolaemia	5 (2.2)	9 (4.0)	2 (0.9)
Gastroenteritis	5 (2.2)	9 (4.0)	1 (0.4)
Oropharyngeal pain	4 (1.7)	9 (4.0)	2 (0.9)
Dizziness	3 (1.3)	7 (3.1)	4 (1.8)
Depression	0	1 (0.4)	8 (3.5)

Number of subjects (%)

The incidence of adverse events in the Japanese subgroup by Week 24 or before change to baricitinib 4 mg was 83.3% (5 of 6 subjects) in the 2 mg group, 100% (7 of 7 subjects) in the 4 mg group, and 50.0% (4 of 8 subjects) in the placebo group. The major adverse events are shown in Table 36.

There were no deaths. The incidence of serious adverse events was 14.3% (1 of 7 subjects; interstitial lung disease) in the 4 mg group. A causal relationship with the study drug could not be ruled out for the event. The outcome of the event was assessed as resolved. The incidence of adverse events leading to treatment discontinuation was 16.7% (1 of 6 subjects; hepatic steatosis) in the 2 mg group and 14.3% (1 of 7 subjects; interstitial lung disease) in the 4 mg group.

The incidence of adverse drug reactions was 50.0% (3 of 6 subjects) in the 2 mg group, 85.7% (6 of 7 subjects) in the 4 mg group, and 25.0% (2 of 8 subjects) in the placebo group.

Table 36. Adverse events that occurred in ≥2 subjects in any group
(by Week 24 or before change to baricitinib 4 mg, Japanese subgroup)

Adverse event	2 mg (N = 6)	4 mg (N = 7)	Placebo (N = 8)
Hepatic function abnormal	2 (33.3)	1 (14.3)	0
Blood creatine phosphokinase increased	1 (16.7)	2 (28.6)	0
Nasopharyngitis	1 (16.7)	2 (28.6)	2 (25.0)
Upper respiratory tract infection	0	3 (42.9)	0
Abdominal pain upper	0	2 (28.6)	0
Eczema	0	1 (14.3)	2 (25.0)
Bronchitis	0	0	2 (25.0)

Number of subjects (%)

7.2.3 Multi-regional study in RA patients with an inadequate response to MTX (Study 14V-MC-JADV [October 2012 to September 2015])

A placebo- and adalimumab (genetical recombination)-controlled, randomized, double-blind, parallel-group study was conducted in RA patients with an inadequate response to MTX[31] (target sample size, 1280 subjects [480 in the baricitinib 4 mg group, 320 in the adalimumab group, and 480 in the placebo group]) in 28 countries including Japan, the US, and South Korea to evaluate the efficacy and safety of baricitinib.

This study consisted of 2 parts (up to Week 24, double-blind placebo- and active-controlled treatment period [Part A]; Weeks 24 to 52, double-blind active-controlled treatment period [Part B]) as shown in Figure 7. In combination with a fixed dose of MTX,[32] baricitinib 4 mg[33] or placebo was administered orally once daily for 52 weeks, and adalimumab (genetical recombination) 40 mg or placebo was administered subcutaneously for 52 weeks at 2-week intervals. Subjects who were assessed as non-responder[34] at Week 16 underwent a regimen change to baricitinib 4 mg once daily in a blinded manner. The change in regimen to baricitinib 4 mg was allowed only once, and subjects who still met the non-responder criteria ≥4 weeks after the change of treatment discontinued the study treatment. Subjects assigned to the placebo group received baricitinib 4 mg at and after Week 24. Subjects were allowed to move onto a long-term study (Study 14V-MC-JADY) after completing the Week-52 visit.

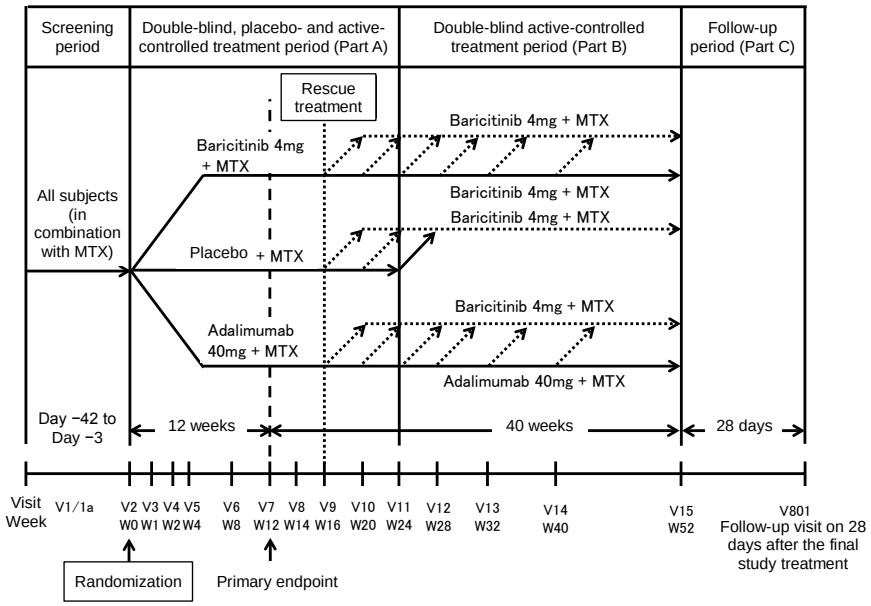

Figure 7. JADV study design

[31] Main inclusion criteria: Patients who have active RA who meet all of the following criteria: (1) ≥6 swollen joints and ≥6 tender joints, (2) CRP (or hsCRP) of ≥0.6 mg/dL, (3) use of MTX for ≥12 months before participating in the study including ≥8 consecutive weeks treated at a fixed dose of 7.5 to 25 mg/week, and (4) no previous use of biological drugs.

[32] Dose adjustment for safety reasons was allowed.

[33] Subjects with eGFR of ≥40 mL/min/1.73 mm^2 to <60 mL/min/1.73 mm^2 received baricitinib 2 mg orally once daily.

[34] Subjects who failed to achieve improvement from baseline by ≥20% in the number of swollen or tender joints at Week 14 and Week 16.

Of 1307 randomized subjects, 1305 subjects receiving the study drug (487 in the baricitinib 4 mg group, 330 in the adalimumab group, and 488 in the placebo group) were included in the safety analysis set and the mITT population. The mITT population also served as the efficacy analysis set. Subjects who discontinued study treatment by Week 24 accounted for 6.0% (29 of 487) of subjects in the 4-mg group, 7.3% (24 of 330) of subjects in the adalimumab group, and 10.9% (53 of 488) of subjects in the placebo group. The major reason for discontinuation was adverse events (3.7% [18 of 487 subjects] in the 4 mg group, 2.1% [7 of 330 subjects] in the adalimumab group, and 3.3% [16 of 488 subjects] in the placebo group). Subjects who experienced a regimen change to baricitinib 4 mg during the period from Week 16 to Week 24 because of inadequate efficacy accounted for 7.2% (35 of 487) of subjects in the 4-mg group, 12.1% (40 of 330) of subjects in the adalimumab group, and 26.2% (128 of 488) of subjects in the placebo group.

The mITT population included 249 Japanese subjects (93 in the 4 mg group, 63 in the adalimumab group, and 93 in the placebo group). Japanese subjects who discontinued study treatment by Week 24 accounted for 6.5% (6 of 93) of subjects in the 4 mg group, 4.8% (3 of 63) of subjects in the adalimumab group, and 8.6% (8 of 93) of subjects in the placebo group. The major reason for discontinuation was adverse events (6 subjects in the 4 mg group, 2 subjects in the adalimumab group, and 4 subjects in the placebo group). Subjects who experienced a regimen change to baricitinib 4 mg during the period from Week 16 to Week 24 because of inadequate efficacy accounted for 8.6% (8 of 93) of subjects in the 4 mg group, 14.3% (9 of 63) of subjects in the adalimumab group, and 34.4% (32 of 93) of subjects in the placebo group.

The primary efficacy endpoint of the ACR20 responder rates at Week 12 [for the definitions of the respective endpoints, see Section “10. Other”] are shown in Table 37. A statistically significant difference between the 4 mg group and the placebo group demonstrated the superiority of baricitinib 4 mg over placebo. The secondary efficacy endpoints, changes from baseline in mTSS at Week 24, HAQ-DI and DAS28-hsCRP at Week 12, and SDAI-based remission rates (SDAI score $\leq$3.3) at Week 12, are also shown in Table 37.

The results in the Japanese subgroup are shown in Table 38.

Table 37. ACR20 responder rates and other endpoints at Week 12 (Week 24 for mTSS only) (mITT population)

	4 mg	Adalimumab	Placebo
ACR20 responders[a)]	69.6 (339/487)	61.2 (202/330)	40.2 (196/488)
Difference from placebo [95% CI][b)] *P* value[c),g)]	29.4 [23.5, 35.4] *P* = 0.001	21.0 [14.2, 27.9]	–
Difference from adalimumab [95% CI][b)]	8.4 [1.7, 15.1]	–	–
Change in mTSS[d)]	0.35 ± 1.59 (470)	0.29 ± 1.47 (312)	0.84 ± 2.32 (452)
Difference from placebo [95% CI][e)] *P* value[e),g)]	-0.49 [-0.73, -0.25] *P* = 0.001	-0.56 [-0.83, -0.29]	–
Change in HAQ-DI[f)]	-0.65 ± 0.59 (487)	-0.56 ± 0.54 (330)	-0.33 ± 0.51 (488)
Difference from placebo [95% CI][e)] *P* value[e),g)]	-0.31 [-0.38, -0.25] *P* = 0.001	-0.21 [-0.28, -0.14]	–
Change in DAS28-hsCRP[f)]	-2.27 ± 1.22 (487)	-1.98 ± 1.28 (330)	-1.01 ± 1.12 (488)
Difference from placebo [95% CI][e)] *P* value[e),g)]	-1.23 [-1.37, -1.09] *P* = 0.001	-0.95 [-1.11, -0.79]	–
SDAI-based remission rate (SDAI ≤3.3)[a)]	8.4 (41/487)	7.3 (24/330)	1.8 (9/488)
Difference from placebo [95% CI][b)] *P* value[c),g)]	6.6 [3.8, 9.3] *P* = 0.001	5.4 [2.4, 8.5]	–

% (number of subjects) or mean ± standard deviation (number of subjects)

a) NRI

b) Newcombe-Wilson method (without continuity correction); non-inferiority margin for the ACR20 responder rate (comparison between the 4 mg group and the adalimumab group) of −12%

c) Logistic regression model with region, baseline bone erosion score (1-2 sites and serum response positive; ≥3 sites), and treatment group as explanatory variables

d) Linear extrapolation approach

e) Analysis of covariance model with region, baseline value, baseline bone erosion score (1-2 sites and serum response positive; ≥3 sites), and treatment group as explanatory variables

f) mBOCF

g) Multiplicity was adjusted by the graphical approach with established test procedures for (1) comparison of ACR20 responder rates between the 4 mg group and the placebo group, (2) comparison of changes in mTSS and HAQ-DI between the 4-mg group and the placebo group, and (3) comparison of changes in DAS28-hsCRP and SDAI-based remission rate (SDAI ≤3.3) between the 4 mg group and the placebo group or a comparison of ACR20 responder rates and changes in DAS28-hsCRP between the 4 mg group and the adalimumab group

Table 38. ACR20 responder rates at Week 12 (Week 24 for mTSS only) (Japanese subgroup)

	4 mg	Adalimumab	Placebo
ACR20 responders[a)]	66.7 (62/93)	60.3 (38/63)	34.4 (32/93)
Difference from placebo [95% CI][b)]	32.3 [18.7, 45.9]	25.9 [10.4, 41.4]	–
Difference from adalimumab [95% CI][b)]	6.3 [-9.1, 21.8]	–	–
Change in mTSS[c)]	0.35 ± 1.40 (91)	0.11 ± 0.60 (61)	1.30 ± 2.80 (90)
Difference from placebo [95% CI][d)]	-0.95 [-1.52, -0.38]	-1.27 [-1.91, -0.63]	–
Change in HAQ-DI[e)]	-0.57 ± 0.50 (93)	-0.53 ± 0.49 (63)	-0.25 ± 0.44 (93)
Difference from placebo [95% CI][d)]	-0.30 [-0.43, -0.17]	-0.27 [-0.42, -0.13]	–
Change in DAS28-hsCRP[e)]	-2.23 ± 1.19 (93)	-2.04 ± 1.14 (63)	-0.86 ± 0.94 (93)
Difference from placebo [95% CI][d)]	-1.38 [-1.69, -1.07]	-1.21 [-1.56, -0.87]	–
SDAI-based remission rate[a)]	12.9 (12/93)	12.7 (8/63)	1.1 (1/93)
Difference from placebo [95% CI][b)]	11.8 [4.7, 19.0]	11.6 [3.1, 20.1]	–

% (number of subjects) or mean ± standard deviation (number of subjects)

a) NRI

b) Newcombe-Wilson method (without continuity correction)

c) Linear extrapolation approach

d) Analysis of covariance model with baseline value, baseline bone erosion score (1-2 sites and serum response positive; ≥3 sites), and treatment group as explanatory variables

e) mBOCF

The incidence of adverse events that occurred by Week 24 or before change to baricitinib 4 mg was 71.3% (347 of 487 subjects) in the 4-mg group, 67.9% (224 of 330 subjects) in the adalimumab group, and 60.5% (295 of 488 subjects) in the placebo group. The major adverse events are shown in Table 39.

The incidence of adverse events that occurred by Week 52 or before change to baricitinib 4 mg was 78.9% (384 of 487 subjects) in the 4-mg group and 76.7% (253 of 330 subjects) in the adalimumab group.

Table 39. Adverse events with an incidence of ≥3% in any group
(by Week 24 or before change to baricitinib 4 mg, safety analysis set)

Adverse event	4_mg (N = 487)	Adalimumab (N = 330)	Placebo (N = 488)
Nasopharyngitis	37 (7.6)	34 (10.3)	35 (7.2)
Urinary tract infection	21 (4.3)	13 (3.9)	17 (3.5)
Bronchitis	19 (3.9)	8 (2.4)	15 (3.1)
Anaemia	18 (3.7)	4 (1.2)	15 (3.1)
Upper respiratory tract infection	15 (3.1)	13 (3.9)	14 (2.9)
Hypercholesterolaemia	15 (3.1)	2 (0.6)	7 (1.4)
Headache	14 (2.9)	13 (3.9)	12 (2.5)
Pharyngitis	12 (2.5)	12 (3.6)	14 (2.9)
Hypertension	9 (1.8)	11 (3.3)	13 (2.7)
Back pain	9 (1.8)	10 (3.0)	9 (1.8)
Rheumatoid arthritis	5 (1.0)	4 (1.2)	15 (3.1)

Number of subjects (%)

Two subjects in the 4 mg group died (pneumonia and circulatory collapse in 1 subject each), 1 subject in the adalimumab group died (acute respiratory failure), and 2 subjects in the placebo group died (acute myocardial infarction and pneumonia in 1 subject each). A causal relationship with the study drug was ruled out for all these events except pneumonia in the placebo group.

The incidence of serious adverse events that occurred by Week 24 or before change to baricitinib 4 mg was 4.7% (23 of 487 subjects) in the 4 mg group, 1.8% (6 of 330 subjects) in the adalimumab group, and 4.5% (22 of 488 subjects) in the placebo group. The major adverse events observed are shown in Table 40. The incidence of serious adverse events that occurred by Week 52 or before change to baricitinib 4 mg was 7.8% (38 of 487 subjects) in the 4 mg group and 3.9% (13 of 330 subjects) in the adalimumab group. The serious adverse events that occurred in ≥2 subjects by Week 52 (before change to baricitinib 4 mg) were cellulitis in 3 subjects and anaemia, myocardial infarction, herpes zoster, and urinary tract infection in 2 subjects each in the 4 mg group.

The incidence of adverse events leading to treatment discontinuation by Week 24 or before change to baricitinib 4 mg was 5.1% (25 of 487 subjects) in the 4 mg group, 2.1% (7 of 330 subjects) in the adalimumab group, and 3.5% (17 of 488 subjects) in the placebo group. The incidence of adverse events leading to treatment discontinuation by Week 52 or before change to baricitinib 4 mg was 7.4% (36 of 487 subjects) in the 4 mg group and 4.5% (15 of 330 subjects) in the adalimumab group.

The incidence of adverse drug reactions that occurred by Week 24 or before change to baricitinib 4 mg was 31.8% (155 of 487 subjects) in the 4 mg group, 27.9% (92 of 330 subjects) in the adalimumab group, and 20.7% (101 of 488 subjects) in the placebo group. The incidence of adverse drug reactions that

occurred by Week 52 (before change to baricitinib 4 mg) was 39.8% (194 of 487 subjects) in the 4 mg group and 33.6% (111 of 330 subjects) in the adalimumab group.

Table 40. Serious adverse events occurring in ≥2 subjects in any group
(by Week 24 or before change to baricitinib 4 mg, safety analysis set)

Adverse event	4 mg (N = 487)	Adalimumab (N = 330)	Placebo (N = 488)
Cellulitis	2 (0.4)	0	0
Anaemia	2 (0.4)	0	0
Herpes zoster	2 (0.4)	0	0
Bile duct stone	0	0	2 (0.4)
Gastroenteritis	0	0	2 (0.4)

Number of subjects (%)

In the Japanese subgroup, the incidence of adverse events that occurred by Week 24 or before change to baricitinib 4 mg was 86.0% (80 of 93 subjects) in the 4 mg group, 82.5% (52 of 63 subjects) in the adalimumab group, and 71.0% (66 of 93 subjects) in the placebo group. The major adverse events are shown in Table 41. The incidence of adverse events that occurred by Week 52 or before change to baricitinib 4 mg was 94.6% (88 of 93 subjects) in the 4 mg group and 93.7% (59 of 63 subjects) in the adalimumab group.

There were no deaths. The incidence of serious adverse events that occurred by Week 24 or before change to baricitinib 4 mg was 3.2% (3 of 93 subjects; herpes zoster, femoral neck fracture/ulna fracture, and interstitial lung disease in 1 subject each) in the 4 mg group, 1.6% (1 of 63 subjects; hypotension) in the adalimumab group, and 3.2% (3 of 93 subjects; large intestine polyp, pyelonephritis/chondrocalcinosis pyrophosphate, and ovarian cancer in 1 subject each) in the placebo group. The incidence of serious adverse events that occurred by Week 52 or before change to baricitinib 4 mg was 5.4% (5 of 93 subjects; neutropenia, herpes zoster, femoral neck fracture/ulna fracture, femur fracture, and interstitial lung disease in 1 subject each) in the 4 mg group and 4.8% (3 of 63 subjects; myocardial infarction, macular fibrosis/retinal detachment, and hypotension in 1 subject each) in the adalimumab group.

The incidence of adverse events leading to treatment discontinuation by Week 24 or before change to baricitinib 4 mg was 6.5% (6 of 93 subjects; herpes zoster in 4 subjects, and hepatitis B DNA assay positive and interstitial lung disease in 1 subject each) in the 4 mg group, 3.2% (2 of 63 subjects; herpes zoster and lymphoproliferative disorder in 1 subject each) in the adalimumab group, and 4.3% (4 of 93 subjects; lymphocyte count decreased, rheumatoid arthritis, ovarian cancer, and skin necrosis in 1 subject each) in the placebo group. The incidence of adverse events leading to treatment discontinuation by Week 52 or before change to baricitinib 4 mg was 9.7% (9 of 93 subjects; herpes zoster in 5 subjects, interstitial lung disease in 2 subjects, and neutropenia and hepatitis B DNA assay positive in 1 subject each) in the 4 mg group, and 7.9% (5 of 63 subjects; herpes zoster in 2 subjects, and lymphoproliferative disorder, pneumonia chlamydial, and myocardial infarction in 1 subject each) in the adalimumab group.

The incidence of adverse drug reactions that occurred by Week 24 or before change to baricitinib 4 mg was 46.2% (43 of 93 subjects) in the 4 mg group, 42.9% (27 of 63 subjects) in the adalimumab group, and 34.4% (32 of 93 subjects) in the placebo group. The incidence of adverse drug reactions that occurred by Week 52 (or before change to baricitinib 4 mg) was 62.4% (58 of 93 subjects) in the 4 mg group and 55.6% (35 of 63 subjects) in the adalimumab group.

Table 41. Adverse events with an incidence of ≥3% in any group
(by Week 24 or before change to baricitinib 4 mg, Japanese subgroup)

Adverse event	4 mg (N = 93)	Adalimumab (N = 63)	Placebo (N = 93)
Nasopharyngitis	16 (17.2)	14 (22.2)	14 (15.1)
Hepatic function abnormal	6 (6.5)	6 (9.5)	0
Constipation	5 (5.4)	2 (3.2)	0
Alanine aminotransferase increased	4 (4.3)	3 (4.8)	0
Blood creatine phosphokinase increased	4 (4.3)	1 (1.6)	1 (1.1)
Herpes zoster	4 (4.3)	1 (1.6)	0
Bronchitis	4 (4.3)	0	4 (4.3)
Pharyngitis	4 (4.3)	0	4 (4.3)
Hyperlipidaemia	3 (3.2)	2 (3.2)	1 (1.1)
Lymphocyte count decreased	3 (3.2)	1 (1.6)	4 (4.3)
Eczema	3 (3.2)	1 (1.6)	3 (3.2)
Stomatitis	3 (3.2)	1 (1.6)	3 (3.2)
Dental caries	3 (3.2)	1 (1.6)	0
Thermal burn	3 (3.2)	0	2 (2.2)
Contusion	3 (3.2)	0	1 (1.1)
Gastrooesophageal reflux disease	3 (3.2)	0	0
Hypertension	2 (2.2)	3 (4.8)	4 (4.3)
Nausea	2 (2.2)	3 (4.8)	1 (1.1)
Aspartate aminotransferase increased	2 (2.2)	2 (3.2)	0
Rash	1 (1.1)	2 (3.2)	2 (2.2)
Transaminases increased	1 (1.1)	2 (3.2)	0
Haemorrhage subcutaneous	1 (1.1)	2 (3.2)	0
Upper respiratory tract infection	1 (1.1)	1 (1.6)	3 (3.2)
Back pain	0	3 (4.8)	0
Rheumatoid arthritis	0	2 (3.2)	2 (2.2)
Iron deficiency anaemia	0	2 (3.2)	1 (1.1)
Pruritus	0	2 (3.2)	0
Lymphopenia	0	0	5 (5.4)
Pulpitis dental	0	0	3 (3.2)

Number of subjects (%)

7.2.4 Multi-regional study in RA patients who had limited or no treatment with cDMARDs (Study 14V-MC-JADZ [January 2013 to August 2015])

An active-controlled, randomized, double-blind, parallel-group study was conducted in RA patients[35)] who were cDMARD-naive or had limited treatment with MTX (within 3 weeks of the start of treatment with MTX) (target sample size, 550 subjects [150 in the baricitinib 4 mg alone group, 200 in the

[35] Main inclusion criteria: Patients with active RA who meet all of the following criteria: (1) positive for rheumatoid factor and/or anti-cyclic citrullinated peptide (anti-CCP) antibody, (2) ≥6 swollen joints and ≥6 tender joints, (3) CRP (or hsCRP) of ≥1.2-fold the ULN, and (4) no or limited (within 3 weeks after the start of) treatment with MTX and no previous use of other cDMARDs or biological drugs.

baricitinib 4 mg/MTX combination group, and 200 in the MTX alone group]) in 17 countries including Japan, the US, and South Korea to verify the non-inferiority of baricitinib 4 mg alone to MTX alone.

Subjects received one of the following 3 oral regimens for 52 weeks: (1) 4 mg[36] of baricitinib once daily and placebo once weekly; (2) 4 mg[27] of baricitinib once daily and MTX[37] once weekly; and (3) MTX[28] once weekly and placebo once daily. For subjects who were assessed as non-responder[38] at Week 24 or later had a regimen change to the combination of baricitinib 4 mg and MTX (4-mg + MTX) in a blinded manner (Figure 8). The change to 4 mg + MTX was allowed only once, and those who showed no improvement in the signs or symptoms of RA ≥4 weeks after the regimen change discontinued the study treatment. Subjects were allowed to move onto a long-term treatment study (Study 14V-MC-JADY) after the Week-52 visit.

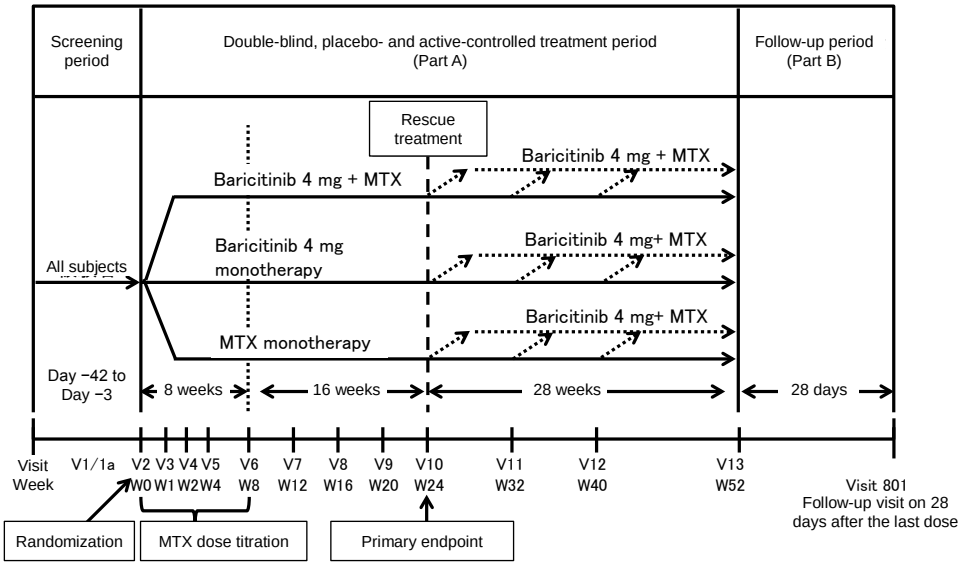

Figure 8. JADZ study design

Of 588 randomized subjects, 584 subjects receiving the study drug (159 in the baricitinib 4 mg alone [4 mg alone] group, 215 in the 4 mg + MTX group, and 210 in the MTX alone group) were included in the safety analysis set and the mITT population. The mITT population also served as the efficacy analysis set. Subjects who discontinued study treatment by Week 24 accounted for 8.8% (14 of 159) of subjects in the 4 mg alone group, 10.7% (23 of 215) of subjects in the 4 mg + MTX group, and 13.3% (28 of 210) of subjects in the MTX alone group. The major reasons for discontinuation were adverse events (3.8% [6 of 159 subjects] in the 4 mg alone group, 6.5% [14 of 215 subjects] in the 4 mg + MTX group, and 1.0% [2 of 210 subjects] in the MTX alone group) and subject's request (2.5% [4 of 159 subjects] in the 4 mg alone group, 2.8% [6 of 215 subjects] in the 4 mg + MTX group, and 4.8% [10 of 210 subjects] in the MTX alone group). Subjects who experienced the regimen change to 4 mg + MTX at or after Week 24 because of inadequate efficacy accounted for 4.4% (7 of 159) of subjects in the 4 mg

36 Subjects with eGFR of ≥40 mL/min/1.73 mm^2 to <60 mL/min/1.73 mm^2 received 2 mg of baricitinib orally once daily.

37 The starting dose of MTX was 10 mg/week and the dose was then increased by 5 mg every 4 weeks up to 20 mg/week. To subjects who were clinically required to adhere to a low dose of MTX it was administered at 7.5 mg/week, and was then increased by 2.5 mg every 4 weeks up to 12.5 mg/week. Subjects enrolled in Japan received a low dose MTX.

38 Subjects who failed to achieve improvement from baseline by ≥20% in the number of swollen or tender joints.

alone group, 2.8% (6 of 215) of subjects in the 4 mg + MTX group, and 12.4% (26 of 210) of subjects in the MTX alone group.

The mITT population included 104 Japanese subjects (29 in the 4 mg alone group, 39 in the 4 mg + MTX group, and 36 in the MTX alone group). Japanese subjects who discontinued study treatment by Week 24 accounted for 13.8% (4 of 29) of subjects in the 4-mg alone group, 15.4% (6 of 39) of subjects in the 4 mg + MTX group, and 11.1% (4 of 36) of subjects in the MTX alone group. The major reason for discontinuation was adverse events (4 subjects in the 4 mg alone group, 6 subjects in the 4 mg + MTX group, and 1 subject in the MTX alone group). Subjects who experienced the regimen change to 4 mg + MTX at or after Week 24 because of inadequate response accounted for 13.8% (4 of 29) of subjects in the 4 mg alone group, 2.6% (1 of 39) of subjects in the 4 mg + MTX group, and 11.1% (4 of 36) of subjects in the MTX alone group.

The primary efficacy endpoint of the ACR20 responder rates at Week 24 are shown in Table 42 [for the definitions of the respective endpoints, see Section "10. Other"]. The lower bound of the 95% confidence interval for the difference between the 4 mg alone group and the MTX alone group (5.5%) exceeded the non-inferiority margin of −12%[39]; therefore, the non-inferiority of baricitinib 4 mg alone to MTX alone was verified. The secondary efficacy endpoints, changes from baseline in HAQ-DI, DAS28-hsCRP, and mTSS at Week 24 and SDAI-based remission rates (SDAI score ≤3.3) at Week 24, are also shown in Table 42.

The results in the Japanese subgroup are shown in Table 43.

[39] This non-inferiority margin was set taking into account that the non-inferiority margin used in clinical studies conducted in RA patients to compare biological drug alone with MTX alone was 10% (*Arthritis Rheum*. 2009;60:2272-83) or 12% (*Ann Rheum Dis*. 2010;69:88-96).

Table 42. ACR20 responder rates and other endpoints at Week 24 (mITT population)

	4 mg alone	4 mg + MTX	MTX alone
ACR20 responders[a)]	76.7 (122/159)	78.1 (168/215)	61.9 (130/210)
Difference from MTX alone [95% CI][b)] *P* value[c),g)]	14.8 [5.5, 24.1]	16.2 [7.7, 24.8] *P* = 0.001	–
Change in HAQ-DI[d)]	-1.01 ± 0.74 (159)	-0.92 ± 0.74 (215)	-0.73 ± 0.71 (210)
Difference from MTX alone [95% CI][e)] *P* value[e),g)]	-0.29 [-0.41, -0.16] *P* = 0.001	-0.23 [-0.35, -0.12] *P* = 0.001	–
Change in DAS28-hsCRP[d)]	-2.74 ± 1.39 (159)	-2.82 ± 1.58 (215)	-2.01 ± 1.51 (210)
Difference from MTX alone [95% CI][e)] *P* value[e),g)]	-0.69 [-0.98, -0.40] *P* = 0.001	-0.78 [-1.05, -0.51] *P* = 0.001	–
Change in mTSS[f)]	0.43 ± 1.18 (152)	0.32 ± 1.14 (198)	0.64 ± 1.81 (191)
Difference from MTX alone [95% CI][e)] *P* value[e),g)]	-0.22 [-0.52, 0.08] *P* = 0.158	-0.32 [-0.60, -0.04] *P* = 0.026	–
SDAI-based remission rate[a)]	22.0 (35/159)	22.8 (49/215)	10.5 (22/210)
Difference from MTX alone [95% CI][b)] *P* value[c),g)]	11.5 [3.9, 19.2] *P* = 0.003	12.3 [5.3, 19.3] *P* = 0.001	–

% (number of subjects) or mean ± standard deviation (number of subjects)

a) NRI

b) Newcombe-Wilson method (without continuity correction)

c) Logistic regression model with region, baseline status of bone erosion, and treatment group as explanatory variables

d) mBOCF

e) Analysis of covariance model with baseline value, region, baseline status of bone erosion, and treatment group as explanatory variables

f) Linear extrapolation approach

g) Multiplicity was adjusted by the graphical approach using test procedures for a comparison between the 4-mg alone group and the MTX alone group in terms of (1) ACR20 responder rate, (2) change in DAS28-hsCRP, (3) change in HAQ-DI, (4) change in mTSS, and (5) SDAI-based remission rate (SDAI ≤3.3) and a comparison between the 4-mg + MTX group and the MTX alone group in terms of (1) ACR20 responder rate, (2) change in DAS28-hsCRP, (3) change in HAQ-DI, (4) change in mTSS, and (5) SDAI-based remission rate (SDAI ≤3.3).

Table 43. ACR20 responder rates and other endpoints at Week 24 (Japanese subgroup)

	4 mg alone	4 mg + MTX	MTX alone
ACR20 responders[a)]	72.4 (21/29)	71.8 (28/39)	69.4 (25/36)
Difference from MTX alone [95% CI][b)]	3.0 [-19.2, 25.1]	2.4 [-18.3, 23.0]	–
HAQ-DI[c)]	-0.97 ± 0.69 (29)	-0.73 ± 0.70 (39)	-0.70 ± 0.68 (36)
Difference from MTX alone [95% CI][d)]	-0.14 [-0.44, 0.16]	-0.12 [-0.39, 0.16]	–
Change in DAS28-hsCRP[c)]	-2.50 ± 1.48 (29)	-2.60 ± 1.67 (39)	-2.07 ± 1.43 (36)
Difference from MTX alone [95% CI][d)]	-0.31 [-1.08, 0.46]	-0.48 [-1.18, 0.22]	–
Change in mTSS[e)]	0.91 ± 1.78 (27)	0.24 ± 0.96 (37)	0.85 ± 1.38 (34)
Difference from MTX alone [95% CI][d)]	0.02 [-0.70, 0.74]	-0.62 [-1.27, 0.03]	–
SDAI-based remission rate[a)]	27.6 (8/29)	28.2 (11/39)	16.7 (6/36)
Difference from MTX alone [95% CI][b)]	10.9 [-9.4, 31.2]	11.5 [-7.1, 30.2]	–

% (Number of subjects) or mean ± standard deviation (N)

a) NRI

b) Newcombe-Wilson method (without continuity correction)

c) mBOCF

d) Analysis of covariance model with baseline value, region, baseline status of bone erosion, and treatment group as explanatory variables

e) Linear extrapolation approach

The incidence of adverse events that occurred by Week 52 or before change to 4 mg + MTX was 71.1% (113 of 159 subjects) in the 4-mg alone group, 77.7% (167 of 215 subjects) in the 4-mg + MTX group, and 71.9% (151 of 210 subjects) in the MTX alone group. The major adverse events observed are shown in Table 44.

A total of 3 subjects in the MTX alone group died (drowning, pulmonary embolism, and pulmonary fibrosis in 1 subject each). A causal relationship with the study drug could not be ruled out for drowning and pulmonary fibrosis in 1 subject each. The incidence of serious adverse events was 7.5% (12 of 159 subjects) in the 4 mg alone group, 7.9% (17 of 215 subjects) in the 4 mg + MTX group, and 9.5% (20 of 210 subjects) in the MTX alone group. The serious adverse events that occurred in ≥2 subjects in any group were herpes zoster (0.6% [1 of 159] of subjects in the 4 mg alone group and 1.0% [2 of 210] of subjects in the MTX alone group), fall (1.0% [2 of 210] of subjects in the MTX alone group), and spinal compression fracture (1.0% [2 of 210] of subjects in the MTX alone group). The adverse events leading to treatment discontinuation was 6.9% (11 of 159) of subjects in the 4 mg alone group, 10.7% (23 of 215) of subjects in the 4 mg + MTX group, and 5.2% (11 of 210) of subjects in the MTX alone group.

The incidence of adverse drug reactions was 31.4% (50 of 159 subjects) in the 4 mg alone group, 45.6% (98 of 215 subjects) in the 4 mg + MTX group, and 34.8% (73 of 210 subjects) in the MTX alone group.

Table 44. Adverse events with an incidence of ≥3% in any group
(by Week 52 or before change to 4 mg + MTX, safety analysis set)

Adverse event	4 mg alone (N = 159)	4 mg + MTX (N = 215)	MTX alone (N = 210)
Nasopharyngitis	16 (10.1)	21 (9.8)	17 (8.1)
Upper respiratory tract infection	12 (7.5)	16 (7.4)	15 (7.1)
Gastroenteritis	10 (6.3)	6 (2.8)	4 (1.9)
Nausea	7 (4.4)	20 (9.3)	13 (6.2)
Influenza	7 (4.4)	11 (5.1)	4 (1.9)
Urinary tract infection	6 (3.8)	14 (6.5)	8 (3.8)
Depression	6 (3.8)	2 (0.9)	4 (1.9)
Bronchitis	5 (3.1)	9 (4.2)	4 (1.9)
Cough	5 (3.1)	6 (2.8)	13 (6.2)
Headache	5 (3.1)	6 (2.8)	3 (1.4)
Vomiting	5 (3.1)	5 (2.3)	6 (2.9)
Blood creatine phosphokinase increased	4 (2.5)	10 (4.7)	2 (1.0)
Fatigue	4 (2.5)	8 (3.7)	5 (2.4)
Back pain	3 (1.9)	9 (4.2)	5 (2.4)
Dyspepsia	3 (1.9)	8 (3.7)	1 (0.5)
Diarrhoea	3 (1.9)	5 (2.3)	12 (5.7)
Rheumatoid arthritis	3 (1.9)	1 (0.5)	7 (3.3)
Hypertension	2 (1.3)	13 (6.0)	7 (3.3)
Dyslipidaemia	2 (1.3)	8 (3.7)	2 (1.0)
Pharyngitis	2 (1.3)	7 (3.3)	4 (1.9)
Constipation	2 (1.3)	7 (3.3)	3 (1.4)
Muscle spasms	2 (1.3)	7 (3.3)	1 (0.5)
Alanine aminotransferase increased	1 (0.6)	13 (6.0)	5 (2.4)
Hepatic function abnormal	1 (0.6)	8 (3.7)	5 (2.4)
Sinusitis	1 (0.6)	7 (3.3)	5 (2.4)
Rhinitis	1 (0.6)	2 (0.9)	7 (3.3)
Aspartate aminotransferase increased	0	7 (3.3)	3 (1.4)
Vulvovaginal candidiasis[a)]	0	6 (3.8)	1 (0.7)

Number of subjects (%)

[a)] Because this was a women-specific event, the number of subjects analyzed as the denominator was adjusted accordingly (N = 121 in the 4-mg alone group, 156 in the 4mg + MTX group, and 148 in the MTX alone group).

The incidence of adverse events that occurred in the Japanese subgroup by Week 52 or before change to 4-mg + MTX was 96.6% (28 of 29 subjects) in the 4-mg alone group, 92.3% (36 of 39 subjects) in the 4-mg + MTX group, and 83.3% (30 of 36 subjects) in the MTX alone group. The major adverse events observed in the Japanese subgroup are shown in Table 45.

One subject in the MTX alone group died (drowning), and a causal relationship with study drug could not be ruled out for the death. The incidence of serious adverse events was 10.3% (3 of 29 subjects; duodenal ulcer, herpes zoster, and cervix carcinoma in 1 subject each) in the 4-mg alone group, 10.3% (4 of 39 subjects; campylobacter gastroenteritis, pneumocystis jirovecii pneumonia, pneumonia/pneumothorax spontaneous, and overdose in 1 subject each) in the 4 mg + MTX group, and 13.9% (5 of 36 subjects; herpes zoster in 2 subjects, and gastric ulcer haemorrhage, drowning, and cerebral haemorrhage in 1 subject each) in the MTX alone group. A causal relationship with study drug could not be ruled out for these events except the duodenal ulcer in the 4-mg alone group and the gastric ulcer haemorrhage and cerebral haemorrhage in 1 subject each in the MTX alone group. The incidence of adverse events leading to treatment discontinuation was 17.2% (5 of 29 subjects) in the 4-mg alone group, 20.5% (8 of 39 subjects) in the 4 mg + MTX group, and 11.1% (4 of 36 subjects) in the MTX alone group.

The incidence of adverse drug reactions was 58.6% (17 of 29 subjects) in the 4-mg alone group, 74.4% (29 of 39 subjects) in the 4 mg + MTX group, and 50.0% (18 of 36 subjects) in the MTX alone group.

Table 45. Adverse events occurring in ≥3 subjects in any group
(by Week 52 or before change to 4-mg + MTX, Japanese subgroup)

Adverse event	4 mg alone (N = 29)	4 mg + MTX (N = 39)	MTX alone (N = 36)
Nasopharyngitis	8 (27.6)	10 (25.6)	9 (25.0)
Gastroenteritis	4 (13.8)	1 (2.6)	1 (2.8)
Herpes zoster	3 (10.3)	3 (7.7)	2 (5.6)
Hepatic function abnormal	1 (3.4)	8 (20.5)	5 (13.9)
Iron deficiency anaemia	1 (3.4)	4 (10.3)	1 (2.8)
Blood creatine phosphokinase increased	1 (3.4)	3 (7.7)	2 (5.6)
Constipation	0	3 (7.7)	2 (5.6)
Lymphocyte count decreased	0	3 (7.7)	1 (2.8)
Dyslipidaemia	0	3 (7.7)	1 (2.8)
Vulvovaginal candidiasis[a)]	0	3 (13.0)	0

Number of subjects (%)

[a)] Because this was a female-specific event, the number of subjects analyzed as the denominator was adjusted accordingly (N = 23 in the 4-mg alone group, 23 in the 4-mg + MTX group, and 27 in the MTX alone group).

7.2.5 Long-term treatment study in patients with RA (Study 14V-MC-JADY [June 2013 to the data cut-off date, September 1, 2016])

An open-label, uncontrolled study was conducted in RA patients who had completed the foreign Phase II study (the JADA study) or a multi-regional Phase III study (the JADZ, JADV, JADX, or JADW study) (target sample size, 2400 to 3500 subjects) in 37 countries including Japan and the US to evaluate the long-term safety of baricitinib.

As shown in Table 46, subjects received baricitinib orally once daily for up to 48 months at a dose of 2 or 4 mg depending on which clinical study they had participated in before enrollment in the JADY study. The dose of subjects who met the specified criteria[40] was changed to 4 mg.

Table 46. Dosing regimens in the JADY study by treatment group in previous studies[a), b)]

Previous study	Treatment group in a previous study	Regimen at the start of JADY
JADZ	4 mg alone	4 mg QD (alone)
	4 mg + MTX	
	MTX alone	
JADV	4 mg	4 mg QD
	Adalimumab	
JADX	2 mg	2 mg QD
	4 mg	4 mg QD
	Placebo	
JADW	2 mg	2 mg QD
	4 mg	4 mg QD
	Placebo	
JADA	4 mg	4 mg QD (open-label)
JAGS	4 mg	4 mg QD

a) Subjects who received rescue therapy with baricitinib 4 mg in the JADZ, JADV, JADX, or JADW study received baricitinib 4 mg QD in the open-label setting.
b) Subjects with eGFR of ≥40 mL/min/1.73 mm^2 to <60 mL/min/1.73 mm^2 received baricitinib 2 mg QD.

All of 2656 treated subjects (83 from the JADA study, 448 from the JADW study, 583 in the JADX study; 1091 from the JADV study, and 451 from the JADZ study) were included in the safety and efficacy analysis sets. Subjects who discontinued study treatment accounted for 16.9% (449 of 2656 subjects). The major reason for discontinuation was adverse events (6.5% [172 of 2656 subjects]).

Among subjects whose treatment was not changed to baricitinib 4 mg in a previous study and who had received treatment for ≥48 weeks in the JADY study as of the data cut-off date (September 1, 2016), the ACR20 responder rates, an efficacy endpoint [for the definitions of the respective endpoints, see "10. Other"], by treatment group to which they had been assigned in a previous study are shown in Table 47.

40 Subjects of the JADV, JADX, or JADW study: At the time point where the CDAI score became >10 at least 3 months after participating in the JADY study. Subjects of the JADZ study: At the discretion of the investigator after participating in the JADY study.

Table 47. ACR20 responder rates at baseline and at Week 48 (NRI)

		JADZ			JADV		
		4 mg→4 mg	4 mg + MTX →4 mg	MTX→4 mg	4 mg→4 mg	Adalimumab→ 4 mg	Placebo→ 4 mg[b)]
ACR20 responders	Baseline[a)]	90.3 (112/124) [83.8, 94.4]	93.3 (152/163) [88.3, 96.2]	83.8 (114/136) [76.7, 89.1]	89.5 (340/380) [86.0, 92.2]	85.3 (203/238) [80.2, 89.2]	86.5 (243/281) [82.0, 90.0]
	Week 48	84.7 (105/124) [77.3, 90.0]	86.5 (141/163) [80.4, 90.9]	88.2 (120/136) [81.7, 92.6]	87.1 (330/379) [83.3, 90.1]	86.1 (205/238) [81.2, 90.0]	82.6 (232/281) [77.7, 86.6]

		JADX			JADW			JADA
		2 mg→2 mg	4 mg→4 mg	Placebo→ 4 mg	2 mg→2 mg	4 mg→4 mg	Placebo→ 4 mg	4 mg→4 mg
ACR20 responders	Baseline[a)]	75.0 (135/180) [68.2, 80.8]	80.6 (145/180) [74.2, 85.7]	66.2 (92/139) [58.0, 73.5]	66.7 (78/117) [57.7, 74.6]	66.9 (83/124) [58.3, 74.6]	56.3 (49/87) [45.9, 66.3]	75.5 (37/49) [61.9, 85.4]
	Week 48	73.9 (133/180) [67.0, 79.8]	70.6 (127/180) [63.5, 76.7]	77.0 (107/139) [69.3, 83.2]	62.4 (73/117) [53.4, 70.6]	58.1 (72/124) [49.3, 66.4]	67.8 (59/87) [57.4, 76.7]	73.5 (36/49) [59.7, 83.8]

% (number of subjects)
a) At the start of the JADY study
b) In the JADV study, the dosing regimen of the placebo group was changed to baricitinib 4 mg at Week 24.

The incidence of adverse events was 77.6% (2062 of 2656 subjects) in all subjects receiving baricitinib (including those who experienced the dose change to baricitinib 4 mg). The major adverse events observed are shown in Table 48.

Table 48. Adverse events with an incidence of ≥3% (safety analysis set, N = 2656)

Adverse event	Baricitinib group
Bronchitis	227 (8.5)
Urinary tract infection	213 (8.0)
Nasopharyngitis	212 (8.0)
Upper respiratory tract infection	182 (6.9)
Herpes zoster	135 (5.1)
Back pain	128 (4.8)
Rheumatoid arthritis	124 (4.7)
Hypertension	114 (4.3)
Blood creatine phosphokinase increased	109 (4.1)
Influenza	104 (3.9)
Arthralgia	103 (3.9)
Sinusitis	96 (3.5)
Pharyngitis	95 (3.6)
Cough	82 (3.1)
Hypercholesterolaemia	80 (3.0)
Osteoarthritis	80 (3.0)

Number of subjects (%)

A total of 18 subjects died (cardio-respiratory arrest in 3 subjects, and cardiac arrest, coagulopathy, pulmonary embolism, acute myocardial infarction, cardiac failure, disseminated tuberculosis, adenocarcinoma pancreas, respiratory failure, pneumonia, squamous cell carcinoma of lung, death, abdominal infection, acute respiratory failure, lung squamous cell carcinoma metastatic, and lung neoplasm malignant in 1 subject each). A causal relationship with the study drug could not be ruled out for 6 deaths (disseminated tuberculosis, adenocarcinoma pancreas, squamous cell carcinoma of lung, abdominal infection, lung squamous cell carcinoma metastatic, and lung neoplasm malignant in 1 subject each).

The incidence of serious adverse events was 14.8% (394 of 2656 subjects). The main serious adverse events observed are shown in Table 49. The incidence of adverse events leading to treatment discontinuation was 5.6% (150 of 2656 subjects).

The incidence of adverse drug reactions was 33.7% (894 of 2656 subjects).

Table 49. Serious adverse events that occurred in ≥5 subjects (safety analysis set, N = 2656)

Adverse event	Baricitinib group
Osteoarthritis	28 (1.1)
Pneumonia	23 (0.9)
Herpes zoster	12 (0.5)
Pulmonary embolism	12 (0.5)
Urinary tract infection	11 (0.4)
Atrial fibrillation	10 (0.4)
Rheumatoid arthritis	10 (0.4)
Fall	9 (0.3)
Deep vein thrombosis	8 (0.3)
Cholelithiasis	7 (0.3)
Cellulitis	6 (0.2)
Haematoma	6 (0.2)
Syncope	6 (0.2)
Acute myocardial infarction	5 (0.2)
Chronic obstructive pulmonary disease	5 (0.2)

Number of subjects (%)

In the Japanese subgroup of all subjects receiving baricitinib (including those who experienced the dose change to baricitinib 4 mg), the incidence of adverse events was 88.7% (291 of 328 subjects). The major adverse events observed are shown in Table 50.

There were no deaths. The incidence of serious adverse events was 12.8% (42 of 328 subjects). The serious adverse events that occurred in ≥2 subjects were herpes zoster (2.4% [8 of 328 subjects]) and enteritis infectious and pneumonia (0.6% [2 of 328 subjects] each). The incidence of adverse events leading to treatment discontinuation was 6.1% (20 of 328 subjects).

The incidence of adverse drug reactions was 58.2% (191 of 328 subjects).

Table 50. Adverse events with an incidence of ≥3% (Japanese subgroup, N = 328)

Adverse event	Baricitinib group
Nasopharyngitis	79 (24.1)
Herpes zoster	29 (8.8)
Blood creatine phosphokinase increased	20 (6.1)
Contusion	20 (6.1)
Upper respiratory tract inflammation	19 (5.8)
Influenza	18 (5.5)
Hypertension	16 (4.9)
Constipation	15 (4.6)
Dental caries	15 (4.6)
Hepatic function abnormal	15 (4.6)
Pharyngitis	15 (4.6)
Bronchitis	14 (4.3)
Dyslipidaemia	12 (3.7)
Hepatic steatosis	12 (3.7)
Periodontitis	12 (3.7)
Rash	12 (3.7)
Tooth extraction	12 (3.7)
Anaemia	11 (3.4)
Gastroenteritis	11 (3.4)
Hyperlipidaemia	11 (3.4)
Chronic gastritis	10 (3.0)
Endoscopy upper gastrointestinal tract	10 (3.0)
Headache	10 (3.0)
Lymphopenia	10 (3.0)
Lymphocyte count decreased	10 (3.0)

Number of subjects (%)

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Development plan

The applicant's explanation about the development plan for baricitinib:

The clinical practice guidelines of Japan College of Rheumatology, ACR, and the European League Against Rheumatism (EULAR) recommend that patients diagnosed as having RA should start receiving treatment with antirheumatic drugs as soon as possible to achieve clinical remission or low disease activity. Treatment-naive RA patients are usually treated with MTX alone or in combination with other cDMARDs, or with a cDMARD alone. For those who have responded inadequately to MTX or other cDMARDs, the use of a biological drug such as a TNF inhibitor with MTX is recommended. The biological drug may be switched to another biological drug in the event of inadequate response (*Guideline for the Management of Rheumatoid Arthritis, Japan College of Rheumatology 2014, Ann Rheum Dis*. 2014;73:492-509, *Ann Rheum Dis*. 2017;0:1-18). In Phase III studies, based on this therapeutic system, the efficacy and safety of baricitinib in combination with MTX or cDMARDs were evaluated in RA patients with an inadequate response to MTX (the JADV study), cDMARDs (the JADX study), or TNF inhibitors (the JADW study). In addition, to confirm the efficacy and safety of baricitinib in MTX- or other cDMARD-naive patients with RA, the efficacy and safety of baricitinib alone were evaluated in the JADZ study conducted in patients with early stage RA, in expectation that baricitinib would become an option for patients intolerant to MTX, .

In Phase II studies (the JADC and JADA studies), the dose-response relationship of the efficacy of baricitinib was relatively flat in dose groups receiving >4 mg, in which a higher incidence of adverse events and a lower hemoglobin level were observed. Benefits from the twice-daily regimen were not greater than from the once-daily regimen. In the JADN study in Japanese patients with RA, while the ACR20, 50, and 70 responder rates at Week 12 were similar among baricitinib groups receiving ≥2 mg [see Section "7.1.1 Japanese study in RA patients with an inadequate response to MTX"], improvement in symptoms was observed earlier in the 4-mg group than in the 1- and 2-mg groups, as shown in Table 51. The earlier improvement in the 4-mg group was also demonstrated in the time courses from baseline in DAS28-hsCRP. Based on these results, the appropriate dosing regimen of baricitinib in RA patients including Japanese patients in Phase III studies would be a 4 mg once daily oral dose. Furthermore, in order to confirm that 4 mg was the optimal dose of baricitinib, 2 of the 4 Phase III studies (JADX and JADW studies) had a group treated with a lower dose regimen, that is, 2 mg once-daily oral baricitinib.

There is no marked difference in the therapeutic system for RA, including the therapeutic algorithm, between Japan and foreign countries. In healthy subjects or subjects with RA, there were no notable differences in the pharmacokinetics of baricitinib that could affect the efficacy and safety of baricitinib between Japanese and non-Japanese subjects [see Section "6.R.1 Ethnic differences in pharmacokinetics of baricitinib"]. The dose-response relationship observed in the JADN study in Japan was similar to that observed in the JADA study overseas, and the results of both studies showed no marked differences. Therefore, the evaluation of the efficacy and safety of baricitinib in Japanese patients with RA was thought to be feasible based on a clinical data package established from multi-regional Phase III studies involving Japanese patients.

Table 51. ACR20 responder rates and changes from baseline in DAS28-hsCRP in the JADN study (FAS)

		1 mg	2 mg	4 mg	8 mg	Placebo
ACR20 responders[a)]	Week 2	20.8 (5/24)	37.5 (9/24)	50.0 (12/24)	50.0 (12/24)	18.4 (9/49)
	Week 4	41.7 (10/24)	45.8 (11/24)	62.5 (15/24)	66.7 (16/24)	30.6 (15/49)
	Week 8	54.2 (13/24)	66.7 (16/24)	79.2 (19/24)	91.7 (22/24)	28.6 (14/49)
	Week 12	66.7 (16/24)	83.3 (20/24)	66.7 (16/24)	87.5 (21/24)	30.6 (15/49)
Change from baseline in DAS28-hsCRP[b)]	Week 2	-0.61 ± 0.62 (24)	-0.98 ± 0.80 (24)	-1.20 ± 0.65 (24)	-1.29 ± 0.79 (24)	-0.41 ± 0.67 (49)
	Week 4	-1.11 ± 0.96 (23)	-1.32 ± 0.97 (24)	-1.66 ± 0.92 (24)	-1.54 ± 0.99 (24)	-0.44 ± 1.03 (49)
	Week 8	-1.33 ± 1.06 (23)	-1.58 ± 1.23 (24)	-1.93 ± 0.96 (24)	-1.94 ± 0.90 (24)	-0.47 ± 1.19 (48)
	Week 12	-1.52 ± 0.99 (23)	-2.02 ± 1.07 (24)	-2.14 ± 1.09 (23)	-1.96 ± 0.95 (24)	-0.61 ± 1.22 (48)

% (number of subjects) or mean ± standard deviation (number of subjects)
a) NRI
b) OC

PMDA accepted the applicant's explanation and considered that it is possible to evaluate the efficacy and safety of baricitinib in RA patients based on the submitted clinical data package with a focus on the results from multi-regional Phase III studies involving Japanese patients.

7.R.1.2 Efficacy against clinical symptoms of RA

The applicant's explanation about the efficacy of baricitinib against the clinical symptoms of RA:

The following 4 multi-regional Phase III studies were conducted involving Japanese patients: the JADZ study in patients who were cDMARD- and biological drug-naive or who had limited treatment with MTX; the JADV study in patients with an inadequate response to MTX; the JADX study in patients with an inadequate response to cDMARDs; and the JADW study in patients with an inadequate response to TFN inhibitors. The results of the primary endpoint in these studies are shown in Table 52. The superiority of baricitinib 4 mg to placebo was verified. Many secondary endpoints demonstrated statistically significant differences between the 4 or 2 mg and placebo [see Section "7.2 Phase III studies"].

Table 52 also shows the proportions of ACR20 responders, the primary endpoint of the JADZ, JADV, JADX, and JADW studies, in the entire subjects and Japanese subjects. In all of these studies, the results in both populations were similar to each other. Therefore, the evaluation of the efficacy of baricitinib in Japanese patients with RA is feasible on the basis of the results of multi-regional Phase III studies.

Table 52. ACR20 responder rates in entire subjects and Japanese subjects in multi-regional Phase III studies (mITT population)[a)]

	Entire subjects	Japanese subjects
JADZ		
4 mg alone	76.7 (122/159)	72.4 (21/29)
4 mg + MTX	78.1 (168/215)	71.8 (28/39)
MTX alone	61.9 (130/210)	69.4 (25/36)
JADV		
4 mg	69.6 (339/487)	66.7 (62/93)
Adalimumab	61.2 (202/330)	60.3 (38/63)
Placebo	40.2 (196/488)	34.4 (32/93)
JADX		
2 mg	65.9 (151/229)	83.3 (5/6)
4 mg	61.7 (140/227)	100.0 (7/7)
Placebo	39.5 (90/228)	50.0 (4/8)
JADW		
2 mg	48.9 (85/174)	50.0 (3/6)
4 mg	55.4 (98/177)	75.0 (6/8)
Placebo	27.3 (48/176)	50.0 (3/6)

% (number of subjects)
a) NRI

PMDA's view:
The superiority of baricitinib 4 mg over placebo in the ACR20 responder rate at Week 12 was verified in the JADV, JADX, and JADW studies. The non-inferiority of baricitinib 4 mg alone to MTX alone in the ACR20 responder rate at Week 24 was verified in the JADZ study. The results of other efficacy endpoints tended to improve in the baricitinib 4-mg group as compared with control groups in all of these studies. Therefore, the efficacy of baricitinib 4 mg against clinical symptoms in RA patients had been demonstrated.

The JADX and JADW studies were not designed to verify the superiority of baricitinib 2 mg to placebo. The efficacy of baricitinib 2 mg on the clinical symptoms of RA tended to be lower than that of

baricitinib 4 mg. However, in both studies, the ACR20 responder rate at Week 12 tended to be higher in the 2-mg group than that in the placebo group, and other endpoints also tended to improve in the 2-mg group as compared with the placebo group. Therefore, baricitinib 2 mg is expected to have a certain degree of efficacy in treating the clinical symptoms of RA.

In addition to the above clinical study results, the results of efficacy endpoints in the Japanese subgroup were similar to those in the entire subjects in any clinical study. Therefore baricitinib is be expected to have efficacy in treating clinical symptoms in Japanese patients with RA.

7.R.1.3 Inhibitory effect on structural joint damage

The applicant's explanation about the inhibitory effect of baricitinib on the progression of joint destruction in RA patients:

In multi-regional Phase III studies, changes from baseline in mTSS at Week 24 in the baricitinib 4 mg group were evaluated as the main secondary endpoint in the JADZ and JADV studies and in an exploratory manner in the JADX study. The changes from baseline in mTSS at Week 24 in each study are shown in Table 53. A statistically significant difference was observed in the 4 mg group as compared with the placebo group in the JADV study. A statistically significant difference was also observed in the baricitinib 4-mg + MTX group as compared with the MTX alone group in the JADZ study, and changes in mTSS tended to be inhibited in the baricitinib 4-mg alone group as compared with the MTX alone group though there was no statistically significant difference between these groups. In the JADX study, changes in mTSS tended to be inhibited in the baricitinib 2- and 4-mg groups as compared to the placebo group, though evaluated in an exploratory manner. The proportions of subjects in whom progression of mTSS was not observed, as presented in Table 53, also showed a similar tendency. The cumulative distribution of changes from baseline in mTSS in each study are shown in Figure 9.

Table 53 also shows the results in the Japanese subgroup in the JADZ, JADV, and JADX studies.

All these results are thought to demonstrate the inhibitory effect of baricitinib administered alone or in combination with MTX on the progression of structural joint damage.

Table 53. Changes from baseline in mTSS at Week 24 and the number of subjects free from structural joint damage progression

	JADZ			JADV			JADX		
	4 mg alone	4 mg + MTX	MTX alone	4 mg	Adalimu-mab	Placebo	2 mg	4 mg	Placebo
Entirel subjects (mITT population)	N = 152	N = 198	N = 191	N = 470	N = 312	N = 452	N = 208	N = 198	N = 190
Change from baseline in mTSS[a)]	0.43 ± 1.18	0.32 ± 1.14	0.64 ± 1.81	0.35 ± 1.59	0.29 ± 1.47	0.84 ± 2.32	0.43 ± 1.19	0.27 ± 0.97	0.80 ± 2.86
Difference from the placebo or MTX alone group [95% CI][b)]	-0.22 [-0.52, 0.08]	-0.32 [-0.60, -0.04]	–	-0.49 [-0.73, -0.25]	–	–	-0.38 [-0.74, -0.01]	-0.55 [-0.92, -0.19]	–
≤0	115 (75.7)	160 (80.8)	130 (68.1)	382 (81.3)	258 (82.7)	318 (70.4)	149 (71.6)	159 (80.3)	141 (74.2)
≤ SDC	134 (88.2)	177 (89.4)	165 (86.4)	430 (91.5)	291 (93.3)	367 (81.2)	180 (86.5)	184 (92.9)	158 (83.2)
Japanese subgroup	N = 27	N = 37	N = 34	N = 91	N = 61	N = 90	N = 5	N = 7	N = 8
Change from baseline in mTSS[a)]	0.91 ± 1.78	0.24 ± 0.96	0.85 ± 1.38	0.35 ± 1.40	0.11 ± 0.60	1.30 ± 2.80	0.00 ± 0.35	0.79 ± 1.65	0.11 ± 0.66
Difference from the placebo or MTX alone group [95% CI][c)]	0.02 [-0.70, 0.74]	-0.62 [-1.27, 0.03]	–	-0.95 [-1.52, -0.38]	-1.27 [-1.91, -0.63]	–	0.06 [-1.69, 1.80]	0.75 [-0.53, 2.03]	–
≤0	17 (63.0)	30 (81.1)	18 (52.9)	75 (82.4)	54 (88.5)	54 (60.0)	4 (80.0)	4 (57.1)	6 (75.0)
≤ SDC	21 (77.8)	34 (91.9)	26 (76.5)	84 (92.3)	58 (95.1)	66 (73.3)	5 (100)	6 (85.7)	7 (87.5)

Mean ± standard deviation, or number of subjects (%)

a) Missing values were imputed by the linear extrapolation method. The number of subjects in each group was the number of subjects analyzed.

b) The JADZ study: an analysis of covariance model with baseline value, region, baseline status of bone erosion, and treatment group as explanatory variables
The JADV study: an analysis of covariance model with region, baseline value, baseline bone erosion score (1-2 sites and serum response positive; ≥3 sites), and treatment group as explanatory variables
The JADX study: an analysis of covariance model with baseline value, region, baseline status of bone erosion, and treatment group as explanatory variables

c) The JADZ study: an analysis of covariance model with baseline value, baseline status of bone erosion, and treatment group as explanatory variables
The JADV study: an analysis of covariance model with baseline value, baseline bone erosion score (1-2 sites and serum response positive; ≥3 sites), and treatment group as explanatory variables
The JADX study: an analysis of covariance model with baseline value, baseline status of bone erosion, and treatment group as explanatory variables

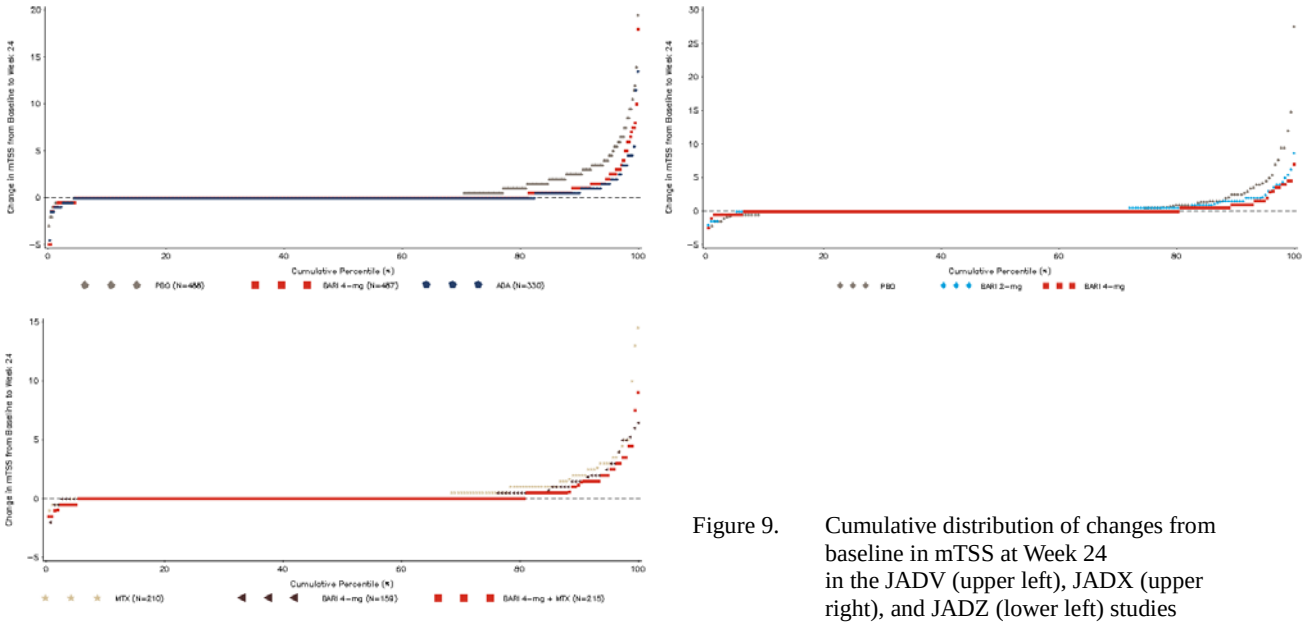

Figure 9. Cumulative distribution of changes from baseline in mTSS at Week 24 in the JADV (upper left), JADX (upper right), and JADZ (lower left) studies

PMDA's view:

Changes from baseline in mTSS tended to be lower in the 4-mg + MTX group than in the MTX alone group in the JADZ study, in the 4-mg group than in the placebo group in the JADV and JADX studies. Therefore, baricitinib 4 mg is expected to have a certain degree of inhibitory effect on structural joint

damage. In the JADX study, while the change from baseline in mTSS in the baricitinib 2-mg group tended to be low as compared to the placebo group, the proportion of subjects free from structural joint damage progression in the 2-mg group was not markedly different from that in the placebo group. These results suggested that the inhibitory effect of baricitinib 2 mg on structural joint damage may be low as compared to that of 4 mg.

Because the efficacy of baricitinib 2 mg given once daily tended to be lower than that of 4 mg given once daily, the dosing regimen should be carefully determined in light of risks and benefits of the respective doses [for dosing regimen, see Section "7.R.5 Dosage and administration"].

7.R.2 Safety

7.R.2.1 Safety summary

The applicant's explanation about the safety of baricitinib based on the pooled data of clinical studies in Japanese and non-Japanese patients with RA:

The safety of baricitinib was evaluated based mainly on the safety results from clinical studies used as evaluation data as well as the results of the pooled analyses, BARI 4-mg RA PC,[41)] BARI 2-mg vs 4-mg RA,[42)] and All BARI RA.[43)]

The summary of adverse events in these pooled analyses is shown in Table 54.

Table 54. Summary of adverse events in pooled analyses

	BARI 4-mg RA PC[a)]		BARI 2-mg vs 4-mg RA[a)]			All BARI RA[b)]
	4 mg	Placebo	2 mg	4 mg	Placebo	All doses of baricitinib in Phase II and III studies
Entire subjects	N = 997	N = 1070	N = 479	N = 479	N = 551	N = 3411
Exposure (person-year)	292.2	300.4	137.6	137.3	150.0	4210.0
Adverse events	635 (63.7)	610 (57.0)	294 (61.4)	315 (65.8)	326 (59.2)	2617 (76.7)
Serious adverse events	39 (3.9)	40 (3.7)	15 (3.1)	22 (4.6)	22 (4.0)	382 (11.2)
Adverse events leading to discontinuation	37 (3.7)	30 (2.8)	17 (3.5)	22 (4.6)	17 (3.1)	250 (7.3)
Adverse drug reactions	286 (28.7)	224 (20.9)	122 (25.5)	148 (30.9)	121 (22.0)	1339 (39.3)
Japanese subgroup	N = 132	N = 156	N = 36	N = 39	N = 63	N = 510
Exposure (person-year)	38.2	42.6	8.6	10.1	15.4	534.0
Adverse events	97 (73.5)	91 (58.3)	24 (66.7)	28 (71.8)	34 (54.0)	448 (87.8)
Serious adverse events	2 (1.5)	3 (1.9)	2 (5.6)	0	1 (1.6)	49 (9.6)
Adverse events leading to discontinuation	5 (3.8)	5 (3.2)	1 (2.8)	1 (2.6)	2 (3.2)	62 (12.2)
Adverse drug reactions	59 (44.7)	44 (28.2)	14 (38.9)	25 (64.1)	17 (27.0)	329 (64.5)

Number of subjects (%)

a) Up to Week 12 or 16

b) Data cut-off on August 10, 2015

41 A pooled analysis of data from 6 studies having a 4 mg group and a placebo group for randomization (the JADA, JADC, and JADN studies [data up to Week 12] and the JADV, JADW, and JADX studies [data up to Week 16])

42 A pooled analysis of data from 4 studies having a 2 mg group and a 4 mg group for randomization (the JADA and JADN studies [data up to Week 12] and the JADW and JADX studies [data up to Week 16])

43 A pooled analysis of data from all the dose groups receiving baricitinib in all clinical studies conducted in RA patients (data cut-off on August 10, 2015)

In the pooled analysis BARI 4-mg RA PC, the adverse event that occurred at an incidence of ≥5% in the 4 mg group was nasopharyngitis (4 mg, 5.3% [53 subjects]; placebo, 4.8% [51 subjects]). The adverse events that occurred with a higher incidence in the 4-mg group than in the placebo group were blood creatine phosphokinase increased (3.5% [35 subjects], 0.6% [6 subjects]) and hypercholesterolaemia (2.8% [28 subjects], 1.3% [14 subjects]). In the pooled analysis BARI 2-mg vs 4-mg RA, the adverse events that occurred at an incidence of ≥5% in any baricitinib group were upper respiratory tract infection (2 mg, 5.6% [27 subjects]; 4 mg, 6.5% [31 subjects]; and placebo, 4.5% [25 subjects]) nasopharyngitis (3.3% [16 subjects], 5.2% [25 subjects], and 4.7% [26 subjects]), blood creatine phosphokinase increased (2.3% [11 subjects], 5.0% [24 subjects], and 0.5% [3 subjects]), and headache (6.3% [30 subjects], 4.2% [20 subjects], and 4.0% [22 subjects]). The adverse events that occurred at a higher incidence in the 4-mg group than in the 2-mg group were blood creatine phosphokinase increased (2.3% [11 subjects], 5.0% [24 subjects], and 0.5% [3 subjects]) and aspartate aminotransferase increased (0.4% [2 subjects], 2.1% [10 subjects], and 0.7% [4 subjects]). In the pooled analysis All BARI RA (data cut-off on August 10, 2015), the adverse events that occurred at an incidence of ≥5% were nasopharyngitis (10.0% [341 subjects]), upper respiratory tract infection (8.1% [277 subjects]), bronchitis (7.5% [257 subjects]), urinary tract infection (7.4% [251 subjects]), and blood creatine phosphokinase increased (5.0% [172 subjects]).

Of all subjects receiving baricitinib, 22 died (0.6%, 0.3/100 person-years; data cut-off on September 1, 2016). The causes of deaths were cardio-respiratory arrest in 3 subjects, pneumonia in 2 subjects, and lung neoplasm malignant, adenocarcinoma pancreas, squamous cell carcinoma of lung, lung squamous cell carcinoma metastatic, myocardial infarction, circulatory collapse, basilar artery thrombosis, pulmonary embolism, cardiac arrest, coagulopathy, acute myocardial infarction, cardiac failure, respiratory failure, acute respiratory failure, death, disseminated tuberculosis, and abdominal infection in 1 subject each.

In the pooled analyses BARI 4-mg RA PC and BARI 2-mg vs 4-mg RA, there was no obvious difference in the incidence of serious adverse events between the 2- or 4-mg group and the placebo group. The serious adverse events that occurred in ≥2 subjects in any group were herpes zoster in 3 subjects, and cellulitis and coronary artery disease in 2 subjects each (4-mg group) in the pooled analysis BARI 4-mg RA PC, and pneumonia and asthma in 2 subjects each (2-mg group) and coronary artery disease in 2 subjects (4-mg group) in the pooled analysis BARI 2-mg vs 4-mg RA. In the pooled analysis All BARI RA (data cut-off on August 10, 2015), the serious adverse events that occurred in ≥10 subjects were herpes zoster and pneumonia in 20 subjects (0.6%) each, osteoarthritis in 17 subjects (0.5%), fall in 15 subjects (0.4%), and urinary tract infection in 13 subjects (0.4%).

There was no obvious difference in the incidence of adverse events leading to treatment discontinuation between the 2- or 4-mg group and the placebo group. The adverse event leading to treatment discontinuation that occurred at an incidence of ≥1% in any group was herpes zoster in any pooled

analysis (1.0% [10 subjects] in the 4-mg group and 0.3% [3 subjects] in the placebo group in the pooled analysis BARI 4-mg RA PC; 1.0% [5 subjects] in the 2 mg group, 1.0% [5 subjects] in the 4-mg group, and 0.4% [2 subjects] in the placebo group in the pooled analysis BARI 2-mg vs 4-mg RA; and 1.7% [58 subjects] in the pooled analysis All BARI RA [data cut-off on August 10, 2015]).

Safety in the Japanese subgroup was analyzed. The incidence of adverse events in the Japanese subgroup tended to be higher than that in the entire subjects in the pooled analyses BARI 2-mg vs 4-mg RA and All BARI RA (data cut-off on August 10, 2015). The incidence of adverse events leading to treatment discontinuation in the Japanese subgroup tended to be higher than in the entire subjects. This outcome was likely to be attributable to herpes zoster that occurred more frequently in the Japanese subgroup. Liver function test abnormal occurred mainly in Japanese subjects. Many of the adverse events observed in Japanese subjects were mild or moderate in severity, and there was no clear difference in safety profile between the Japanese subgroup and the entire subjects that could affect tolerability.

7.R.2.2 Adverse events that may be related to baricitinib

Taking into account the incidences of adverse events in clinical studies and the pharmacological actions of baricitinib, PMDA reviewed adverse events that may be related to baricitinib with a focus on the events summarized in the subsections below. In order to conduct a more detailed review of the safety of baricitinib 2 mg and 4 mg, PMDA asked the applicant to perform pooled analyses including long-term treatment data in addition to the 3 pooled analyses mentioned in Section "7.R.2.1 Safety summary." In response, the applicant additionally submitted the results of pooled analyses Modified Bari 4-mg RA[44)] (data cut-off on September 1, 2016) and Modified Ext BARI 2-mg vs 4-mg[45)] (data cut-off on September 1, 2016).

(a) Infection

(1) Serious infection

The applicant's explanation about the occurrence of serious infection:

The incidences of serious infection in the respective pooled analyses are shown in Table 55. In the pooled analysis BARI 2-mg vs 4-mg RA, the incidence of serious infection in the 4-mg group tended to be higher than that in the 2-mg group but was similar to that in the placebo group. In the pooled analysis Modified Ext BARI 2-mg vs 4-mg, while the incidence of serious infection in the 4-mg group tended to be higher than that in the 2-mg group, no marked increase in incidence was observed compared to the pooled analysis BARI 2-mg vs 4-mg RA. The incidence in the pooled analysis Modified 4-mg RA did not exceed the incidence in the pooled analysis BARI 4-mg RA PC or BARI 2-mg vs 4-mg RA. These

44 To remove the effect of regimens other than baricitinib 4 mg from the pooled analysis All BARI RA, data from subjects starting treatment with baricitinib 4 mg and those who had a change from placebo or other drugs to baricitinib 4 mg were combined. Data from subjects who started treatment with baricitinib at a dose other than 4 mg and underwent dose modification to 4 mg were excluded. When a subject receiving baricitinib 4 mg underwent dose modification to another dose level, data of the subject was cut off at the time point of dose modification.

45 The pooled analysis BARI 2-mg vs 4-mg RA had additional data obtained later than the placebo-control period and data from the long-term treatment study (the JADY study). Data obtained at and after Week 24 in the JADA study and at and after Week 12 in the JADN study, which did not have a 2-mg group, were excluded.

results suggest no possibility of an increase in the exposure-adjusted incidence of serious infection with increased duration of administration.

Table 55. Exposure-adjusted incidences of serious infection in pooled analyses

	BARI 4-mg RA PC[a)]		BARI 2-mg vs 4-mg RA[a)]			Modified Ext BARI 2-mg vs 4-mg[b)]		Modified 4-mg RA[b)] (N = 2658)	ALL BARI-RA[b)] (N = 3492)
	4-mg (N = 997)	Placebo (N = 1070)	2-mg (N = 479)	4-mg (N = 479)	Placebo (N = 551)	2-mg (N = 479)	4-mg (N = 479)		
Number of subjects (%)	11 (1.1)	13 (1.2)	5 (1.0)	7 (1.5)	7 (1.3)	18 (3.8)	29 (6.1)	140 (5.3)	194 (5.6)
Incidence rate per 100 person-years [95% CI]	3.76 [1.88, 6.74]	4.33 [2.30, 7.40]	3.64 [1.18, 8.50]	5.09 [2.05, 10.48]	4.67 [1.88, 9.62]	3.27 [1.94, 5.17]	5.45 [3.59, 7.93]	3.04 [2.55, 3.58]	2.94 [2.54, 3.39]

a) Up to Week 16
b) Data cut-off on September 1, 2016

Table 56 shows the exposure-adjusted incidences of serious infection by ethnicity and by age in the pooled analyses Modified Ext BARI 2-mg vs 4-mg and Modified 4-mg RA. The incidence of serious infection in the Asian subgroup of the 4-mg group was higher than that in other ethnic groups in the pooled analysis Modified Ext BARI 2-mg vs 4-mg. However, no marked difference was observed in the incidence of serious infection among ethnic groups in the pooled analysis Modified 4-mg RA. In the pooled analysis Modified 4-mg RA, the incidence of serious infection in the Japanese subgroup of the 4-mg group was largely similar to that in the Asian subgroup or the entire subjects.

When subjects were stratified by age (≥65 years, <65 years) in the pooled analysis Modified 4-mg RA, the incidence of serious infection was higher in those aged ≥65 years. Since elderly people are generally susceptible to infection, this may have been reflected in the higher incidence of serious infection in elderly subjects than in non-elderly subjects in clinical studies of baricitinib (*Ann Rheum Dis*. 2011;70:1914-20, *Mod Rheumatol*. 2014;24:572-9).

Table 56. Exposure-adjusted incidences of serious infection by age and by ethnicity

	Modified Ext BARI 2-mg vs 4-mg[a)]		Modified 4-mg RA[a)]
	2 mg	4 mg	
<65 years	12/397 (3.0) 2.66 [1.37, 4.64]	22/392 (5.6) 5.57 [3.49, 8.44]	94/2179 (4.3) 2.45 [1.98, 3.00]
≥65 years	6/82 (7.3) 5.96 [2.19, 12.97]	5/87 (5.7) 4.95 [1.61, 11.54]	46/479 (9.6) 5.90 [4.32, 7.87]
Japanese	2/36 (5.6) 8.48 [1.03, 30.62]	2/39 (5.1) 8.50 [1.03, 30.72]	23/407 (5.7) 3.54 [2.24, 5.31]
Asian (including Japanese)	6/102 (5.9) 5.62 [2.06, 12.23]	12/101 (11.9) 13.82 [7.14, 24.13]	45/698 (6.4) 4.11 [3.00, 5.50]
Caucasian	11/340 (3.2) 2.71 [1.35, 4.84]	13/332 (3.9) 3.54 [1.89, 6.06]	81/1729 (4.7) 2.59 [2.06, 3.22]
Other	1/37 (2.7) 2.57 [0.07, 14.33]	2/42 (4.8) 5.06 [0.61, 18.26]	13/226 (5.8) 3.39 [1.81, 5.80]

Upper, number of subjects (%); lower, incidence rate (100 person-years) [95% CI]
a) Data cut-off on September 1, 2016

In the JADV study, there was no obvious difference among the 4-mg, adalimumab, and placebo groups in the incidence of serious infection up to Week 24. The incidences of serious infection up to Week 52

in the JADV and JADZ studies are presented in Table 57, showing that the incidence in any baricitinib group was not substantially higher than that in the adalimumab group or the MTX alone group. Moreover, according to published papers on clinical studies of other drugs in RA patients, the incidence rates of serious infection were 0.8 to 3.79 per 100 person-years in patients receiving cDMARDs, 2.68 to 18.1 per 100 person-years in patients receiving TNF inhibitors, and 0 to 5.2 per 100 person-years in patients receiving biological drugs other than TNF inhibitors. These results suggest that the risk of serious infection in patients receiving baricitinib is lower than the historical incidence rates of the disease in RA patients receiving other antirheumatic drugs.

Table 57. Exposure-adjusted incidences of serious infection in the JADV and JADZ studies (by Week 52 or before change to baricitinib 4 mg due to inadequate efficacy)

	JADV		JADZ		
	4 mg (N = 487)	Adalimumab (N = 330)	4 mg alone (N = 159)	4 mg + MTX (N = 215)	MTX alone (N = 210)
Number of subjects (%)	10 (2.1)	5 (1.5)	6 (3.8)	5 (2.3)	8 (3.8)
Incidence rate (per 100 person-years) [95% CI]	2.29 [1.10, 4.21]	1.79 [0.58, 4.19]	4.13 [1.51, 8.98]	2.61 [0.85, 6.10]	4.61 [1.99, 9.08]

The pooled analysis All BARI RA (data cut-off on August 10, 2015) identified suspected opportunistic infection in 10 subjects[46)] (oesophageal candidiasis in 5 subjects, pneumocystis pneumonia in 3 subjects, and wound infection with *Coccidioides* and Blood beta-D-glucan increased in 1 subject each). Pneumocystis pneumonia in 3 subjects, who were all Japanese women, was diagnosed by computed tomographic (CT) images of the chest and slightly increased beta-D-glucan, and was either asymptomatic or mild.

Baricitinib's inhibitory effect on the JAK-STAT pathway may affect the immune response, and serious infection occurred in clinical studies of baricitinib as often as in clinical studies of other antirheumatic drugs. The applicant therefore will remind healthcare professionals of the importance of close attention to possible onset or worsening of infection during treatment with baricitinib and careful treatment of patients with risk factors for infection.

PMDA views on the risk of baricitinib causing serious infection:
The action mechanism of baricitinib suggest that its immunosuppressive action may cause infection. In clinical studies, a certain number of subjects experienced serious infections including opportunistic infection, and some had a fatal outcome. The incidence of serious infection in the 4-mg group was not markedly higher than that in the placebo, adalimumab, or MTX alone group. The incidence of serious infection in the pooled analyses was largely similar to the incidences in clinical studies of other drugs in RA patients as reported in published papers. However, in the pooled analysis Modified Ext BARI 2-mg vs 4-mg, the incidence rate of serious infection tended to be high in the 4-mg group (5.45 per 100 person-years) as compared to the 2-mg group (3.27 per 100 person-years), being particularly high in the

[46] After a detailed assessment, the number of affected subjects was revised from 16 to 10.

Asian subgroup of the 4-mg group including Japanese subjects (13.82 per 100 person-years). These results suggest that baricitinib may increase the risk of serious infection in a dose-dependent manner.

Based on the above, the risk of serious infection caused by baricitinib is considered to be similar to that caused by other JAK activity inhibitors and biological drugs used for treating RA. Therefore, stringent safety measures should be taken against the potential risk of serious infection when using baricitinib similarly to these drugs. Because of a small number of subjects evaluated in the clinical studies and uncertainty about whether long-term use of baricitinib will increase the risk and about differences in such risk between baricitinib and the similar drugs, the occurrence of serious infection during treatment with baricitinib in its clinical use, including in long-term use, should be further investigated through post-marketing surveillance. New findings should be communicated to healthcare professionals accordingly.

(2) Herpes zoster

The applicant's explanation about the occurrence of herpes zoster:

The incidences of herpes zoster calculated by pooled analyses are shown in Table 58. In the pooled analyses BARI 4-mg RA PC and BARI 2-mg vs 4-mg RA, herpes zoster tended to occur more frequently in the 4-mg group than in the placebo group. In the pooled analyses including the long-term treatment data, Modified Ext BARI 2-mg vs 4-mg and Modified 4-mg RA, no trend towards an increase in the exposure-adjusted incidence of herpes zoster was identified. In the pooled analysis All BARI RA (data cut-off on September 1, 2016), herpes zoster was found in 212 subjects. The event was mild or moderate in most subjects affected but serious in 27 of the 212 subjects. Herpes zoster occurred with nerve paralysis in 4 subjects (0.1%), with dissemination of lesions outside the primary or adjacent dermatomes in 18 subjects (0.5%), but with no internal organ dissemination in any subjects. The incidences of herpes zoster in the JADZ and JADV studies[47)] are presented in Table 59, showing that the incidence in the baricitinib group was higher than that in the adalimumab or MTX alone group.

In the pooled analysis All BARI RA (data cut-off on September 1, 2016), the incidence rate of herpes zoster in the Japanese subgroup was 6.5 per 100 person-years and was higher than that in the entire population. The incidences of herpes zoster in the entire population and the Japanese subgroup in the JADZ and JADV studies are presented in Table 59, showing that the incidence in the Japanese subgroup was higher than that in the entire population.

The above results may have reflected a general tendency towards frequent herpes zoster in Japanese patients with RA, which was supported by the following results: (1) in Phase III studies of tofacitinib, a drug with an inhibitory effect on JAK activity, the incidence rate of herpes zoster in Asian subjects was 7.7 per 100 person-years (9.2 per 100 person-years in Japanese and Korean subjects), which was ≥2-fold the corresponding incidence rates in Western subjects, which were 2.7 to 3.7 per 100 person-years (*Arthritis Rheumatol*. 2014;66:2675-84); and (2) in clinical studies of baricitinib, while the incidence

[47] Up to Week 52 or before change to baricitinib 4 mg due to inadequate efficacy

rate of herpes zoster in Japanese subjects in the baricitinib group tended to be higher than that in non-Japanese subjects, that in Japanese subjects in the MTX alone or adalimumab group was also high compared to non-Japanese subjects.

Accordingly, the risk for causing herpes zoster will be highlighted in the package insert.

Table 58. Exposure-adjusted incidences of herpes zoster in pooled analyses

	BARI 4-mg RA PC[a)]		BARI 2-mg vs 4-mg RA[a)]			Modified Ext BARI 2-mg vs 4-mg[b)]		Modified 4-mg RA[b)] (N = 2658)	ALL BARI RA[b)] (N = 3492)
	4 mg (N = 997)	Placebo (N = 1070)	2 mg (N = 479)	4 mg (N = 479)	Placebo (N = 551)	2 mg (N = 479)	4 mg (N = 479)		
Number of subjects (%)	18 (1.8)	4 (0.4)	6 (1.3)	10 (2.1)	2 (0.4)	15 (3.1)	20 (4.2)	146 (5.5)	212 (6.1)
Incidence rate per 100 person-years [95% CI]	4.32 [2.56 ,6.82]	0.99 [0.27, 2.53]	3.11 [1.14, 6.76]	5.18 [2.48, 9.52]	1.02 [0.12, 3.68]	2.72 [1.52, 4.49]	4.02 [2.45, 6.20]	3.18 [2.68, 3.74]	3.22 [2.80, 3.68]

a) Up to Week 24
b) Data cut-off on September 1, 2016

Table 59. Incidence of herpes zoster in the JADZ and JADV studies (up to Week 52)

	JADZ			JADV	
	4 mg alone	4 mg + MTX	MTX alone	4 mg	Adalimumab
Entire population	2.5 (4/159)	2.3 (5/215)	1.0 (2/210)	2.3 (11/487)	1.5 (5/330)
Japanese subgroup	10.3 (3/29)	7.7 (3/35)	5.6 (2/36)	5.4 (5/93)	3.2 (2/63)

% (number of subjects)

PMDA's view:

The incidence of herpes zoster increased dose-dependently, and was higher in the 4-mg group than that in the MTX alone or adalimumab group. In addition, the incidence of herpes zoster in Japanese patients tends to be high as compared to non-Japanese patients. Therefore, healthcare professionals should be reminded of the importance of the signs and symptoms of reactivation of viruses such as herpesvirus during treatment with baricitinib and appropriate measures taken for such signs and symptoms as with its analogues with an inhibitory effect on JAK activity. The occurrence of herpes zoster during treatment with baricitinib, including in its long-term use, should be further investigated through post-marketing surveillance, and any new findings should be communicated to healthcare professionals accordingly.

(3) Viral reactivation

The applicant's explanation about the occurrence of reactivation of viruses including hepatitis B virus (HBV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV):

In Phase III studies, an HBV test was performed during the screening period to ascertain whether candidate subjects met the exclusion criteria[48)] for the studies. In 4 Phase III studies (the JADV, JADX, JADW, and JADZ studies), HBV DNA was detected in 16 of 227 subjects treated with baricitinib who tested positive for the HBV antibody during at screening and underwent HBV DNA measurement during

48 Patients who fell under any of the following criteria were excluded: (1) hepatitis B surface antigen (HBsAg) positive; (2) hepatitis B core antibody (HBcAb) positive and hepatitis B surface antibody (HBsAb) negative; (3) in some participating countries, HBsAb-positive and HBV deoxyribonucleic acid (DNA) positive [in Japan, (1) HBsAg-positive; (2) HBcAb-positive and/or HBsAb-positive and HBV DNA-positive]

the study period. A total of 3 of the 16 subjects exhibited HBV DNA levels of 31 IU/mL, 36 IU/mL, and 257 IU/mL, respectively, which were all higher than the lower limit of quantitation (<29 IU/mL), and received treatment with antiviral agents. In the JADV study, HBV DNA was detected in 1 subject for whom regimen was changed to baricitinib 4 mg because of inadequate efficacy. HBV DNA was detected only once in most of these subjects, and there were no cases of obvious reactivation of HBV. Although CMV infection was reported in 1 subject (woman aged 4[redacted] years) in the JADY study and EBV infection in 1 subject (man, aged 6[redacted] years) in the JADV study, both subjects continued to receive baricitinib 4 mg and the outcomes of both events were assessed as resolved.

The limited number of cases reported and data on patient characteristics available preclude a conclusion on the relationship between viral reactivation and baricitinib. However, considering the pharmacological actions of baricitinib and advice given for the use of similar drugs, healthcare professionals will be reminded of the importance of screening prior to treatment with baricitinib and careful administration of the drug to patients carrying a virus or have a history of viral infection.

PMDA's view:
HBV carriers and patients infected with HBV, who were HBV DNA-positive, were excluded from clinical studies. Therefore, during the study period, there were no cases of continuous HBV DNA detection or *de novo* hepatitis B induced by HBV reactivation, but HBV DNA was detected from some patients treated with baricitinib. The mechanism of action of baricitinib, the incidence of herpes zoster in clinical studies, and the occurrence of CMV-infection and EBV-infection in subjects suggest the possibility that baricitinib may trigger the reactivation of viruses including HBV. Therefore, the possibility of viral reactivation and the importance of screening and monitoring in the use of baricitinib should be communicated well to healthcare professionals, as practiced for other JAK activity inhibitors. Given the limited number of subjects evaluated in the clinical studies, the risk of viral reactivation during treatment with baricitinib, including in its long-term use, must be further investigated in post-marketing surveillance. These viruses are suggested to be associated with not only infections but also malignant tumors. A relationship between viral reactivation following treatment with baricitinib and the development of malignant tumors should also be investigated in post-marketing surveillance.

(4) Tuberculosis

The applicant's explanation about the occurrence of tuberculosis:
In the pooled analysis All BARI RA, tuberculosis infection was found in a total of 9 subjects (in 7 subjects by the date of data cut-off, January 1, 2016, and in 2 subjects through the individual case safety report by April 26, 2016). All these subjects belonged to the 4-mg group. The incidence rate of tuberculosis was 0.14 per 100 person-years in the pooled analysis All BARI RA and 0.44 per 100 person-years in the pooled analysis Modified 4-mg RA. In the JADV study, tuberculosis was found in 1 subject in the adalimumab group, and its incidence rate was 3.6 per 100 person-years.

Of 7 subjects who were found to have tuberculosis in the pooled analysis All BARI RA (data cut-off on January 1, 2016), 4 subjects had extrapulmonary tuberculosis and 1 subject had miliary tuberculosis. Reports on the 9 affected subjects including 2 subjects found through the individual case safety report were all from regions with a high incidence of tuberculosis (Argentina, Taiwan, Russia, South Korea, India, and South Africa). The incidence rates (per 100 person-years) of tuberculosis in RA patients in these regions are 0.10 to 0.24 in Argentina, 0.20 to 0.49 in Taiwan, 0.34 to 0.84 in Russia, 0.34 to 0.86 in South Korea, 0.67 to 1.67 in India, and 3.34 to 8.34 in South Africa, which were not markedly different from the rates of tuberculosis in the clinical studies (*Arthritis Rheum*. 2009;61(3):300-304). All the subjects who experienced tuberculosis received cDMARDs concomitantly and 4 of them also received steroids.

The above observations preclude a clear conclusion on a relationship between the onset of tuberculosis and baricitinib. However, in light of the action mechanism of baricitinib, as practiced for the use of similar drugs, the importance of checking for tuberculosis prior to treatment and non-use of baricitinib in patients with active tuberculosis will be highlighted in the package insert.

PMDA's view:
Tuberculosis infection was observed in the 4-mg group, and active tuberculosis was reported in some subjects receiving baricitinib who tested negative for tuberculin, etc. Furthermore, its action mechanism suggest a possibility that baricitinib may cause tuberculosis by extensively inhibiting key cytokines involved in the prevention of tuberculosis infection. Therefore, the use of baricitinib requires close attention to the onset of tuberculosis as practiced in the use of other JAK activity inhibitors and biological drugs for RA. In other words, healthcare professionals should be reminded of the importance of screening for tuberculosis before starting treatment and cooperation with physicians experienced in the treatment of infections including tuberculosis to adhere to the safety measures for baricitinib as per the practice in the use of the similar drugs. The occurrence of tuberculosis during treatment with baricitinib, including in its long-term use, should be further investigated in post-marketing surveillance, and any new findings should be communicated appropriately to healthcare professionals.

(b) Malignant tumor

The applicant's explanation about the occurrence of malignant tumors:
The incidence rates of malignant tumors excluding nonmelanoma skin cancers (NMSCs) in pooled analyses are shown in Table 60. In the pooled analysis Modified Ext BARI 2-mg vs 4-mg RA, while the point estimate of the incidence of non-NMSC malignant tumors in the 4-mg group was higher than in the 2- mg group, the rate was extremely low in both groups with 95% confidence intervals that largely overlapped. The incidences of non-NMSC malignant tumors that occurred by Week 52 in the JADZ study are shown in Table 61. There was no marked difference in the incidences of non-NMSC malignant tumors between any baricitinib group and the adalimumab or MTX alone group.

In the pooled analysis of All BARI RA (data cut-off on August 10, 2015), NMSCs occurred in 17 subjects (0.5%), and the NMSCs that occurred in ≥3 subjects were basal cell carcinoma in 10 subjects and squamous cell carcinoma in 5 subjects. Later, by data cut-off on January 1, 2016, NMSCs were reported in 2 subjects (basal cell carcinoma and squamous cell carcinoma in 1 subject each).

In all the clinical studies (data cut-off on January 1, 2016) included in the data package for application, lymphoproliferative disorder was reported in 3 subjects, consisting of 2 subjects in the baricitinib group and 1 subject in the adalimumab group.

Table 60. Incidences of non-NMSC malignant tumors in pooled analyses

	BARI 4-mg RA PC[a)]		Modified Ext BARI 2-mg vs 4-mg RA[b)]		Modified 4-mg RA[b)] (N = 2658)	All BARI RA[b)] (N = 3492)
	4 mg (N = 997)	Placebo (N = 1070)	2 mg (N = 479)	4 mg (N = 479)		
Number of subjects (%)	2 (0.2)	2 (0.2)	3 (0.6)	6 (1.3)	37 (1.4)	52 (1.5)
Incidence rate per 100 person-years [95% CI]	0.48 [0.06, 1.72]	0.49 [0.06, 1.78]	0.53 [0.11, 1.56]	1.19 [0.44, 2.58]	0.79 [0.55, 1.08]	0.77 [0.58, 1.01]

a) Up to Week 24
b) Data cut-off on September 1, 2016

Table 61. Exposure-adjusted incidences of non-NMSC malignant tumors in the JADV and JADZ studies (by Week 52 or before change to baricitinib 4 mg due to inadequate efficacy)

	JADV		JADZ		
	4 mg (N = 487)	Adalimumab (N = 330)	4 mg alone (N = 159)	4 mg + MTX (N = 215)	MTX alone (N = 210)
Number of subjects (%)	3 (0.6)	0	1 (0.6)	3 (1.4)	1 (0.5)
Incidence rate per 100 person-years [95% CI]	0.68 [0.14, 2.00]	0	0.68 [0.02, 3.79]	1.55 [0.32, 4.53]	0.57 [0.01, 3.18]

The incidences of non-NMSC malignant tumors by treatment period in the pooled analysis All BARI RA (data cut-off on September 1, 2016) are shown in Table 62. Although the number of subjects evaluated in clinical studies was limited, there was no trend towards an increase in the incidence of non-NMSC malignant tumors with the increased treatment period with baricitinib.

Table 62. Incidences of non-NMSC malignant tumors by treatment period in the pooled analysis All BARI RA (Data cut-off on September 1, 2016)

	All (N = 3492)	Weeks 0-24 (N = 3492)	Weeks 24-48 (N = 3162)	Weeks 48-72 (N = 2818)	Weeks 72-96 (N = 2380)	Weeks 96-120 (N = 1999)	Weeks 120-144 (N = 1429)	>Week 144 (N = 707)
Number of subjects (%)	52 (1.5)	7 (0.2)	10 (0.3)	12 (0.4)	7 (0.3)	5 (0.3)	10 (0.7)	1 (0.1)
Incidence rate per 100 person-years [95% CI]	0.77 [0.58, 1.01]	0.46 [0.18, 0.94]	0.74 [0.35, 1.36]	1.00 [0.52, 1.74]	0.69 [0.28, 1.43]	0.62 [0.20, 1.44]	2.09 [1.00, 3.84]	0.28 [0.01, 1.54]

In observational studies, the incidence rates of non-NMSC malignant tumors were 0.67 to 1.77 per 100 person-years in RA patients treated with MTX in combination with other cDMARDs or biological drugs and 0.74 to 1.30 per 100 person-years in RA patients treated with TNF inhibitors and other biological drugs. In the pooled analysis All BARI RA (data cut-off on August 10, 2015) (number of subjects evaluated, 3469 subjects; observation person-year, 4304 person-years), the incidence rate of non-NMSC malignant tumors, 0.72 per 100 person-years, did not exceed that in observational studies or other

clinical studies (*Ann Rheum Dis*. 2009;68:1819-26, *Arthritis Rheum*. 2007;56:2886-95, etc.). Using the Surveillance Epidemiology and End Result (SEER) program, the age- and sex-adjusted standardized incidence rate (SIR) of non-NMSC malignant tumors [95% CI] in the pooled analysis All BARI RA was 0.96 [0.67, 1.35]. The SIR [95% CI] of non-NMSC malignant tumors in the pooled analysis Ext BARI 2-mg vs 4-mg RA (data cut-off on August 10, 2015) was 1.30 [0.42, 3.02] in the 4-mg group and 0.59 [0.071, 2.14] in the 2-mg group. Meanwhile, the SIR of non-NMSC malignant tumors in RA patients receiving existing antirheumatic drugs was 1.05 [1.01, 1.09] (*Arthritis Res Ther*. 2008;10:R45) and that in RA patients receiving biological drugs was 1.0 [1.0, 1.1] (*Arthritis Rheum*. 2007;56:2886-95). These results showed that the SIR of non-NMSC malignant tumors in pooled analyses of clinical study data of baricitinib was not markedly different from that in RA patients receiving existing antirheumatic drugs.

As shown above, there was no trend towards increased incidence of non-NMSC malignant tumors in patients receiving baricitinib as compared to those receiving other eDMARDs or biological drugs. However, the incidence of non-NMSC malignant tumors in patients receiving baricitinib is expected to be similar to that in patients receiving existing antirheumatic drugs, and this will be highlighted in the package insert of baricitinib as practiced for the similar drugs and biological drugs for RA.

PMDA's view:

Given the limited observation period in clinical studies, currently available data is not sufficient enough to come to a conclusion on the risk of baricitinib causing malignant tumors. As shown in Table 62, there was no trend towards increased incidence of non-NMSC malignant tumors with increased treatment duration. The incidences of malignant tumors in clinical studies were not markedly different from those in RA patients treated with existing drugs. However, the pooled analysis Modified Ext BARI 2-mg vs 4-mg RA revealed that malignant tumors occurred in 6 of 479 subjects (1.19 per 100 person-years) in the 4-mg group, which was more frequent than in the 2-mg group (3 of 479 subjects [0.53 per 100 person-years]), and that NMSCs also occurred at a certain rate. In light of these results and the pharmacological action of baricitinib, the possibility remains that baricitinib may induce malignant tumors, as with the similar drugs and biological drugs for RA. In addition, lymphoproliferative disorders are known to occur in overly immunosuppressed patients. While a dose-dependent increase in the incidence of lymphoproliferative disorder was not observed in the clinical studies, there was a trend towards a dose-dependent increase in serious infection that may have been related to an immunosuppressive action. Therefore, the possibility cannot be rule out that lymphoproliferative disorders occur more frequently in patients receiving baricitinib in combination with an antirheumatic drug or steroid. The potential risk of baricitinib for causing malignant tumor and lymphoproliferative disorder should be communicated well to healthcare professionals, as practiced for similar JAK activity inhibitors. The package insert of baricitinib should also warn of the risk of malignant tumors, as practiced for the similar drugs and existing biological drugs for RA. In addition, the relationship between baricitinib and malignant tumors or lymphoproliferative disorder must be investigated through a long-term survey that allows a comparison with existing drugs, to continue to pay attention to such risks.

(c) Gastrointestinal perforation

The applicant's explanation about the occurrence of gastrointestinal perforation:

Gastrointestinal perforation is a serious adverse event that is infrequently reported in patients with RA (*Arthritis Rheum*. 2011;63:346-51, *Ann Rheum Dis*. 2014;73:252-5). Known risk factors for the event include the use of steroids or NSAIDs, concurrent diverticulitis, aging, and coexisting severe diseases.

In pooled analyses BARI 4-mg RA PC and BARI 2-mg vs 4-mg RA, there were no events corresponding to the Preferred Terms falling under the Standardised MedDRA Queries (SMQ) of gastrointestinal perforation by Week 16. In the pooled analysis All BARI RA (data cut-off on January 1, 2016; 3492 subjects), events corresponding to the Preferred Terms falling under the SMQ of gastrointestinal perforation were reported in 6 subjects (0.2%; abdominal wall abscess in 2 subjects and diverticular perforation, ruptured appendix, anal abscess, and rectal abscess in 1 subject each). Of these, 2 subjects were confirmed to have gastrointestinal perforation (diverticular perforation and ruptured appendix in 1 subject each). Both events were serious but resolved. The exposure-adjusted incidence rate (EAIR) of gastrointestinal perforation was 0.04 per 100 person-years, which was not markedly different from that in RA patients (0.17 per 100 person-years) *(Arthritis Care Res*. 2012;64:1819-28), in patients receiving a similar drug (0.13 per 100 person-years) (*J Rheumatol*. 2014;41:837-52), in patients receiving biological drugs without steroids (0.05 per 100 person-years), or in patients receiving biological drugs in combination with steroids (0.11 per 100 person-years) (*Arthritis Rheum*. 2011;63:346-51).

PMDA's view:

Gastrointestinal perforation is a serious event that can lead to a fatal outcome. An increase in the incidence of lower gastrointestinal perforation was suggested in RA patients treated with tocilizumab (genetical recombination) or tofacitinib, an IL-6-mediated signal transduction inhibitor similar to baricitinib (*Arthritis Rheumatol*. 2016;68:2612-7). NSAIDs and steroids are frequently used in RA patients and are thus known to have a risk for causing gastrointestinal perforation. The risk can be enhanced when baricitinib is used in combination with these drugs. Therefore, baricitinib should be administered carefully to patients with colonic diverticulitis, a suspected risk factor for gastrointestinal perforation. This should also be mentioned in the "Careful Administration" section of the package insert, as practiced for tocilizumab (genetical recombination) and tofacitinib. Given a small number of subjects evaluated in the clinical studies and limited data on increased risk for gastrointestinal perforation during long-term treatment, further data collection through post-marketing surveillance is essential to understand the characteristics of patients who may suffer gastrointestinal perforation and to investigate the occurrence of the event during treatment with baricitinib, including in its long-term use. New findings should be communicated to healthcare professionals appropriately.

(d) Interstitial lung disease

The applicant's explanation about the occurrence of interstitial lung disease:

The incidences of interstitial lung disease and pulmonary fibrosis calculated in pooled analyses are shown in Table 63. Serious events occurred in 5 (including 3 Japanese) subjects treated with baricitinib

4 mg in any clinical study of baricitinib, and their outcomes were all assessed as resolved or resolving. In many cases, a prior disease or concomitant drug could be a contributory factor. The incidence rates of interstitial lung disease and pulmonary fibrosis in the pooled analysis All BARI RA (data cut-off on January 1, 2016) were lower than those reported in published papers (0-4.7 per 100 person-years) (Curtis et al. *Arthritis Res Ther*. 2015;17:319) or from clinical studies on other antirheumatic drugs (<0.1%-1.0%) (Review Report of Xeljanz Tablets 5 mg dated February 28, 2013).

Based on the above, baricitinib is unlikely to increase the risk of interstitial lung disease or pulmonary fibrosis.

Table 63. Incidences of interstitial lung disease and pulmonary fibrosis in pooled analyses

		BARI 4-mg RA PC[a)]		BARI 2-mg vs 4-mg RA[a)]			All BARI RA[b)]
		4 mg (N = 997)	Placebo (N = 1070)	2 mg (N = 479)	4 mg (N = 479)	Placebo (N = 551)	All doses of baricitinib in Phase I to III studies (N = 3492)
Interstitial lung disease	Adverse event	2 (0.20) 0.49 [0.06, 1.76]	0	0	0	0	10 (0.29) 0.19 [0.09, 0.36]
	Adverse event leading to discontinuation	0	0	0	0	0	2 (0.06) 0.04 [0.00, 0.14]
	Serious adverse event	0	0	0	0	0	2 (0.06) 0.04 [0.00, 0.14]
Pulmonary fibrosis	Adverse event	0	0	0	0	0	3 (0.09) 0.06 [0.01, 0.17]
	Adverse event leading to discontinuation	0	0	0	0	0	0
	Serious adverse event	0	0	0	0	0	0

Upper, N (%); lower, incidence rate per 100 person-years [95% CI]
a) Up to Week 24
b) Data cut-off on January 1, 2016

PMDA's view:

Interstitial lung disease and pulmonary fibrosis occurred in some subjects in clinical studies, and Japanese patients with RA suffered serious events. Because the possibility cannot be ruled out that such risk may be enhanced by the combination of baricitinib with other antirheumatic drugs, healthcare professionals should be informed of the potential risk for interstitial lung disease in patients treated with baricitinib. Drug-induced lung injury occurred more frequently in Japanese patients than in non-Japanese patients (*Guidelines for Diagnosis and Management of Drug-induced Lung Injury*. first ed. Medical Review Co., Ltd.; 2012:7-10). Given that the number of Japanese subjects and the duration of evaluation in clinical studies were insufficient to assess the risk for causing interstitial lung disease, the investigation on interstitial lung disease occurring during treatment with baricitinib including in its long-term use is essential through post-marketing surveillance. New findings should be communicated to healthcare professionals appropriately.

(e) Abnormal lipid and cardiovascular events

The applicant's explanation about abnormal lipid and cardiovascular events:

In RA patients treated with antirheumatic drugs such as tofacitinib, an analogue of baricitinib (*Arthritis Rheumatol*. 2015;67:117-27), tocilizumab (genetical recombination) (*Nat Rev Rheumatol*. 2013;9:513-23), or MTX (*Arthritis Rheum*. 2013;65:1430-8), increased total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were observed. Furthermore, RA patients were at high risk of a cardiovascular disease associated with accelerated inflammation-induced atherosclerosis (*J Rheumatol*. 2011;38:1601-6, *Rheum Dis Clin North Am*. 2014;40:27-49). Because elevated lipid level was observed in the clinical studies of baricitinib, association of changes in lipid levels with cardiovascular events was investigated to clarify the effects of baricitinib in RA patients.

The time courses of LDL cholesterol, HDL cholesterol, and triglyceride levels in the 4-mg group in 3 Phase III studies (the JADV, JADX, and JADW studies) and the JADY study, a long-term treatment study, are presented in Figure 10. LDL and HDL cholesterol levels increased within 12 weeks of the start of treatment with baricitinib and remained high afterward. Triglyceride increased within 12 weeks from the start of treatment with baricitinib and decreased afterward.

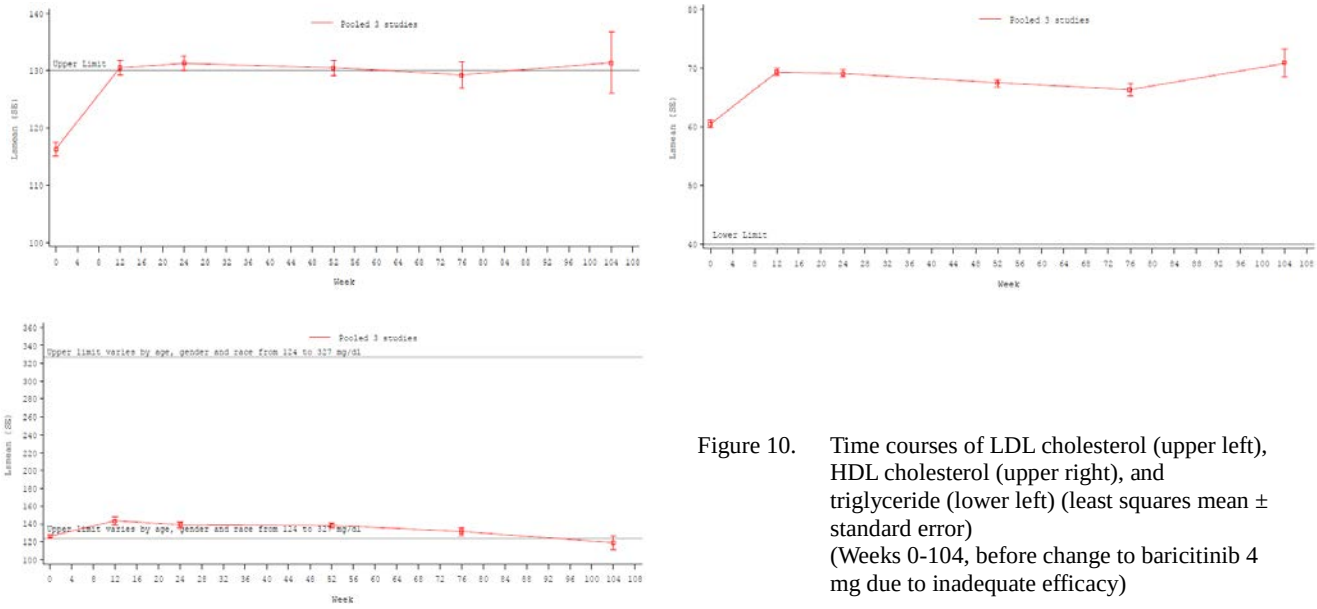

Figure 10. Time courses of LDL cholesterol (upper left), HDL cholesterol (upper right), and triglyceride (lower left) (least squares mean ± standard error)
(Weeks 0-104, before change to baricitinib 4 mg due to inadequate efficacy)

The incidences of hyperlipidemia-related adverse events (e.g., hypercholesterolaemia, hyperlipidaemia, and dyslipidaemia) in pooled analyses are shown in Table 64. While the incidence in the 4-mg group tended to be higher than that in the placebo or 2-mg group, there were no serious events or events leading to treatment discontinuation. The incidence of hyperlipidemia-related adverse events in the Japanese subgroup was 11.1% (4 subjects) in the 2-mg group, 23.1% (9 subjects) in the 4-mg group, 3.2% (2 subjects) in the placebo group in the pooled analysis BARI 2-mg vs 4-mg RA, and 15.2 per 100 person-years in the pooled analysis All BARI RA (data cut-off on August 10, 2015), tending to be high as compared to the entire subjects.

Table 64. Hyperlipidemia-related adverse events in pooled analyses

	BARI 4-mg RA PC[a)]		BARI 2-mg vs 4-mg RA[a)]			All BARI RA[b)]
	4 mg (N = 997)	Placebo (N = 1070)	2 mg (N = 479)	4 mg (N = 479)	Placebo (N = 551)	All doses of baricitinib in Phase I to III studies (N = 3464)
≥1 adverse event	69 (6.9) 23.6 [18.4, 29.9]	37 (3.5) 12.3 [8.7, 17.0]	20 (4.2) 14.6 [8.9, 22.5]	37 (7.7) 26.9 [18.9, 37.1]	23 (4.2) 15.3 [9.7, 23.0]	370 (10.7) 8.8 [7.9, 9.7]
Serious adverse event	0	0	0	0	0	0
Adverse event leading to discontinuation	0	0	0	0	0	0

Upper, number of subjects (%); lower, incidence rate per 100 person-years [95% CI]
a) Up to Week 16
b) Data cut-off on August 10, 2015

The incidences of MACE and other cardiovascular events in pooled analyses were assessed by the external clinical endpoint committee (CEC) established by the sponsor. The results are shown in Table 65. The incidences were lower in the baricitinib groups than in the placebo group, and the results of the pooled analysis All BARI RA (data cut-off on August 10, 2015) including long-term treatment data showed no trend towards increased incidences of cardiovascular events. The incidences of MACE by treatment duration in the pooled analysis All BARI RA (data cut-off on August 10, 2015) are presented in Table 66. The results were similar irrespective of the duration of treatment. The incidence rate of MACE in the pooled analysis All BARI RA (0.46 per 100 person-years; data cut-off on August 10, 2015) was lower than that in an observational study (*Arthritis Rheumatol*. 2015;67:327-9) in a similar patient population (TNF inhibitors, 1.1 per 100 person-years; MTX, 1.0 per 100 person-years; cDMARDs, 1.5 per 100 person-years [*Arthritis Care & Research*. 2014;66:355-63]). The incidence rate of MACE in the pooled analysis All BARI RA (data cut-off on September 1, 2016) was 0.51 per 100 person-years.

Accordingly, the following reminders will be given to healthcare professionals: (1) the possibility that baricitinib may cause lipid test abnormality and (2) the importance of regular lipid level check during treatment and appropriate measures taken from a clinical point of view.

Table 65. MACE and non-MACE cardiovascular events[a)] in pooled analyses

	BARI 4-mg RA PC[b)]		BARI 2-mg vs 4-mg RA[b)]			All BARI RA[c)]
	4 mg (N = 891)	Placebo (N = 892)	2 mg (N = 404)	4 mg (N = 403)	Placebo (N = 404)	All doses of baricitinib of Phase III studies (N = 2862)
MACE	2 (0.2) 0.75 [0.09, 2.70]	2 (0.2) 0.77 [0.09, 2.77]	0	2 (0.5) 1.66 [0.20, 6.01]	2 (0.5) 1.71 [0.21, 6.16]	16 (0.6) 0.46 [0.26, 0.74]
Non-MACE cardiovascular event	2 (0.2) 0.75 [0.09, 2.70]	3 (0.3) 1.15 [0.24, 3.36]	1 (0.2) 0.84 [0.02, 4.66]	2 (0.5) 1.66 [0.20, 6.01]	2 (0.5) 1.71 [0.21, 6.16]	25 (0.9) 0.72 [0.47, 1.07]

Upper, number of subjects (%); lower, incidence rate per 100 person-years [95% CI]
a) Subjects included in the respective pooled analysis sets excluding those who were evaluated in studies other than Phase III studies evaluated by the CEC (the JADW, JADX, JADV, and JADZ studies) and the JADY study
b) Up to Week 16
c) Data cut-off on August 10, 2015 (including the follow-up period)

Table 66. Incidence of MACE by treatment duration in the pooled analysis All BARI RA (Data cut-off on August 10, 2015)

	All (N = 2861)	Weeks 0-24 (N = 2861)	Weeks 24-48 (N = 2509)	Weeks 48-72 (N = 2011)	Weeks 72-96 (N = 1180)	>Week 96 (N = 469)
Number of subjects (%)	16 (0.6)	5 (0.2)	5 (0.2)	5 (0.2)	1 (0.1)	0
Incidence rate per 100 person-years [95% CI]	0.46 [0.26, 0.74]	0.40 [0.13, 0.94]	0.48 [0.16, 1.13]	0.68 [0.22, 1.58]	0.27 [0.01, 1.50]	0

PMDA's view:

The applicant's explanation is generally acceptable. However, the limited number of subjects evaluated and short observation period in clinical studies preclude the determination of the effect of baricitinib-induced prolonged abnormal lipid on the cardiovascular system. Hyperlipidemia-related adverse events tended to occur in the Japanese subgroup frequently. Baricitinib may be administered to RA patients in combination with steroids, which are known to cause hyperlipidemia as an adverse reaction, and RA itself is suggested to be a risk factor of arteriosclerosis. Therefore, RA patients are at high risk of cardiovascular events. Because baricitinib-induced lipid test abnormality may increase the risk of cardiovascular events, obtaining long-term safety data through post-marketing surveillance is essential to further investigate the relationship between lipid test abnormality and cardiovascular events. New findings should be communicated to healthcare professionals appropriately.

(f) Bone marrow depression

The applicant's explanation about the occurrence of bone marrow depression:

Erythropoietin, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and thrombopoietin are hematopoietic growth factors transducing signals via the JAK-STAT pathway. Therefore, baricitinib's inhibition of the signaling pathway may reduce the production of red blood cells, white blood cells, or platelets. In clinical studies, exclusion criteria and criteria for treatment discontinuation or suspension related to hematology test values[49] were established.

[49] Exclusion criteria: hemoglobin <10.0 g/dL, total white blood cell count <2500/μL, absolute neutrophil count <1200/μL, lymphocyte count <750/μL, and platelet count <100,000/μL. Discontinuation criteria: white blood cell count <1000/μL, absolute neutrophil count <500/μL, lymphocyte count <200/μL, and hemoglobin <6.5 g/dL. Treatment suspension criteria: white blood cell count <2000/μL, absolute neutrophil count <1000/μL, lymphocyte count <500/μL, platelet count <75,000/μL, and hemoglobin <8 g/dL.

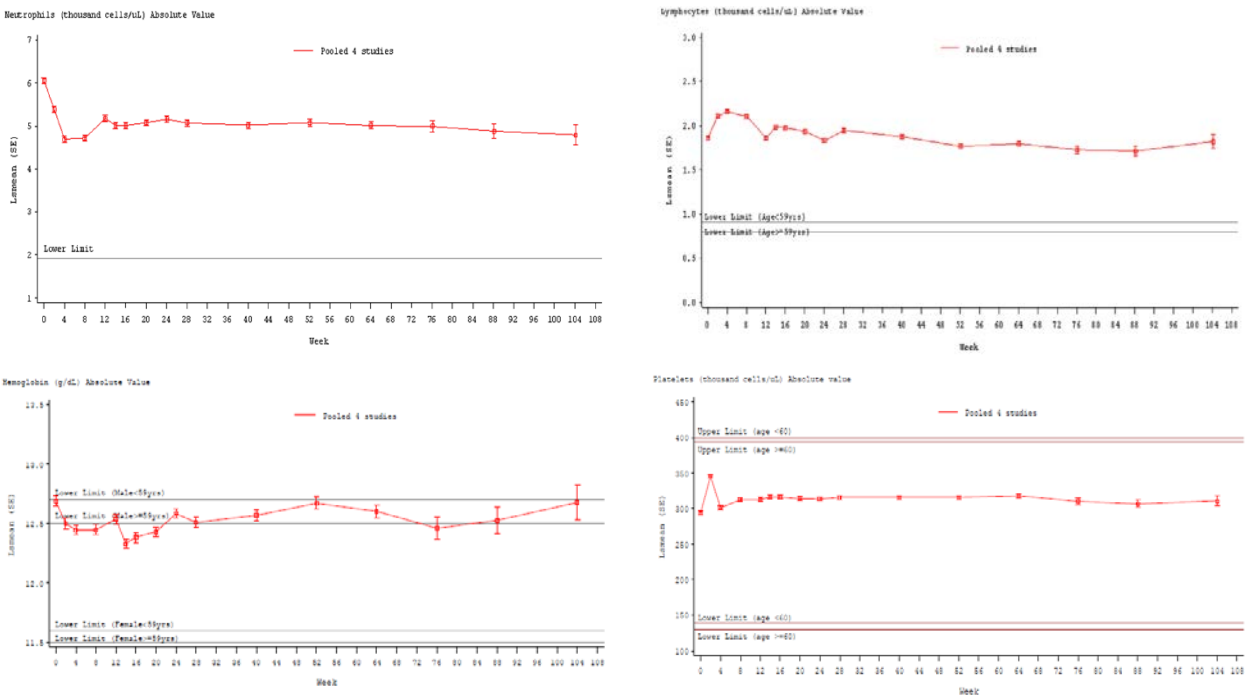

Figure 11. Time courses of neutrophil count (upper left), lymphocyte count (upper right), hemoglobin level (lower left), and platelet count (lower right) (least squares mean ± standard error)
(Weeks 0-104, before change to baricitinib 4 mg due to inadequate efficacy)

(1) White blood cell count (neutrophil count, lymphocyte count)

The applicant's explanation about the effect of baricitinib on white blood cell count:

The time courses of neutrophil count and lymphocyte count in subjects in the 4-mg group from a Phase II study (the JADA study), 3 Phase III studies (the JADV, JADX, and JADW studies), and a long-term treatment study (the JADY study) are shown in Figure 11. The neutrophil count decreased during the first month of the study. After that, it was stable throughout the treatment period while remaining below baseline. The lymphocyte count increased during the first week and recovered to baseline afterward. After falling below baseline from Week 12 to Week 24 it was stable Week 24 onward.

The proportions of subjects who were found to have decreased neutrophil or lymphocyte count in pooled analyses are shown in Table 67. The incidence of neutrophil count decreased was high in the 2- and 4-mg groups, particularly in the 4-mg group, as compared to the placebo group. Grade ≥3 neutrophil count decreased according to the common terminology criteria for adverse events (CTCAE) (version 3), although not many, tended to occur more frequently in the baricitinib group than in the placebo group. There was no clear difference in the incidence of lymphocyte count decreased between baricitinib and placebo.

Table 67. Subjects with neutrophil or lymphocyte count decreased in pooled analyses

	BARI 4-mg RA PC[a]		BARI 2-mg vs 4-mg RA[a]			All BARI RA[b] All doses of baricitinib in Phase I to III studies
	4 mg	Placebo	2 mg	4 mg	Placebo	
Low neutrophil count	78/943 (8.3)	27/1016 (2.7)	31/474 (6.5)	35/467 (7.5)	15/535 (2.8)	403/3236 (12.5)
Worsened CTCAE Grade of neutrophil count decreased	88/957 (9.2)	30/1029 (2.9)	35/477 (7.3)	38/474 (8.0)	17/544 (3.1)	455/3286 (13.8)
Worsened neutrophil count decreased from CTCAE Grade ≤2 to ≥3	3/957 (0.3)	0	3/477 (0.6)	1/474 (0.2)	0	23/3286 (0.7)
Neutropenia (PT)	5/997 (0.5) 1.71 [0.56, 3.99]	0	0	2/479 (0.4) 1.45 [0.18, 5.25]	0	33/3464 (1.0) 0.78 [0.54, 1.10]
Neutrophil count decreased (PT)	3/997 (0.3) 1.03 [0.21, 3.00]	1/1070 (0.1) 0.33 [0.01, 1.85]	0	3/479 (0.6) 2.18 [0.45, 6.37]	1/551 (0.2) 0.67 [0.02, 3.71]	11/3464 (0.3) 0.26 [0.13, 0.47]
Low lymphocyte count	71/920 (7.7)	89/966 (9.2)	29/444 (6.5)	38/442 (8.6)	48/499 (9.6)	469/3225 (14.5)
Worsened CTCAE Grade of lymphocyte count decreased	151/988 (15.3)	196/1059 (18.5)	66/477 (13.8)	78/474 (16.5)	97/544 (17.8)	970/3406 (28.5)
Worsened lymphocyte count decreased from CTCAE Grade ≤2 to ≥3	7/987 (0.7)	9/1052 (0.9)	4/476 (0.8)	3/473 (0.6)	2/541 (0.4)	66/3403 (1.9)
Lymphopenia (PT)	6/997 (0.6) 2.05 [0.75, 4.47]	4/1070 (0.4) 1.33 [0.36, 3.41]	2/479 (0.4) 1.46 [0.18, 5.26]	3/479 (0.6) 2.18 [0.45, 6.37]	1/551 (0.2) 0.67 [0.02, 3.71]	33/3464 (1.0) 0.78 [0.54, 1.10]
Lymphocyte count decreased (PT)	3/997 (0.3) 1.03 [0.21, 3.00]	8/1070 (0.7) 2.66 [1.15, 5.25]	3/479 (0.6) 2.18 [0.45, 6.39]	2/479 (0.4) 1.45 [0.18, 5.25]	2/551 (0.4) 1.33 [0.16, 4.82]	41/3464 (1.2) 0.97 [0.70, 1.32]

Upper, number of subjects (%); lower, incidence rate per 100 person-years [95% CI]
[a] Up to Week 16
[b] Data cut-off on August 10, 2015

The incidences of infection by the worst CTCAE Grade of neutrophil or lymphocyte count decreased in the pooled analysis BARI 4-mg RA PC are shown in Table 68. There was no clear trend towards increased incidence of infection or serious infection with worsened Grade of neutrophil count decreased. In terms of lymphocyte count decreased, the incidence of infection in the 4-mg group increased with worsened Grade.

Based on the above, the potential risk of neutrophil and lymphocyte counts decreased and its relationship with infection are to be communicated to healthcare professionals along with advice to the effect that (1) baricitinib should be carefully administered to patients with a low neutrophil or lymphocyte count; and (2) patients receiving baricitinib should be monitored for neutrophil and lymphocyte counts on a regular basis, and treatment should be suspended or discontinued if a low neutrophil or lymphocyte count is detected.

Table 68. Incidences of infection by the worst CTCAE Grade of neutrophil or lymphocyte count decreased (Pooled analysis BARI 4-mg RA PC; up to Week 24)

		Infection		Serious infection	
		4 mg	Placebo	4 mg	Placebo
Neutrophil count decreased	0 (≥2000/mm^3)	313/853 (36.7)	279/985 (28.3)	13/853 (1.5)	16/985 (1.6)
	1 (1500-<2000/mm^3)	32/74 (43.2)	10/34 (29.4)	1/74 (1.4)	0/34
	2 (1000-<1500/mm^3)	11/27 (40.7)	0/9	0/27	0/9
	3 (500-<1000/mm^3)	1/3 (33.3)	1/1 (100.0)	0/3	0/1
	4 (<500/mm^3)	0/0	0/0	0/0	0/0
Lymphocyte count decreased	0 (≥1100/mm^3)	246/704 (34.9)	201/710 (28.3)	8/704 (1.1)	12/710 (1.7)
	1 (800-<1100/mm^3)	81/205 (39.5)	65/233 (27.9)	2/205 (1.0)	2/233 (0.9)
	2 (500-<800/mm^3)	31/71 (43.7)	30/103 (29.1)	3/71 (4.2)	1/103 (1.0)
	3 (200-<500/mm^3)	4/8 (50.0)	3/13 (23.1)	1/8 (12.5)	1/13 (7.7)
	4 (<200/mm^3)	0/0	0/0	0/0	0/0

Number of subjects (%)

PMDA's view:

The proportion of patients experiencing neutrophil count decreased increased in a dose-dependent manner and the incidence of infection in patients experiencing neutrophil count decreased increased with worsening CTCAE Grade of the event. Healthcare professionals, therefore, should be informed of the potential risk of decreased neutrophil or lymphocyte count during treatment with and its association with infection. In light of the exclusion criteria and the criteria for treatment suspension or discontinuation established for the clinical studies, healthcare professionals should also be advised not to administer baricitinib to patients having severely decreased neutrophil or lymphocyte count before or during treatment. A small number of subjects evaluated and limited time period given for evaluation in the clinical studies precluded adequate assessment of the risk of infection associated with decreased neutrophil or lymphocyte count. Therefore, the occurrence of decreased neutrophil or lymphocyte count and infection in clinical use of baricitinib should be further investigated through post-marketing surveillance, and new findings should be communicated to healthcare professionals accordingly.

(2) Hemoglobin

The applicant's explanation about the effect of baricitinib on hemoglobin level:

The time course of hemoglobin level in the 4-mg group in a Phase II study (the JADA study), 3 Phase III studies (the JADV, JADX, and JADW studies), and a long-term treatment study (the JADY study) is shown in Figure 11. The hemoglobin decreased after the start of baricitinib and reached its lowest level at Week 12. After that, it recovered to baseline.

Table 69 shows the proportions of subjects who were found to have haemoglobin decreased in pooled analyses. While the proportion of affected subjects was higher in the baricitinib groups than in the placebo group, only a small number of subjects had CTCAE Grade ≥3 haemoglobin decreased. There were no marked differences in the incidence of adverse events such as anemia among treatment groups.

Based on the above, the potential risk of decreased hemoglobin will be highlighted to healthcare professionals along with the cautions that (1) baricitinib should be carefully administered to patients

with decreased hemoglobin level and (2) patients receiving baricitinib should be monitored for hemoglobin level on a regular basis, and treatment should be discontinued if a low hemoglobin level is detected.

Table 69. Subjects with hemoglobin decreased in pooled analyses

	BARI 4-mg RA PC[a)]		BARI 2-mg vs 4-mg RA[a)]			All BARI RA[b)] All doses of baricitinib in Phase I to III studies
	4 mg	Placebo	2 mg	4 mg	Placebo	
Low hemoglobin level	191/696 (27.4)	183/747 (24.5)	86/343 (25.1)	95/360 (26.4)	95/407 (23.3)	829/2451 (33.8)
Worsened CTCAE grade of hemoglobin decreased (anaemia)	262/988 (26.5)	233/1059 (22.0)	125/477 (26.2)	142/474 (30.0)	122/544 (22.4)	1131/3408 (33.2)
Worsened CTCAE grade from ≤2 to ≥3	0/988	2/1059 (0.2)	2/477 (0.4)	0/473	1/544 (0.2)	16/3407 (0.5)
Anaemia	20/997 (2.0) 6.84 [4.18, 10.57]	22/1070 (2.1) 7.32 [4.59, 11.09]	8/479 (1.7) 5.83 [2.52, 11.48]	6/479 (1.3) 4.36 [1.60, 9.49]	8/551 (1.5) 5.33 [2.30, 10.51]	97/3464 (2.8) 2.30 [1.87, 2.81]
Haemorrhagic anaemia	0	1/1070 (0.1) 0.33 [0.01, 1.85]	0	0	1/551 (0.2) 0.67 [0.02, 3.71]	2/3464 (0.1) 0.05 [0.01, 0.17]
Normochromic normocytic anaemia	0	1/1070 (0.1) 0.33 [0.01, 1.85]	0	0	0	4/3464 (0.1) 0.09 [0.03, 0.24]
Haemoglobin decreased	2/997 (0.2) 0.68 [0.08, 2.47]	2/1070 (0.2) 0.67 [0.08, 2.41]	3/479 (0.6) 2.18 [0.45, 6.39]	2/479 (0.4) 1.45 [0.18, 5.25]	2/551 (0.4) 1.33 [0.16, 4.82]	15/3464 (0.4) 0.36 [0.20, 0.59]
Haematocrit decreased	0	2/1070 (0.2) 0.67 [0.08, 2.41]	2/479 (0.4) 1.46 [0.18, 5.26]	0	1/551 (0.2) 0.67 [0.02, 3.71]	7/3464 (0.2) 0.17 [0.07, 0.34]
Red blood cell count decreased	3/997 (0.3) 1.03 [0.21, 3.00]	0	2/479 (0.4) 1.46 [0.18, 5.26]	2/479 (0.4) 1.45 [0.18, 5.25]	0	10/3464 (0.3) 0.24 [0.11, 0.44]

Upper, number of subjects (%); lower, incidence per 100 person-years [95% CI]
a) Up to Week 16
b) Data cut-off on August 10, 2015

PMDA's view:

As shown in Figure 11, the hemoglobin level in the 4-mg group decreased after the start of treatment with baricitinib until around Week 24. The proportion of subjects experiencing worsening of the CTCAE grade for haemoglobin low and haemoglobin decreased was slightly higher in the baricitinib groups than in the placebo group. A dose-dependent increase in the incidence of such events was also observed. Therefore, healthcare professionals should be informed of a possible decrease in hemoglobin caused by baricitinib and advised not to administer baricitinib to patients having severely decreased hemoglobin before or during treatment. The occurrence of adverse events related to low hemoglobin or anemia in clinical use of baricitinib should be further investigated through post-marketing surveillance, and new findings should be communicated to healthcare professionals accordingly.

(3) Platelet count

The applicant' explanation about the effect of baricitinib on platelet count:

The time course of platelet count in the 4-mg group in a Phase II study (the JADA study), 3 Phase III studies (the JADV, JADX, and JADW studies), and a long-term treatment study (the JADY study) is shown in Figure 11. After an increase within 2 weeks after the start of treatment, the platelet count (mean) decreased close to baseline, and remained stable throughout the rest of the treatment period.

The proportions of subjects in whom abnormal platelet count was observed are shown in Table 70. In pooled analyses BARI 4-mg RA PC and BARI 2-mg vs 4-mg RA, the proportion of subjects showing high platelet count was higher in the 4-mg group than in the placebo and 2-mg groups. There were no CTCAE Grade ≥3 events. In the pooled analysis All BARI RA (data cut-off on August 10, 2015), the incidence of platelet count increased (thrombocytosis) from ≤600,000/mm^3 to >600,000/mm^3 was 2.4% (80 subjects). Most of the 80 subjects had a high baseline platelet count, which was >400,000/mm^3 in the majority of the subjects. Deep vein thrombosis, peripheral artery thrombosis, and peripheral vascular disorder were observed in 1 subject each out of the 80 subjects. Based on the time course of platelet count before and after the start of treatment, the timing of onset of the adverse events, and the known risk factors, these 3 events were assessed as not related to increased platelet count. Because of thrombocytosis, treatment was suspended in 2 subjects and discontinued in 5 subjects. A cerebrovascular accident in 1 subject also led to treatment suspension.

Table 70. Subjects with platelet count abnormal in pooled analyses

	BARI 4-mg RA PC[a)]		BARI 2-mg vs 4-mg RA[a)]			All BARI RA[b)] All doses of baricitinib in Phase II and III studies
	4 mg	Placebo	2 mg	4 mg	Placebo	
Low platelet count	8/977 (0.8)	12/1039 (1.2)	2/470 (0.4)	4/469 (0.9)	6/530 (1.1)	42/3364 (1.2)
High platelet count	201/854 (23.5)	82/923 (8.9)	65/420 (15.5)	98/426 (23.0)	37/482 (7.7)	775/2996 (25.9)

Number of subjects (%)
a) Up to Week 16
b) Data cut-off on August 10, 2015

PMDA's view:

The proportion of subjects experiencing increased platelet count tended to increase in a dose-dependent manner. Healthcare professionals should be informed of the risk of increased platelet count by baricitinib. Baricitinib must be administered to patients with thrombocytosis carefully. The occurrence of platelet count increase and other related adverse events in the clinical use of baricitinib should be further investigated through post-marketing surveillance, and new findings should be communicated appropriately to healthcare professionals. A relationship between baricitinib and thromboembolism is unclear. However, some subjects with increased platelet count suffered serious thromboembolism, and 1 subject died of pulmonary embolism, even though its relationship with baricitinib was ruled out. Thus, a risk for thromboembolism should also be reminded to healthcare professionals.

(g) Effects on liver function

The applicant's explanation about the effect of baricitinib on liver function:

In clinical studies conducted at an early stage of the development of baricitinib, increased mean ALT and AST and a high ALT or AST were observed in some subjects. Similar phenomena have been reported from patients treated with tofacitinib, an analogue of baricitinib (*J Rheumatol*. 2014;41:837-52, *Arthritis Care Res*. 2011;63:1150-8, etc.) and MTX (*Ann Rheum Dis*. 2009;68:1100-4), and commonly from RA patients (*Br J Rheumatol*. 1997;36:210-3). Exclusion criteria and criteria for

treatment suspension or discontinuation related to liver function test values[50)] were established for the clinical studies

The liver function test parameters in the pooled analyses are summarized in Table 71 with the incidences of liver disorder-related adverse events.[51)] The incidences of liver disorder-related adverse events tended to be high in the baricitinib groups as compared to the placebo and in the 4-mg group as compared to the 2-mg group. A total of 30 subjects had increased ALT to ≥5-fold the upper limit of normal (ULN) by Week 24 in the pooled analysis All BARI RA (data cut-off on August 10, 2015). Of these, 24 subjects had their treatment discontinued or suspended, resulting in a recovery in 23 subjects. In Phase II and III studies in the pooled analysis All BARI RA (data cut-off on August 10, 2015), the incidence of liver disorder-related adverse events was 7.1% (241 of 3411 subjects) and that of serious cases of such events was 0.2% (7 subjects). Most of these adverse events were mild or moderate in severity, and not many serious events or events leading to treatment discontinuation or suspension occurred. In the Japanese subgroup, the incidence of liver disorder-related adverse events was 17.6% (90 of 510 subjects), which tended to be higher than that in the entire population.

Based on the above, increases in liver function test values during treatment with baricitinib will be highlighted to healthcare professionals along with the cautions that (1) baricitinib should be carefully administered to patients with hepatic impairment; and (2) baricitinib should be discontinued in patients showing increased liver function test value with suspected drug-induced liver injury during treatment.

50 Exclusion criteria: Patients with previous or concurrent chronic liver disease with the latest AST or ALT of >1.5-fold the ULN and the latest total bilirubin of ≥1.5-fold the ULN. Discontinuation criteria: ALT or AST of >8-fold the ULN; ALT or AST of >5-fold the ULN for ≥2 consecutive weeks after treatment suspension; ALT or AST of >3-fold the ULN and total bilirubin of >2-fold the ULN; or ALT or AST of >3-fold the ULN with fatigue, nausea, vomiting, right upper quadrant pain or tenderness, pyrexia, rash and/or eosinophilia (>5%). Treatment suspension criteria: ALT or AST of >5-fold the ULN.

51 MedDRA PTs searched by the following SMQs were assessed as liver disorder-related adverse events: (1) broad and narrow terms for liver related investigations, signs and symptoms (SMQ) (SMQ20000008), (2) broad and narrow terms for cholestasis and jaundice of hepatic origin (SMQ) (SMQ20000009), (3) broad and narrow terms for hepatitis, non-infectious (SMQ) (SMQ20000010), (4) broad and narrow terms for hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ) (SMQ20000013), (5) broad and narrow terms for liver-related coagulation and bleeding disturbances (SMQ) (SMQ20000015)

Table 71. Liver function test parameters and liver function-related adverse events in pooled analyses

	BARI 4-mg RA PC[a)]		BARI 2-mg vs 4-mg RA[a)]			All BARI RA[b)]
	4 mg	Placebo	2 mg	4 mg	Placebo	All doses of baricitinib in Phase I to III studies
ALT						
≥3 × ULN	15/988 (1.5)	14/1059 (1.3)	8/477 (1.7)	6/474 (1.3)	2/544 (0.4)	98/3407 (2.9)
≥5 × ULN	7/988 (0.7)	4/1059 (0.4)	3/477 (0.6)	4/474 (0.8)	0	29/3407 (0.9)
≥10 × ULN	2/988 (0.2)	0	1/477 (0.2)	1/474 (0.2)	0	7/3407 (0.2)
ALT (subjects with normal baseline ALT)						
≥3 × ULN	10/902 (1.1)	10/932 (1.1)	2/431 (0.5)	1/435 (0.2)	0	60/3109 (1.9)
≥5 × ULN	4/902 (0.4)	4/932 (0.4)	0	1/435 (0.2)	0	15/3109 (0.5)
≥10 × ULN	1/902 (0.1)	0	0	0	0	3/3109 (0.1)
Bilirubin						
≥2 ×	0	1/1059 (0.1)	0	0	0	1/3407 (0.0)
Adverse events						
Liver function-related adverse events	42 (4.2) 14.37 [10.36, 19.43]	25 (2.3) 8.32 [5.39, 12.29]	13 (2.7) 9.47 [5.04, 16.19]	21 (4.4) 15.26 [9.45, 23.33]	9 (1.6) 6.00 [2.74, 11.39]	241 (7.0) 5.72 [5.02, 6.49]
Liver function-related serious adverse events	3 (0.3) 1.03 [0.21, 3.00]	0	0	1 (0.2) 0.73 [0.02, 4.05]	0	7 (0.2) 0.17 [0.07, 0.34]
Liver function-related adverse events leading to discontinuation	4 (0.4) 1.37 [0.37, 3.50]	0	1 (0.2) 0.73 [0.02, 4.06]	2 (0.4) 1.45 [0.18, 5.25]	0	16 (0.5) 0.38 [0.22, 0.62]

Upper, number of subjects (%); lower, incidence rate per 100 person-years [95% CI]
a) Up to Week 24 for ALT and bilirubin, and up to Week 16 for adverse events
b) Data cut-off on August 10, 2015

PMDA's view

The incidences of adverse events likely related to liver disorder tended to increase in a dose-dependent manner, and such adverse events tended to occur more frequently in the Japanese subgroup than in the entire subjects. Therefore, healthcare professionals should be informed of the effect of baricitinib on liver function and advised that baricitinib should be administered to patients with hepatic impairment carefully, and that treatment discontinuation or suspension should be considered when the patient's liver function test results are abnormal during treatment with baricitinib. RA patients may receive baricitinib in combination with MTX or NSAIDs, and these drugs have a risk of causing hepatic dysfunction. The possibility therefore cannot be ruled out that baricitinib or the concomitant drugs increase the risk of hepatic dysfunction. The effect of baricitinib on liver function in its clinical use should be further investigated via post-marketing surveillance, and new findings should be communicated to healthcare professionals accordingly.

(h) Creatine phosphokinase increased

The applicant's explanation about creatine phosphokinase (CPK) increased:

In early-stage clinical studies of baricitinib, increased mean CPK and high CPK were observed in some subjects. Similar phenomena were reported from patients treated with tofacitinib, an analogue of baricitinib (*J Rheumatol*. 2014;41:837-52).

The time course of CPK level in the 4-mg group in a Phase II study (the JADA study), 3 Phase III studies (the JADV, JADX, and JADW studies), and a long-term treatment study (the JADY study) is shown in Figure 12. CPK increased within 4 to 8 weeks after the start of treatment, and remained high but stable throughout the rest of the treatment period.

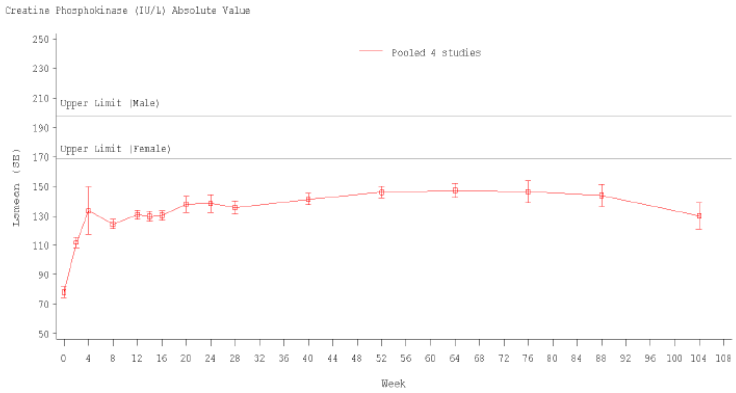

Figure 12. Time course of CPK (least squares mean ± standard error)
(Weeks 0-104, before change to baricitinib 4 mg due to inadequate efficacy)

The percentages of subjects in whom a high CPK level was detected and the incidences of muscle symptom-related adverse events in pooled analyses are shown in Table 72. The proportion of subjects with a high CPK level and that of subjects experiencing worsening of CTCAE grade for CPK were high in the 2- and 4-mg groups, particularly in the 4-mg group, as compared to the placebo group. Common muscle symptom-related adverse events in the pooled analysis All BARI RA (data cut-off on August 10, 2015) were muscle twitching (2.0%, 68 of 3464 subjects) and myalgia (1.0%, 33 of 3464 subjects), but there was no clear temporal relationship between CPK increased and myalgia. Eight of 3464 subjects (0.2%) discontinued the treatment due to a high CPK level at laboratory test or muscle symptoms. There were not many subjects with CTCAE Grade 3 CPK increased and those who were led to treatment discontinuation or suspension due to the event. Increased CPK in most of the affected subjects was accompanied by no muscle symptoms. Moreover, there were no events confirmed as rhabdomyolysis. Based on the above, increased CPK caused by baricitinib is not considered of clinical concern.

Table 72. Proportions of subjects with a high CPK level and the incidences of muscle symptom-related adverse events

	BARI 4-mg RA PC[a)]		BARI 2-mg vs 4-mg RA[a)]			All BARI RA[b)]
	4 mg	Placebo	2 mg	4 mg	Placebo	All doses of baricitinib in Phase I to III studies
High CPK level	302/893 (33.8)	79/954 (8.3)	90/451 (20.0)	153/438 (34.9)	48/494 (9.7)	1322/3059 (43.2)
Worsened CTCAE grade for CPK increased	322/957 (33.6)	85/1029 (8.3)	95/476 (20.0)	166/474 (35.0)	51/544 (9.4)	1396/3234 (43.2)
Worsened CPK increased from CTCAE Grade ≤2 to ≥3	8/956 (0.8)	3/1028 (0.3)	4/476 (0.8)	7/474 (1.5)	3/543 (0.6)	60/3226 (1.9)
Muscle symptom-related adverse events	16/997 (1.6) 5.48 [3.13, 8.89]	12/1070 (1.1) 3.99 [2.06, 6.98]	11/479 (2.3) 8.01 [4.00, 14.34]	10/479 (2.1) 7.27 [3.49, 13.37]	6/551 (1.1) 4.00 [1.47, 8.71]	110/3464 (3.2) 2.61 [2.15, 3.15]
Serious muscle symptom-related adverse events	0	0	0	0	0	2/3464 (0.1) 0.05 [0.01, 0.17]
Muscle symptom-related adverse events leading to discontinuation	0	1/1070 (0.1) 0.33 [0.01, 1.85]	0	0	1/551 (0.2) 0.67 [0.02, 3.71]	1/3464 (0.0) 0.02 [0, 0.13]

Upper, number of subjects (%); lower, incidence rate per 100 person-years [95% CI]
a) Up to Week 16
b) Data cut-off on August 10, 2015

PMDA's view:

As of now, there have been no confirmed cases of rhabdomyolysis, and muscle symptom-related adverse events assessed as serious or led to treatment discontinuation are extremely rare. However, high CPK was detected in many subjects. CPK increased in a dose-dependent manner, and the long-term effect of baricitinib on patients with persistent high CPK is unknown. Further investigation on whether increased CPK can induce clinically significant changes, such as rhabdomyolysis and myopathy, should be conducted through post-marketing surveillance. New findings should be communicated to healthcare professionals accordingly.

(i) Effects on renal function

The applicant's explanation about the effect of baricitinib on renal function:

A reversible, dose-dependent increase in serum creatinine (Cr) was observed in patients treated with tofacitinib, an analogue of baricitinib, and a compound with an inhibitory effect on JAK activity under development (*Arthritis Rheumatol*. 2015;67:334-43, *J Rheumatol*. 2014;41:837-52). RA patients receiving the analogue experienced a mild decrease in glomerular filtration rate (GFR), and it reversed to baseline after treatment discontinuation (*Arthritis Res Ther*. 2015;17:95).

The time course of serum Cr in the 4-mg group in a Phase II study (the JADA study), 3 Phase III studies (the JADV, JADX, and JADW studies), and a long-term treatment study (the JADY study) is shown in Figure 13. Serum Cr increased from Week 2 to Week 12, and remained high but stable throughout the rest of the treatment period.

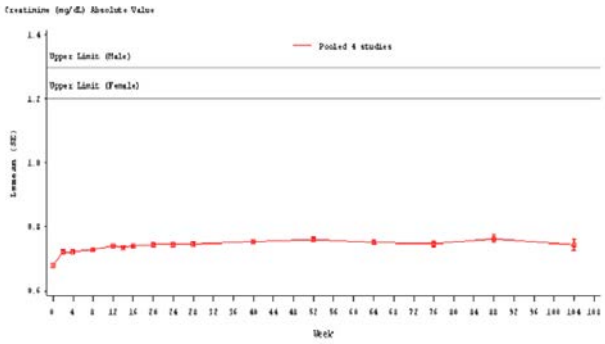

Figure 13. Time course of serum Cr (least squares mean ± standard error)
(Weeks 0-104, before change to baricitinib 4 mg due to inadequate efficacy)

The proportions of subjects with a high serum Cr in pooled analyses are presented in Table 73, showing no marked difference among treatment groups. In the pooled analysis All BARI RA (data cut-off on August 10, 2015), the incidence of Grade ≥3 serum Cr increased was 0.1% (4 of 3211 subjects). Of 6 subjects who experienced treatment discontinuation or suspension due to renal adverse events, 2 subjects had moderate renal impairment at baseline. The serum Cr (mean and median, respectively) in 979 subjects who were followed up after the completion of study were 73.0 and 71.0 μmol/L after the final dose and 69.9 and 68.0 μmol/L at follow-up, showing a trend towards reversing to baseline.

Table 73. Subjects with a high serum Cr in pooled analyses

	BARI 4-mg RA PC[a)]		BARI 2-mg vs 4-mg RA[a)]			All BARI RA[b)] All doses of baricitinib in Phase I to III studies
	4 mg	Placebo	2 mg	4 mg	Placebo	
High serum Cr level	23/951 (2.4)	19/989 (1.9)	11/444 (2.5)	16/441 (3.6)	11/484 (2.3)	156/3166 (4.9)
Worsened CTCAE Grade	23/964 (2.4)	21/1010 (2.1)	11/453 (2.4)	16/450 (3.6)	12/495 (2.4)	157/3211 (4.9)
Worsened CTCAE Grade from ≤2 to ≥3	2/964 (0.2)	0/1010	0/453	2/450 (0.4)	0/495	4/3211 (0.1)

Number of subjects (%)
a) Up to Week 16
b) Data cut-off on August 10, 2015

Based on *in vitro* studies on renal transporters using cells, it is suggested that baricitinib inhibited OCT2-mediated Cr uptake and MATE1- and MATE2-K-mediated transport of Cr and that tubular secretion of Cr was competitively inhibited.

Accordingly, an increase in serum Cr caused by baricitinib is unlikely to be of clinical concern, and giving advice for use in patients with increased serum Cr, e.g., dose adjustment, is not necessary.

PMDA's view:
The incidence of increased serum Cr tended to be high in the baricitinib groups as compared to the placebo group. Nevertheless, because of no clinical study data of baricitinib suggesting a relationship between high serum Cr and renal function-related events, the applicant's explanation about increased serum Cr is largely acceptable. However, given the dose-dependent increase in serum Cr, and because baricitinib may be used in combination with a drug with the potential to cause renal dysfunction such as MTX and NSAIDs, the possibility remains that baricitinib or the concomitant drug may increase the risk for renal dysfunction. The effect of baricitinib on renal function should be further investigated through post-marketing surveillance, and new findings should be communicated to healthcare professionals accordingly.

7.R.2.3 Use in the elderly

The applicant's explanation about the occurrence of adverse events in elderly subjects:
Table 74 shows adverse events and laboratory abnormalities in which an interaction between treatment group and a stratification factor (age) was observed in the pooled analysis BARI 2-mg vs 4-mg RA. The incidences of serious infection and herpes zoster by age in the pooled analysis Modified Ext BARI 2-mg vs 4-mg are shown in Table 75. The incidences of these events tended to be higher in subjects aged ≥65 years than in subjects aged <65 years.

Table 74. Adverse events and laboratory abnormalities in which interactions between treatment groups and a stratification factor (age) were observed (Pooled analysis BARI 2-mg vs 4-mg RA, up to Week 16)

	<65 years	≥65 years
Oropharyngeal pain	1.9 (0.7, 5.1)	0
Neutrophil count low	0.9 (0.5, 1.6)	7.8 (1.0, 62.7)

Odds ratio (95% CI)
Interaction, *P* value ≤0.1

Table 75. Adverse events by age group (Modified Ext BARI 2-mg vs 4-mg[a])

	<65 years		≥65 years	
	2 mg (N = 397)	4 mg (N = 392)	2 mg (N = 82)	4 mg (N = 87)
Serious infection	12 (3.0%) 2.67 [1.38, 4.66]	22 (5.6%) 5.58 [3.50, 8.44]	6 (7.3%) 5.97 [2.19, 12.98]	5 (5.7%) 4.96 [1.61, 11.58]
Herpes zoster	11 (2.8%) 2.45 [1.22, 4.38]	13 (3.3%) 3.25 [1.73, 5.56]	4 (4.9%) 3.92 [1.07, 10.03]	7 (8.0%) 7.14 [2.87, 14.71]

Number of subjects (%); incidence rate per 100 person-years [95% CI]
[a] Data cut-off on September 1, 2016

The incidences of adverse events by age in the pooled analysis All BARI RA (data cut-off on August 10, 2015) are shown in Table 76. The incidences of serious adverse events; adverse events leading to treatment discontinuation; adverse events related to cardiac disorders (SOC), renal and urinary disorders (SOC), and vascular disorders (SOC); events related to accidents and injuries (SMQ), central nervous system haemorrhages and cerebrovascular conditions (SMQ), malignancies (SMQ), and bone marrow depression-related adverse events (several SMQs); and events categorized as hypotension, fall, or fracture in the group aged ≥65 years tended to be higher than those in the group aged <65 years, although the group aged ≥65 years consisted of a limited number of subjects (the group aged ≥85 years consisted of 1 subject only, and the group aged 75 to 84 years consisted of 76 subjects).

Table 76. Adverse events by age group (Pooled analysis All BARI RA[a]; Overall subjects)

	<65 years (N = 2859)	65-74 years (N = 528)	75-84 years (N = 76)	≥85 years (N = 1)
All adverse events	2161 (75.6)	423 (80.1)	63 (82.9)	1 (100)
Serious adverse events	263 (9.2)	99 (18.8)	22 (28.9)	0
Adverse events resulting in death	2 (0.1)	1 (0.2)	3 (3.9)	0
Adverse events leading to discontinuation	182 (6.4)	61 (11.6)	12 (15.8)	0

Number of subjects (%)
[a] Data cut-off on August 10, 2015

PMDA's view:

Limited data preclude a clear conclusion on the effect of baricitinib on aging-related safety at present. However, the incidence of serious adverse events tended to be high in elderly subjects in the clinical studies. Elderly patients are more likely to have renal impairment, and subjects with renal impairment had increased exposure to baricitinib. Healthcare professionals must be advised to follow elderly patients carefully during treatment with baricitinib. Given the limited number of elderly subjects in the clinical studies, relevant data should be further collected of elderly patients through post-marketing surveillance, and new findings should be communicated to healthcare professionals accordingly.

Based on the review in the Sections from "7.R.2.1 Safety summary" through "7.R 2.3 Use in the elderly" and the safety profile and pharmacological actions of baricitinib observed in the clinical studies, patients treated with baricitinib should be closely monitored for serious infection, including herpes zoster and tuberculosis, malignant tumors, gastrointestinal perforation, cytopenia, lipids abnormal, and other events. Because baricitinib has the risks similar to those of its analogues and biological drugs for RA, the adverse events will be managed by physicians with a thorough understanding of baricitinib and adequate knowledge and experience in RA drug therapy according to appropriate advice given as practiced for these similar drugs. However, serious infection, herpes zoster, malignant tumor, bone marrow depression, and liver function test abnormal tended to occur more frequently in the 4-mg group than in the 2-mg group, and therefore the 4-mg QD regimen may have a relatively high risk compared to the 2-mg QD regimen. The dosing regimen of baricitinib should be carefully determined in light of the benefits and risks of each regimen [for dosage and administration, see Section "7.R.5 Dosage and administration"].

The above PMDA's conclusion on the safety of baricitinib will be further discussed at the Expert Discussion.

7.R.3 Clinical positioning

The applicant's explanation about the expected clinical positioning of baricitinib:

In the clinical practice guidelines of the Japan College of Rheumatology published in 2014, a weak recommendation is made for JAK inhibitors as an option for patients with an inadequate response to ≥1 biological drug (*Guideline for the Management of Rheumatoid Arthritis, Japan College of Rheumatology 2014*). The 2015 ACR guidelines strongly recommend JAK inhibitors for patients with prolonged RA who have inadequate response to a cDMARD alone, and conditionally recommend for patients with an inadequate response to biological drugs (*Arthritis Care Res*. 2016;68:1-25). The 2016 EULAR recommendations recognize JAK inhibitors as equivalent to biological drugs and recommend then as a therapeutic option for patients inadequately responding to cDMARDs with unfavorable prognostic factors, such as high autoantibody titer and high disease activity, or for patients inadequately responding to 2 cDMARDs or the first biological drug without unfavorable prognostic factors (*Ann Rheum Dis*. 2017;0:1-18).

In clinical studies in patients with an inadequate response to cDMARDs including MTX (the JADV and JADX studies), thus who are regarded as target patients of JAK inhibitors in the above-mentioned guidelines, and in a clinical study in patients with an inadequate response to biological drugs (the JADW study), the baricitinib 4 mg once daily regimen was proven to be effective as compared to placebo in terms of efficacy endpoints such as ACR20 responder rate and changes in DAS28-hsCRP with acceptable tolerability. In the JADZ study in patients who were cDMARD-naive or who had limited treatment with MTX, the non-inferiority of baricitinib 4 mg alone to MTX alone was demonstrated, suggesting that baricitinib is expected to be effective in the treatment of MTX- or other cDMARD-naive RA patients who are likely to be intolerant to existing treatments.

Based on the above, baricitinib may serve as a treatment option for RA patients inadequately responding to cDMARDs or biological drugs as recommended by the above-mentioned guidelines, as well as for MTX- or other cDMARD-naive RA patients who are likely to be intolerant to existing treatments.

PMDA's view:
The current preferred treatment for RA is to begin with a cDMARD, mainly MTX, as early as possible after a diagnosis of RA. Biological drugs are used for patients with moderate to severe RA who have shown an inadequate response to or who are intolerant of cDMARDs (*Guideline for the Management of Rheumatoid Arthritis, Japan College of Rheumatology 2014*, *Arthritis Care Res*. 2016;68:1, *Ann Rheum Dis*. 2017;0:1-18).

As shown in Section "7.R.1 Efficacy," the clinical study data submitted demonstrate the efficacy of baricitinib in studies in patients with an inadequate response to cDMARDs including MTX (the JADV and JADX studies) and a study in patients with an inadequate response to TNF inhibitors (the JADW study). Despite that, because of its risks noted in (a) to (c) below, baricitinib should not be actively used in MTX- or other cDMARD-naive RA patients, but it is instead an option for treating RA patients with an inadequate response to existing cDMARDs such as MTX, as with biological drugs:

(a) As shown in Section "7.R.2 Safety," baricitinib is considered similar to biological drugs in terms of its safety and magnitude of risk at present.
(b) Given the limited availability of long-term safety data from the clinical studies, potential risks in the long-term use of baricitinib, such as for serious infection and malignant tumors, cannot be ruled out.
(c) In the JADZ study in RA patients who were cDMARD-naive and had limited treatment with MTX, the non-inferiority of baricitinib 4 mg to MTX alone was demonstrated while the incidence of herpes zoster in the baricitinib groups was higher than that in the MTX alone group.

Besides, baricitinib is considered to pose risks similar to biological drugs. Because of no clinical experience, baricitinib should not be used in combination with biological drugs. Furthermore, baricitinib should not be prescribed easily because of being a handy oral tablet form. Healthcare professionals should be reminded that the use of baricitinib must be determined carefully by physicians with adequate knowledge and experience in RA drug therapy at medical centers equipped for serious infection, weighing the benefit-risk balance of the product and other available medication, according to the condition of each patient and his or her treatment history and prognostic factors.

The above PMDA's conclusion on the clinical positioning of baricitinib will be further discussed at the Expert Discussion.

7.R.4 Indication

As explained in Section "7.R.1 Efficacy," PMDA considers that the clinical study data submitted demonstrated the efficacy of baricitinib in inhibiting the main clinical symptoms of RA such as arthralgia

and structural joint damage. Meanwhile, as discussed in Section "7.R.3 Clinical positioning," baricitinib should be used in patients with an inadequate response to existing treatments as a rule. Therefore, the indication of baricitinib should be "rheumatoid arthritis in patients who have had an inadequate response to existing treatments (including prevention of structural joint damage)." However, baricitinib should be used only in patients who have persistent symptoms clearly attributable to RA despite previous appropriate medication including antirheumatic drugs. This reminder should be given in the "Precautions for indications" section of the package insert as it was given for biological drugs for RA and tofacitinib, an analogue of baricitinib.

The above PMDA's conclusion on the indication of baricitinib will be further discussed at the Expert Discussion.

7.R.5 Dosage and administration

7.R.5.1 Dosage and administration

The applicant's rationale for the proposed dosage and administration:

The dosage and administration was proposed as "The usual adult dosage is 4 mg of baricitinib administered orally once daily. The dose may be reduced to 2 mg according to symptoms. "As shown in Section "7.R.1 Efficacy," the efficacy of baricitinib was demonstrated at both 2 mg and 4 mg, and was superior at 4 mg than with placebo at 2 mg. The latest clinical practice guidelines for RA aim to meet stringent remission criteria earlier (*Ann Rheum Dis*. 2016;75:3-15), and early improvement of DAS28-hsCRP was proven to contribute to a decrease in change in mTSS (*BMC Musculoskelet Disord*. 2011;12:120, *Medicine [Baltimore]*. 2016;95:e3476, etc.) For these reasons, the dose of 4 mg is considered more effective than 2 mg.

As explained in Section "7.R.2 Safety," the safety profiles of baricitinib 2 mg and 4 mg are acceptable. Although the incidences of adverse events such as herpes zoster and serious infection tended to increase dose-dependently, there was no marked difference between the 2 doses. Until now, there has been no increase in the incidences of serious infection and malignant tumor, etc. due to prolonged treatment. Baricitinib 2 mg and 4 mg are both tolerable with no obvious clinically significant risks.

In the JADY study, a long-term treatment study, subjects who had achieved sustained low disease activity or remission[52)] after receiving baricitinib at 4 mg once daily for ≥15 months were re-randomized to continue baricitinib at 4 mg once daily or to receive a reduced dose of baricitinib at 2 mg once daily in a double-blind setting. As shown in Table 77, although changes in CDAI, HAQ-DI, DAS28-hsCRP, and SDAI, disease activity endpoints, in the 2-mg group tended to increase as compared with the 4-mg group, the proportions of subjects who maintained low disease activity (CDAI score of ≤10) were high in both groups, and, as shown in Table 78, a similar tendency was observed in the Japanese subgroup.

[52] Subjects from the JADV, JADX, or JADW study who maintained low disease activity (CDAI score ≤10) for ≥3 months in the JADY study or subjects from the JADZ study who maintained remission (CDAI score ≤2.8) for ≥3 months in the JADY study

These results suggest that the dose for some patients in whom disease activity is well controlled by treatment with baricitinib 4 mg may be reduced to 2 mg.

In the Japanese phase II study (the JADN study), the primary efficacy endpoint at Week 12 showed no clear difference between the 2- and 4-mg groups. This was probably because of a difficulty in detecting a between-group difference in the evaluation based on the proportion of patients achieving the improvement criteria because relatively many of the patients enrolled in this study had mild RA with low ACR component scores, such as for tender joint count (TJC), swollen joint count (SJC), patient and physician global assessments by visual analog scale (VAS), and high-sensitivity C-reactive protein (hsCRP), compared to patients enrolled in other studies.

Based on the above, the dosage and administration was proposed as "The usual adult dosage is 4 mg of baricitinib administered orally once daily. The dose may be reduced to 2 mg according to symptoms."

Table 77. Comparison between the baricitinib 2- and 4-mg groups at Week 12 after re-randomization (NRI; mLOCF)

	Pooled data from JADV, JADX, and JADW		JADZ	
Treatment group after re-randomization	2 mg (reduced dose)	4 mg (maintained dose)	2 mg (reduced dose)	4 mg (maintained dose)
CDAI-based low disease activity (CDAI ≤10)	83.0 (326/393)	90.7 (359/396)	90.2 (55/61)	95.2 (60/63)
CDAI-based remission (CDAI ≤2.8)	36.4 (143/393)	39.9 (158/396)	67.2 (41/61)	74.6 (47/63)
ΔCDAI	1.84 ± 5.92 (383)	0.58 ± 3.75 (390)	1.67 ± 4.15 (58)	1.22 ± 3.42 (63)
ΔHAQ-DI	0.05 ± 0.29 (383)	0.02 ± 0.26 (390)	0.04 ± 0.22 (59)	0.04 ± 0.21 (63)
ΔDAS28-hsCRP	0.33 ± 0.83 (379)	0.09 ± 0.70 (387)	0.31 ± 0.69 (58)	0.17 ± 0.71 (63)
ΔSDAI	2.08 ± 6.08 (379)	0.68 ± 4.06 (387)	1.87 ± 4.39 (57)	1.17 ± 3.61 (63)

% (number of subjects) or mean ± standard deviation (number of subjects)
Data cut-off on September 1, 2016

Table 78. Comparison between the baricitinib 2- and 4-mg groups at 12 weeks after re-randomization (Japanese subgroup; mLOCF)

	Pooled data from JADV, JADX, and JADW		JADZ	
Treatment group after re-randomization	2 mg (reduced dose)	4 mg (maintained dose)	2 mg (reduced dose)	4 mg (maintined dose)
ΔCDAI	0.08 ± 2.19 (61)	0.18 ± 2.34 (61)	1.74 ± 5.41 (14)	0.84 ± 2.97 (14)
ΔHAQ-DI	0.01 ± 0.16 (61)	-0.03 ± 0.20 (61)	0.04 ± 0.15 (15)	0.01 ± 0.08 (14)
ΔDAS28-hsCRP	0.10 ± 0.60 (61)	0.05 ± 0.53 (61)	0.30 ± 0.75 (14)	-0.01 ± 0.59 (14)
ΔSDAI	0.20 ± 2.45 (61)	0.23 ± 2.41 (61)	1.85 ± 5.71 (13)	0.67 ± 3.07 (14)

Mean ± standard deviation (number of subjects)
Data cut-off on September 1, 2016

PMDA's view:

As explained in Section "7.R.1 Efficacy," both 2 mg and 4 mg of baricitinib are expected to have efficacy in treating RA, and 4 mg is expected to be more effective based on the following observations:

(a) In the JADX and JADW studies, in which the 2-mg and 4-mg groups were compared, the ACR20 responder rate and scores for other efficacy endpoints including SDAI-based remission rate were

higher and DAS28-hsCRP tended to improve earlier in the 4-mg group than in the 2-mg group. These results suggested that improvement in clinical symptoms was greater at 4 mg than at 2 mg.

(b) In the JADZ, JADV, and JADX studies, progression of the change in mTSS was inhibited in the 4-mg group, suggesting that the inhibitory effect of baricitinib 2 mg on structural joint damage may be lower than that of baricitinib 4 mg.

(c) While there was no clear difference in the ACR20 responder rate at Week 12 between the 2- and 4-mg groups in the JADN study, the time course of the DAS28-hsCRP score and the results of other efficacy endpoints and in the Japanese subgroup of the JADW and JADX studies suggested that greater efficacy of 4 mg than 2 mg.

As explained in Section "7.R.2 Safety," based on (d) and (e) below, the incidences of adverse events of baricitinib 2 or 4 mg have not been markedly higher than the existing similar drugs or biological drugs until now. Therefore, risk in 2 or 4 mg baricitinib is considered similar to that in those drugs.

(d) The safety profile and pharmacological actions of baricitinib in the clinical studies suggest that baricitinib may cause serious infection including herpes zoster and tuberculosis, malignant tumor, cytopenia, and lipids abnormal, etc. However, these events are similar to those observed with existing biological drugs RA or tofacitinib, an analogue of baricitinib.

(e) The Modified Bari 4-mg RA and Modified Ext BARI 2-mg vs 4-mg pooled analyses involved a substantial number of patients and long-term observation, the incidence of serious infection including herpes zoster in the 4-mg group did not tend to be notably higher than that in patients receiving existing drugs.

Based on the above review and the therapeutic goal in RA that is earlier and deeper clinical remission according to the recent clinical practice guidelines for RA, baricitinib 4 mg is an acceptable starting dose in RA patients with inadequate response to existing treatments.

Meanwhile, the incidences of serious infection and malignant tumor in the 4-mg group were relatively high, and a similar tendency was observed in the incidence of herpes zoster in the pooled analysis Modified Ext BARI 2-mg vs 4-mg, although not markedly higher incidences than in patients receiving existing drugs, and dose-dependent abnormal changes in laboratory values were also observed in the pooled analysis BARI 2-mg vs 4-mg RA. Therefore, the risk of baricitinib causing adverse events such as serious infection and herpes zoster may increase in a dose-dependent manner. Given the limited availability of long-term data, it is difficult to rule out the possibility that the risk of adverse drug reactions increases with the increase in the duration of baricitinib administration.

Based on the above, PMDA considers that the dose of baricitinib should preferably be reduced to 2 mg in patients with specific conditions, in particular, those who have achieved clinical remission or low disease activity after treatment with baricitinib 4 mg, those who are at high risk of adverse drug reactions, and those who are expected to have high systemic exposure to the drug [see Sections "6.R.2 Drug interactions" and "7.R.5.2 Pharmacokinetics of baricitinib in patients with renal impairment"],

according to their condition. The description of the dosage and administration of baricitinib should be as follows: “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.”

The above conclusion by PMDA will be finalized, taking account of comments from the Expert Discussion.

7.R.5.2 Pharmacokinetics of baricitinib in patients with renal impairment

The applicant’ explanation about the necessity of adjusting the dose of baricitinib for patients with renal impairment:

After administration of baricitinib to patients with moderate renal impairment, the C_{max} and $AUC_{0-\infty}$ of baricitinib in these patients were approximately 1.5- and 2.2-fold, respectively, and AUC tended to increase with increasing severity of renal impairment [see Section “6.2.2.1 Pharmacokinetics in subjects with renal impairment”]. Figure 14 shows the $AUC_{\tau,ss}$ in RA patients with normal renal function after once daily dose of baricitinib 4 mg and RA patients with moderate renal impairment after once daily dose of baricitinib 2 mg estimated from the population pharmacokinetic model established using the results from phase II and III studies [see Section “6.2.3.1 Pharmacokinetics in patients”]. The AUC in RA patients with moderate renal impairment after the once daily 2 mg dose did not exceed the AUC in those with normal renal function treated with once daily 4 mg.

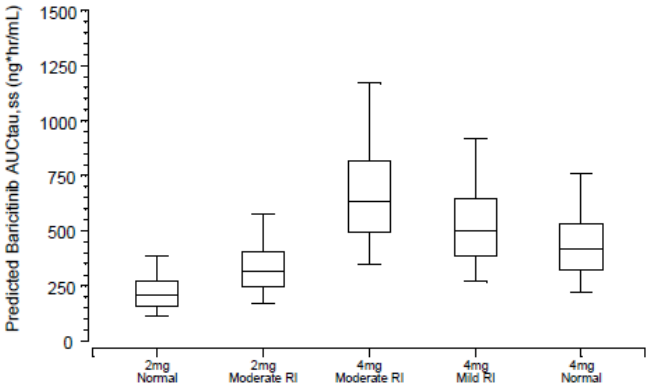

Figure 14. Estimated steady-state exposure by severity of renal impairment (normal to moderate)

In 4 Phase III studies (the JADV, JADX, JADW, and JADZ studies), the dose of baricitinib for RA patients with moderate renal impairment[53] who were assigned to the 4-mg group were reduced to 2 mg. The results of subgroup analyses of ACR20 responder rates, the primary endpoint of each studies, by renal function are shown in Table 79. The results in RA patients with moderate renal impairment were similar to those in RA patients with normal renal function or mild renal impairment.

[53] RA patients with eGFR of <40 mL/min/1.73m^2 were excluded.

Table 79. ACR20 responder rates[a)] by severity of renal impairment in the multi-regional Phase III studies

	4 mg		2 mg	
	RA patients with moderate renal impairment[b)] (eGFR <60 mL/min/1.73m^2)	RA patients with normal renal function or mild renal impairment (eGFR ≥60 mL/min/1.73m^2)	RA patients with moderate renal impairment (eGFR <60 mL/min/1.73m^2)	RA patients with normal renal function or mild renal impairment (eGFR ≥60 mL/min/1.73m^2)
JADZ (Baricitinib + MTX)	6/10 (60.0%)	162/205 (79.0%)	−	−
JADZ (Baricitinib alone)	4/5 (80.0%)	118/154 (76.6%)	−	−
JADV	11/15 (73.3%)	328/472 (69.5%)	−	−
JADX	8/19 (42.1%)	131/207 (63.3%)	7/15 (46.7%)	144/214 (67.3%)
JADW	5/10 (50.0%)	93/167 (55.7%)	5/12 (41.7%)	80/162 (49.4%)

Number of subjects (%)

a) ACR20 response was evaluated at Week 24 in the JADZ study and at Week 12 in the JADV, JADX, and JADW studies.

b) Baricitinib 2 mg was administered to RA patients with moderate renal impairment.

The safety analysis in the 4-mg groups (n = 2579) of a Phase II study (the JADA study), 4 Phase III studies (the JADV, JADX, JADW, and JADZ studies), and a long-term treatment study (the JADY study; data cut-off on January 1, 2016) revealed that the incidence of adverse events was 85.9% (116 of 135 subjects) in the subgroup[54)] of eGFR <60 mL/min/1.73 m^2, which was higher than the incidence in the subgroup with an eGFR ≥60 mL/min/1.73 m^2, 78.1% (1909 of 2444 subjects). A similar tendency was observed in the incidence of serious adverse events, which was 25.9% (35 of 135 subjects) in the subgroup with an eGFR <60 mL/min/1.73 m^2 and 11.7% (286 of 2444 subjects) in the subgroup with an eGFR ≥60 mL/min/1.73 m^2. The major concurrent diseases (SOC) at baseline were musculoskeletal and connective tissue disorders (subgroup with an eGFR ≥60 mL/min/1.73 m^2, 33.0%; subgroup with an eGFR<60 mL/min/1.73 m^2, 57.0%), gastrointestinal disorders (23.1%; 40.7%), respiratory, thoracic and mediastinal disorders (12.3%; 21.5%), nervous system disorders (10.5%; 24.4%), cardiac disorders (7.2%; 14.8%), and infections and infestations (13.4%; 16.3%). The proportions of patients with a concurrent disease tended to be high in the subgroup with an eGFR <60 mL/min/1.73 m^2. This indicates that the higher incidence of adverse events in RA patients with moderate renal impairment may be partly attributable to their baseline condition that is worse than those with normal renal function.

Based on the above, the dose adjustment for RA patients with moderate renal impairment to once-daily 2 mg is appropriate. In the JADL study, patients with severe renal impairment had their CL/F approximately one-fourth of that in patients with normal renal function, showing increased baricitinib exposure. In addition, the efficacy and safety of baricitinib in this patient population have not been evaluated. Therefore, healthcare professionals should be reminded not to administer baricitinib to RA patients with severe renal impairment.

54 The dose for patients with eGFR of <60 mL/min/1.73m^2 who were assigned to the 4-mg group was adjusted to 2 mg once daily in these studies except for the JADA study. Patients who had a reduction of dose to 2 mg once daily were analyzed in pooled analyses.

Table 80. Incidences of adverse events (SOC) by severity of renal impairment

SOC	RA patients with normal renal function or mild renal impairment (eGFR ≥60 mL/min/1.73m^2) (N = 2444)	RA patients with moderate renal impairment (eGFR <60 mL/min/1.73m^2) (N = 135)
Blood and lymphatic system disorders	204 (8.3)	9 (6.7)
Cardiac disorders	68 (2.8)	10 (7.4)
Congenital, familial and genetic disorders	5 (0.2)	1 (0.7)
Ear and labyrinth disorders	66 (2.7)	1 (0.7)
Endocrine disorders	17 (0.7)	1 (0.7)
Eye disorders	127 (5.2)	10 (7.4)
Gastrointestinal disorders	563 (23.0)	39 (28.9)
General disorders and administration site conditions	215 (8.8)	17 (12.6)
Hepatobiliary disorders	100 (4.1)	5 (3.7)
Immune system disorders	25 (1.0)	1 (0.7)
Infections and infestations	1185 (48.5)	74 (54.8)
Injury, poisoning and procedural complications	321 (13.1)	22 (16.3)
Investigations	421 (16.9)	26 (19.3)
Metabolism and nutrition disorders	303 (12.4)	17 (12.6)
Musculoskeletal and connective tissue disorders	511 (20.9)	47 (34.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	66 (2.7)	5 (3.7)
Nervous system disorders	280 (11.5)	21 (15.6)
Pregnancy, puerperium and perinatal conditions	4 (0.2)	0
Psychiatric disorders	119 (4.9)	9 (6.7)
Renal and urinary disorders	74 (3.0)	16 (11.9)
Reproductive system and breast disorders	82 (3.4)	1 (0.7)
Respiratory, thoracic and mediastinal disorders	271 (11.1)	26 (19.3)
Skin and subcutaneous tissue disorders	264 (10.8)	17 (12.6)
Social circumstances	6 (0.2)	0
Surgical and medical procedures	133 (5.4)	18 (13.3)
Vascular disorders	177 (7.2)	12 (8.9)

Number of subjects (%)

PMDA's view:

Systemic exposure in patients with moderate renal impairment increased to approximately 2-fold that in patients with normal renal function, and the dose for the patient population in Phase III studies was adjusted to baricitinib 2 mg once daily. No clear difference was observed in the efficacy of baricitinib between this patient population and patients with normal renal function or mild renal impairment receiving 4 mg once daily. In addition, because RA patients with moderate renal impairment receiving baricitinib 2 mg once daily, though limited in number, did not experience adverse events indicative of intolerance to the dose, 2 mg once daily may be recommended for RA patients with moderate renal impairment. However, given that the incidence of adverse events reported in RA patients with moderate renal impairment tended to be higher than that in those with normal renal function or mild renal impairment, healthcare professionals should be advised to administer baricitinib to RA patients with moderate renal impairment with careful monitoring of their condition and to make a deliberate decision on whether to continue treatment.

While the efficacy and safety of baricitinib in RA patients with severe renal impairment have not been evaluated, the results of the JADL study suggested increased baricitinib exposure in this patient

population. Healthcare professionals should be advised not to administer baricitinib to RA patients with severe renal impairment. Furthermore, given the limited number of RA patients with renal impairment evaluated in the clinical studies, the efficacy and safety of baricitinib in this patient population should be further investigated in post-marketing surveillance, and new findings should be communicated to healthcare professionals accordingly.

7.R.6 Post-marketing safety measures

The applicant plans to conduct post-marketing surveillance to investigate the safety of baricitinib in its post-marketing use, including long-term safety. Data on adverse events such as malignant tumor and serious infection will be collected to further assess the safety of baricitinib in a way that allows comparison with appropriate external controls.

PMDA's view:

The possibility cannot be ruled out that baricitinib may cause similar adverse events as observed with other JAK activity inhibitors. The incidences of serious infection (e.g., herpes zoster, tuberculosis), malignant tumor, gastrointestinal perforation, cytopenia, and lipids abnormal observed in the clinical studies are similar to those occurring in patients receiving existing biological drugs used for RA or tofacitinib, an analogue of baricitinib. Therefore, the level of safety measures of baricitinib should be at least the same as those taken for the existing drugs. In particular, baricitinib, as practice for the existing biological drugs and tofacitinib, should be used by physicians with a thorough understanding of the profile of baricitinib and knowledge and experience in RA drug therapy. Healthcare professionals should be warned about the occurrence of serious infection or malignant tumor, and a tuberculin skin test should be performed before starting treatment with baricitinib.

Considering its effects on the embryos and fetuses observed in the toxicity studies, baricitinib should be contraindicated in pregnant and possibly pregnant women, and effective measures need to be taken to ensure that women of childbearing potential use effective contraception during and for a certain period after the completion of treatment [see Section "5.R.1 Administration to pregnant or possibly pregnant women"].

Because of the limited experience with long-term use of baricitinib and its pharmacological actions, the possibility cannot be ruled out that baricitinib may cause serious infection including herpes zoster and tuberculosis, malignant tumor, cytopenia, lipids abnormal, and other serious adverse events as well as unknown events that have not been identified in the clinical studies. Therefore, post-marketing surveillance should be conducted covering all patients treated with baricitinib as early as possible to clarify the safety profile of the drug, including the occurrence of unknown adverse events, and to continue to assess the safety of the drug in its clinical use in a way that allows comparisons with appropriate external controls.

The above PMDA's conclusion on the post-marketing investigations will be further discussed at the Expert Discussion.

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

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

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

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

The new drug application data (CTD 5.3.5.1.4, CTD 5.3.5.1.5, CTD 5.3.5.1.6, CTD 5.3.5.1.7, and CTD 5.3.5.2.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA acknowledged that the conduct of clinical studies were conducted generally in compliance with GCP and concluded that there were no obstacles to conducting its review based on the application documents submitted. However, the following areas for improvement were discovered at some study sites and the sponsor, albeit with no significant impact on the overall study evaluation. The areas for improvement were notified to the head of each study sites and the applicant (sponsor).

Areas for improvement

Study sites

- Some subjects were enrolled in a study and received the study drug despite not meeting a prior therapy-related inclusion criterion.
- Some subjects were enrolled in a study and received the study drug despite meeting a thyroid function-related exclusion criterion.
- Protocol deviations were found (non-compliance with the specified duration of use of concomitant drugs before participating in a study, non-compliance with the restriction of use of prior medication, and unnecessary blood collection and X-ray examination).

Sponsor

- The sponsor failed to appropriately identify some ineligible patients not meeting a prior therapy-related inclusion criterion enrolled in a study and received the study drug and the protocol deviations (non-compliance with the specified duration of use of concomitant drugs before participating in a study and non-compliance with the restriction of use of prior medication) through monitoring.

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

On the basis of the data submitted, PMDA has concluded that baricitinib has efficacy in the treatment for patients RA inadequately responding to existing treatments, and that baricitinib has acceptable safety in view of the benefits. However, in light of the efficacy and safety profiles identified in the clinical studies and the potential risks that are likely to be related to the pharmacological actions of baricitinib, any treatment options other than baricitinib should be selected for patients with RA who are expected to respond to the existing therapies. Baricitinib offers a new treatment option for RA patients inadequately responding to conventional therapies and is of a certain clinical significance.

Stringent safety measures should be taken during the use of baricitinib as practiced in the use of biological drugs for RA and tofacitinib, an analogue of baricitinib, for possible serious adverse drug reactions such as infection and malignant tumor. A post-marketing use-results survey should be conducted covering all patients treated with the baricitinib to clarify its safety profile early. The assessment of the safety and efficacy of baricitinib should be continued in a careful manner. In particular, incidences of serious adverse events, including serious infection and malignant tumor, in prolonged use of the product must be assessed by comparison with appropriate external controls. Any findings should be communicated to physicians, nurses, and pharmacists promptly and appropriately.

Provided that the above-mentioned safety measures are followed, 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.

10. Other

The definitions of the main efficacy endpoints used in multi-regional Phase III studies:

Endpoint	Definition
ACR20, ACR50, or ACR70 response rate	The proportion of subjects achieving ≥20%, ≥50%, or ≥70% reduction from baseline in the tender joint count out of 68 joints and swollen joint count out of 66 joints, and ≥20%, ≥50%, or ≥70% improvement in ≥3 of the following: patient assessment pain by VAS, patient global assessment by VAS, physician global assessment by VAS, daily activity assessment (health assessment questionnaire disability index [HAQ-DI; an RA-specific health assessment questionnaire]), and high-sensitivity C-reactive protein (hsCRP) level or erythrocyte sedimentation rate (ESR)
CDAI	Disease activity assessment score calculated by the following formula based on tender joint count (TJC) and swollen joint count (SJC) out of 28 joints, physician (estimator) global assessment by VAS (EGA), and patient global assessment by VAS (PGA): CDAI = TJC + SJC + EGA + PGA
CDAI remission	CDAI of ≤2.8 at assessment
CDAI low disease activity	CDAI of ≤10 at assessment
DAS28-hsCRP	Disease activity assessment score calculated by the following formula based on tender joint count (TJC) and swollen joint count (SJC) out of 28 joints , high-sensitivity C-reactive protein (hsCRP) level, and patient global assessment by VAS (GH): DAS28 = $0.56\sqrt{\mathrm{TJC}} + 0.28\sqrt{\mathrm{SJC}} + 0.36\{\ln(\mathrm{hsCRP} + 1)\} + 0.014 \times \mathrm{GH} + 0.96$
HAQ-DI	Physical function assessment score of RA patients calculated based on subjective difficulty in daily activities of 8 categories (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities [errands and chores]) assessed on a scale of 0 to 3 (the mean score of each category)
mTSS	Structural joint damage score based on the sum of quantified degrees of bone erosion (44 joints) and joint space narrowing (42 joints) in X-ray images of both hands/wrists and feet
SDAI	Disease activity assessment score calculated by the following formula based on tender joint count (TJC) and swollen joint count (SJC) out of 28 joints, high-sensitivity C-reactive protein (hsCRP) level, physician (estimator) global assessment by VAS (EGA), and patient global assessment by VAS (PGA): CDAI = TJC + SJC + hsCRP + EGA + PGA
SDAI remission	SDAI of ≤3.3 at assessment

VAS, Visual analog scale

Review Report (2)

May 19, 2017

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	March 11, 2016

1. Content of the Review

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

On April 14, 2017, Eli Lilly and Company in the US announced that the U.S. Food and Drug Administration (FDA) had issued a complete response letter for the new drug application of Olumiant Tablets [redacted] indicating that the FDA was unable to approve the application for Olumiant for the treatment of rheumatoid arthritis (RA) (http://lilly.mediaroom.com/index.php?s=9042&item=137646).

[redacted]

and PMDA's view are presented below. These views were also discussed at the Expert Discussion.

[redacted]

FDA [redacted] indicated that additional clinical data are needed to determine doses.

The applicant's explanation about venous thromboembolism (VTE):

The incidences of deep vein thrombosis and pulmonary embolism are shown in Table 81. Both events were observed in subjects treated with baricitinib. All subjects who experienced either event had a VTE risk factor such as obesity and previous diseases, and all cases with the events were assessed as not

related to baricitinib. One subject died from pulmonary embolism. The subject had a history of chronic cardiac failure and obesity, and a causal relationship with baricitinib was ruled out for the death.

In the Japanese subgroup, deep vein thrombosis occurred in 3 of 514 subjects. Although the event in 1 of the 3 subjects was serious, it resolved with anticoagulant therapy after discontinuation of baricitinib. All 3 affected subjects had risk factors including obesity and smoking history (2 subjects each), and previous deep vein thrombosis, varicose veins, and lower leg edema (1 subject each). A causal relationship with baricitinib was ruled out for all cases. Pulmonary embolism was not observed in any subjects.

Of all 3492 subjects treated with baricitinib, 24 subjects experienced VTE (including 4 subjects who had both deep vein thrombosis and pulmonary embolism). Of the 24 subjects, 2 experienced increased platelet count (>600,000/mm^3) before the onset of VTE. One of the 2 subjects received baricitinib 4 mg from the start of the study and had a baseline platelet count of 589,000/mm^3, which increased after the start of treatment up to 652,000/mm^3 by the onset of the event. The subject had lower leg edema, a risk factor for deep vein thrombosis. The other subject received placebo at the start of the study and baricitinib 4 mg from Week 20 due to inadequate efficacy. The platelet count of this subject was 302,000/mm^3 at baseline, 341,000/mm^3 at the start of baricitinib 4 mg, and 608,000/mm^3 at peak (Week 96). At Week 104, treatment was suspended due to gastroenteritis. Deep vein thrombosis (platelet count unknown) occurred at Week 107, but it improved with treatment. Baricitinib was resumed 4 days after the onset of the event.

The incidence rate of VTE reported in observational studies in RA patients was 0.59 per 100 person-years (*JAMA*. 2012;308:1350-6) or 0.61 per 100 person-years (*Arthritis Care Res*. 2013;65:1600-7), which was not markedly different from the incidence rate of VTE (0.53 per 100 person-years) in the pooled analysis All BARI RA (data cut-off on January 1, 2016).

Despite the above-mentioned occurrence of VTE in the clinical studies, there are no data from the clinical studies and observational studies clearly indicating an increased risk of VTE following treatment with baricitinib.

Table 81. Incidences of deep vein thrombosis and pulmonary embolism in pooled analyses

		BARI 4-mg RA PC[a]		BARI 2-mg vs 4-mg RA[a]			All BARI RA[b]
		4 mg (N = 997)	Placebo (N = 1070)	2 mg (N = 479)	4 mg (N = 479)	Placebo (N = 551)	All doses of baricitinib in Phase I to III studies (N = 3492)
Deep vein thrombosis	Adverse event	2 (0.2) 0.49 [0.06, 1.76]	0	0	0	0	13 (0.4) 0.25 [0.13, 0.43]
	Adverse event leading to discontinuation	0	0	0	0	0	1 (0.0) 0.02 [0.00, 0.11]
	Serious adverse event	0	0	0	0	0	8 (0.2) 0.16 [0.07, 0.31]
Pulmonary embolism	Adverse event	2 (0.2) 0.49 [0.06, 1.76]	0	0	1 (0.2) 0.53 [0.01, 2.97]	0	15 (0.4) 0.29 [0.16, 0.48]
	Adverse event leading to discontinuation	0	0	0	0	0	2 (0.1) 0.04 [0.00, 0.14]
	Serious adverse event	1 (0.1) 0.24 [0.01, 1.36]	0	0	1 (0.2) 0.53 [0.01, 2.97]	0	12 (0.3) 0.23 [0.12, 0.41]

Upper, number of subjects (%); lower, incidence rate per 100 person-years [95% CI]
[a] Up to Week 24
[b] Data cut-off on January 1, 2016

Time courses of the efficacy endpoints of the JADX study are shown in Figure 15. The applicant commented that, although there was no obvious difference in some endpoints between the 2- and 4-mg groups at some time points, ACR tended to improve in the 4-mg group from an early stage of treatment. The efficacy endpoints including DAS28-hcCRP, SDAI, and CDAI [for the definitions of the respective endpoints, see "10. Other" of Review Report (1)] tended to be better in the 4-mg group than in the 2-mg group. Moreover, great benefits of the baricitinib 4 mg once-daily regimen in the clinical studies are indicated by the following observations:

- Consistent efficacy of the regimen was observed in RA patients with different treatment histories.
- Greater efficacy of the regimen than of methotrexate or adalimumab (genetical recombination) was suggested.
- Efficacy was observed from an early stage of treatment.
- Reduced efficacy tended to be observed more often in subjects in the 2-mg dose-reduction group than in those in the 4-mg dose-maintenance group.

[redacted], the applicant plans to have further discussions with FDA.

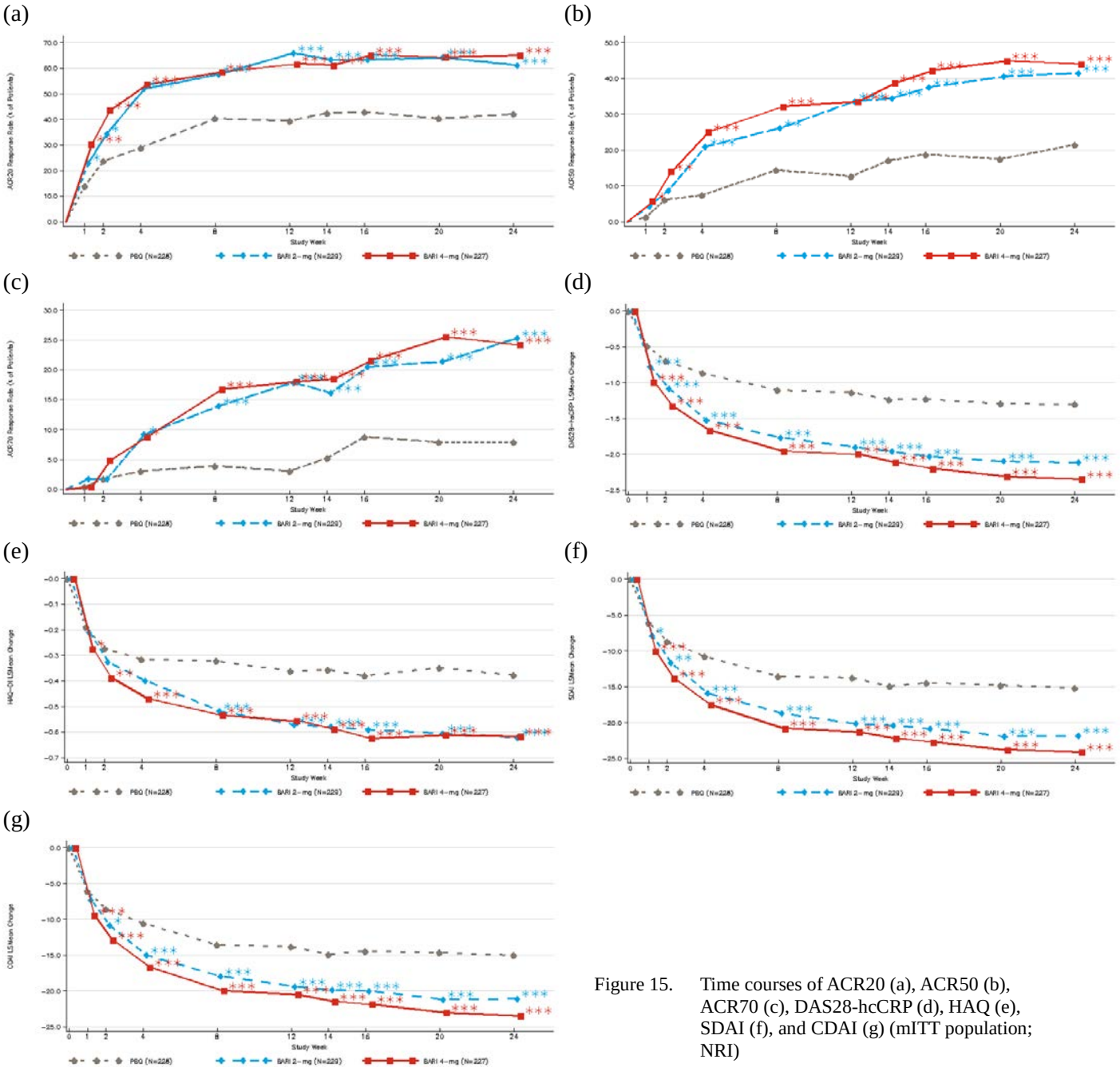

Figure 15. Time courses of ACR20 (a), ACR50 (b), ACR70 (c), DAS28-hcCRP (d), HAQ (e), SDAI (f), and CDAI (g) (mITT population; NRI)

PMDA's view:

As mentioned in Section "7.R.2 Safety" of Review Report (1) and based on the following observations, the applicant should warn of the occurrence of VTE, with a reminder of the importance of adequate monitoring of patient condition during treatment with baricitinib and careful follow-up of those who are at risk for VTE:

- Increased platelet count was observed in subjects receiving baricitinib.
- One subject died of pulmonary embolism.
- In the pooled analyses BARI 4-mg RA PC and BARI 2-mg vs 4-mg RA, VTE occurred only in the 4-mg group, although in a short term.

Given the limited number of subjects in the clinical studies, the occurrence of VTE during treatment with baricitinib including its long-term use should be further investigated in post-marketing surveillance. New findings should be communicated to healthcare professionals accordingly.

While some endpoints showed no clear differences between the 2- and 4-mg groups at some time points, the percentage of ACR responders tended to increase from an early stage of treatment with baricitinib 4 mg, and 4 mg tended to achieve better results than 2 mg in other efficacy endpoints. As mentioned in Section "7.R.1 Efficacy" of Review Report (1), the results suggest greater efficacy of baricitinib 4 mg than of baricitinib 2 mg.

1.1 Efficacy and safety

At the Expert Discussion, PMDA's conclusions about the efficacy and safety of baricitinib presented in Review Report (1) were supported. The following comments were raised by the expert advisors:

- In light of the impact of early withdrawal on the results, baricitinib's inhibitory effect on structural joint damage should also be evaluated at Week 16.
- The JADX study [see Section"7.2.2 Multi-regional study in RA patients with an inadequate response to cDMARDs" of Review Report (1)] and the JADW study [see Section "7.2.1 Multi-regional study in RA patients with an inadequate response to TNF inhibitors" of Review Report (1)] evaluated baricitinib 2 and 4 mg, and the efficacy of 2 mg was assessed as a secondary analysis in these studies. The results suggested a certain efficacy of baricitinib 2 mg.
- The difference [95% CI] from the placebo group in the change in bone erosion score at Week 24 was −0.17 [−0.42, 0.07] in the 2-mg group and −0.36 [−0.61, −0.11] in the 4-mg group, indicating lower efficacy of baricitinib 2 mg than of 4 mg.
- Attaching importance to the high incidences of serious adverse events and adverse events leading to discontinuation in elderly subjects, healthcare professionals should be advised to administer baricitinib carefully to elderly patients.

The over-time changes from baseline in mTSS in the clinical studies are shown in Table 82.

Any groups including the control groups showed a small change from baseline in the early stage of treatment. However, the changes in the baricitinib groups tended to be smaller than those in control groups at any evaluation time point. PMDA therefore concluded that baricitinib is expected to have some inhibitory effect on structural joint damage.

Table 82. Changes from baseline in mTSS[a)]

	JADZ			JADV			JADX		
	4 mg alone	4 mg + MTX	MTX alone	4 mg	Adalimu-mab	Placebo	2 mg	4 mg	Placebo
Week 12 or 16[b)]	0.35 ± 0.92 (146)	0.30 ± 1.13 (191)	0.50 ± 1.74 (185)	0.33 ± 1.33 (454)	0.26 ± 1.13 (300)	0.66 ± 1.86 (444)	–	–	–
Difference from placebo or MTX alone [95% CI][c)]	-0.14 [-0.43, 0.14]	-0.19 [-0.46, 0.08]	–	-0.33 [-0.53, -0.14]	-0.40 [-0.63, -0.18]	–	–	–	–
Week 24	0.43 ± 1.18 (152)	0.32 ± 1.14 (198)	0.64 ± 1.81 (191)	0.35 ± 1.59 (470)	0.29 ± 1.47 (312)	0.84 ± 2.32 (452)	0.43 ± 1.19 (208)	0.27 ± 0.97 (198)	0.80 ± 2.86 (190)
Difference from placebo or MTX alone [95% CI][c)]	-0.22 [-0.52, 0.08]	-0.32 [-0.60, -0.04]	–	-0.49 [-0.73, -0.25]	-0.56 [-0.83, -0.29]	–	-0.38 [-0.74, -0.01]	-0.55 [-0.92, -0.19]	–
Week 52	0.81 ± 2.22 (154)	0.41 ± 1.68 (199)	1.03 ± 2.43 (192)	0.60 ± 2.54 (473)	0.51 ± 2.78 (312)	1.70 ± 4.72 (452)	–	–	–
Difference from placebo or MTX alone [95% CI][c)]	-0.23 [-0.67, 0.22]	-0.62 [-1.04, -0.20]	–	-1.10 [-1.55, -0.64]	-1.20 [-1.71, -0.69]	–	–	–	–

Mean ± standard deviation (number of subjects)

a) Missing values were imputed by the linear extrapolation method. The number of subjects in each group was the number of subjects analyzed.

b) At Week 12 in the JADZ study and Week 16 in the JADV study

c) The JADZ study: an analysis of covariance model with baseline value, region, baseline status of bone erosion, and treatment group as explanatory variables
The JADV study: an analysis of covariance model with baseline value, baseline bone erosion score (1-2 sites and serum response positive; ≥3 sites), and treatment group as explanatory variables
The JADX study: an analysis of covariance model with baseline value, baseline status of bone erosion, and treatment group as explanatory variables

1.2 Clinical positioning and indication

At the Expert Discussion, PMDA's conclusions about the clinical positioning and indication of baricitinib presented in Review Report (1) were supported. The following comments were made by the expert advisors:

- Based on the efficacy and safety results from the clinical studies, baricitinib should only be used in patients with an inadequate response to ≥1 antirheumatic drug.
- The use of baricitinib alone or in combination with DMARDs other than MTX is possible. However, baricitinib should be indicated for RA patients inadequately responding to appropriate treatment with MTX as a rule.

Based on the comments at the Expert Discussion, PMDA concluded that the indication and precautions for indications of baricitinib should be described as follows:

Indication

Rheumatoid arthritis in patients who have had an inadequate response to conventional treatments (including the prevention of structural joint damage)

Precautions for indications

Baricitinib should be administered only to patients who have persistent symptoms clearly attributable to rheumatoid arthritis despite previous appropriate medication with ≥1 antirheumatic drug such as methotrexate.

1.3 Dosage and administration

At the Expert Discussion, PMDA's conclusions about the dosage and administration of baricitinib presented in Review Report (1) were supported. The following comments were made by the expert advisors:

- Baricitinib 4 mg tended to cause adverse events more frequently than 2 mg in the clinical studies, and baricitinib may have sufficient effect even at a low dose. Therefore, the 2-mg dose should also be included in treatment options.
- Based on the clinical study data, healthcare professionals should be informed of patient characteristics suitable for the 2-mg dose, e.g., their clinical symptoms, concomitant diseases such as renal impairment, and age.

Taking into account the comments from the Expert Advisors, PMDA concluded that treatment with baricitinib should start with the usual starting dose of 4 mg once daily, and dose reduction to 2 mg once daily should be considered when low disease activity is achieved, depending on clinical symptoms of the patient. Further, treatment may be started with baricitinib at 2 mg once daily depending on the patient's condition including concomitant disease such as renal impairment, age, and concomitant drugs. Accordingly, dosage and administration should be described as follows:

Dosage and administration

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.

1.4 Risk management plan (draft)

At the Expert Discussion, PMDA's conclusions about post-marketing safety measures presented in Review Report (1) were supported. The following comments were made by the expert advisors:

- Baricitinib may pose similar risks to those caused by existing JAK activity inhibitors and biological drugs for treating RA. Therefore, similar safety measures should be taken for baricitinib; for example, use of baricitinib by physicians knowledgeable about baricitinib and have adequate knowledge and experience in RA drug therapy.
- Given the limited number of underweight subjects in clinical studies, the safety and efficacy of baricitinib alone in this patient population should be further investigated through post-marketing surveillance.

Based on the review presented in Section "7.R.6 Post-marketing safety measures" of Review Report (1) and the discussion at the Expert Discussion, PMDA concluded that the draft risk management plan for baricitinib should include the safety and efficacy specifications listed in Table 83 and that additional pharmacovigilance activities and risk minimization activities listed in Table 84 should be conducted.

Table 83. Safety and efficacy specifications in the risk management plan (draft)

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

Table 84. Summary of additional pharmacovigilance activities and risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (all-case surveillance) • Post-marketing clinical study (the JADY study)[a)] • Pharmacovigilance activities using the medical information database (serious infection) • Pharmacovigilance activities using the medical information database (malignant tumor)	• Early post-marketing phase vigilance • Preparation and distribution of reference materials for healthcare professionals • Preparation and distribution of reference materials for patients • Ensuring provision of information on proper use before product supply

a) The ongoing JADY study will be continued as a post-marketing clinical study after approval.

PMDA instructed the applicant to conduct post-marketing surveillance to investigate the above specifications.

The applicant's explanation about the main survey items:

As shown in Table 85, a specified use-results survey will be conducted covering all patients receiving baricitinib. The survey will continue until data from a certain number of patients on baricitinib (planned sample size, 3000) are accumulated. All patients registered will be observed for a total of 3 years, including the first 6-month follow-up, to assess the safety and efficacy of baricitinib in routine clinical settings. The priority survey items of this survey will be herpes zoster, serious infection (including tuberculosis), neutrophil count decreased and neutropenia, lymphocyte count decreased and lymphopenia, haemoglobin decreased and anaemia, hepatitis B virus reactivation, gastrointestinal perforation, hepatic dysfunction, lipids increased and hyperlipidaemia, interstitial pneumonia, malignant tumor (including lymphoma), cardiovascular events, rhabdomyolysis and myopathy, and venous thromboembolism. The risk of malignant tumor and serious infection caused by baricitinib will be compared against the medical information database for further investigation.

Table 85. Outline of specified use-results survey (all-case survey) (draft)

Objective	To assess the safety and efficacy of baricitinib in its clinical use
Survey method	All-case survey
Population	RA patients with an inadequate response to existing treatments
Observation period	3 years
Planned sample size	3000 patients
Main survey items	• Priority survey items: herpes zoster, serious infection (including tuberculosis), neutrophil count decreased and neutropenia, lymphocyte count decreased and lymphopenia, haemoglobin decreased and anaemia, gastrointestinal perforation, hepatitis B virus reactivation, hepatic dysfunction, lipids increased and hyperlipidaemia, interstitial pneumonia, malignant tumor (including lymphoma), cardiovascular events, rhabdomyolysis and myopathy, and venous thromboembolism • Patient characteristics (e.g., body weight, age, duration of disease, complications, and medical history) • Previous treatments for RA • Use status of baricitinib • Concomitant drugs and therapies • Laboratory tests • Adverse events • Efficacy assessment

PMDA accepted the applicant's planned actions including the survey and concluded that the applicant should keep providing safety information including the latest incidence and severity of malignant tumor and serious infection to healthcare professionals and patients appropriately and promptly via printed materials, website, and any other means.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the descriptions of the proposed indication and dosage and administration as shown below and with the following conditions attached. The product, a drug with a new active ingredient, is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Indication

Rheumatoid arthritis <u>in patients who have had an inadequate response to conventional treatments</u> (including the prevention of structural joint damage)

(Underline denotes additions)

Dosage and Administration

The usual adult dosage is 4 mg of baricitinib administered orally once daily. The dose ~~may~~ <u>should</u> be reduced to 2 mg according to ~~symptoms~~ <u>the patient's condition</u>.

(Underline denotes additions, and strike-through denotes deletion)

Conditions of Approval

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

2. A post-marketing use-results survey must be conducted covering all patients treated with the product until data are gathered from a certain number of patients so that the safety and efficacy data of the product are available early. The applicant is required to take any necessary measures to ensure proper use of the product based on data obtained through the survey.