Report on the Deliberation Results

February 28, 2019

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

Brand Name	Smyraf Tablets 50 mg, Smyraf Tablets 100 mg
Non-proprietary Name	Peficitinib Hydrobromide (JAN*)
Applicant	Astellas Pharma Inc.
Date of Application	May 31, 2018

Results of Deliberation

In its meeting held on February 22, 2019, 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. The applicant is required to conduct a drug use-results survey covering all patients treated with the product after its market launch until data from a certain number of patients have been accumulated, to early collect the safety and efficacy data on the product and to take necessary measures to facilitate the proper use of the product.

**Japanese Accepted Name (modified INN)*

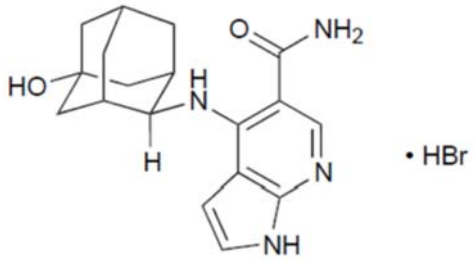
Review Report

February 14, 2019
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Smyraf Tablets 50 mg, Smyraf Tablets 100 mg
Non-proprietary Name	Peficitinib Hydrobromide
Applicant	Astellas Pharma Inc.
Date of Application	May 31, 2018
Dosage Form/Strength	A tablet containing 62.4 mg of peficitinib hydrobromide (50 mg of peficitinib) or 124.8 mg of peficitinib hydrobromide (100 mg of peficitinib)
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{18}H_{22}N_4O_2 \cdot HBr$

Molecular weight: 407.30

Chemical name: 4-{[(*1R, 2s, 3S, 5s, 7s*)-5-Hydroxyadamantan-2-yl]amino}-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxamide monohydrobromide

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 (including prevention of structural joint damage) in patients who have an inadequate response to conventional therapies and that the product has acceptable safety in view of its benefits.

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. In view of the risk of serious infections or serious adverse reactions such as malignancy associated with the product, safety measures required in its clinical use are the same as that taken for approved Janus kinase (JAK) inhibitors or biological products for the treatment of rheumatoid arthritis. The applicant should conduct a drug use-results survey covering all patients

treated with the product after its market launch until data from a certain number of patients have been accumulated to early grasp the safety profile of the product including unknown adverse events. The applicant also should conduct a survey to trace the occurrence of serious infections and malignant tumors, etc. in prolonged use of the product.

Indication	Treatment of rheumatoid arthritis (including prevention of structural joint damage) in patients who have an inadequate response to conventional therapies.
Dosage and Administration	The usual adult dosage is 150 mg of peficitinib administered orally once daily after a meal. A 100-mg dose may be administered once daily according to the patient's condition.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a drug use-results survey covering all patients treated with the product after its market launch until data from a certain number of patients have been accumulated, to early collect the safety and efficacy data on the product and to take necessary measures to facilitate the proper use of the product.

Attachment

Review Report (1)

January 25, 2019

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

Product Submitted for Approval

Brand Name	Smyraf Tablets 50 mg, Smyraf Tablets 100 mg
Non-proprietary Name	Peficitinib Hydrobromide
Applicant	Astellas Pharma Inc.
Date of Application	May 30, 2018
Dosage Form/Strength	A tablet containing 62.4 mg of peficitinib hydrobromide (50 mg of peficitinib) or 124.8 mg of peficitinib hydrobromide (100 mg of peficitinib)
Proposed Indication	Treatment of rheumatoid arthritis (including prevention of structural joint damage) in patients who have an inadequate response to conventional therapies.
Proposed Dosage and Administration	The usual adult dosage is 100 to 150 mg of peficitinib administered orally once daily after a meal. The dose can be reduced to 50 mg per dose according to the patient's condition.

Table of Contents

List of Abbreviations

See Appendix.

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

Peficitinib hydrobromide (to be referred as to peficitinib), the active ingredient of Smyraf Tablets 50 mg or 100 mg, is a Janus kinase (JAK) inhibitor developed by Astellas Pharma Inc.

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory, and autoimmune disease that is characterized by destruction of the synovial membrane of joints. The currently recommended treatment for RA aims to relieve arthritis symptoms as soon as possible to induce sustainable remission (Japan College of Rheumatology [JCR], *Clinical Practice Guidelines for Rheumatoid Arthritis 2014*). In pharmacotherapy for RA, use of conventional disease-modifying antirheumatic drugs (cDMARDs) including methotrexate (MTX) is recommended as soon as RA is confirmed, and biological agents including tumor necrosis factor (TNF) inhibitors are recommended for patients responding insufficiently to these cDMARDs. JAK inhibitors are recommended as alternative therapeutic options (*Ann Rheum Dis.* 2017;76:960-77). In Japan, tofacitinib and baricitinib were approved as JAK inhibitors in 2013 and 2017, respectively, for the indication of treatment in RA patients with an inadequate response to conventional therapies.

The JAK family is a family of intracellular tyrosine kinases consisting of JAK1, JAK2, JAK3, and TYK2, and involves in signal transduction mediated by type I and II cytokine receptors. JAKs associate with intracellular domains of various cytokine receptors and growth factor receptors and play an important role in signal transduction of cytokines and growth factors. In response to the suggested association of the signaling pathway of the Janus kinase/signal transduction and activator of transcription (JAK-STAT) with the pathogenesis of autoimmune diseases including RA (*Drugs*. 2017;77:521-46), Astellas developed peficitinib for the treatment of RA.

The clinical development of peficitinib was started overseas in July 2008 and in Japan in November 2009. The marketing application for peficitinib has been filed based on data from global and Japanese phase III clinical studies. Outside Japan, the applications for peficitinib are currently under review in Korea and Taiwan, and [redacted] as of January 2019.

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 white powder. The determined general properties of the drug substance include description, solubility, hygroscopicity, thermal analysis, melting point, dissociation constant (pyridinium group), partition coefficient, and particle size distribution. A total of 6 crystalline forms ([redacted]) of the drug substance have been identified. Only [redacted], however, has been confirmed to be produced during the manufacturing process at commercial scale.

The proposed specifications for the drug substance include powder X-ray diffractometry to control the crystalline form.

The chemical structure of the drug substance has been elucidated by elemental analysis, ultraviolet and visible absorption spectrometry (UV-VIS), infrared spectrophotometry (IR), hydrogen (^{1}H-) and carbon (^{13}C-) nuclear magnetic resonance spectrometry (NMR), mass spectrometry, and single-crystal X-ray crystallography.

2.1.2 Manufacturing process

The drug substance is synthesized from [redacted] and [redacted] as the starting materials.

A quality by design (QbD) approach has been applied to the following to formulate the quality control strategy (Table 1).

- Identification of critical quality attributes
- Identification of critical process parameters based on the quality risk assessment

Table 1. Outline of the quality control strategy for the drug substance

Critical quality attributes	Control methods
[redacted]	[redacted]

The [redacted] process has been specified as a critical step. The [redacted] and [redacted] have been controlled as a critical intermediate.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (UV-VIS, IR, powder X-ray diffractometry, and qualitative test for bromides), purity (related substances [high performance liquid chromatography (HPLC)] and residual solvents and [redacted] [gas chromatography]), residue on ignition, and assay (HPLC).

2.1.4 Stability of drug substance

The main stability studies performed for the drug substance are shown in Table 2. The photostability testing showed that the drug substance is photostable.

Table 2. Main stability studies for the drug substance

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term testing	3 batches at commercial scale	25°C	60% RH	Low-density polyethylene bag (double-layer) + low-density polyethylene tube + high-density polyethylene drum	36 months
Accelerated testing		40°C	75% RH		6 months

Based on the above and in compliance with the Guidelines for Evaluation of Stability Data (Notification No. 0603004 of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau [PFSB/ELD], the Ministry of Health, Labour and Welfare [MHLW], dated June 3, 2003), a re-test period of 48 months has been proposed for the drug substance when stored in a double-layer low-density polyethylene bag, then in a low-density polyethylene tube, and further packed in a high-density polyethylene drug at room temperature. The long-term testing will be continued for up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is film-coated tablets each containing 62.4 mg of the drug substance (50 mg of peficitinib) or 124.8 mg of the drug substance (100 mg of peficitinib). It contains the following as excipients: D-mannitol, hydroxypropyl cellulose, crystalline cellulose, low-substituted hydroxypropyl cellulose, sodium stearyl fumarate, light anhydrous silicic acid, hypromellose, talc, macrogol [redacted], titanium oxide, and yellow iron sesquioxide (only for 50 mg tablets) or iron sesquioxide (only for 100 mg tablets).

2.2.2 Manufacturing process

The drug product is manufactured in a process consisting of the [redacted] and [redacted] steps. The [redacted] step is as a [redacted] step, and the process controls and action limits are specified for [redacted] and [redacted] steps.

A QbD approach is employed to the following to formulate the quality control strategy (Table 3).

- Identification of critical quality attributes based on the quality target product profile
- Identification of critical process parameters based on the quality risk assessment

Table 3. Outline of control strategy for the drug product

Critical quality attributes	Control methods
[redacted]	[redacted]

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description (appearance), identification (UV-VIS), purity (related substance [HPLC]), dissolution (HPLC), microbial limit test, and assay (HPLC).

As for [redacted] and [redacted], near-infrared spectroscopy is performed for [redacted] as in-process controls, which are included in the real time release testing (RTRT) and used as testing for the drug product release. If the RTRT is not applicable for release testing, specification tests are to be performed according to prespecified suitability criteria and implementation procedures to determine the release.

2.2.4 Stability of drug product

The main stability studies performed for the drug product are shown in Table 4. The photostability testing showed that the drug product is photostable.

Table 4. Main stability studies for the drug product

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term testing	3 batches at pilot scale	25°C	60% RH	Blister pack＋aluminum bag (with desiccant)	24 months
Accelerated testing		40°C	75% RH		6 months

Based on the above and in compliance with the Guidelines for Evaluation of Stability Data (PFSB/ELD Notification No. 0603004, dated June 3, 2003), a shelf-life of 36 months has been proposed for the drug product when stored in a blister pack (polyvinyl chloride file/aluminum foil) and further in an aluminum bag with desiccant. The long-term testing will be continued for up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA has 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

For the evaluation of primary pharmacodynamics, the applicant submitted study data on the inhibitory effect of peficitinib on the JAK family and effects on animal models of rheumatoid arthritis. For the evaluation of secondary pharmacodynamics, the applicant submitted study data on the effects of peficitinib on kinases, receptors, ion channels, enzymes, and transporters. For the evaluation of safety pharmacology, the applicant submitted study data on the effects of peficitinib on the central nerve, cardiovascular, and respiratory systems, and data from follow-up studies were also submitted for the effects on the cardiovascular system.

In this section, unless otherwise specified, peficitinib hydrobromide is described, the dose is expressed as an equivalent dose of peficitinib, and the pharmacodynamic parameters are expressed as the mean.

3.1 Primary pharmacodynamics

3.1.1 Inhibitory effects on the JAK family (CTD 4.2.1.1-1 to -3, 4.2.1.2-3)

Table 5 shows the half-maximal inhibitory concentration (IC_{50}) of peficitinib and its metabolites (M1, M2, and M4) in assays of recombinant human JAK1, JAK2, JAK3, and TYK2 kinase domains.

Table 5. IC_{50} of Peficitinib and its metabolites for the JAK family

	Peficitinib	Metabolites		
		M1	M2	M4
JAK1 (200 μmol/L in the presence of ATP)	3.92	>500	101	>1000
JAK2 (10 μmol/L in the presence of ATP)	5.01	>500	14.0	>1000
JAK3 (8 μmol/L in the presence of ATP)	0.71	>500	0.655	>1000
TYK2 (10 μmol/L in the presence of ATP)	4.79	>500	43.1	>1000

IC_{50}: nmol/L

3.1.2 Effects on signal transduction of and proliferation of T cells mediated by IL-2 (CTD 4.2.1.1-4 to -9)

Peficitinib (30, 100, 300, or 1000 nmol/L) inhibited phosphorylation of the signal transducer and activator of transcription 5 (STAT5) in a concentration-dependent manner in the stimulation of human blood T cells with human interleukin (IL) 2 (10 ng/mL).

The IC_{50} of peficitinib for proliferation of T cells derived from human peripheral blood mononuclear cells (PBMC) induced by stimulation with human IL-2 (1 ng/mL), cynomolgus PBMC-derived T cells induced by stimulation with human IL-2 (3 ng/mL), and rat spleen-derived T cells induced by stimulation with human IL-2 (3 ng/mL) was 18.2, 39.9, and 10.2 nmol/L, respectively. In a similar study with human PBMC-derived T cells, while no cell proliferation was inhibited by M1 and M4 up to a concentration of 1000 nmol/L and up to 100 nmol/L by M2, M2 at 1000 nmol/L inhibited cell proliferation by approximately 20%.

3.1.3 Effects on cytokine production of human PBMC (CTD 4.2.1.1.10, 4.2.1.1.11)

The IC_{50} of peficitinib for production of interferon (IL)-13, granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN-γ, and TNFα induced by stimulation of human PBMC with human IL-2 (100 ng/mL) was 2.43, 2.11, 0.203, and 15.7 nmol/L, respectively. The IC_{50} of peficitinib for production of IL-4, IL-5, IL-13, GM-CSF, IFN-γ, and TNFα induced by stimulation of human PBMC with anti-CD28 antibodies (0.5 μg/mL) using an anti-CD3 antibody-coated plate was 25.0, 10.9, 173, 469, 79.0, and 136 nmol/L, respectively.

3.1.4 Effects on adjuvant-induced arthritis in rats (CTD 4.2.1.1-12, 4.2.1.1-13)

Adjuvant containing killed *Mycobacterium tuberculosis* was inoculated into footpads of female rats, and beginning from the same day, peficitinib 0 (vehicle), 1, 3, 10, or 30 mg/kg was orally administered once daily for 24 days. Footpad edema formation was inhibited in a dose-dependent manner, and the ED_{50} was 2.7 mg/kg. The radiographic evaluation of bone destruction of left hind limbs demonstrated decreases in radiographic bone destruction scores[1)] in the 10 and 30 mg/kg groups

In another study, adjuvant containing killed *Mycobacterium tuberculosis* was inoculated into footpads of female rats to induce edema in their footpads, and 15 days after the inoculation, peficitinib 0 (vehicle), 1, 3, 10 or 30 mg/kg was orally administered once daily for 10 days. Footpad edema was ameliorated in the 10 and

[1)] For evaluation of the bone destruction of left hind limbs, the severity of bones and joints were evaluated for radiographic 5 signs (destruction of calcaneus, destruction of tarsal bones, destruction of intertarsal joints and joints between the tarsal bones and ankle bones, destruction of metatarsal bones, and destruction of distal tibiae) and were classified into 3 grades (0, no change; 1, moderate change; and 2, severe change). A total score of the severity serves as the bone destruction score for each animal.

30 mg/kg groups with an ED_{50} of 5.6 mg/kg. The radiographic evaluation of bone destruction of left hind limbs demonstrated decreases in radiographic bone destruction scores[1)] in the 30 mg/kg group.

3.2 Secondary pharmacodynamics

3.2.1 Effects on cell proliferation induced by erythropoietin (CTD 4.2.1.2-1)

The IC_{50} of peficitinib for proliferation of human erythroleukemia cells (TF-1 cells) induced by stimulation with erythropoietin (1 U/mL) was 248 nmol/L.

3.2.2 Effects on kinases (CTD 4.2.1.2-2, 4.2.1.2-3)

As for kinases other than the JAK family, the IC_{50} of peficitinib for lymphocyte-specific protein tyrosine kinase, protein kinase C-alpha, and cyclin-dependent kinase 2/cyclin A complex was 750, 680, and 707 nmol/L, respectively. The inhibition rate of peficitinib up to 1 μmol/L for other studied kinases (including EGFR, CHUK, and MAPK11) was <50%.

3.2.3 Effects on receptors, ion channels, enzymes, and transporters (CTD 4.2.1.2-4)

Among studied receptors, ion channels, enzymes, and transporters, only the rat GABA-A receptor was inhibited by ≥50% by peficitinib (10 μmol/L) with an IC_{50} 6.74 μmol/L.

3.3 Safety pharmacology

3.3.1 Effects on the central nervous system (CTD 4.2.1.3-1)

A single oral dose of peficitinib 10, 30, or 100 mg/kg was administered to male rats (6/group). General symptoms and behavior were assessed by the modified Irwin test, and no effects were observed in any groups. In a 4-week oral toxicity study in rats [see Section 5.2], the C_{max} and $AUC_{0\text{-}24h}$ after the initial dosing of peficitinib in male rats in the 100 mg/kg group was 6400 ng/mL and 23,913 ng·h/mL, respectively, which were 10.4 times and 9.0 times, respectively, those observed in Japanese healthy adults receiving repeated doses of peficitinib 150 mg orally administered once daily in Study CL-PK20 (C_{max} of 613.2 ng/mL and AUC_{24h} of 2643 ng·h/mL) [see Section 6.2.1.2].

3.3.2 Effects on the cardiovascular and respiratory systems (CTD 4.2.1.3-2 to -4)

3.3.2.1 Effects on hERG current and cardiac action potential

Human embryonic kidney 293 cells expressing the human ether-à-go-go related gene (hERG) channel were treated with peficitinib 0.1, 1, and 10 μmol/L, and the rate of inhibition of hERG current (measured by patch-clamp technique) after the treatment was −0.1%, −3.2%, and 11.7%, respectively. No statistically significant differences in the current inhibition rate were observed between peficitinib at the above concentrations and the vehicle. Based on the findings, the applicant concluded that peficitinib up to 10 μmol/L has no obvious inhibitory effects on hERG current.

Peficitinib 0.1, 1, and 10 μmol/L was demonstrated to have no effects on the action potential duration, upstroke amplitude, maximum upstroke velocity of the action potential, or resting membrane potential as measured by the glass microelectrode method with isolated guinea pig papillary muscles.

Peficitinib 10 μmol/L (3264 ng/mL) was 19.6 times the plasma concentration of the unbound peficitinib (166.6 ng/mL), which was calculated from the C_{max} (613.2 ng/mL) and the plasma protein-binding rate (72.83% to 75.20%, CTD 4.2.2.3-5) after repeated administration of peficitinib 150 mg once daily to Japanese healthy adults in Study CL-PK20 [see Section 6.2.1.2].

3.3.2.2 Effects on the cardiovascular and respiratory systems

In studies investigating the effects of peficitinib on the cardiovascular and respiratory systems, a single dose of peficitinib 15, 30, or 60 mg/kg was administered to male cynomolgus monkeys (4/group). In the 60 mg/kg group, soft stools and watery stools were observed in one animal at 2 and 4 hours after dosing, and blood potassium levels tended to decrease in 3 animals in 1 to 4 hours after dosing. No other effects were observed for general observation of symptoms, temperature, heart rate, blood pressure, electrocardiograms, blood gas parameters, or blood electrolytes. Based on these findings, the applicant concluded that peficitinib up to 60 mg/kg has no obvious effects on the cardiovascular or respiratory system. The C_{max} (879 ng/mL) and $AUC_{0\text{-}24h}$ (7,331 ng·h/mL) after administration of peficitinib 60 mg/kg was 1.4 times the C_{max} (613.2 ng/mL) and the 2.8 times the AUC_{24h} (2643 ng·h/mL), respectively, after repeated administration of peficitinib 150 mg once daily to Japanese healthy adults in Study CL-PK20 [see Section 6.2.1.2].

3.4 Follow-up studies

3.4.1 Effects on myocardial ion channels and Na^+/Ca^{2+} exchanger (CTD 4.2.1.3-5, 4.2.1.3-6 to -8 [reference data])

Table 6 shows the effects of peficitinib and its metabolites (M1, M2, and M4) on human myocardial ion channels and channel currents of NCX1 (type 1 Na^+/Ca^{2+} exchange transporter) expressing cells (human embryonic kidney 293 cells or Chinese hamster ovary cells) (as measured by patch-clamp technique).

Table 6. Effects of peficitinib and its metabolites on myocardial ion channels and Na^+/Ca^{2+} exchanger

Myocardial ion channels	Test substances	Concentrations (μmol/L)	Results
hERG	M2, M4	0.1, 1, 10	No effects were observed for any concentrations tested.
	M1	0.01, 0.03, 0.1	
hNav1.5	Peficitinib [a], M2, M4	0.1, 1, 10	
	M1	0.01, 0.03, 0.1	
hCav1.2-β2-α2δ	Peficitinib [b], M2, M4	0.1, 1, 10	
	M1	0.01, 0.03, 0.1	
hKvLQT1/hminK	Peficitinib [c], M2, M4	0.1, 1, 10	
	M1	0.01, 0.03, 0.1	
hKv4.3	Peficitinib [d], M2, M4	0.1, 1, 10	
	M1	0.01, 0.03, 0.1	
hKir6.2/SUR2A	Peficitinib, M2, M4	0.1, 1, 10	
	M1	0.01, 0.03, 0.1	
hKir2.1	Peficitinib, M2, M4	0.1, 1, 10	
	M1	0.01, 0.03, 0.1	
NCX1	Peficitinib, M1, M2, M4	0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10	

hERG, human ether-a-go-go related gene; hNav1.5, human Nav1.5 sodium channel; hCav1.2-β2-α2δ, human Cav1.2-β2-α2δ calcium channel; hKvLQT1/hminK, human KvLQT1/mink potassium channel; hKv4.3, human Kv4.3 potassium channel; hKir6.2/SUR2A, human Kir6.2/SUR2A potassium channel; hKir2.1, human Kir2.1 potassium channel; and NCX1, type 1 Na^+/Ca^{2+} exchanger
a) The actually exposed concentrations of peficitinib were 0.12, 1.10, and 10.8 μmol/L.
b) The actually exposed concentrations of peficitinib were 0.11, 1.01, and 10.1 μmol/L.
c) The actually exposed concentrations of peficitinib were 0.12, 1.07, and 10.7 μmol/L.
d) The actually exposed concentrations of peficitinib were 0.13, 1.04, and 10.4 μmol/L.

3.R Outline of the review by PMDA

The applicant's explanation about the mechanism of action of peficitinib on RA:

Various inflammatory cytokines, such as IL-2, IFN-γ, TNF-α, and GM-CSF, produced by T cells invading to synovial RA lesions play a key role in the persistence of inflammatory response and progression of bone destruction (*Rheumatology [Oxford]*. 1999;38:202-13; *Nat Rev Rheumatol*. 2013;9:24-33). Since peficitinib has been demonstrated to inhibit the kinase activity of the JAK family (JAK1, JAK2, JAK3, and TYK2) and their signal transduction mediated by IL-2, peficitinib is expected to inhibit the signal transduction of cytokines important for the pathological condition of RA. In an *in vitro* study, an inhibitory effect on the kinase activity of the JAK family was observed for M2, a metabolite of peficitinib [see Section 3.1.1]. Meanwhile, peficitinib up to 100 nmol/L showed no inhibitory effects on the proliferation of PBMC-derived T cells induced by stimulation with IL-2 [see Section 3.1.2]. In light of the plasma concentration of the unbound peficitinib (107-112 nmol/L[2)]) after repeated administration of peficitinib 150 mg once daily to Japanese healthy adults, the role of M2 in the pharmacological action of peficitinib is considered limited.

The applicant's explanation about the difference or similarity in action mechanism between peficitinib and similar drugs, e.g., tofacitinib citrate and baricitinib, and their clinical effects:

While peficitinib inhibits enzymes of the JAK family (JAK1, JAK2, JAK3, and TYK2), tofacitinib selectively inhibits JAK1, JAK2, and JAK3, and baricitinib selectively inhibits JAK1 and JAK2. This suggests that the inhibitory profile for the JAK family differs between peficitinib and the similar drugs. However, studies with cells demonstrated that the signal transduction of cytokines which are inhibited by peficitinib was inhibited also by tofacitinib and baricitinib (J *Med Chem*. 2014;57:5023-38; *Ann Rheum Dis*. 2018;77:A38), suggesting that peficitinib and the similar drugs will exhibit their therapeutic effects with the similar mechanisms.

[2)] Calculated with the C_{max} (1,112 ng/mL) and the plasma protein-binding rate (95.9% to 96.1% [see Section 4.2.2]) of M2 after oral repeated-dose administration of peficitinib 150 mg once daily in Japanese healthy adults in Study CL-PK20.

The signal transduction of IL-2, IL-7, and IL-15, which are important for the maturation and activation of T cells and natural killer (NK) cells, is mediated by JAK1/JAK3 (*Immunity*. 2012;36:515-28; *Front Immunol*. 2018;9:1869), and the signal transduction of erythropoietin, which plays an important role in the production of erythrocytes, is mediated by JAK2 (*Drugs*. 2017;77:521-46). These findings suggest that peficitinib may also decrease the number and activity of T cells and NK cells and the number of erythrocytes.

PMDA's view;
Based on the submitted data, the pharmacological action of peficitinib has been demonstrated and that peficitinib is expected to have efficacy in the treatment of RA mainly on the ground of its pharmacological action.

Based on the anticipated effects of peficitinib on the immune and hematopoietic systems due to its pharmacological action, peficitinib is presumed to have risks that are similarly seen in the use of tofacitinib citrate and baricitinib. During the treatment, attention should be paid to the occurrence of serious infections and malignant tumors and the effects on the hematopoietic system [for safety, see Section 7.R.3].

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

The applicant submitted data from studies of oral and intravenous administration of peficitinib to rats and cynomolgus monkeys for evaluation of absorption, distribution, metabolism, and excretion. The concentrations of peficitinib and its metabolites in plasma were measured with liquid chromatography-tandem mass spectrometry (LC-MS/MS; with a lower limit of quantification of 0.25 ng/mL), and the radioactivity concentrations in biospecimens were measured with a liquid scintillation counter.

The dose is expressed as that of peficitinib, and pharmacokinetic parameters are expressed as a mean or a mean ± standard deviation, unless otherwise specified.

4.1 Absorption

4.1.1 Single dose studies (CTD 4.2.2.2-1, 4.2.2.2-2)

Table7 shows the pharmacokinetic parameters after single-dose oral and intravenous administration of peficitinib to male rats and cynomolgus monkeys. The absolute bioavailability after oral administration of peficitinib was 39.8% to 46.4% in rats and 18.9% to 19.2% in cynomolgus monkeys.

Table7. Pharmacokinetic parameters after single-dose oral and intravenous administration of peficitinib

Animal species	Route of administration	Dose (mg/kg)	Number	C_{max} (ng/mL)	T_{max} (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	CL_{tot} (L/h/kg)	V_{ss} (L/kg)
Rat	Oral	1	3 males/time point	125.7	0.25	263.7	2.12	—	—
		3	3 males/time point	721.7	0.10	800.2	2.59	—	—
		10	3 males/time point	2051	0.10	2289	3.01	—	—
	Intra-venous	1	3 males/time point	—	—	574.5	4.72	1.74	1.83
Cynomol-gus monkey	Oral	1	4 males	20.2 ± 8.86	3.25 ± 3.20	183.3 ± 59.22	6.40 ± 1.43	—	—
		3	4 males	74.1 ± 38.5	3.00 ± 2.00	548.2 ± 124.5	5.58 ± 0.44	—	—
		10	4 males	286 ± 116	2.50 ± 1.00	1802 ± 591.9	5.78 ± 0.74	—	—
	Intra-venous	1	4 males	—	—	978.9 ± 119.6	6.44 ± 1.31	1.03 ± 0.12	2.80 ± 0.41

Mean or mean ± standard deviation; CL_{tot}, total clearance; V_{ss}, volume of distribution at steady state; —, not calculated

4.1.2 Repeated-dose studies (toxicokinetics) (CTD 4.2.3.2-4, 4.2.3.2-8, 4.2.3.7.5-2, 4.2.3.7.5-4)

Table 8 shows the pharmacokinetic parameters of peficitinib and its metabolites after repeated-dose oral administration of peficitinib once daily in male and female rats and cynomolgus monkeys.

In the pharmacokinetics of peficitinib, there were no consistent sex difference among doses or accumulation associated with repeated-doses of peficitinib in either animal species.

In the pharmacokinetics of M2, C_{max} and $AUC_{0\text{-}24}$ were higher in female rats than in male rats, showing sex difference,[3)] and C_{max} $AUC_{0\text{-}24}$ after repeated-dose decreased only in male rats.[4)] In cynomolgus monkeys, the exposure tended to be higher in female monkeys than in male monkeys, which was attributed to the differences of exposure to peficitinib due to the inter-individual variability.

[3)] The metabolic activity of sulfate conjugation of peficitinib hydrobromide was investigated in rat liver cytosol. The metabolic activity of sulfate conjugation from the unchanged peficitinib to M2 was higher in female rats than in male rats (*Xenobiotica*. 2015;45:488-94), and the mRNA expression level of SULT2A1 in the rat liver was higher in female rats than in male rats (*J Pharmacol Exp Ther*. 1997;282:1117-21). Based on these findings, the applicant explained that the sex difference in the metabolic activity of SULT2A1 caused the sex difference in the M2 exposure.

[4)] Decreased M2 exposure after repeated-dose administration in male rats was due to the depletion of active sulfate (PAPS), a coenzyme, which caused activity of sulfate conjugation to decrease in male rats (*J Pharmacol Exp Ther*. 1995;275:654-8). The applicant explained that a similar phenomenon had occurred in the study.

Table 8. Pharmacokinetic parameters after repeated-dose oral administration of peficitinib

Animal species	Dose (mg/kg /day)	Target entity	Number	Time point	C_{max} (ng/mL)		t_{max} (h)		AUC_{0-24} (ng·h/mL)	
					Males	Females	Males	Females	Males	Females
Rat	30	Peficitinib	3/sex/time point	Day 1	1390	2584	0.25	0.25	4768	7942
			3/sex/time point	Day 28	1516	3006	0.25	0.25	6500	8443
		M2	3/sex/time point	Day 1	154.1	1665	1.0	1.0	368.4	6931
			3/sex/time point	Day 28	2.638	2177	1.0	0.25	16.37	6788
	100	Peficitinib	3/sex/time point	Day 1	7111	6648	1.0	1.0	21,090	23,750
			3/sex/time point	Day 28	5309	6068	1.0	0.25	19,940	17,160
		M2	3/sex/time point	Day 1	921.5	6957	1.0	1.0	2452	20,260
			3/sex/time point	Day 28	109	5400	1.0	1.0	203.1	12,410
	1	Peficitinib	3/sex/time point	Day 1	32.1	94.5	1.0	1.0	210.1	301.3
			3/sex/time point	Week 13	71.2	113	0.25	1.0	190.4	356.9
			3/sex/time point	Week 26	39.9	146	1.0	1.0	226.1	466.6
	3		3/sex/time point	Day 1	119	389	1.0	0.25	511.8	822.1
			3/sex/time point	Week 13	179	322	0.25	0.25	663.8	826.6
			3/sex/time point	Week 26	269	430	0.25	0.25	849.5	935.8
	10		3/sex/time point	Day 1	365	1150	1.0	0.25	2070	2937
			3/sex/time point	Week 13	713	1440	0.25	0.25	2393	2722
			3/sex/time point	Week 26	393	2230	0.25	0.25	2886	3057
	100		3/sex/time point	Day 1	6110	8430	1.0	1.0	23,455	25,687
			3/sex/time point	Week 13	6530	6860	2.0	0.25	36,655	21,147
			3/sex/time point	Week 26	9880	10,100	2.0	1.0	40,902	30,984
Cynomolgus monkey	15	Peficitinib	3/sex	Day 1	313 ± 238	663 ± 525	1.8 ± 1.9	1.2 ± 0.8	2774 ± 1557	3508 ± 1868
			3/sex	Day 28	300 ± 119	633 ± 220	2.3 ± 1.5	1.7 ± 0.6	2283 ± 911	4001 ± 2240
		M2	3/sex	Day 1	47.5 ± 39.0	202 ± 176	1.2 ± 0.8	1.2 ± 0.8	407 ± 235	913 ± 675
			3/sex	Day 28	50.6 ± 32.7	182 ± 99.3	1.5 ± 0.9	1.7 ± 0.6	332 ± 161	1103 ± 843
	30	Peficitinib	3/sex	Day 1	260 ± 159	447 ± 130	1.7 ± 2.0	1.8 ± 1.9	1536 ± 1362	3335 ± 1893
			3/sex	Day 28	174 ± 244	451 ± 315	2.2 ± 1.8	1.8 ± 1.9	869 ± 837	2778 ± 1226
		M2	3/sex	Day 1	37.4 ± 24.7	82.3 ± 28.4	1.8 ± 1.9	3.2 ± 4.2	183 ± 77.1	607 ± 437
			3/sex	Day 28	32.1 ± 46.4	78.8 ± 59.2	1.5 ± 0.9	1.2 ± 0.8	137 ± 169	427 ± 197
	2	Peficitinib	4/sex	Day 1	28.9 ± 7.8	25.3 ± 5.9	1.5 ± 0.6	1.9 ± 1.6	211 ± 20.3	306 ± 40.9
			4/sex	Week 26	34.3 ± 14.0	29.9 ± 8.0	1.0 ± 0.7	1.5 ± 0.6	270 ± 30.5	316 ± 91.6
			4/sex	Week 52	26.6 ± 2.3	22.0 ± 8.0	2.8 ± 3.6	6.3 ± 3.5	291 ± 53.0	316 ± 133
	4		4/sex	Day 1	187 ± 125	153 ± 79	1.1 ± 0.6	1.0 ± 0.7	664 ± 236	811 ± 269
			4/sex	Week 26	176 ± 83	71.6 ± 92.4	0.9 ± 0.3	3.1 ± 3.3	704 ± 302	478 ± 364
			4/sex	Week 52	136 ± 46	72.3 ± 48.5	0.9 ± 0.3	3.0 ± 1.2	706 ± 147	664 ± 328
	8		4/sex	Day 1	225 ± 73	90.7 ± 58.2	2.5 ± 1.0	3.1 ± 3.3	1472 ± 322	898 ± 408
			4/sex	Week 26	211 ± 75	114 ± 30	2.3 ± 1.3	1.6 ± 0.8	1688 ± 341	948 ± 296
			4/sex	Week 52	212 ± 66	77.2 ± 36	2.3 ± 1.3	2.1 ± 1.4	1784 ± 552	763 ± 274
	15		4/sex	Day 1	300 ± 76	414 ± 394	2.0 ± 1.4	2.8 ± 3.6	2596 ± 753	2265 ± 1034
			4/sex	Week 26	418 ± 142	343 ± 239	2.3 ± 1.3	1.6 ± 0.8	2456 ± 570	1680 ± 622
			4/sex	Week 52	361 ± 155	160 ± 102	2.0 ± 1.4	3.0 ± 1.2	2887 ± 1117	1521 ± 572

Mean or mean ± standard deviation

4.1.3 Membrane permeability *in vitro* (CTD 5.3.2.3-20 [reference data])

The membrane permeability of peficitinib in human colon tumor-derived Caco-2 cells was evaluated, and the permeability coefficient in the absorption direction from the apical to basolateral membrane ($P_{app\ A\ to\ B}$) for ^{14}C-peficitinib was $1.85 \pm 0.06 \times 10^{-6}$ to $2.47 \pm 0.06 \times 10^{-6}$ cm/s in the concentrations tested (0.3 to 30 µmol/L). The $P_{app\ A\ to\ B}$ of control compounds with a low membrane permeability (^{3}H-atenolol, 20 µmol/L) and a high membrane permeability (^{3}H-levocabastine, 20 µmol/L) was $0.36 \pm 0.02 \times 10^{-6}$ and $11.3 \pm 0.66 \times 10^{-6}$ cm/s, respectively.

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.3-1, 4.2.2.3-2, 4.2.2.3-3)

A single dose of ^{14}C-peficitinib 3 mg/kg was orally administered to male albino rats (3/time point). The tissue

radioactivity concentration[5)] peaked in tissues other than the small intestine, large intestine, and testis at 0.25 hours post-dose. The tissue radioactivity concentration at 0.25 hours post-dose was highest in the liver, followed by the kidney and the adrenal gland (excluding the gastrointestinal tract). Radioactivity was detected in the liver, kidney, adrenal gland, large intestine, skin, and thoracic aorta 24 hours post-dose.

Repeated-doses of ^{14}C-peficitinib 3 mg/kg were orally administered once daily for 21 days to male albino rats (3/time point). The tissue distribution[5)] was similar to that observed after the single-dose administration, and the tissue radioactivity concentrations at 0.25 and 24 hours post-dose on Day 21 did not markedly differ from those on Day 1. The tissue radioactivity concentration on Day 21 peaked at 0.25 hours post-dose in all tissues and subsequently decreased over time to ≤19% of the maximum concentration (at 0.25 hours post-dose) for individual tissues at 168 hours post-dose in all tissues, except for the thoracic aorta (61.0%).

A single dose of ^{14}C-peficitinib 3 mg/kg was orally administered to pigmented male rats (3/time point). The tissue radioactivity concentration[6)] in tissues, except eyeballs, showed a similar radioactivity distribution to that observed in albino rats. The intraocular radioactivity concentration peaked at 24 hours post-dose, and radioactivity was still detected at 2184 hours post-dose, with the $t_{1/2}$ of 1105.8 hours for intraocular radioactivity. After a single oral administration of ^{14}C-peficitinib 3 mg/kg to a pigmented male rat, the radioactivity distribution to the ciliary body, choroid, and iris, which contain a lot of melanin, was identified with whole-body autoradioluminography performed at 24 hours post-dose.

There were no remarkable ocular findings in the ophthalmological and histopathological examinations performed in repeated oral dose toxicity studies in cynomolgus monkeys [see Section 5.2]. In phase III clinical studies conducted in and outside Japan [see Section 7.R.3], among adverse events related to tissues containing melanin (Eye disorders [system organ class (SOC)] and Skin and subcutaneous tissue disorders [SOC]), serious adverse events or adverse events assessed as Grade ≥3 of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) occurred in 1 patient (retinal detachment) in the peficitinib 100 mg group and 1 patient (drug eruption) in the peficitinib 150 mg group. A causal relationship between the adverse event of drug eruption and peficitinib was not ruled out. However, the patient continued to receive the study treatment after recovering from the adverse event. No clinically significant adverse events have been identified so far. Based on the above, the applicant explains that no safety concerns have been suggested by the accumulation of peficitinib in melanin-containing tissues such as eyeballs.

4.2.2 Plasma protein binding and distribution in blood cells (CTD 4.2.2.3-5, 4.2.2.3-6, 4.2.2.3-7)

The plasma protein-binding rate of peficitinib at the tested concentrations (0.2-20 μg/mL) measured by an equilibrium dialysis method was 58.6% to 60.6% in mice, 79.7% to 86.5% in rats, 94.5% to 95.1% in rabbits, 65.4% to 68.2% in dogs, and 79.4% to 80.0% in cynomolgus monkeys. The plasma protein-binding rate in human was 72.8% to 75.2%.

[5)] Examined in the plasma, blood, brain, lung, heart, liver, kidney, spleen, pancreas, femoral muscle, adrenal gland, stomach, small intestine, large intestine, skin, lipid, pituitary, submandibular gland, thymus, eyeball, Harderian gland, thyroid, testis, bone marrow, and thoracic aorta.
[6)] Examined in the plasma, blood, cerebrum, eyeball, pigmented skin, non-pigmented skin, lung, heart, liver, kidney, adrenal gland, thymus, thyroid, testis, and bone marrow.

The plasma protein-binding rate of M2 at the tested concentrations (0.2 to 20 μg/mL) measured by the ultrafiltration was 91.2% to 96.9% in mice, 95.2% to 96.6% in rats, 91.0% to 91.9% in rabbits, 84.4% to 85.3% in dogs, and 98.7% to 98.8% in cynomolgus monkeys, Plasma protein-binding rate in human was 95.9% to 96.1%.

The binding rate of peficitinib and M2 (both at 2 μg/mL) to human plasma proteins[7)] was highest in human serum albumin with a respective rate of 69.2% and 97.6%. The binding rate of peficitinib and M2 to other serum proteins was <20%.

4.2.3 Placental transfer (CTD 4.2.2.3-4)

A single dose of ^{14}C-peficitinib 3 mg/kg was orally administered to albino female rats on gestation day 14 (3 females/time point), and the maternal tissue radioactivity concentration[8)] was evaluated. At 0.25 hours post-dose, the maternal plasma radioactivity level was 0.576 ± 0.185 μg eq./mL, and radioactivity was detected also in the uterus, placenta, and amniotic fluid of the dams (0.221 ± 0.065, 0.173 ± 0.060, 0.002 ± 0.000 μg eq./mL or μg eq./g, respectively). At 24 hours after post-dose, radioactivity was below the lower limit of quantification in all tissues except the liver, kidney, placenta, and spleen. The fetal tissue radioactivity concentration reached a peak (0.023 ± 0.008 μg eq./g) at 0.25 hours post-dose and decreased to below the lower limit of quantification at 24 hours post-dose.

4.3 Metabolism

4.3.1 *In vitro* studies (CTD 4.2.2.4-1, 5.3.2.2-1, 5.3.2.2-2, 5.3.2.2-3, 5.3.2.2-4)

The metabolic profiles of murine, rat, rabbit, dog, simian, and human hepatic microsomes or frozen hepatocytes were evaluated with ^{14}C-peficitinib (10 μmol/L). The metabolites observed in the human hepatocytes and hepatic microsomes were also observed in ≥1 animal species, and no human-specific metabolites were detected.

In human clinical studies [see Section 6.2.1], the main plasma metabolites of peficitinib were M2 (sulfate conjugation of the hydroxyl groups), M4 (*N*-methylation of the hydroxyl groups), and M1 (sulfate conjugation and *N*-methylation of the hydroxyl groups). Isoforms of sulfotransferase (SULT) and *N*-methyltransferase (NMT) that contribute to their metabolic reaction were evaluated.

In human recombinant SULT-expressing cell lines (SULT1A1*1, SULT1A1*2, SULT1A2, SULT1A3, SULT1B1, SULT1C2, SULT1C4, SULT1E1, and SULT2A1), ^{14}C-peficitinib (1 μmol/L) was incubated in the presence of a coenzyme, namely adenosine 3'-phosphate 5'-phosphosulfate, and M2 was produced in the SULT2A1-expressing cell line.

[7)] Examined in human serum albumin (40 mg/mL), alpha 1-acid glycoprotein (1 mg/mL), high-density lipoprotein (3 mg/mL), low-density lipoprotein (3 mg/mL), and gamma-globulin (10 mg/mL for peficitinib, 15 mg/mL for M2)

[8)] Examined in the plasma, blood, liver, kidney, lung, spleen, heart, pancreas, mammary gland, ovary, uterus, placenta, fetus, brain, and amniotic fluid

In human liver cytosols and the SULT2A1-expressing cell line, peficitinib (2 μmol/L) was incubated. M2 was produced for both cell lines, and the K_m for the M2 production reaction was 34.5 and 24.6 μmol/L, respectively.

In human liver cytosols and the SULT2A1-expressing cell line, M4 (3 μmol/L) was incubated. M1 was produced for both cell lines, and the K_m of the M1 production reaction was 128 and 216 μmol/L, respectively.

In human liver cytosols, peficitinib and M2 (both at 1 μmol/L) were incubated in the presence of a coenzyme, namely S-adenosylmethionine, and M4 and M1 were produced respectively.

In cell lines expressing nicotinamide *N*-methyltransferase (NNMT) and glycine *N*-methyltransferase in human liver cytosols, peficitinib and M2 (both at 1 μmol/L) were incubated, and M4 and M1 were produced in the NNMT-expressing cell line.

4.3.2 *In vivo* studies (CTD 4.2.2.4-2, 4.2.2.4-3, 4.2.3.7.5-2, 4.2.3.7.5-4, 5.3.2.3-17, 5.3.2.3-18, 5.3.2.3-19)

A single dose of ^{14}C-peficitinib 3 mg/kg was orally administered to male rats to evaluate metabolites in the plasma, urine, and bile. In plasma, at 0.25 hours post-dose, peficitinib was mainly detected, and M6 and M9 were also detected. By 6 hours post-dose, peficitinib was mainly detected, and M3, M4, M6, M9, and M11 were also detected in urine. By 6 hours post-dose, M6 was mainly detected, and peficitinib, M3, M4, M7, M8, M9, M10, M12, and M13 were detected in bile. Peficitinib 30 and 100 mg/kg was repeatedly administered once daily for 28 days to rats (3/sex/time point), and the ratio of the exposure of M1, M2, and M4 (AUC_{0-24}) to peficitinib was 0.00034 to 0.029, 0.0025 to 0.80, and 0.0065 to 0.013, respectively.

A single dose of ^{14}C-peficitinib 3 mg/kg was orally administered to cynomolgus monkeys (3 males) to evaluate metabolites in the plasma, urine, and bile. In plasma, peficitinib and M6 were mainly detected, and M2, M12, M14, and M15 were also detected. By 72 hours post-dose, M6 was mainly detected, followed by peficitinib, in urine, and the percentage relative to the administered dose was 12.7% and 3.7% for M6 and peficitinib, respectively. M2, M3, M12, M14, M15, and M16 were also detected in urine. By 72 hours post-dose, M6 was mainly detected in bile, and the percentage relative to the administered dose was 17.8%. M2, M4, M12, M14, M15, and M16 were also detected in bile. Peficitinib 15 and 30 mg/kg was repeatedly administered orally once daily to cynomolgus monkeys for 28 days, and the ratio of the exposure of M1, M2, and M4 (AUC_{0-24}) to peficitinib was 0 to 0.0019, 0.15 to 0.28, and 0.0022 to 0.0050, respectively.

In a foreign mass balance study (Study CL-PK03), a single dose of ^{14}C-peficitinib 100 mg was orally administered after a meal to healthy adult men (n = 6). By 24 hours post-dose, peficitinib, M1, M2, and M4 were detected in plasma, and the percentage relative to total radioactivity was 32.5%, 4.3%, 34.2%, and 7.5%, respectively. Other 2 metabolites with an undetermined structure were also detected (≤1.1%). In urine (by 24 hours after post-dose), peficitinib, M1, M2, and M4 were detected, and the percentage relative to the administered dose was 14.2%, 2.6%, 13.7%, and 4.1%, respectively. In feces (by 96 hours post-dose), peficitinib,

M2, and M4 were detected, and the percentage relative to the administered dose was 29.8%, 5.8%, and 10.7%, respectively. Other 2 metabolites with an undetermined structure were also detected (<1.0%).

In foreign phase I studies (Studies CL-HV01 and CL-HV02), peficitinib was once or repeatedly administered to healthy adults. Peficitinib, M1, M2, and M4 were detected in plasma and urine, and M3 and M5 were also detected as minor metabolites in urine.

Based on the results of the above metabolism studies, the metabolic activation pathway for peficitinib[9)] is supposed as shown in Figure 1.

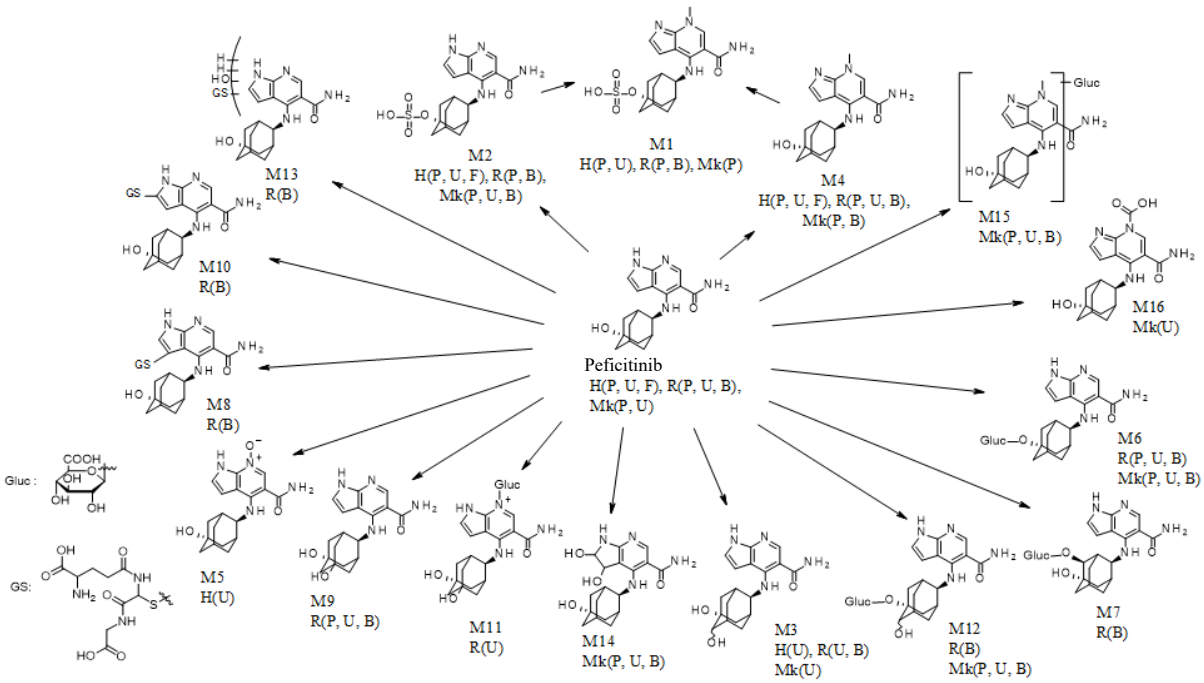


Figure 1. Possible metabolic pathways of peficitinib in rats (R), cynomolgus monkeys (Mk), and humans (H) (cited from CTD 2.6.5.11)
B, bile; P, plasma; U, urine; and F, feces

4.4 Excretion

4.4.1 Excretion in urine and feces and excretion into bile (CTD 4.2.2.2-3, 4.2.2.3-1)

A single dose of ^{14}C-peficitinib 3 mg/kg was orally administered to bile duct-cannulated rats (4 males) and intact rats (4 males). The cumulative excretion rate of radioactivity in urine and feces in intact rats was 8.2% and 76.9%, respectively, by 24 hours post-dose and 9.9% and 87.3%, respectively, by 168 hours post-dose. In the bile duct-cannulated rats, the cumulative excretion rate of radioactivity in urine and bile by 72 hours post-dose was 25.2% and 46.7%, respectively. The 0.5 mL bile obtained from these rats (bile collected by 6 hours post-

[9)] The following metabolites are mentioned in this section: M1, methylation of the 7th position of the pyrrolo-[2,3-*b*]-pyridine ring and sulfate conjugation of the hydroxyl group at the 5th position of the adamantane ring; M2, sulfate conjugation of the hydroxyl group at the 5th position of the adamantane ring; M3, hydroxylation of the 6th position of the adamantane ring; M4, methylation of 7th position of the pyrrolo-[2,3-*b*]-pyridine ring; M5, oxidation of the 7th position of the pyrrolo-[2,3-b]-pyridine ring; M6, glucuronate conjugation of the hydroxy at the 5th position of the adamantane ring; M7, a hydroxylation and glucuronate conjugation of the 4th position of the adamantane ring; M8, glutathione conjugation of the 3rd position of the pyrrolo-[2,3-*b*]-pyridine ring; M9, hydroxylation of the 7th position of the adamantane ring; M10, glutathione conjugation of the 2nd position of the pyrrolo-[2,3-*b*]-pyridine ring2; M11, hydroxylation of the 7th position of the adamantane ring and glucuronate conjugation of the 7th position of the pyrrolo-[2,3-*b*]-pyridine ring; M12, hydroxylation of the 6th position and glucuronate conjugation of the hydroxy group at the 5th position of the adamantane ring; M13, glutathione conjugation of the dihydrohydroxy peficitinib; M14, dihydrodiolation of the 2nd and 3rd positions of the pyrrolo-[2,3-*b*]-pyridine ring; M15, methylation and glucuronate conjugation of the 7th position of the pyrrolo-[2,3-*b*]-pyridine ring; and M16, carboxylation of the 7th position of the pyrrolo-[2,3-*b*]-pyridine ring.

dose) was administered into the duodenum of other rats, and the cumulative excretion rate of radioactivity in urine and bile by 72 hours post-dose was 9.6% and 19.1%, respectively. These findings suggest that compounds derived from ^{14}C-peficitinib may undergo enterohepatic circulation in rats.

A single dose of ^{14}C-peficitinib 3 mg/kg was orally administered to bile duct-cannulated cynomolgus monkeys (3 males) and intact cynomolgus monkeys (3 males). The cumulative excretion rates of radioactivity in urine and feces in the intact cynomolgus monkeys was 19.6% and 52.5%, respectively, by 24 hours post-dose and 20.7% and 76.1%, respectively, by 168 hours post-dose. In bile duct-cannulated cynomolgus monkey, the cumulative excretion rate of radioactivity in urine and bile by 72 hours post-dose was 22.3% and 26.4%, respectively.

4.4.2 Excretion in milk (CTD 4.2.2.3-4)

A single dose of ^{14}C-peficitinib 3 mg/kg was orally administered to lactating rats (3 females on postpartum day 14). The maternal plasma peficitinib concentration and the radioactivity concentration in milk peaked (0.154 ± 0.098 μg eq./mL and 0.841 ± 0.376 μg eq./mL, respectively) at 1 hour after the administration and decreased below the lower limit of quantification at 24 hours post-dose. Radioactivity was detected in the liver, kidney, lung, and milk curd in the stomach of the breast-fed rats.[10)]

4.5 Pharmacokinetic interactions

4.5.1 Inhibitory and inducing effects on enzymes (CTD 5.3.2.2-5, 5.3.2.2-6, 5.3.2.2-7, 5.3.2.2-8, 5.3.2.2--9, 5.3.2.2-10, 5.3.2.2-11)

Inhibitory effects of peficitinib on CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A)[11)] were evaluated by using human hepatic microsomes. The IC_{50} of peficitinib for testosterone and midazolam as substrates of CYP3A was 29.4 and 46.5 μmol/L, respectively, and the IC_{50} of peficitinib for other isoforms exceeded 100 μmol/L. M2 did not inhibit any of the isoforms (IC_{50} >100 μmol/L).

The time-dependent inhibitory effects of peficitinib and M2 were evaluated for these CYP isoforms. Peficitinib inhibited CYP2C8 and CYP3A (testosterone and midazolam) in a time-dependent manner (with an IC_{50} of 22.2 μmol/L for CYP2C8 and 7.91 and 9.96 μmol/L for CYP3A4 after 30-min preincubation), and M2 inhibited CYP2C8 in a slightly time-dependent manner (with an IC_{50} of 80 μmol/L after 30-min preincubation). Peficitinib and M2 did not show time-dependent inhibitory effects on other isoforms.

The time-dependent inhibitory effects of peficitinib on CYP2C8 and CYP3A were evaluated also in other studies. The concentration producing 50% maximum inactivation (K_I) of peficitinib on the metabolic activity of amodiaquine, a substrate of CYP2C8, was 5.95 μmol/L, and the maximum inactivation rate constant (K_{inact}) was 0.0558 min^{-1}. The K_I of peficitinib on the metabolic activity of tacrolimus, testosterone, and midazolam as

[10)] Examined in the plasma, blood, milk curd in the stomach, brain, lung, heart, liver, and kidney
[11)] Compounds used as the substrate for each isoform: phenacetin for CYP1A2; bupropion for CYP2B6; amodiaquine for CYP2C8; diclofenac for CYP2C9; (*S*)-mephenytoin for CYP2C19; bufuralol for CYP2D6; chlorzoxazone for CYP2E1; and testosterone and midazolam for CYP3A.

substrates of CYP3A was 142, 82.4, and 153 μmol/L, respectively, and the K_{inact} thereof was 0.215, 0.178, and 0.226 min^{-1}, respectively.

The induction effects of peficitinib (0.1, 1, 10, and 100 μmol/L) on the activity and mRNA expression of CYP isoforms (CYP1A2, 2B6, 2C8, 2C9, 2C19, and 3A)[12)] were evaluated by using primary cultured human hepatocytes. In the presence of peficitinib at 10 μmol/L, which is the maximum concentration with no evident extracellular efflux of lactate dehydrogenase, the enzyme activity and mRNA expression of CYP1A2 was 1.52 to 2.19 times and 2.89 to 21.1 times those in the presence of the vehicle control (0.1% DMSO), respectively. The enzyme activity and mRNA expression for other CYP isoforms in the presence of peficitinib were both <2 times those in the presence of vehicle control (0.1% DMSO).

The induction effects of peficitinib (0.01 to 22.3 μmol/L) on the mRNA expression of CYP1A2 were evaluated by using human frozen hepatocytes. In the presence of peficitinib at a concentration of ≥1.7 μmol/L which is nearly equivalent to the exposure (C_{max} of 613.2 ng/mL, "1.88 μmol/L," Study CL-PK20 [see Section 6.2.1.2]) obtained after repeated administration of peficitinib 150 mg once daily to Japanese healthy adults, the mRNA expression was ≥2 times that in the presence of the vehicle control (0.1% DMSO) but, at the tested concentrations, the mRNA expression was ≤13% of that in the presence of the positive controls, beta-naphthoflavone and omeprazole (both at 50 μmol/L), suggesting that peficitinib has no clinically significant enzyme-inducing effects.

The above findings suggest that peficitinib may inhibit CYP2C8 and CYP3A.

4.5.2 Peficitinib's likelihood of being a substrate for drug transporters (CTD 5.3.2.3-1, 5.3.2.3-2, 5.3.2.3-5, 5.3.2.3-8, 5.3.2.3-9, 5.3.2.3-11, 5.3.2.3-13, 5.3.2.3-15)

An investigation was conducted by using MDCKII cells or LLC-PK1 cells expressing human P-gp, membrane vesicles prepared from Sf9 cells expressing human BCRP, MRP2, or MRP4, HEK293 cells expressing human transporters (MATE1, MATE2-K, OATP1B1, OATP1B3, OCT1, or OCT2), and S_2 cells expressing human OAT1 or OAT3. The results suggested the possibility that peficitinib is a substrate of P-gp and M2 is a substrate of BCRP, OAT3, OATP1B1, OATP1B3, and MRP4.

4.5.3 Inhibitory effects on drug transporters (CTD 5.3.2.3-2, 5.3.2.3-3, 5.3.2.3-4, 5.3.2.3-6, 5.3.2.3-7, 5.3.2.3-10, 5.3.2.3-12, 5.3.2.3-14, 5.3.2.3-16)

Table 9 shows the results of the investigation conducted by using MDCKII cells or LLC-PK1 cells expressing human P-gp, membrane vesicles prepared from Sf9 cells expressing human BCRP, MRP2, or MRP4, HEK293 cells expressing human transporters, and S_2 cells expressing human OAT1 or OAT3. Based on the inhibitory effects of peficitinib on individual transporters (IC_{50}) and the exposures of unchanged peficitinib and M2 (peficitinib, C_{max} 613.2 ng/mL; M2, C_{max} 1112 ng/mL [Study CL-PK20 (see Section 6.2.1.2)]) after multiple

[12)] Compounds used as the substrate for each isoform: phenacetin for CYP1A2; bupropion for CYP2B6; amodiaquine for CYP2C8; diclofenac for CYP2C9; (*S*)-mephenytoin for CYP2C19; and testosterone for CYP3A

doses of peficitinib 150 mg once daily to Japanese healthy adults, peficitinib may inhibit BCRP, OATP1B1, and OCT1 in clinical use.

Table 9 Inhibitory effects of peficitinib and M2 on transporters

Transporter	Substance	Concentration	IC_{50} (μmol/L) (maximum inhibition rate)	Transporter	Substance	Concentration	IC_{50} (μmol/L) (maximum inhibition rate)
P-gp	Peficitinib	1-100	>100	OATP1B1	Peficitinib	1-100	19.2
	M2	1-100	>100		M2	1-100	11.5
BCRP	Peficitinib	3-100	13.5	OATP1B3	Peficitinib	1-100	>100 (18%)
	M2	3-100	32.1		M2	1-100	84.4
MRP2	Peficitinib	3-100	No inhibition	OAT1	Peficitinib	1-100	>100 (29.7%)
	M2	3-100	No inhibition		M2	1-100	75.6
MRP4	Peficitinib	3-100	>100 (<50%)	OAT3	Peficitinib	1-100	5.01
	M2	3-100	30.4		M2	1-100	4.55
MATE 1	Peficitinib	1-100	10	OCT1	Peficitinib	0.1-10	0.247
	M2	1-100	>100 (23.9%)		M2	1-100	>100 (29.6%)
MATE2-K	Peficitinib	1-100	20.8	OCT2	Peficitinib	1-100	71.4
	M2	1-100	>100 (16%)		M2	1-100	No inhibition

4.R Outline of the review by PMDA

PMDA has concluded that the *in vivo* kinetics of peficitinib have been elucidated to a certain extent by the study data submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

The following toxicity studies of peficitinib were conducted: single-dose toxicity studies, repeat-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, and other toxicity studies (repeated-dose toxicity studies of the metabolite M4, immunophenotyping studies, a 13-week repeated-dose toxicity study with a combined use with tacrolimus, mycophenolate mofetil [MMF], or MTX, and phototoxicity studies). A 0.5% w/v methylcellulose solution was used as a vehicle in *in vivo* studies unless otherwise specified.

5.1 Single-dose toxicity

Single-dose toxicity studies were conducted in rats and cynomolgus monkeys (Table 10). No deaths or acute symptoms were observed.

Table 10. Outline of results of single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg/day)	Attachment CTD
Male and female rat (SD)	Oral	500, 1000, 2000	≥1000 mg/kg: dark-red spots in the glandular stomach; basophilic change, calcification, and focal hemorrhage of mucosal epithelial cells of the glandular stomach 2000 mg/kg: transient weight loss	>2000	4.2.3.1-1
Male and female cynomolgus monkey	Oral	500, 2000	≥500 mg/kg: vomiting, high blood AST, and low blood potassium 2000 mg/kg: high total bilirubin in blood, low blood sodium	>2000	4.2.3.1-2

5.2 Repeat-dose toxicity

Oral toxicity studies were conducted in rats (4, 13, and 26 weeks) and cynomolgus monkeys (4, 13, and 52 weeks) (Table 11).

In the 13-week oral toxicity study in cynomolgus monkeys, death occurred. The main systemic toxicity findings in the dead monkeys include gastrointestinal injury-related changes and increased activities of creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) in blood, which were suggested to be derived from musculoskeletal tissues, but no histological abnormalities were found.

Abnormalities related to the pharmacological effects of peficitinib [see Section 3.1.1] included decreased blood lymphocytes and white blood cells and atrophic changes in the lymphoid tissues (e.g., thymus, spleen, and lymph nodes) in rats and cynomolgus monkeys. These changes representing the suppression of the immune system induced increased susceptibility to infections, which included ulceration of the skin tissues, increased granulocytic hematopoiesis, and proliferation of plasma cells in the lymph nodes in rats, and mononuclear cell infiltration in the lung, liver, and kidney and abscess of the lung, skin, and bone marrow in cynomolgus monkeys. Other observed changes were decreased myelopoiesis and extramedullary hematopoiesis in the spleen in rats and cynomolgus monkeys and decreased levels of erythroid parameters in cynomolgus monkeys. These findings were considered to be related to the suppression of erythropoietin signal transduction due to the JAK2 inhibition by peficitinib (*Blood 2001*. 98:2948-57). Other systemic toxicity included gastrointestinal injury-related changes in rats and cynomolgus monkeys and necrotic changes of the corpus luteum of the ovary and femoral epiphysis and hyperplasia of the renal papillary epithelium in rats.

The no-observed-adverse-effect level (NOAEL) in the 26-week repeated oral dose toxicity study in rats and the 52-week repeated oral dose toxicity study in cynomolgus monkeys was determined to be 3 and 2 mg/kg, respectively. $AUC_{0\text{-}24}$ (849.5 and 316.4 ng·h/mL) at the NOAEL was 0.3 and 0.1 times the clinical exposure ($AUC_{0\text{-}24}$, 2643 ng·h/mL)[13)], respectively.

Table 11. Summary of repeated-dose toxicity study results

Test system	Route of administration	Duration of administration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attachment CTD
Male and female rat (SD)	Oral	4 weeks (once daily) + 4-week interval	0, 3, 10, 30, 100	10 mg/kg/day: low leukocytes (males) ≥30 mg/kg/day: low lymphocytes; low weight of thymus and spleen; atrophy of thymus; low bone marrow cells (males and females); low basophils; atrophy of mesenteric lymph node; decreased extramedullary hematopoiesis in spleen; focal basophilic change in superficial mucosal epithelial cells of glandular stomach (males); low eosinophils; erosion of glandular stomach (males) 100: low large achromatic cells; decreased size of thymus and spleen; atrophy of spleen lymphoid follicle (males and females); low eosinophils; atrophy of mandibular lymph node; erosion of glandular stomach; focal necrosis of trabecular bone associated with aggregation of osteoclasts in femoral metaphysis (males); low leukocytes and basophils; atrophy of mesenteric lymph node; cell necrosis of corpus luteum of ovary (females) Reversibility: reversible	10	4.2.3.2-2
Male and female rat (SD)	Oral	13 weeks (once daily) +	0, 1, 3, 10, 100	≥10 mg/kg/day: atrophy of the mesenteric lymph node (males and females); single-cell necrosis of cecal mucosal epithelium (males); low spleen weight; atrophy of Peyer's patch (females)	3	4.2.3.2-3

[13)] Exposure after multiple doses of peficitinib 150 mg once daily to Japanese healthy adults (Study CL-PK20, [see Section 6.2.1.2])

Test system	Route of administration	Duration of administration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attachment CTD
		4-week interval		100 mg/kg/day: low leukocytes and lymphocytes; low thymus weight; hemosiderosis of spleen and atrophy of splenic white pulp; atrophy of thymus (males and females); low spleen weight; atrophy of mandibular lymph node; atrophy of Peyer's patch; decreased extramedullary hematopoiesis in spleen; single-cell necrosis and focal regeneration of rectal mucosal epithelium (males); skin ulcer; spleen congestion; increased size and septic granuloma of mandibular lymph node; single-cell necrosis of cecal mucosal epithelium; cell necrosis of corpus luteum of ovary; subcutaneous mass; septic granuloma; multiple septic pneumonia; high bone marrow cells (mainly granulocytes) (females) Reversibility: reversible (except for atrophy and septic granuloma of mandibular lymph node)		
Male and female rat (SD)	Oral	26 weeks (once daily)	0, 1, 3, 10, 100	Deaths: 100 mg/kg/day (1 of 10 males) [a)] ≥1 mg/kg/day: low lymphocytes (females) ≥3 mg/kg/day: low lymphocytes and atrophy of splenic white pulp (males) ≥10 mg/kg/day: atrophy of mesenteric lymph node; spleen congestion (males); low spleen weight; atrophy of splenic white pulp (females) 100 mg/kg/day: skin ulcer and crusts; low leukocytes; decreased size of spleen; atrophy of mandibular lymph node; increased hemosiderosis in spleen; hypertrophy and hyperplasia of epithelial cells of renal papillary collecting duct; low bone marrow cells (males and females); red urine; low spleen weight; decreased size and atrophy of thymus (males); spleen congestion; low levels of blood total protein, albumin, and A/G ratio; subcutaneous mass and granuloma formation, the mesenteric lymph node atrophy (females)	3	4.2.3.2-4
Male and female cynomolgus monkey	Oral	4 weeks (once daily) + 4-week interval	0, 8, 15, 30, 60	≥30 mg/kg/day: low food consumption and body weight; loose stool; diarrhea (watery stool); atrophy of thymus; slightly increased bone-marrow granulocytes (males) 60 mg/kg/day: low leukocytes, hematocrit, and hemoglobin; high neutrophils and leukocytes; high blood creatinine and chloride (males and females); vomiting; high blood LDH and CPK; low blood albumin; low urine pH and chloride excretion; urinary cast (males); salivation; loose stool; diarrhea (watery stool); low food consumption and low body weight; atrophy of thymus; slightly increased bone-marrow granulocytes (females) Reversibility: reversible	15 (males) 30 (females)	4.2.3.2-6
Male and female cynomolgus monkey	Oral	13 weeks (once daily) + 4-week interval	0, 4, 8, 15, 60/30 [b)]	Deaths: 60 mg/kg/day (2 of 6 females, 1 of 6 males), 60/30 mg/kg/day (1 of 6 females) [c)], Dead animals Decreased spontaneous motility; decreased response to stimulation; abnormal body posture (sitting position, squatting position, lateral position, prone position); decreased body temperature; pale oral mucosa; emaciation; red stool; positive fecal occult blood; low blood lymphocytes; prolonged prothrombin time and activated partial thromboplastin time; high hematocrit and mean corpuscular hemoglobin; low mean corpuscular volume; high blood ALP, urea nitrogen, inorganic phosphorus, glucose, total bilirubin, CPK (CPK MM type), and LDH (LDH type 5); low blood globulin, total protein, potassium, and calcium; high adrenal gland weight; atrophy of spleen follicle; atrophy of thymus; atrophy and single-cell necrosis of follicle of mandibular lymph node; low bone marrow cells of sternum; inflammatory cell infiltration, erosion, mucosal hemorrhage, and epithelial regeneration of proper mucosal layer of stomach, duodenum,	8 (males) 4 (females)	4.2.3.2-7

Test system	Route of administration	Duration of administration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attachment CTD
				ileum, and colon; decreased lipid droplet and hyperplasia of zona fasciculata of adrenal gland. Surviving animals ≥8 mg/kg/day: low blood inorganic phosphorus; inflammatory cell infiltration into proper mucosal layer of rectum and colon; erosion, mucosal hemorrhage, and epithelial regeneration of rectum (females). ≥15 mg/kg/day: low hematocrit (males); high neutrophils; low reticulocyte ratio (females). 60/30 mg/kg/day: loose stool; diarrhea; low body weight; low urine sodium and chloride excretion; low erythrocytes and hemoglobin; high monocytes (males and females); vomiting; salivation; high neutrophils; high blood troponin T and I (males); low food consumption; low hematocrit; high platelets; high blood total protein, globulin, creatinine, and triglyceride; low blood albumin, A/G ratio, sodium, and chloride (females) Reversibility: reversible		
Male and female cynomolgus monkey	Oral	52 weeks (once daily)	0, 2, 4, 8, 15	≥2 mg/kg/day: atrophy of spleen germinal center (males) ≥4 mg/kg/day: high neutrophils; low blood albumin and A/G ratio; high blood globulin; atrophy of spleen germinal center (females) 15 mg/kg/day: loose stool; diarrhea; atrophy of cecal epithelium (males and females); inflammatory cell infiltration into proper mucosal layer of cecum and rectum; colitis (males); atrophy of colonic epithelium (females).	8 (males) 2 (females)	4.2.3.2-8

a) The cause of death was unknown.
b) Because of deaths due to poor clinical conditions, the dose was reduced on Day 29 in female animals and Day 32 in male animals.
c) The animal died after a dose reduction to 30 mg/kg.

5.3 Genotoxicity

The following genotoxicity studies were conducted: bacterial reverse mutation test, a chromosomal aberration assay with fibroblasts derived from Chinese hamster lung, an unscheduled DNA synthesis assay with rat livers, and peripheral blood micronucleus tests in mice (Table 12).

Bacterial reverse mutation, unscheduled DNA synthesis with rat livers, and peripheral blood micronucleus in mice were negative, whereas chromosomal aberration was observed in the presence or absence of metabolic activation in the chromosomal aberration assay with fibroblasts derived from Chinese hamster lung. However, the peripheral blood micronucleus test by oral administration to mice resulted in no micronucleus induction at the highest dose which was equivalent to approximately 60 times the clinical exposure (C_{max}, 613.2 ng/mL, Study CL-PK20 [see Section 6.2.1.2]), indicating that peficitinib is unlikely to induce chromosomal aberration.

Table 12. Summary of genotoxicity study results

Types of study		Test system	Metabolic activation	Concentration or dose	Study results	Attachment CTD
In vitro	Bacterial reverse mutation test	Salmonella typhimurium: TA98, TA100, TA1535, TA1537	S9−/+	0, 156, 313, 625, 1250, 2500, 5000 μg/plate	Negative	4.2.3.3.1-1
		Escherichia coli: WP2*uvr*A				
	Chromosomal aberration assay with mammalian cultured cells	Fibroblasts derived from Chinese hamster lung	S9− (6 hours)	0, 120, 140, 160, 180, 200[a)] μg/mL	Positive ≥120: structural alteration	4.2.3.3.1-2
				0, 10, 30, 60, 90, 120 μg/mL	Positive 120: structural alterations ≥10: numerical alteration	
				0, 0.156, 0.313, 0.625, 1.25, 2.5, 5, 10 μg/mL	Positive ≥2.5: numerical alteration	
			S9+ (6 hours)	0, 80, 100, 120, 140, 160 μg/mL	Positive ≥140: structural alteration ≥80: numerical alteration	
				0, 10, 20, 40, 60, 80 μg/mL	Positive 80: numerical alteration	
In vivo	Unscheduled DNA synthesis assay	Male rats(SD) Hepatocytes		0, 250, 500, 1000 mg/kg/day (oral, single dose)	Positive	4.2.3.3.2-1
	Micronucleus test in rodents	Male and female mice (ICR) Peripheral blood		0, 250, 500, 1000 mg/kg/day (oral, single dose)	Positive	4.2.3.3.2-3

a) No middle stage of cell division was observed due to cytotoxicity.

5.4 Carcinogenicity

A carcinogenicity study by oral administration to mice was conducted (Table 13). The incidence and extent of foci of clear cell changes increased in male animals in the 100 mg/kg group, but no effects on the incidence of hepatocellular adenoma or hepatocellular carcinoma were observed, leading to a conclusion that peficitinib is unlikely to be carcinogenic. The incidence of Harderian adenocarcinoma significantly increased in male animals in the 10 mg/kg group, but the incidence of Harderian adenocarcinoma in the 40 and 100 mg/kg groups was similar to that observed in the control group. The increased incidence of Harderian adenocarcinoma in the 10 mg/kg group was considered not to be toxicologically significant. Based on the above, the noncarcinogenic level was determined to be 100 mg/kg. The plasma exposure ($AUC_{0\text{-}24}$) at the noncarcinogenic level was 9921 ng·h/mL, which was 3.8 times the clinical exposure ($AUC_{0\text{-}24}$: 2643 ng·h/mL).[13)] Major nonneoplastic changes observed in the peficitinib group included erosions/ulcers in the anterior stomach and hyperplasia of the squamous epithelium.

Table 13. Summary of results of a carcinogenicity study in mice

Test system	Route of administration	Duration of administration	Main lesion	Sex	Dose (mg/kg/day)					Noncarcinogenic level (mg/kg/day)	Attachment CTD
					0	0	10	40	100		
				n	55	55	55	55	55		
Male and female mouse (B6C3F1)	Oral	24 months (once daily)	Benign thymoma	Male	1	0	0	0	0	100	4.2.3.4.1-3
				Female	0	0	1	1	2		
			Hepatocellular adenoma	Male	26	28	21	20	29		
				Female	16	7	16	20	13		
			Hepatocellular carcinoma	Male	16	8	10	8	11		
				Female	4	2	5	2	5		
			Hepatocellular adenoma/Hepatocellular carcinoma	Male	35	33	25	27	35		
				Female	20	9	18	21	17		
			Harderian adenocarcinoma	Male	0	2	3	3	1		
				Female	1	1	5	2	1		
			Malignant lymphoma	Male	17	9	10	7	4		
				Female	18	19	18	19	16		
			Non-neoplastic lesions	≥40 mg/kg/day: vacuolation of hepatocytes (females) 100 mg/kg/day: elevated lesion in the anterior stomach; hyperplasia of squamous epithelium (males and females); erosions/ulcers of anterior stomach; foci of clear cell changes (males)							

A carcinogenicity study by oral administration to rats was conducted (Table 14). The incidence of benign/malignant thymoma increased in females in the ≥20 mg/kg or higher groups. In peficitinib groups, the incidence of following events significantly increased: hyperplasia of oval cells, foci of eosinophilic cellular alterations, and hepatocellular adenoma in the liver; urothelial hyperplasia, and urothelial papilloma/cancer in the kidney; malignant astrocytoma/malignant oligodendroglial tumor in the brain; and squamous cell papilloma/keratoacanthoma of the skin. However, these findings were not markedly dose-related, and they were thus considered coincidental and unlikely to be related to the administration of peficitinib. The noncarcinogenic level was determined to be 5 mg/kg in females and 50 mg/kg in males. The plasma exposure ($AUC_{0\text{-}24}$) at the noncarcinogenic level was 1269 ng·h/mL in females, which was 0.5 times the clinical exposure ($AUC_{0\text{-}24}$: 2643 ng·h/mL).[13)] Major nonneoplastic changes observed in the peficitinib group included keratitis, erosions/ulcers of the glandular stomach and the duodenum, and squamous hyperplasia of the stomach.

Table 14. Summary of results of a carcinogenicity study in rats

Test system	Route of administration	Duration of administration	Main lesion	Sex	Dose (mg/kg/day)					Noncarcinogenic level (mg/kg/day)	Attachment CTD
					0	0	5	20	50		
				n	55	55	55	55	55		
Male and female rat (Wistar)	Oral	24 months (once daily)	Benign thymoma	Male	6	5	7	7	6	50 (males) 5 (females)	4.2.3.4.1-6
				Female	5	8	13	18	26		
			Malignant thymoma	Male	0	1	0	0	0		
				Female	0	0	1	1	2		
			Benign thymoma/Malignant thymoma	Male	6	6	7	7	6		
				Female	5	8	14	19	28		
			Hepatocellular adenoma	Male	8	1	3	5	3		
				Female	1	0	5	0	2		
			Urothelial papilloma	Male	0	0	0	0	0		
				Female	0	0	3	0	1		
			Urothelial carcinoma	Male	0	0	0	0	0		
				Female	0	0	0	3	0		
			Urothelial papilloma/ carcinoma	Male	0	0	0	0	0		
				Female	0	0	3	3	1		
			Brain: Malignant astrocytoma/Malignant oligodendroglial tumor	Male	0	0	3	0	1		
				Female	0	0	0	0	0		
			Skin: Squamous cell papilloma/Keratoacanthoma	Male	1	2	5	2	0		
				Female	0	0	0	0	0		
			Skin: Squamous cell carcinoma [a)]	Male	0	0	0	0	0		
				Female	0	4	3	3	5		
			Non-neoplastic lesions	≥20 mg/kg/day: Keratitis (males); infection-related changes [b)] (males and females). 50 mg/kg/day: Plasmacytosis of spleen and mandibular lymph node (males and females); hepatocellular degeneration (microvacuolation, inclusion) of liver; oval cell hyperplasia; foci of eosinophilic cellular alterations; erosions/ulcers of glandular stomach and duodenum; squamous hyperplasia of stomach; pyelitis; renal urothelial hyperplasia (males); keratitis; multinucleated acinar cells of Harderian gland; paracortical lymphoid hyperplasia of mesenteric lymph node (females).						

a) Skin (including subcutaneous tissue), clitoral gland, oral cavity, and nose.
b) Included are septic granulomatous inflammation and septic inflammation in systemic organs and tissues and increased granulocytic hematopoiesis of the bone marrow and spleen.

5.5 Reproductive and developmental toxicity

Fertility and early embryonic development to implantation in rats, embryo-fetal development in rats and rabbits, and effects on pre- and postnatal development including maternal function in rats were studied (Table 15).

Main embryo-fetal effects due to fetal exposure of peficitinib [see Section 4.2.3] included increased post-implantation embryonal mortality, decreased number of live conceptuses, and skeletal and visceral teratogenicity at an exposure 4.1 times the clinical exposure ($AUC_{0\text{-}24}$, 2643 ng·h/mL)[13)] in rats and embryonic/fetal deaths at an exposure 5.4 times the clinical exposure ($AUC_{0\text{-}24}$, 2643 ng·h/mL)[13)] in rabbits. The skeletal malformation observed in the rat fetuses was observed also in the offspring. The $AUC_{0\text{-}24}$ (3236.6 ng·h/mL in rats and 2478.7 ng·h/mL in rabbits) at the NOAEL (10 mg/kg in rats and 3 mg/kg in rabbits) for embryo-fetal development was 1.2 and 0.9 times the clinical exposure ($AUC_{0\text{-}24}$, 2643 ng·h/mL),[13)] respectively. The observed effects on rat offspring included decreased survival rate and decreased body weight in offspring due to excretion of peficitinib in milk [see Section 4.4.2].

Table 15. Summary of results of reproduction toxicity studies

Types of study	Test system	Route of administration	Duration of administration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attachment CTD
Study of fertility and early embryonic development to implantation	Male and female rat (SD)	Oral	Males: 2 weeks pre-mating to Mating Week 2 (once daily) Females: 2 weeks pre-mating to Gestation Day 7 (once daily)	0, 10, 30, 100	Parents: No abnormalities Early embryonic development: 100 mg/kg/day: High post-implantation embryonal mortality; decreased number of live conceptuses; tendency toward increases in the total number of dead conceptuses, number of retained placenta, and number of early macerated fetuses.	Parents (general toxicity, fertility): 100 Early embryonic development: 30	4.2.3.5.1-1
Embryo-fetal development study	Female rat (SD)	Oral	Gestation Days 7 to 17 (once daily)	0, 30, 100, 300	Dams: No abnormalities Embryos and fetuses: ≥30 mg/kg/day: Increased number of fetuses with skeletal malformation [a)]; high incidence of skeletal mutation (cervical rib); decreased number of sternal segmentation ≥100 mg/kg/day: Low body weight of fetuses; increased incidence of skeletal malformation (defect of cervical vertebral arch, defect of cervical vertebra, fusion of rib)/skeletal mutation (incomplete ossification of supraoccipital bone, altered number of lumbar vertebra, wavy rib, short 13th rib) 300 mg/kg/day: Increased incidence of skeletal malformation (rib defect); increased number of fetuses with skeletal mutation; increased incidence of skeletal mutation (incomplete ossification of calvarial bone and interparietal bone, lumbar hemivertebra); increased number of fetuses with organ malformation; increased incidence of organ malformation (aberrant origin of the subclavian artery, defect of pars membranacea septi interventricularis); increased incidence of visceral alteration (thymic remnant in the neck, left umbilical artery); increased number of fetuses with gross external abnormalities (including generalized edema, nail absent, micronychia, brachydactyly, ectrodactyly); increased number of resorptions	Dams (general toxicity): 300 embryo-fetal development: <30 (visceral development: 30)	4.2.3.5.2-2
	Female rat (SD)[b)]	Oral	Gestation Days 7 to 17 (once daily)	0, 1, 3, 10	Dams: No effects Embryos and fetuses [c)]: 10 mg/kg/day: No effects	Dams (general toxicity): 10 Embryo-fetal development: 10	4.2.3.5.2-3
	Female rabbit (NZW)	Oral	Gestation Days 6 to 18 (once daily)	0, 1, 3, 10	Dams: Death: 10 (1 of 19 animals [d)]) 10 mg/kg/day: Low food consumption; abortion (2 of 19 animals); vulvar hemorrhage after administration period Fetuses: 10 mg/kg/day: Increased number of dead embryos and fetuses; increased number of postimplantation loss; increased postimplantation mortality; decreased number of mean live fetuses; increased incidence of sternal fusion and thread-like sternal fusion.	Dams (general toxicity): 3 Embryo-fetal development: 3	4.2.3.5.2-5
Study for effects on pre- and postnatal development, including maternal function	Female rat (SD)	Oral	Dams: Gestation Day 7 to Postpartum Day 20 (once daily)	0, 3, 10, 100	Dams: Death: 100 mg/kg/day (1 of 20 animals [e)]) F1 offspring: 100 mg/kg/day: Low body weight; decreased survival rate at Postnatal Day 4; skeletal malformation (defect of cervical vertebra, defect of cervical vertebral arch, fusion of rib and thoracic vertebral arch)	Dams (general toxicity): 10 Survivability and body weight of F1 offspring: 10 Development, behavior, and reproductive function of FI offspring: 100	4.2.3.5.3-1

a) Skeletal malformation in the 30 mg/kg group: defect of the cervical vertebral arch, defect of the cervical vertebra, and fusion of the ribs

b) The study was additionally conducted to determine the NOAEL of peficitinib for embryo-fetal development because the effects on embryo-fetal

development were observed even at the lowest dose in an embryo-fetal development study in rats (CTD4.2.3.5.2-2).

c) The NOAEL for visceral development was determined in the embryo-fetal development toxicity study in rats (CTD4.2.3.5.2-2). Visceral examinations had not been performed.

d) The blood exposure level (AUC_{0-24}, 30,286.3 ng·h/mL) was higher than the mean blood exposure level (AUC_{0-24}, 14,318.6 ng·h/mL) in this group.

e) The rat died of difficult delivery due to delayed labor, and the death was considered unlikely to be related to peficitinib.

5.6. Other toxicity studies

5.6.1 Evaluation of safety of Metabolite 2 (M2)

M2 is a major human metabolite of peficitinib, and AUC_{0-24} of M2 after multiple oral doses of peficitinib 150 mg to Japanese healthy adults was 5175 ng·h/mL [see Section 6.2.1.2]. General toxicity and embryo-fetal development toxicity were investigated in a toxicokinetics study with peficitinib and metabolites in SD rats (CTD 4.2.3.7.5-2). In the study, AUC_{0-24} of M2 after the administration of peficitinib 100 mg/kg was 12,410 ng·h/mL in female rats [see Section 4.1.2]. It was thus concluded that the toxicity characteristics was evaluated in the repeated-dose toxicity studies (CTD4.2.3.2-2, 4.2.3.2-3, and 4.2.3.2-4) and the embryo-fetal development study in rats (CTD4.2.3.5.2-2). M2 is an alcohol sulfate conjugate and has no structure suggestive of concerns for genotoxicity. Carcinogenicity was evaluated in the toxicokinetics study (CTD 4.2.3.7.5-3) in Wistar rats used in the carcinogenicity study (CTD4.2.3.4.1-6), and AUC_{0-24} of M2 after the oral administration of peficitinib 30 mg/kg was 4268 ng·h/mL in female rats. It was thus concluded that the toxicity characteristics of M2 were evaluated in the carcinogenicity study.

5.6.2 Four-week oral toxicity study of Metabolite 4 (M4) in rats

A 4-week oral toxicity study of Metabolite 4 (M4[14)]) was conducted in rats (Table 16).

Table 16. Summary of results of a toxicity study of M4

Test system	Route of administration	Duration of administration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attachment CTD
Male and female rat (SD)	Oral	4-week administration (once daily) + 4-week interval	0, 100, 300, 1,000	1000 mg/kg/day: Dilatation of cecum with increased cecal contents (males and females); high body weight and low food consumption; decreased urinary pH; liver low weight (males); increased blood AST/ALT (females). Reversibility: Reversible	300	4.2.3.7.5-6

5.6.3 Immunophenotyping study in cynomolgus monkeys

An immunophenotyping study was conducted with peripheral blood lymphocytes of cynomolgus monkeys orally administered peficitinib to evaluate the effects of peficitinib on lymphocytes (Table 17). Decreases in blood T cells and NK cells were observed as the effects of peficitinib on immune cells.

[14)] Accounted for <10% (7.5%) of the total of unchanged peficitinib and metabolites in human plasma.

Table 17. Summary of the results of the immunophenotyping study

Test system	Test method	Main findings	Attachment CTD
Male cynomolgus monkey	Analysis of lymphocyte subsets in peripheral blood after 6-week repeated oral administration of peficitinib at 0, 1, 3, 10 mg/kg/day with a 3-week interval with flow cytometry	≥3 mg/kg/day: Decreased NK cell ratio 10 mg/kg/day: Decreased NK cell count ≥3 mg/kg/day: Decreased naïve T cell ratio in helper T cells 10 mg/kg/day: Decreased naïve T cell count Reversibility: Reversible	Reference data 4.2.3.7.7-1

5.6.4 Thirteen-week oral toxicity study of peficitinib used in combination with tacrolimus in rats

A toxicity study of peficitinib with tacrolimus was conducted (Table 18). There was no new toxicity associated with the combination use or increased toxicity of individual active ingredients.

Table 18. Summary of results of 13-week oral toxicity study of peficitinib used in combination with tacrolimus in rats

Test system	Route of administration	Duration of administration	Dose (mg/kg/day)	Main findings	Attachment CTD
Male and female rat (SD)	Oral	13 weeks (once daily)	Vehicle/tacrolimus [a)] 0/0[b, c)] 0/3.2	0/3.2 mg/kg/day: Decreased food intake; low lymphocytes; low gamma-globulin ratio; high blood urea nitrogen; vacuolation of pancreatic islet cells; increased thymic cortex/medulla ratio and ·lysis of lymphocytes; calcinosis of renal cortico-medullary junction and basophilic change of cortical tubule; follicular atrophy of mandibular/mesenteric lymph node; focal mononuclear cell infiltration in cerebral meninges (males and females); decreased feces; low body weight gain; low leukocytes; high blood cholesterol; low blood potassium/chloride; high urinary output; increased urinary glucose; low total urinary sodium excretion; ocular lens opacification and cortical degeneration; low prostate weight; high kidney weight; encephalitis; myelitis; focal mononuclear cell infiltration in spinal meninges and sciatic nerve; prostate atrophy (males); low body weight; low blood lymphocyte ratio; low blood glucose; high ovary weight; basophilic change of gastric epithelial cells (females).	4.2.3.7.7-3
			Peficitinib/vehicle [a)] 0/0[b, c)] 30/0	30/0 mg/kg/day: Low lymphocytes and eosinophils; low spleen weight, follicular atrophy of spleen/mesenteric lymph node; basophilic change of gastric epithelial cells (males and females); low leukocytes and low lymphocyte ratio; thymus atrophy; basophilic change of renal cortical tubule (males); low food consumption; subcutaneous mass and granulomatous inflammation (females)	
			Peficitinib/tacrolimus [a, d)] 3/3.2 [c)] 10/3.2 30/3.2	≥3/3.2 mg/kg/day: vacuolation of pancreatic islet cells; calcinosis of renal cortico-medullary junction and basophilic change of ·cortical tubule; thymus atrophy, increased cortico-medullary ratio, and lysis of lymphocytes; follicular atrophy of mandibular/mesenteric lymph node; focal mononuclear cell infiltration of cerebral meninges [e)]; encephalitis [e)] (males and females); decreased feces; increased urinary glucose; prostate atrophy; ocular lens opacification; degeneration of ocular lens cortex; basophilic change of gastric epithelial cells [e)] (males). ≥10/3.2 mg/kg/day: low spleen weight; rough surface of kidney (males). ≥30/3.2 mg/kg/day: spleen follicle atrophy (males and females), low blood lymphocyte ratio and low eosinophils (males); rough surface of kidney; low spleen weight; subcutaneous granulomatous inflammation; basophilic change of gastric epithelial cells (females).	

a) Tacrolimus was suspended in water for injection.
b) 0.5% w/v methylcellulose solution/water for injection
c) Tacrolimus or water for injection was administered within 1 minute post-dose of peficitinib or vehicle.
d) Compared with the group of animals treated with tacrolimus alone.
e) Not observed in the 10/3.2 mg/kg/day group.

5.6.5 Thirteen-week oral toxicity study of peficitinib used in combination with MMF in rats

Toxicity of peficitinib in combination use with MMF was studied (Table 19). Toxicity findings in the combination use were suggestive of increased changes related to thymus atrophy and anemia, which are known pharmacological effects of individual active ingredients, but no new toxicity was identified.

Table 19. Summary of results of a 13-week oral toxicity study of peficitinib used in combination with MMF in rats

Test system	Route of administration	Duration of administration	Dose (mg/kg/day)	Main findings	Attachment CTD
Male and female rat (SD)	Oral	13 weeks (once daily)	Vehicle/MMF 0/0 [a)] 0/20	0/20 mg/kg/day: Low erythrocytes, low hematocrit, low hemoglobin, low mean corpuscular hemoglobin, and low mean corpuscular hemoglobin; follicle atrophy of spleen; thymus atrophy (males and females); high reticulocyte ratio; increased extramedullary hematopoiesis in spleen (males); high platelets; follicular atrophy of Peyer's patch (females).	4.2.3.7.7-5
			Peficitinib/vehicle 0/0 [a)] 30/0	30/0 mg/kg/day: Thymus atrophy; low spleen weight; follicular atrophy of spleen/mesenteric lymph node (males and females); low leukocytes, low lymphocytes, low lymphocyte ratio, and low eosinophils; low thymus weight (males); basophilic change of glandular stomach epithelial cells (females)	
			Peficitinib/MMF [a), b)] 3/20 10/20 30/20	≥3/20 mg/kg/day: Thymus atrophy (males and females); increased extramedullary hematopoiesis in spleen (males); follicular atrophy of Peyer's patch (females). ≥10/20 mg/kg/day: Low spleen weight (males and females); low lymphocytes and low lymphocyte ratio (males). 30/20 mg/kg/day: Low leukocytes; low thymus weight; follicular atrophy of spleen/mesenteric lymph node (males and females); low eosinophils; low sternal bone marrow cells (males); low lymphocytes, low erythrocytes, low hematocrit, low hemoglobin, low mean corpuscular volume, and low mean corpuscular hemoglobin (females).	

a) MMF or vehicle was administered within 1 minute after administration of peficitinib or vehicle.
b) Compared with the group of animals treated with MMF alone.

5.6.6 Thirteen-week oral toxicity study of peficitinib in combination with MTX in rats

A toxicity study of peficitinib in combination with MTX was conducted (Table 20), and there was no new toxicity associated with the combination or increased toxicity of individual active ingredients.

Table 20. Summary of results of a 13-week oral toxicity study of peficitinib in combination with MTX in rats

Test system	Route of administration	Duration of administration	Dose (mg/kg/day)	Main findings	Attachment CTD
Male and female rat (SD)	Oral	13 weeks (once daily)	Vehicle/MTX 0/0 [a)] 0/0.1	0/0.1 mg/kg/day: Low erythrocytes, low reticulocyte ratio, low hematocrit, and low hemoglobin; high platelets; high blood AST and ALT; low prostate weight; low femoral/sternal bone marrow cells (males)	4.2.3.7.7-8
			Peficitinib/vehicle 0/0 [a)] 30/0	30/0 mg/kg/day: Low leukocytes; low lymphocytes; low spleen weight; follicular atrophy of spleen/mesenteric lymph node; decreased sternal bone marrow cells (males and females); low lymphocyte ratio and low eosinophils; low thymus weight; thymus atrophy (males).	
			Peficitinib/MTX [a,b)] 3/0.1 10/0.1 30/0.1	≥3/0.1 mg/kg/day: Low sternal bone marrow cells (males and females) [c)]. ≥10/0.1 mg/kg/day: follicular atrophy of mesenteric lymph node (males); low spleen weight, low femoral bone marrow cells [d)] (females). 30/0.1 mg/kg/day: Low lymphocyte ratio; follicle atrophy of spleen (males and females); low spleen weight; thymus atrophy (males); low leukocytes and low lymphocytes (females).	

a) MTX or vehicle was administered within 1 minute after administration of peficitinib or vehicle.
b) Compared with the group of animals treated with MTX alone.
c) Observed in females in the 3/0.1 and 10/0.1 groups and males in the 30/0.1 group.
d) Observed only in the 10/0.1 group.

5.6.7 Phototoxicity

Peficitinib has the absorption maximum at 300 nm in the photoabsorption spectrum, and the molar absorptivity at the wavelength is 12,100 L $mol^{-1}cm^{-1}$. A phototoxicity study was thus conducted (Table 21), and peficitinib is considered to have no phototoxicity.

Table 21. Summary of phototoxicity study results

Types of study	Test system	Test method	Main findings	Attachment CTD
Phototoxicity study	Murine fibroblasts Balb/c 3T3	0, 3.35, 5.36, 8.58, 13.7, 22.0, 35.2, 56.3, 90 µg/mL, UV-A at 5 J/cm^2	No phototoxicity (mean light action: 0.011)	4.2.3.7.7-9

5.R Outline of the review by PMDA

5.R.1 Effects of immunosuppression

The applicant's explanation about the human relevance of the data from the rat carcinogenicity study [see Section 5.4] and a risk of carcinogenicity of peficitinib in humans:

The data from the genotoxicity study [see Section 5.3] indicate that peficitinib is not genotoxic in the body, and the increased incidence of benign thymoma in the rat carcinogenicity study is attributable to a non-genotoxic mechanism.

In rodents, the incidence of spontaneous tumors increases in an immunosuppressed state. Long-term administration of immunosuppressive drugs such as leflunomide and sirolimus caused lymphoma in mice (*Int J Toxicol*. 2010;29:435-66). In addition, thymoma and lymphoid tumors spontaneously occurred with a higher incidence in the Wistar rat strain, which was used in the carcinogenicity study of peficitinib, than in other rat strains (*Toxicol Pathol*. 2017;45:64-75). Peficitinib is a JAK inhibitor, and findings related to immunosuppression were observed in the toxicity studies in rats and cynomolgus monkeys [see Section 5.2]. In the immunophenotyping study in cynomolgus monkeys, the counts of blood lymphocytes and NK cells decreased in association with the administration of peficitinib [see Section 5.6.3]. Until now, there has been no report that the inhibition of the JAK-STAT signal transduction may promote the proliferation of lymphocyte-derived tumor cells. Therefore, the increased incidence of lymphocyte-predominant thymoma observed in rats in the carcinogenicity study of peficitinib is attributed not to the direct effects of peficitinib but to the increases in the incidence of spontaneous thymoma due to the immunosuppressive effects of peficitinib.

In clinical studies of peficitinib, no clear relationship has been indicated between the treatment with peficitinib and the onset of malignant tumors so far [see Section 7.R.3.]. In light of the immunosuppressive effects of peficitinib, however, a possible increase in the carcinogenic risk cannot be excluded in the setting of prolonged treatment with peficitinib in humans. Malignant tumors reported in the clinical studies and the occurrence of thymoma in rats will be highlighted in the package insert, and data collection will be continued on the occurrence of malignant tumors associated with peficitinib therapy in post-marketing surveys and studies.

PMDA's view:
From the following viewpoints, long-term treatment with peficitinib in humans requires a careful approach based on the benefit-risk discussion for patients in clinical practice in Section 7.R.3.2 for the associated risk of malignant tumors.

- There is no safety margin in the carcinogenicity study in rats.
- Generally, the immunosuppressive effects increase the risk of malignant tumors, and patients treated with immunosuppressive drugs were more susceptible to lymphoproliferative diseases (*Int J Toxicol*. 2010;29:435-66).
- Given the reported an increased incidence of thymoma in a rat carcinogenicity study and the occurrence of malignant tumors in clinical studies on tofacitinib, also a JAK inhibitor, (Xeljanz Tablets 5 mg Review Report dated February 28, 2013), peficitinib's JAK inhibition-related immunosuppression may increase the risk of malignant tumors in humans as well.

Changes related to the increased susceptibility to infections due to the immunosuppressive effects of peficitinib were observed in the repeated-dose toxicity studies in rats and cynomolgus monkeys. The safety of peficitinib therapy in patients with infectious diseases should be thoroughly discussed in the clinical sections in light of the incidence of infectious diseases in clinical studies.

5.R.2 Effects on embryo and fetus

The applicant's explanation on the relationship with the administration of peficitinib based on the reproductive and developmental toxicity studies in rats and rabbits [see Section 5.5]:
Leukemia inhibitory factors (LIFs) are involved in the endometrial development (*Reproduction*. 2009;138:827-36). The activation of LIFs is mediated by the JAK-STAT signal transduction (*PLos One*. 2016;11:e0153086). Given these, the increased post-implantation embryonal mortality in rats is attributable to the poor endometrial development due to blocked LIF signal transduction by the preimplantation exposure to peficitinib. Since LIFs are expressed also in human endometrium (*Proc Natl Acad Sci USA*. 1996;93:3115-20), the possibility cannot be excluded that peficitinib may exert similar effects in humans.

The visceral and skeletal malformations observed in rat fetuses are likely to be caused by the direct effects of peficitinib on the fetuses based on the findings suggestive of the possible placental transfer of peficitinib [see Section 4.2.3].

As shown above, skeletal and visceral malformations were observed in rats, and embryocidal effects were observed in rabbits. These facts should be informed via the package insert, etc. along with cautionary advice on the use of peficitinib for women, i.e., women of childbearing potential to be treated with peficitinib should avoid pregnancy; peficitinib should not be administered to pregnant women or those who may be pregnant; and

women of childbearing potential should avoid pregnancy during peficitinib therapy and for ≥1 menstrual cycle after the termination of peficitinib therapy.

PMDA's view:
Additional cautionary advice is required about contraception during peficitinib therapy in women of childbearing potential, in light of the teratogenicity and other embryo/fetal toxicity of peficitinib and a safety margin yet to be defined. The observation about the effects of peficitinib on embryo-fetal development is presented below.

The mechanism of the increased incidence of early embryonic deaths and post-implantation embryonic deaths in rats, including peficitinib's action mechanism on the placenta, remains unclear. Nevertheless, peficitinib may possibly affect the post-implantation embryo development as well, in view of the increasing tendency of retained placenta and the number of early macerated fetuses. The possibility cannot be denied that peficitinib is related to the visceral and skeletal teratogenicity in rats, the effects on embryo-fetal deaths in rabbits, and the following sternal abnormalities in rabbit fetuses.

- There is difficulty in clearly distinguishing sternal fusion from thread-like sternal fusion in rabbits, which is a different type of abnormality.
- The sum of the percentages of animals with sternal fusion and those with thread-like sternal fusion is greater than the historical data in the study site.
- Sternal fusion was observed even in an embryo-fetal study of tofacitinib in rabbits (Xeljanz Tablets 5 mg Review Report dated February 28, 2013).
- The JAK-STAT signal transduction is involved in osteogenesis, and the defect/inhibition of the JAK-STAT signal transduction may influence osteogenesis [see Section 5.R.3 Effects on osteogenesis].

5.R.3 Effects on osteogenesis

PMDA's view on necrotic changes at femoral metaphysis [see Section 5.2] and skeletal malformations and mutations in fetuses and offspring [see Section 5.5] in repeated-dose toxicity studies in rats:
Abnormal bone growth was observed in Jak-1-deficient mice and Stat-mutant mice in which gens for the JAK-STAT signal transduction were mutated (JAK-STAT 2013; 2: e23930), and fetal skeletal abnormalities were observed with other JAK inhibitors (Xeljanz Tablets 5 mg Review Report dated February 28, 2013; Olumiant Tablets 2 mg and 4 mg Review Report dated May 19, 2017). These findings suggest that the inhibition of the JAK-STAT signal transduction may affect bone development and growth. Although the effects are considered insignificant in adults with mature bone growth, safety considerations should be given when drugs with inhibitory effects on the JAK-STAT signal transduction, including peficitinib, are used in patients undergoing rapid bone growth.

5.R.4 Effects on gastrointestinal tract

The applicant's explanation about the cause of gastrointestinal damages observed during repeated dosing of peficitinib in rats and cynomolgus monkeys, and safety in humans:

In cynomolgus monkeys, gastrointestinal toxicity with peficitinib was observed extensively in the upper and lower gastrointestinal tract, indicating that the gastrointestinal damages are associated with the systemic exposure of peficitinib but not due to local effects, such as irritation of peficitinib. Gastrointestinal perforation was reported in clinical studies of another JAK inhibitor (*Nat Rev Rheumatol*. 2017;13:234-43), and the gastrointestinal toxicity might have been related to the JAK inhibition of peficitinib. Also, in clinical studies of peficitinib, the incidence of gastrointestinal disorders was slightly higher in the peficitinib group than in the control group or the etanercept (ETN) group [see Section 7.R.3].

Based on the above, attention will be called to gastrointestinal perforation and gastrointestinal disorders via the package insert, and data on the occurrence of serious adverse drug reactions such as gastrointestinal perforation in the use of peficitinib will be further collected in the post-marketing setting.

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 Biopharmaceutic Studies and Associated Analytical Methods

Data from bioequivalence studies and food effect studies in Japanese healthy adults were submitted for evaluation.

In the clinical development program of peficitinib, 5 formulations (Formulation 1 [[redacted], [redacted], [redacted], and [redacted] mg]; Formulation 2 [[redacted], [redacted], [redacted], and [redacted] mg]; Formulation 3 [Formulation in which [redacted] and [redacted] were changed from those for Formulation [redacted], [redacted], [redacted], and [redacted] mg], Formulation 4 [[redacted], [redacted], [redacted], and 150 mg], and Formulation 5 [[redacted] formulation in which [redacted] in Formulation [redacted] was changed because of [redacted], 150 mg]) were mainly used.[15)] In Japanese phase III studies, Formulation 4 was used, and a bioequivalence study comparing Formulations 4 and 5 demonstrated the bioequivalence between these formulations [see Section 6.1.1]. The commercial formulations in Japan (50 and 100 mg) were Formulation 5 and [redacted] Formulation which is [redacted], and dissolution equivalence between these formulations was

[15)] The following clinical studies were conducted for individual formulations:
Formulation 1, Phase [redacted] studies (Studies [redacted], [redacted], [redacted], [redacted], and [redacted]); Formulation 2, Phase [redacted] studies (Studies [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]) and Phase [redacted] study (Study [redacted]); Formulation 3, Phase [redacted] studies (Studies [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]), Phase [redacted] studies (Studies [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]), and a [redacted] study (Study [redacted]); Formulation 4, Phase [redacted] studies (Studies [redacted], [redacted], CL-PK27, and [redacted]), Phase III studies (Studies CL-RAJ3 and CL-RAJ4), and a [redacted] study (Study [redacted]); and Formulation 5, Phase [redacted] studies (Studies [redacted], CL-PK12, [redacted], CL-PK27, and [redacted]).

confirmed in an *in vitro* dissolution study.[16] The dissolution equivalence between the proposed formulations 50 mg and 100 mg was confirmed in an *in vitro* dissolution study.[17]

The plasma and urinary concentrations of peficitinib and its metabolites were determined with LC-MS/MS (a lower limit of quantification in plasma and urine, 0.25 ng/mL and 2.5 ng/mL, respectively, for peficitinib; and a lower limit of quantification in plasma, 0.25 ng/mL for metabolites [M1, M2, and M4]). Unless otherwise specified, the dose is expressed as an equivalent dose of peficitinib, and the pharmacodynamic parameters and measurements are expressed as the mean or mean ± standard deviation.

6.1.1 Bioequivalence study (CTD 5.3.1.2-1: Study CL-PK27 [June 2015 to July 2015])

In a randomized, open-label, 2-treatment, 2-period, crossover study in Japanese healthy adult men (n = 40), the single-dose of Formulation 4 (one 150 mg tablet) and Formulation 5 (one 150 mg tablet) were administered under fasting conditions. Results of the bioequivalence of the formulations are shown in Table 22. The ratio of least squares geometric mean [90% confidence interval] of C_{max} and AUC_t of peficitinib after administration of Formulation 5 to that after administration of Formulation 4 was 1.11 [0.99, 1.24] and 1.05 [0.95, 1.16], respectively, and fell within the range of the prespecified criteria for bioequivalence (0.80 to 1.25).

Table 22. Pharmacokinetic parameters of peficitinib (a single oral dose of Formulation 4 or 5, fasted)

	N	C_{max} (ng/mL)	AUC_t (ng·h/mL)	AUC_{inf} (ng·h/mL)	t_{max} (h) [a]	$t_{1/2}$ (h)
Formulation 4 (150 mg)	39	466.6 ± 139.7	1843 ± 450.6	1832 ± 440.9 [b]	1.50 [1.0, 6.0]	10.58 ± 9.787 [b]
Formulation 5 (150 mg)	39	524.5 ± 183.8	1924 ± 410.3	1932 ± 417.5 [c]	1.50 [1.0, 3.0]	9.35 ± 7.427 [c]

Mean ± standard deviation; a) Median [range]; b) n = 38; c) n = 37.

6.1.2 Study on effects of food (CTD 5.3.1.1-1: Study CL-PK12 [November 2015 to February 2016])

In a 2-treatment, 2-period, crossover study in 18 Japanese healthy adult men, a single dose of peficitinib 150 mg (Formulation 5) was orally administered under fasting conditions or after a high-fat meal (with ≥900 kcal and fat accounting for ≥35% of total calories). The pharmacokinetic parameters are shown in Table 23. Based on the results, it was concluded that foods influenced the pharmacokinetics of peficitinib, and it was decided that peficitinib was to be administered after a meal in clinical studies.

Table 23. Pharmacokinetic parameters of peficitinib 150 mg (fasted or fed)

Fed/fasted	N	C_{max} (ng/mL)	AUC_{last} (ng·h/mL)	t_{max} (h) [a]	Ratio of least squares geometric mean (90% confidence interval [CI]) of C_{max} and AUC_{last} after fasted administration to that after fed administration	
					C_{max}	AUC_{last}
Fasted	18	447.6 ± 138.7	1645 ± 506.5	1.5 [1.0, 3.0]	1.56 [1.39, 1.76]	1.37 [1.23, 1.53]
Fed	17	698.5 ± 213.2	2217 ± 441.9	2.0 [1.0, 3.0]		

Mean ± standard deviation
a) Median [range]

[16] Dissolution studies for Formulation 5 (150 mg) and the proposed formulation (50 mg) were conducted with the [redacted] dissolution procedure (testing media [[redacted]], [redacted], [redacted] rotation/min, [redacted] tablets, [redacted] mL). Dissolution studies for Formulation 5 (150 mg) and the proposed formulation (100 mg) were conducted with the [redacted] ([redacted] rotation/min, testing media [150 mg [redacted] tablets, [redacted] mL; 100 mg [redacted] tablets, [redacted] mL or [redacted] mL]) with the use of the testing media ([redacted], [redacted], [redacted], and [redacted]).

[17] They were evaluated with [redacted] ([redacted] rotation/min, testing media [[redacted] mL (100 mg tablets [redacted] tablets, 50 mg tablets [redacted] or [redacted] tablets)]) with the use of the testing media ([redacted], [redacted], [redacted], and [redacted]).

6.2 Clinical Pharmacology

To evaluate clinical pharmacology, data were submitted from studies conducted in healthy adults and subjects with hepatic or renal impairment, pharmacokinetic interaction studies, and population pharmacokinetics (PPK) analyses. *In vitro* studies with human biospecimens are described on the sections of non-clinical pharmacokinetics [see Sections 4.2 to 4.5]. Unless otherwise specified, the dose of peficitinib hydrobromide is expressed as an equivalent dose of peficitinib, and the PK parameters are expressed as the mean or mean ± standard deviation.

6.2.1 Studies in healthy adults

6.2.1.1 Phase I study (CTD 5.3.3.1-3: Study CL-HV03 [November 2009 to March 2010])

A single dose of placebo or peficitinib 20, 60, or 200 mg was orally administered under fasting conditions in a total of 48 Japanese and non-Japanese healthy adults. The pharmacokinetics and the inhibitory activity against the phosphorylation of STAT5 are shown in Table 24. The ratio of geometric means of C_{max} and AUC_{inf} in Japanese subjects and that in non-Japanese subjects was 1.57 to 1.77 and 1.35 to 1.66, respectively. The inhibitory activity against the phosphorylation of STAT5 peaked at 2 hours post-dose, and the maximum inhibitory activity was higher in Japanese subjects than in non-Japanese subjects.

Placebo or peficitinib 10, 30, or 100 mg was repeatedly administered orally twice daily after meal for 7 days in 24 Japanese healthy adults. The pharmacokinetics and the inhibitory activity against the phosphorylation of STAT5 are shown in Table 25. The accumulation ratio (Day 7/Day 1) of C_{max} and AUC_{0-12} on Day 1 to that on Day 7 was 1.13 to 1.28 and 1.25 to 1.37, respectively.

Table 24. Pharmacokinetic parameters and inhibitory activity against STAT5 phosphorylation of a single oral dose of peficitinib in Japanese and non-Japanese healthy adults

Dose (mg)	Subjects	N	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	t_{max} (h) [a]	$t_{1/2}$ (h)	CL/F (L/h)	Maximum inhibitory activity against STAT5 phosphorylation (%)
20	Japanese	6	76.9 ± 24.2	259.5 ± 42.9	1.0 [1.0, 3.0]	3.7 ± 0.7	78.9 ± 13.5	68.4 ± 7.59
	Non-Japanese	6	48.9 ± 16.9	196.3 ± 54.6	1.0 [1.0, 1.5]	7.3 ± 10.0	108.5 ± 30.0	56.6 ± 7.78
60	Japanese	6	241.1 ± 74.7	782.8 ± 158.6	1.3 [1.0, 1.5]	4.0 ± 1.0	79.8 ± 19.2	89.6 ± 3.88
	Non-Japanese	6	130.9 ± 19.4	528.6 ± 118	1.0 [1.0, 1.5]	10.0 ± 5.0	117.8 ± 23.6	81.2 ± 2.70
200	Japanese	6	648.7 ± 55.5	2525 ± 234.5	2.0 [1.0, 2.0]	7.5 ± 4.9	79.8 ± 8.2	97.2 ± 0.95
	Non-Japanese	6	381.2 ± 114.4	1520 ± 186.5	1.8 [1.5, 3.0]	6.9 ± 3.2	133.1 ± 15.0	93.2 ± 3.70

Mean ± standard deviation; CL/F, apparent total clearance.
a) Median [range]

Table 25. Pharmacokinetic parameters and inhibitory activity against STAT5 phosphorylation of multiple oral doses of peficitinib in Japanese healthy adults

Dosing regimen	N	Time point	C_{max} (ng/mL)	AUC_{0-12} (ng·h/mL)	t_{max} (h) [a]	$t_{1/2}$ (h)	CL/F (L/h)	Maximum inhibitory activity against STAT5 phosphorylation (%)
Multiple doses of 10 mg BID	6	Day 1	28.5 ± 6.1	114.5 ± 29.1	1.5 [1.0, 2.0]	—	87.7 ± 23.6	72.2 ± 2.36
		Day 7	36.4 ± 8.2	144.6 ± 24.1	2.5 [1.0, 4.0]	6.0 ± 1.2	71.0 ± 13.6	49.2 ± 12.7
Multiple doses of 30 mg BID	6	Day 1	93.5 ± 21.2	353.9 ± 60.8	2.0 [2.0, 3.0]	—	83.3 ± 14.6	74.4 ± 7.08
		Day 7	106.2 ± 25.8	443.6 ± 80.1	2.0 [1.0, 3.0]	6.1 ± 3.6	69.6 ± 13.5	77.3 ± 5.40
Multiple doses of 100 mg BID	6	Day 1	383.4 ± 26.0	1336 ± 135.1	2.0 [2.0, 3.0]	—	71.2 ± 8.7	94.2 ± 1.96
		Day 7	482.8 ± 77.3	1833 ± 261.3	2.0 [2.0, 3.0]	7.4 ± 3.5	55.7 ± 9.3	95.5 ± 1.32

Mean ± standard deviation; —, not calculated; CL/F, apparent total clearance; BID, twice daily.
a) Median [range]

6.2.1.2 Phase I study (CTD 5.3.3.4-4: Study CL-PK20 [May 2016 to June 2016])

In a Japanese study conducted in 24 Japanese healthy adults, peficitinib 150 mg was orally administered after the meal as a single dose or once daily for 5 days. The pharmacokinetic parameters are shown in Table 26. The exposure of peficitinib reached a steady state on Day 3. The ratio of C_{max} and AUC_{0-24} after the single oral dose to that of the multiple doses on Day 5 was 1.18 and 1.22, respectively.

Table 26. Pharmacokinetic parameters after a single or multiple oral dose(s) of peficitinib in Japanese healthy adults

Dosing regimen	Test substance	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	t_{max} (h) [a]	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
Single dose of 150 mg	Peficitinib	532 ± 155	2185 ± 532	3.0 [1.5, 4.0]	6.45 ± 3.38	70.9 ± 15.9	656 ± 376
Multiple doses of 150 mg (for 5 days)		613 ± 168	2643 ± 590	3.0 [1.5, 4.0]	—	59.5 ± 13.0	—
Single dose of 150 mg	M1	47.9 ± 22.0	380 ± 183	4.0 [3.0, 6.0]	6.47 ± 2.18	—	—
Multiple doses of 150 mg (for 5 days)		39.8 ± 19.0	363 ± 172	4.0 [3.0, 6.0]	—	—	—
Single dose of 150 mg	M2	992 ± 267	4382 ± 945	3.0 [2.0, 4.0]	6.83 ± 3.46	—	—
Multiple doses of 150 mg (for 5 days)		1112 ± 320	5175 ± 1,152	3.0 [2.0, 4.0]	—	—	—
Single dose of 150 mg	M4	44.5 ± 13.9	407 ± 103	4.0 [3.0, 6.0]	6.17 ± 1.37	—	—
Multiple doses of 150 mg (for 5 days)		44.0 ± 13.8	449 ± 111	4.0 [3.0, 8.0]	—	—	—

Mean ± standard deviation; —, not calculated; CL/F, apparent total clearance; V_z/F, apparent distribution volume
a) Median [range]

6.2.1.3 Phase I study (CTD 5.3.3.4-3: Study CL-PK26 [May 2013 to July 2013])

In foreign studies conducted in non-Japanese healthy adults, Table 27 shows the pharmacokinetic parameters of multiple doses of peficitinib 150 mg once daily after meal.

Table 27. Pharmacokinetic parameters of multiple oral doses of peficitinib after meal in non-Japanese healthy adults

Test substance	Population	N	C_{max} (ng/mL)	AUC_{24h} (ng·h/mL)
Peficitinib	Asian	5	726.3 ± 139.7	2562 ± 293.5
	Non-Asian	18	433.9 ± 142.5	1768 ± 434.6
M2	Asian s	5	1329 ± 162.5	5.266 ± 602.7
	Non-Asian	18	707.4 ± 276.3	3316 ± 1220

Mean ± standard deviation

6.2.1.4 Mass balance study (CTD 5.3.3.1-5: Stud CL-PK03 [December to January 2010])

In a foreign study conducted in 6 non-Japanese healthy adult men, a single dose of ^{14}C-peficitinib 100 mg was orally administered after meal. The t_{max} of plasma radioactivity and plasma peficitinib was 2.0 and 1.75,

respectively, and the proportion of peficitinib in the total plasma radioactivity was 36% in AUC_{last}. The ratio of C_{max} and AUC_{last} of the whole blood radioactivity to that of the plasma radioactivity was 0.77 and 0.66, respectively. A total of 93.2% of the administered dose was excreted in urine by 120 hours post-dose, and 93.4% in feces by 216 hours post-dose. The cumulative urinary excretion rate by 216 hours post-dose was 36.8% of the administered radioactivity, and peficitinib accounted for 36% of the urinary radioactivity. The cumulative fecal excretion rate by 216 hours post-dose was 56.6% of the administered radioactivity.

6.2.2 Intrinsic factor pharmacokinetic studies

6.2.2.1 Study in subjects with hepatic impairment (CTD 5.3.3.3-2: Study CL-PK10 [December 2015 to September 2016])

A single dose of peficitinib 150 mg was administered under fasting conditions in 16 Japanese subjects with mild (Child-Pugh class A, 8 subjects) or moderate (Child-Pugh class B, 8 subjects) hepatic impairment and 8 subjects with normal hepatic function. The pharmacokinetic parameters of peficitinib are shown in Table 28. In subjects with moderate hepatic impairment, the peficitinib exposure increased with decreased capacity to metabolize peficitinib into M2 due to decreased sulfate conjugation activity in the liver.

Table 28. Pharmacokinetic parameters of a single oral dose of peficitinib in subjects with hepatic impairment

Severity of hepatic impairment	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	Ratio of least squares geometric mean [90% CI] (hepatic impairment/normal hepatic function)	
				C_{max}	AUC_{inf}
Normal hepatic function	350 ± 129	1149 ± 231 [a)]	10.4 ± 6.22 [a)]	—	—
Mild	372 ± 147	1435 ± 525	13.7 ± 9.93	1.04 [0.71, 1.53]	1.19 [0.86, 1.64]
Moderate	674 ± 332	2332 ± 896	11.2 ± 8.88	1.82 [1.24, 2.69]	1.92 [1.39, 2.66]

Mean ± standard deviation; —, not calculated; a) 7 subjects.

6.2.2.2 Study in subjects with renal impairment (CTD 5.3.3.3-1: Study CL-PK11 [November 2015 to December 2016)

A single dose of peficitinib 150 mg was administered under fasting conditions in 24 Japanese subjects with renal impairment (8 each with mild [eGFR of 60 to 90 mL/min/1.73m^2], moderate [eGFR of 30 to 60 mL/min/1.73m^2], and severe [eGFR of 15 to 30 mL/min/1.73m^2] impairment) and 8 Japanese subjects with normal renal function (eGFR of ≥90 mL/min/1.73m^2). The pharmacokinetic parameters of peficitinib are shown in Table 29. No marked differences in peficitinib exposure were observed between subjects with and without renal impairment.

Table 29. Pharmacokinetic parameters of a single oral dose of peficitinib in subjects with renal impairment

Severity of renal impairment	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	Ratio of least squares geometric mean [90% CI] (renal impairment/normal renal function)	
				C_{max}	AUC_{inf}
Normal renal function	426 ± 157	1595 ± 360	6.80 ± 4.34	—	—
Mild	377 ± 120	1419 ± 385	15.0 ± 8.33	0.90 [0.60, 1.35]	0.87 [0.61, 1.25]
Moderate	342 ± 135	1427 ± 563	14.4 ± 14.3	0.78 [0.52, 1.18]	0.83 [0.58, 1.19]
Severe	387 ± 260	1933 ± 985 [a)]	10.8 ± 5.13 [a)]	0.78 [0.51, 1.20]	1.09 [0.74, 1.60]

Mean ± standard deviation; —, not calculated; a) 6 subjects

6.2.3 Investigation of pharmacokinetic interactions[18)]

A total of 8 studies were conducted to investigate drug interaction between peficitinib and other drugs used in combination. The ratio of least squares geometric mean of PK parameters of peficitinib and concomitant drugs administered alone to that of drugs administered concomitantly are shown in Table 30 and Table 31.

Table 30. Effects of concomitant drugs on the pharmacokinetic parameters of peficitinib

Concomitant drug	Dosing regimen		N	Ratio of least squares geometric mean [90% CI] (concomitant use/no concomitant use)	
	Concomitant drug	Peficitinib		AUC_{0-12}	C_{max}
Verapamil	80 mg, 3 times daily, PO	150 mg, once, PO	24	1.27 [1.22, 1.32] a)	1.39 [1.26, 1.53]
Midazolam	3 mg, once, PO	60 mg BID PO	28	1.07 [1.03, 1.12]	0.97 [0.90, 1.04]
		100 mg BID PO	29	1.05 [1.01, 1.09]	1.03 [0.96, 1.11]
Rosuvastatin	10 mg, once, PO	150 mg QD PO	23	1.16 [1.06, 1.28] b)	1.28 [1.13, 1.45]
Metformin	750 mg, once, PO	150 mg QD PO	24	1.15 [1.13, 1.17] b)	1.20 [1.11, 1.30]
MTX	15 to 25 mg, once, PO	100 mg BID	14	0.98 [0.91, 1.06]	0.92 [0.78, 1.08]
MMF	1 g, once, PO	100 mg BID PO	24	1.08 [1.04, 1.12]	1.05 [0.95, 1.16]
Tacrolimus	5 mg, once, PO	100 mg BID PO	24	1.13 [0.96, 1.33]	1.12 [0.92, 1.37]
	5 mg, once, PO	60 mg BID PO	28	1.07 [1.05, 1.10]	0.96 [0.90, 1.03]
		100 mg BID PO	27	1.06 [1.03, 1.10]	1.06 [0.97, 1.16]
	1 mg, once, IV	100 mg BID PO	12	1.0 [0.95, 1.06]	0.88 [0.79, 0.99]

PO, oral administration; IV, intravenous administration; QD, once daily; BID, twice daily; a) AUC_{inf}; b) AUC_{0-24}.

Table 31. Effects of peficitinib on pharmacokinetic parameters of concomitant drugs

Concomitant drug	Dosing regimen		N	Ratio of least squares geometric mean [90% CI] (concomitant use/no concomitant use)	
	Concomitant drug	Peficitinib		AUC_{inf}	C_{max}
Midazolam	3 mg, once, PO	60 mg BID PO	30[a)]	1.19 [1.11, 1.27]	1.04 [0.97, 1.11]
		100 mg BID PO	30[b)]	1.37 [1.28, 1.46]	1.13 [1.06, 1.21]
Rosuvastatin	10 mg, once, PO	150 mg QD PO	24[c)]	0.94 [0.56, 1.58]	1.15 [1.01, 1.31]
Metformin	750 mg, once, PO	150 mg QD PO	24	0.83 [0.78, 0.87]	0.83 [0.79, 0.88]
MTX	15 to 25 mg, once	100 mg BID	15[d)]	1.03 [0.93, 1.13] e)	0.92 [0.83, 1.03] f)
MMF	1 g, once, PO	100 mg BID PO	24	1.02 [0.96, 1.09]	0.95 [0.80, 1.12]
Tacrolimus	5 mg, once, PO	100 mg BID PO	24	1.63 [1.50, 1.78]	1.57 [1.40, 1.75]
	5 mg, once, PO	60 mg BID PO	28	1.23 [1.14, 1.31]	1.40 [1.24, 1.58]
		100 mg BID PO	27	1.39 [1.27, 1.53]	1.60 [1.40, 1.84]
	1 mg, once, IV	100 mg BID PO	12	1.03 [0.98, 1.08]	1.01 [0.93, 1.09]

PO, oral administration; IV, intravenous administration;
a) Concomitant use in 28 subjects; b) Concomitant use in 29 subjects; c) Concomitant use in 23 subjects; d) Concomitant use in 14 subjects; e) AUC_{inf}/Dose; f) C_{max}/Dose

6.2.4 Thorough QT/QTc study (CTD 5.3.4.1-1: Study CL-QT01 [June 2014 to September 2014])

In a 4-treatment, 4-period crossover study in 56 non-Japanese healthy adults, a single dose of placebo or peficitinib 150 or 450 mg was orally administered with a positive control of moxifloxacin (400 mg, single oral dose) to evaluate the effects on QT interval. The maximum difference [90% confidence interval] in the mean change from baseline in QT interval between peficitinib 150 mg or 450 mg and placebo was −12.0 ms [−14.0, −10.0] (150 mg, 2 hours post-dose) and −14.7 ms [−16.8, −12.6] (450 mg, 4 hours post-dose), showing shortened QT interval. The maximum difference [90% confidence interval] in the mean changes from baseline in QT interval between moxifloxacin (3 hours post-dose) and placebo was 9.3 ms [7.2, 11.3] (3 hours post-dose).

6.2.5 Population pharmacokinetic analysis (CTD 5.3.3.5-2)

[18)] CTD 5.3.3.4-1, Study CL-PK04 [October 2013 to November 2013]; CTD 5.3.3.4-2, Study CL-PK05 [June 2010 to July 2010]; CTD 5.3.3.4-3, Study CL-PK26 [May 2013 to July 2013]; CTD 5.3.3.4-4, Study CL-PK20 [May 2016 to June 2016]; CTD 5.3.3.4-5, Study CL-PK13 [January 2010 to March 2010]; reference data, CTD 5.3.3.4-6, Study CL-PK01 [May 2009 to June 2009]; reference data, CTD 5.3.3.4-7, Study CL-PK02 [June 2009 to June 2009]; reference data, CTD 5.3.3.4-8, Study CL-PK16 [July 2010 to September 2010]

A population pharmacokinetics analysis was performed (NONMEM version 7.3) with the use of a model based on data on plasma peficitinib concentrations from the Japanese and foreign phase I study in healthy adults (98 subjects, 2464 time points)[19] and data on plasma peficitinib concentrations in RA patients from the phase III studies (Studies CL-RAJ3 and CL-RAJ4, 989 subjects, 4919 time points).

A 2-compartment model with sequential zero- and first-order absorption was used as a basic model. As a result of evaluation,[20] eGFR and lymphocyte count at baseline for the apparent total clearance (CL/F) were selected as covariates for the final model. Table 32 shows the pharmacokinetic parameters of peficitinib 150 mg at steady state in Japanese RA subjects estimated with the final model.

Table 32. Estimated PK parameters of multiple oral doses of peficitinib 150 mg in Japanese RA patients

Dosing regimen		N	C_{max} (ng/mL)	$AUC_{0\text{-}24}$ (ng/h/mL)
Peficitinib 150 mg QD		424	377.7 [299.5, 451.2]	1695 [1115, 2353]

Mean [90% CI]

6.R Outline of the review by PMDA

6.R.1 Ethnic differences in pharmacokinetics of peficitinib

The applicant's explanation about ethnic differences in the pharmacokinetics of peficitinib:
In the single and repeated dose study in Japan (Study CL-HV03), exposure to peficitinib tended to be higher in Japanese subjects than in Caucasian subjects [see Table 21].

In a Japanese phase I study (Study CL-PK20) and a foreign phase I study (Study CL-PK26), peficitinib 150 mg was repeatedly administered orally once daily in Japanese, Asian, and non-Asian healthy adults. The pharmacokinetic parameters of peficitinib in these population are shown in Table 33. The levels of exposure to peficitinib and M2 were similar between Japanese and Asian subjects, and both populations tended to have higher exposure levels than non-Asian subjects. Based on the results from the population pharmacokinetic analysis performed on data from the Japanese phase II study (Study CL-RAJ1) and phase III studies (Studies CL-RAJ3 and CL-RAJ4) [see Section 6.2.5], the study region (Japan, Korea, or Taiwan) was not selected as covariate for description of the pharmacokinetic model of peficitinib.

Table 33 Pharmacokinetic parameters of multiple doses of peficitinib 150 mg once daily in Japanese, Asian, and non-Asian healthy adults

Test substance	PK parameters	Study CL-PK20	Study CL-PK26	
		Japanese subjects (n = 24)	Non-Asian subjects (n = 18)	Asian subjects (n = 5)
Peficitinib	C_{max} (ng/mL)	613.2 ± 167.9	433.9 ± 142.5	726.3 ± 139.7
	AUC_{24h} (ng·h/mL)	2643 ± 590.4	1768 ± 434.6	2562 ± 293.5
M2	C_{max} (ng/mL)	1112 ± 320.1	707.4 ± 276.3	1329 ± 162.5
	AUC_{24h} (ng·h/mL)	5175 ± 1,152	3316 ± 1,220	5266 ± 602.7

Mean ± standard deviation

[19] Phase I study (Studies 015K-CL-PK12, 015K-CL-PK27, and 015K-CL-PK20 [all subjects]; Studies 015K-CL-PK10 and 015K-CL-PK11 [subjects with normal hepatic function and subjects with normal renal function])
[20] The following factors were investigated as covariates: age, body weight, sex (male or female), study region (Japan, Korea, and Taiwan), C-reactive protein, neutrophil count, lymphocyte count, erythrocyte count, platelet count, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin, total bilirubin, hemoglobin, hematocrit, creatinine, uric acid, and eGFR for CL/F of peficitinib hydrobromide; and body weight, C-reactive protein, neutrophil count, and lymphocyte count for V2/F of peficitinib hydrobromide.

These results demonstrate no evident differences in the pharmacokinetics of peficitinib between Japanese and Asian subjects.

PMDA accepted the above explanation.

6.R.2 Dose adjustment of peficitinib in patients with hepatic impairment

The applicant's explanation about dose adjustment of peficitinib in patients with moderate hepatic impairment:
The data from a clinical study in subjects with hepatic impairment (Study CL-PK10 [see Section 6.2.2.1]) are shown in Table 28. Exposure to peficitinib in subjects with moderate hepatic impairment, namely, C_{max} and AUC, increased by 82.4% and 92.3%, respectively, as compared to those in subjects with normal hepatic function.

No clinical study has been conducted to evaluate the efficacy and safety of peficitinib in RA patients with moderate hepatic impairment. However, the exposure to peficitinib after a 50-mg dose in RA patients with moderate hepatic impairment is estimated to be nearly equal to that after a 100-mg oral dose RA patients with normal hepatic function. Thus peficitinib should be administered to RA patients with moderate hepatic impairment at a reduced dose of 50 mg once daily. Peficitinib has never been administered to subjects with severe hepatic impairment, and data of subjects with moderate hepatic impairment are indicative of a risk of severe adverse drug reactions in patients with severe hepatic impairment. Accordingly, peficitinib should be contraindicated for patients with severe hepatic impairment.

PMDA's view:
The above applicant's explanation is acceptable. Nevertheless, patients with moderate hepatic impairment should be closely monitored during peficitinib therapy to determine whether the therapy be continued. As of now, there are no data on long-term use of peficitinib in patients with moderate hepatic impairment, which should be further investigated via post-marketing surveillance and studies. Once available, information should be communicated to healthcare professionals. At the same time, patients with severe hepatic impairment have never been treated with peficitinib and are presumably be at risk of severe adverse drug reactions in light of the data of subjects with moderate hepatic impairment. Therefore, contraindicating peficitinib for RA patients with severe hepatic impairment is appropriate.

6.R.3 Drug interactions

The applicant's explanation about the drug interactions between peficitinib and CYP2C8 substrates:
Data from *in vitro* studies suggest that peficitinib may inhibit CYP2C8 [see Section 4.5.1]. No study has been conducted to investigate the drug interactions between CYP2C8 substrates and peficitinib. However, the incidence of adverse events (in the entire period) with and without a concomitant drug that is a substrate of CYP2C8 was 87.7% (57 of 65 subjects) and 88.1% (431 of 489 subjects), respectively, in the peficitinib group and 87.2% (34 of 39 subjects) and 89.4% (144 of 161 subjects), respectively, in the ENT group, showing no

marked differences in the incidence of adverse events between subjects receiving peficitinib with and without a concomitant drug that is a CYP2C8 substrate.

Based on the above, drug interactions between peficitinib and CYP2C8 are considered to be clinically insignificant.

PMDA's view:
No marked differences in the incidence of adverse events were observed between treatment with peficitinib with and without a concomitant CYP2C8 substrate in the clinical studies at present. However, the inhibitory effects of peficitinib on CYP2C8 have not been evaluated with actual data, and only limited information is available on the drug interactions between peficitinib and CYP2C8 substrates. Therefore, new findings on the safety of the use of peficitinib with concomitant CYP2C8 substrates should be communicated to healthcare professionals once available after the market launch of peficitinib.

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

The applicant submitted data from 4 clinical studies shown in Table 34 for the main evaluation of the efficacy and safety.

Table 34. List of main clinical studies evaluating the efficacy and safety

Region	Study ID	Phase	Subjects	Number of subjects [b]	Outline of a dosing regimen (Peficitinib was orally administered after meals)	Primary endpoint
Japan	CL-RAJ1	II	RA patients who are treatment-naïve or with prior antirheumatic therapy	(a) 55 (b) 57 (c) 55 (d) 58 (e) 56	(a) Peficitinib 25 mg once daily (b) Peficitinib 50 mg once daily (c) Peficitinib 100 mg once daily (d) Peficitinib 150 mg once daily (e) Placebo once daily	Efficacy Safety
Global	CL-RAJ3	III	RA patients with an inadequate response to cDMARDs including MTX	(a) 104 (b) 102 (c) 101 (d) 200	(a) Peficitinib 100 mg once daily (b) Peficitinib 150 mg once daily (c) Placebo once daily (d) Etanercept (ETN) 50 mg QW (subcutaneous)	Efficacy Safety
Japan	CL-RAJ4	III	RA patients with an inadequate response to MTX	(a) 175 (b) 174 (c) 170	(a) Peficitinib 100 mg once daily (b) Peficitinib 150 mg once daily (c) Placebo once daily	Efficacy Safety
Global	CL-RAJ2	III	RA patients who completed any of the preceding studies (Studies CL-RAJ1, CL-RAJ3, or CL-RAJ4)	843	Peficitinib 50, 100, or 150 mg once daily [a]	Efficacy Safety

a) Subjects who had completed preceding Study CL-RAJ1 started at 50 mg, and those who had completed Study CL-RAJ3 or CL-RAJ4 at 100 mg. The doses were reduced or increased to 50, 100, or 150 mg as specified.
b) Number of patients receiving the study drug

7.1 Phase II studies

7.1.1 Japanese study in RA patients (5.3.5.1-1: Study CL-RAJ1 [March 2012 to July 2013])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of peficitinib in patients with moderate to severe RA with or without cDMARDs[21)] (target sample size, 275 subjects [55/group]).

[21)] Main inclusion criteria: 1) Confirmed RA diagnosed according to the ACR criteria ≥6 months before the screening; 2) at screening, ≥6 swollen joints, ≥6 tender joints, and CRP of >0.5 mg/dL or erythrocyte sedimentation rate (ESR) of ≥28 mm/h; 3) classified as Class I, II, or III according to the 1991 ACR Revised Criteria for the Classification of Global Functional Status in RA; and 4) aged between 20 and 75 years

Peficitinib 25, 50, 100, or 150 mg or placebo was orally administered once daily after breakfast for 12 weeks without other concomitant RA drugs.

All randomized 281 patients (55 in the 25 mg group, 57 in the 50 mg group, 55 in the peficitinib 100 mg group, 58 in the peficitinib 150 mg group, and 56 in the placebo group) were included in the full analysis set (FAS) and the safety analysis set, and the FAS was used for efficacy analyses. The study treatment was discontinued in 20.0% (11 of 55) of patients in the peficitinib 25 mg group, 14.0% (8 of 57) of patients in the peficitinib 50 mg group, 18.2% (10 of 55) of patients in the peficitinib 100 mg group, 8.6% (5 of 58) of patients in the peficitinib 150 mg group, and 26.8% (15 of 56) of patients in the placebo group. The main reasons for discontinuation included inadequate response (9.1% [5 of 55] of patients in the peficitinib 25 mg group, 10.5% [6 of 57] of patients in the peficitinib 50 mg group, 9.1% [5 of 55] of patients in the peficitinib 100 mg group, 1.7% [1 of 58] of patients in the peficitinib 150 mg group, and 16.1% [9 of 56] of patients in the placebo group).

The primary efficacy endpoint of this study was the American College of Rheumatology (ACR)-20 responder index [for definition, see Section "10. Other"] at Week 12, and the results of the ACR20 responder index are shown in Table 35. Statistically significant differences in the ACR20 responder index were observed with a pair-comparison between the peficitinib 50 mg, 100 mg, and 150 mg groups and the placebo group, showing the superiority of peficitinib over placebo.

Table 35. ACR20 responder index at Week 12 (FAS, LOCF)

	Peficitinib 25 mg	Peficitinib 50 mg	Peficitinib 100 mg	Peficitinib 150 mg	Placebo
ACR20 responder index	23.6 (13/55)	31.6 (18/57)	54.5 (30/55)	65.5 (38/58)	10.7 (6/56)
Difference from placebo [95% CI] [a)]	12.9 [−2.7, 28.6]	20.9 [4.6, 37.2]	43.8 [26.6, 61.1]	54.8 [38.4, 71.2]	—
Adjusted *p*-value [b)]	0.082	0.021	<0.001	<0.001	

% (number of patients)
a) Based on normal approximation of binominal distribution (continuity correction).
b) Two-sided significance level of 5%, Fisher's exact test, and Hochberg procedure for multiplicity adjustment were used.

Adverse events occurred in 70.9% (39 of 55) of patients in the peficitinib 25 mg group, 64.9% (37 of 57) of patients in the peficitinib 50 mg group, 52.7% (29 of 55) of patients in the peficitinib 100 mg group, and 67.2% (39 of 58) of patients in the peficitinib 150 mg group, and 64.3% (36 of 56) of patients in the placebo group. The main adverse events are shown in Table 36.

Table 36. Adverse events occurring in ≥2 patients in any group (safety analysis set)

Event term	Peficitinib 25 mg (n = 55)	Peficitinib 50 mg (n = 57)	Peficitinib 100 mg (n = 55)	Peficitinib 150 mg (n = 58)	Placebo (n = 56)
Rheumatoid arthritis	12 (21.8)	8 (14.0)	4 (7.3)	4 (6.9)	18 (32.1)
Nasopharyngitis	11 (20.0)	9 (15.8)	1 (1.8)	9 (15.5)	3 (5.4)
Diarrhea	4 (7.3)	1 (1.8)	1 (1.8)	2 (3.4)	1 (1.8)
Blood triglycerides increased	3 (5.5)	0	2 (3.6)	1 (1.7)	0
Blood creatine phosphokinase increased	2 (3.6)	1 (1.8)	1 (1.8)	7 (12.1)	0
Nausea	2 (3.6)	1 (1.8)	0	2 (3.4)	0
Pharyngitis	2 (3.6)	1 (1.8)	0	1 (1.7)	2 (3.6)
Upper respiratory tract infection	2 (3.6)	0	2 (3.6)	2 (3.4)	0
Herpes zoster	2 (3.6)	0	2 (3.6)	0	0
Cystitis	1 (1.8)	2 (3.5)	0	2 (3.4)	3 (5.4)
Constipation	1 (1.8)	1 (1.8)	3 (5.5)	0	0
Headache	1 (1.8)	1 (1.8)	1 (1.8)	2 (3.4)	1 (1.8)
Malaise	1 (1.8)	0	2 (3.6)	1 (1.7)	0
Oropharyngeal pain	1 (1.8)	0	2 (3.6)	1 (1.7)	0
Contact dermatitis	1 (1.8)	0	2 (3.6)	0	2 (3.6)
Stomatitis	0	3 (5.3)	0	0	1 (1.8)
Back pain	0	2 (3.5)	0	1 (1.7)	2 (3.6)
Joint sprain	0	2 (3.5)	0	0	1 (1.8)
Pyrexia	0	2 (3.5)	0	0	0
Bronchitis	0	1 (1.8)	1 (1.8)	0	2 (3.6)
Liver function test abnormal	0	0	1 (1.8)	2 (3.4)	0
Dyspepsia	0	0	0	3 (5.2)	0
Lipids increased	0	0	0	3 (5.2)	0
Hyperlipidemia	0	0	0	2 (3.4)	0

Number of patients (%)

Death occurred in 1 patient in the peficitinib 50 mg group (cerebral hemorrhage). A causal relationship with the study drug was ruled out for the death.

Serious adverse events occurred in 1.8% (1 of 55 [abortion spontaneous]) of patients in the peficitinib 25 mg group, 3.5% (2 of 57 [rheumatoid arthritis and cerebral hemorrhage in 1 each]) of patients in the peficitinib 50 mg group, 5.5% (3 of 55 [cholecystitis, femoral neck fracture, and rheumatoid arthritis in 1 each]) of patients in the peficitinib 100 mg group, and 1.8% (1 of 56 [atrial fibrillation/cardiac failure/hepatic function abnormal]) of patients in the placebo group. Adverse events led to discontinuation of the study drug in 12.7% (7 of 55) of patients in the peficitinib 25 mg group, 8.8% (5 of 57) of patients in the peficitinib 50 mg group, 10.9% (6 of 55) of patients in the peficitinib 100 mg group, 6.9% (4 of 58) of patients in the peficitinib 150 mg group, and 17.9% (10 of 56) of patients in the placebo group.

Adverse drug reactions occurred in 38.2% (21 of 55) of patients in the peficitinib 25 mg group, 43.9% (25 of 57) of patients in the peficitinib 50 mg group, 29.1% (16 of 55) of patients in the peficitinib 100 mg group, 55.2% (32 of 58) of patients in the peficitinib 150 mg group, and 28.6% (16 of 56) of patients in the placebo group.

7.2 Phase III studies

7.2.1 Global study in RA patients with inadequate response to cDMARDs (5.3.5.1-2: Study CL-RAJ3 [August 2014 to November 2017])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in Japan, Korea, and Taiwan to evaluate the efficacy and safety of peficitinib in RA patients with inadequate response to cDMARDs

including MTX[22] (target sample size, 500 patients [100 each for peficitinib and placebo groups and 200 for reference group]).

Peficitinib 100 or 150 mg or placebo was orally administered once daily after breakfast for 12 weeks. In the peficitinib 100 mg and 150 mg groups, peficitinib was administered by the same dosing regimen after Week 12. At Week 12, patients in the placebo group were switched to peficitinib in a blinded manner, at a dose determined randomly at baseline in advance. Etanercept (ETN) 50 mg, an open-label reference drug, was subcutaneously administered once weekly. The total treatment duration was 52 weeks.

Of 509 randomized patients, 507 patients who received the study drug (104 in the peficitinib 100 mg group, 102 in the peficitinib 150 mg group, 101 in the placebo group, and 200 in the ETN group) were included in the FAS and the safety analysis set, and the FAS was used for efficacy analyses.

The study drug was discontinued by Week 12 in 7.7% (8 of 104) of patients in the peficitinib 100 mg group, 6.9% (7 of 102) of patients in the peficitinib 150 mg group, 10.8% (11 of 102) of patients in the placebo group, and 4.0% (8 of 201) of patients in the ETN group. The main reasons for discontinuation included inadequate response (1.0% [1 of 104] of patients in the peficitinib 100 mg group, 1.0% [1 of 102] of patients in the peficitinib 150 mg group, 6.9% [7 of 102] of patients in the placebo group, and 0.5% [1 of 201] of patients in the ETN group). During the whole study period (52 weeks), the study drug was discontinued in 29.8% (31 of 104) of patients in the peficitinib 100 mg group, 17.6% (18 of 102) of patients in the peficitinib 150 mg group, 28.0% (14 of 50) of patients in the placebo/peficitinib 100 mg group, 25.0% (13 of 52) of patients in the placebo/peficitinib 150 mg group, and 16.9% (34 of 201) of patients in the ETN group. The main reasons for discontinuation included inadequate response (10.6% [11 of 104] of patients in the peficitinib 100 mg group, 2.9% [3 of 102] of patient in the peficitinib 150 mg group, 16.0% [8 of 50] of patients in the placebo/peficitinib 100 mg group, 7.7% [4 of 52] of patients in the placebo/peficitinib 150 mg group, and 3.0% [6 of 201] of patients in the ETN group).

The results of the ACR20 responder index at Week 12, which was the primary efficacy endpoint of this study, are shown in Table 37. Statistically significant differences in the ACR20 responder index were observed in pairwise comparison between the peficitinib 100 mg or 150 mg group and the placebo group, showing the superiority of peficitinib over placebo. The efficacy results in the Japanese subgroups are shown in Table 38.

[22] Main inclusion criteria: 1) Confirmed RA diagnosed according to the 1987 ACR criteria or the 2010 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) criteria; 2) inadequate response to ≥1 DMARD administered for ≥90 days prior to screening; 3) at screening, ≥6 swollen joints, ≥6 tender joints, and CRP of >0.5 mg/dL; 4) classified as Class I, II, or III according to the 1991 ACR Revised Criteria for the Classification of Global Functional Status in RA; and 5) aged ≥20 years

Table 37. ACR20 responder index at Week 12 (FAS, LOCF)

	Peficitinib 100 mg	Peficitinib 150 mg	Placebo	ETN
ACR20 responder index	57.7 (60/104)	74.5 (76/102)	30.7 (31/101)	83.5 (167/200)
Difference from placebo [95% CI]	27.0 [12.9, 41.1]	43.8 [30.5, 57.1]	—	52.8 [41.7, 63.9]
Odds ratio [95% CI] [a)]	3.13 [1.76, 5.58]	6.59 [3.56, 12.20]		—
p-value [a),b)]	<0.001	<0.001		

% (number of patients)
a) A logistic regression model with region, therapeutic response to previous biologic therapy, co-administration of cDMARDs, and treatment groups as explanatory variables.
b) A two-sided significance level of 5% and a closed testing procedure were used to consider multiplicity,

Table 38. ACR20 responder index at Week 12 (Japanese subgroup, LOCF)

	Peficitinib 100 mg	Peficitinib 150 mg	Placebo	ETN
ACR20 responder index	61.2 (52/85)	74.7 (62/83)	28.9 (24/83)	84.8 (139/164)
Difference from placebo [95% CI]	32.3 [16.8, 47.7]	45.8 [31.1, 60.5]	—	55.8 [43.7, 67.9]
Odds ratio [95% CI] [a)]	3.89 [2.04, 7.43]	7.26 [3.65, 14.41]		—

% (number of patients)
a) A logistic regression model with therapeutic response to previous biologic therapy, co-administration of cDMARDs, and treatment groups as explanatory variables.

Adverse events occurred by Week 12 in 56.7% (59 of 104) patients in the peficitinib 100 mg group, 53.9% (55 of 102) of patients in the peficitinib 150 mg group, 53.5% (54 of 101) of patients in the placebo group, and 59.5% (119 of 200) of patients in the ETN group. The main adverse events are shown in Table 39.

No deaths occurred. Serious adverse events occurred in 2.9% (3 of 104 [duodenal ulcer, malaise, and rheumatoid arthritis in 1 each]) of patients in the peficitinib 100 mg group, 2.0% (2 of 102 [*Pneumocystis jirovecii* infection, and foot fracture in 1 each]) of patients in the peficitinib 150 mg group, 4.0% (4 of 101 [rheumatoid arthritis, febrile neutropenia/thrombocytopenia, tendon rupture, and vertigo in 1 each]) of patients in the placebo group, 2.0% (4 of 200 [interstitial lung diseases, pneumonia, rhabdomyolysis/hepatic function abnormal, and hypereosinophilic syndrome in 1 each]) of patients in the ETN group. Adverse events led to discontinuation of the study drug in 5.8% (6 of 104) of patients in the 100 mg group, 2.9% (3 of 102) of patients in the peficitinib 150 mg group, 4.0% (4 of 101) of patients in the placebo group, and 2.5% (5 of 200) of patients in the ETN group. Adverse drug reactions occurred in 31.7% (33 of 104) of patients in the peficitinib 100 mg group, 37.3% (38 of 102) of patients in the peficitinib 150 mg group, 28.7% (29 of 101) of patients in the placebo group, and 37.5% (75 of 200) of patients in the ETN group.

Table 39. Adverse events occurring at an incidence of ≥3% in any group (by Week 12, safety analysis set)

Event term	Peficitinib 100 mg (n = 104)	Peficitinib 150 mg (n = 102)	Placebo (n = 101)	ETN (n = 200)
Nasopharyngitis	10 (9.6)	19 (18.6)	6 (5.9)	16 (8.0)
Nausea	5 (4.8)	0	2 (2.0)	2 (1.0)
Bronchitis	4 (3.8)	1 (1.0)	1 (1.0)	1 (0.5)
Blood creatine phosphokinase increased	4 (3.8)	4 (3.9)	0	1 (0.5)
Lymphocyte count decreased	4 (3.8)	1 (1.0)	0	0
Rheumatoid arthritis	3 (2.9)	2 (2.0)	11 (10.9)	3 (1.5)
Stomatitis	2 (1.9)	4 (3.9)	2 (2.0)	4 (2.0)
Cough	1 (1.0)	3 (2.9)	4 (4.0)	2(1.0)
Hepatic function abnormal	0	7 (6.9)	3 (3.0)	10 (5.0)
Injection site reaction	0	0	0	25 (12.5)
Injection site erythema	0	0	0	6 (3.0)

Number of patients (%)

Adverse events occurred between Weeks 12 and 52 in 81.3% (78 of 96) of patients in the peficitinib 100 mg group, 84.9% (79 of 93) of patients in the peficitinib 150 mg group, 95.3% (41 of 43) of patients in the

placebo/peficitinib 100 mg group, 78.7% (37 of 47) of patients in the placebo/peficitinib 150 mg group, and 81.7% (156 of 191) of patients in the ETN group. Main adverse events are shown in Table 40. No deaths occurred. Serious adverse events occurred in 5.2% (5 of 96 [benign prostatic hyperplasia, colon cancer, radius fracture, pneumonia pneumococcal, and gastric ulcer/gastric cancer in 1 each]) of patients in the peficitinib 100 mg group, 6.5% (6 of 93 [spinal compression fracture in 2; pharyngitis, vertigo/drug hypersensitivity/bronchoscopy, anaphylactic shock, and hepatic enzyme increased in 1 each]) of patients in the peficitinib 150 mg group, 9.3% (4 of 43 [prostatectomy, hypertension/colonic polyp, breast cancer, and eczema herpeticum in 1 each]) of patients in the placebo/peficitinib 100 mg group, 10.6% (5 of 47 [renal disorder, gastric ulcer hemorrhage, social stay hospitalisation, pneumonia, and colitis in 1 each]) of patients in the placebo/peficitinib 150 mg group, and 7.3% (14 of 191 [cataract operation and organising pneumonia in 2 each; pharyngotonsillitis, enteritis infectious, patella fracture, thyroid cancer, hepatic steatosis, pneumonia, humerus fracture, osteoarthritis, migraine, and spinal column stenosis in 1 each]) of patients in the ETN group. Adverse events led to discontinuation of the study drug in 7.3% (7 of 96) of patients in the peficitinib 100 mg group, 3.2% (3 of 93) of patients in the peficitinib 150 mg group, 4.7% (2 of 43) of patients in the placebo/peficitinib 100 mg group, 8.5% (4 of 47) of patients in the placebo/peficitinib 150 mg group, and 4.2% (8 of 191) of patients in the ETN group. Adverse drug reactions occurred in 52.1% (50 of 96) of patients in the peficitinib 100 mg group, 50.5% (47 of 93) of patients in the peficitinib 150 mg group, 62.8% (27 of 43) of patients in the placebo/peficitinib 100 mg group, 55.3% (26 of 47) of patients in the placebo/peficitinib 150 mg group, and 48.7% (93 of 191) of patients in the ETN group.

Table 40. Adverse events occurring at an incidence of ≥5% in any group (between Weeks 12 and 52, safety analysis set)

Event term	Peficitinib 100 mg (n = 96)	Peficitinib 150 mg (n = 93)	Placebo/ peficitinib 100 mg (n = 43)	Placebo/ peficitinib 150 mg (n = 47)	ETN (n = 191)
Nasopharyngitis	21 (21.9)	15 (16.1)	13 (30.2)	8 (17.0)	49 (25.7)
Pharyngitis	7 (7.3)	3 (3.2)	0	4 (8.5)	6 (3.1)
Blood creatine phosphokinase increased	6 (6.3)	7 (7.5)	3 (7.0)	3 (6.4)	4 (2.1)
Cough	5 (5.2)	4 (4.3)	1 (2.3)	3 (6.4)	8 (4.2)
Influenza	4 (4.2)	5 (5.4)	2 (4.7)	2 (4.3)	8 (4.2)
Herpes zoster	4 (4.2)	4 (4.3)	4 (9.3)	1 (2.1)	3 (1.6)
Bronchitis	4 (4.2)	0	1 (2.3)	5 (10.6)	7 (3.7)
Upper respiratory tract inflammation	3 (3.1)	5 (5.4)	1 (2.3)	0	9 (4.7)
Upper respiratory tract infection	3 (3.1)	4 (4.3)	4 (9.3)	5 (10.6)	3 (1.6)
Hypertension	3 (3.1)	4 (4.3)	3 (7.0)	2 (4.3)	8 (4.2)
Constipation	3 (3.1)	2 (2.2)	3 (7.0)	1 (2.1)	3 (1.6)
Stomatitis	3 (3.1)	1 (1.1)	1 (2.3)	3 (6.4)	3 (1.6)
Gastroenteritis	1 (1.0)	2 (2.2)	3 (7.0)	0	5 (2.6)
Arthralgia	0	0	0	3 (6.4)	1 (0.5)

Number of patients (%)

In the Japanese subgroup, adverse events occurred by Week 12 in 58.8% (50 of 85) of patients in the peficitinib 100 mg group, 57.8% (48 of 83) of patients in the peficitinib 150 mg group, 55.4% (46 of 83) of patients in the placebo group, and 61.6% (101 of 164) of patients in the ETN group, and main adverse events are shown in Table 41.

No deaths occurred. Serious adverse events occurred in 2.4% (2 of 85 [duodenal ulcer and malaise in 1 each]) of patients in the peficitinib 100 mg group, 2.4% (2 of 83 [pneumocystis jirovecii infection and foot fracture in

1 each]) of patients in the peficitinib 150 mg group, 3.6% (3 of 83 [rheumatoid arthritis, febrile neutropenia/thrombocytopenia, and vertigo in 1 each]) of patients in the placebo group, and 1.8% (3 of 164 [interstitial lung diseases, pneumonia, and rhabdomyolysis/hepatic function abnormal in 1 each]) of patients in the ETN group. Adverse events led to discontinuation of the study drug in 4.7% (4 of 85) of patients in the peficitinib 100 mg group, 3.6% (3 of 83) of patients in the peficitinib 150 mg group, 4.8% (4 of 83) of patients in the placebo group, and 2.4% (4 of 164) of patients in the ETN group. Adverse drug reactions occurred in 36.5% (31 of 85) of patients in the peficitinib 100 mg group, 41.0% (34 of 83) of patients in the peficitinib 150 mg group, 32.5% (27 of 83) of patients in the placebo group, and 41.5% (68 of 164) of patients in the ETN group.

Table 41. Adverse events occurring at an incidence of ≥3% in any group (by Week 12, Japanese subgroup)

Event term	Peficitinib 100 mg (n = 85)	Peficitinib 150 mg (n = 83)	Placebo (n = 83)	ETN (n = 164)
Nasopharyngitis	9 (10.6)	18 (21.7)	6 (7.2)	13 (7.9)
Blood creatine phosphokinase increased	4 (4.7)	4 (4.8)	0	1 (0.6)
Nausea	4 (4.7)	0	2 (2.4)	2 (1.2)
Lymphocyte count decreased	4 (4.7)	1 (1.2)	0	0
Influenza	3 (3.5)	1 (1.2)	2 (2.4)	2 (1.2)
Bronchitis	3 (3.5)	1 (1.2)	1 (1.2)	1 (0.6)
Gastritis	3 (3.5)	0	1 (1.2)	1 (0.6)
Stomatitis	2 (2.4)	4 (4.8)	2 (2.4)	4 (2.4)
Upper respiratory tract infection	2 (2.4)	3 (3.6)	2 (2.4)	2 (1.2)
Upper respiratory tract inflammation	2 (2.4)	3 (3.6)	1 (1.2)	3 (1.8)
Cough	1 (1.2)	3 (3.6)	3 (3.6)	2 (1.2)
Rheumatoid arthritis	1 (1.2)	0	11 (13.3)	2 (1.2)
Hepatic function abnormal	0	6 (7.2)	2 (2.4)	8 (4.9)
Injection site reaction	0	0	0	25 (15.2)
Injection site erythema	0	0	0	6 (3.7)

Number of patients (%)

In the Japanese subgroup, adverse events occurred between Weeks 12 and 52 in 82.7% (67 of 81) of patients in the peficitinib 100 mg group, 88.3% (68 of 77) of patients in the peficitinib 150 mg group, 100.0% (35 of 35) of patients in the placebo/peficitinib 100 mg group, 81.6% (31 of 38) of patients in the placebo/peficitinib 150 mg group, and 82.3% (130 of 158) of patients in the ETN group. Main adverse events are shown in Table 42.

No deaths occurred.

Serious adverse events occurred in 4.9% (4 of 81 [benign prostatic hyperplasia, colon cancer, radius fracture, and pneumonia pneumococcal in 1 each]) of patients in the peficitinib 100 mg group, 6.5% (5 of 77 [spinal compression fracture in 2; pharyngitis, vertigo/drug hypersensitivity/bronchoscopy and anaphylactic shock in 1 each]) of patients in the peficitinib 150 mg group, 8.6% (3 of 35 [prostatectomy, hypertension and colonic polyp, and breast cancer in 1 each]) of patients in the placebo/peficitinib 100 mg group, 13.2% (5 of 38 [renal disorder, gastric ulcer hemorrhage, social stay hospitalisation, pneumonia, and colitis in 1 each]) of patients in the placebo/peficitinib 150 mg group, and 7.6% (12 of 158 [cataract operation and organising pneumonia in 2 each; pharyngotonsillitis, enteritis infectious, patella fracture, thyroid cancer, hepatic steatosis, pneumonia, humerus fracture, and osteoarthritis in 1 each]) of patients in the ETN group.

Adverse events led to discontinuation of the study drug in 6.2% (5 of 81) of patients in the peficitinib 100 mg group, 2.6% (2 of 77) of patients in the peficitinib 150 mg group, 5.7% (2 of 35) of patients in the placebo/peficitinib 100 mg group, 10.5% (4 of 38) of patients in the placebo/peficitinib 150 mg group, and 4.4% (7 of 158) of patients in the ETN group. Adverse drug reactions occurred in 55.6% (45 of 81) of patients in the 100 mg group, 55.8% (43 of 77) of patients in the 150 mg group, 74.3% (26 of 35) of patients in the placebo/peficitinib 100 mg group, 57.9% (22 of 38) of patients in the placebo/peficitinib 150 mg group, and 54.4% (86 of 158) of patients in the ETN group.

Table 42. Adverse events occurring at an incidence of ≥5% in any group (between Week 12 and Week 52, Japanese subgroup)

Event term	Peficitinib 100 mg (n = 81)	Peficitinib 150 mg (n = 77)	Placebo/peficitinib 100 mg (n = 35)	Placebo/peficitinib 150 mg (n = 38)	ETN (n = 158)
Nasopharyngitis	19 (23.5)	12 (15.6)	11 (31.4)	7 (18.4)	46 (29.1)
Pharyngitis	6 (7.4)	3 (3.9)	0	3 (7.9)	6 (3.8)
Blood creatine phosphokinase increased	5 (6.2)	7 (9.1)	3 (8.6)	3 (7.9)	4 (2.5)
Influenza	4 (4.9)	5 (6.5)	2 (5.7)	2 (5.3)	8 (5.1)
Nausea	4 (4.9)	4 (5.2)	2 (5.7)	1 (2.6)	2 (1.3)
Cough	4 (4.9)	4 (5.2)	1 (2.9)	2 (5.3)	7 (4.4)
Bronchitis	4 (4.9)	0	1 (2.9)	4 (10.5)	7 (4.4)
Upper respiratory tract inflammation	3 (3.7)	5 (6.5)	1 (2.9)	0	9 (5.7)
Herpes zoster	3 (3.7)	4 (5.2)	4 (11.4)	0	2 (1.3)
Hypertension	3 (3.7)	4 (5.2)	2 (5.7)	1 (2.6)	6 (3.8)
Upper respiratory tract infection	3 (3.7)	3 (3.9)	3 (8.6)	5 (13.2)	2 (1.3)
Rheumatoid arthritis	3 (3.7)	3 (3.9)	2 (5.7)	0	6 (3.8)
Back pain	3 (3.7)	3 (3.9)	1 (2.9)	2 (5.3)	5 (3.2)
Constipation	3 (3.7)	2 (2.6)	3 (8.6)	1 (2.6)	2 (1.3)
Stomatitis	3 (3.7)	1 (1.3)	1 (2.9)	3 (7.9)	3 (1.9)
Contusion	3 (3.7)	1 (1.3)	1 (2.9)	2 (5.3)	1 (0.6)
Eczema	2 (2.5)	4 (5.2)	1 (2.9)	2 (5.3)	8 (5.1)
Periodontitis	2 (2.5)	4 (5.2)	1 (2.9)	2 (5.3)	1 (0.6)
Hepatic function abnormal	2 (2.5)	2 (2.6)	2 (5.7)	0	3 (1.9)
Gastroenteritis	1 (1.2)	2 (2.6)	3 (8.6)	0	4 (2.5)
Pyrexia	1 (1.2)	1 (1.3)	0	2 (5.3)	1 (0.6)
Keratitis	1 (1.2)	0	2 (5.7)	0	0
Contact dermatitis	1 (1.2)	0	1 (2.9)	0	8 (5.1)
Rhinitis allergic	1 (1.2)	0	0	2 (5.3)	1 (0.6)
Conjunctivitis	0	2 (2.6)	0	2 (5.3)	1 (0.6)
Stomach discomfort	0	2 (2.6)	0	2 (5.3)	1 (0.6)
Lymphocyte count decreased	0	2 (2.6)	1 (2.9)	2 (5.3)	0
Oropharyngeal pain	0	1 (1.3)	2 (5.7)	0	2 (1.3)
Dehydration	0	0	0	2 (5.3)	1 (0.6)
Duodenal ulcer	0	0	0	2 (5.3)	0
Infected epidermal cyst	0	0	0	2 (5.3)	0
Administration site reaction	0	0	0	0	9 (5.7)

Number of patients (%)

7.2.2 Japanese study in RA patients with inadequate response to MTX (5.3.5.1-3: Study CL-RAJ4 [July 2014 to November 2017])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of peficitinib used in combination with MTX in RA patients with inadequate response to MTX[23)] (target sample size, 510 [170/group]).

[23)] Main inclusion criteria: 1) Confirmed RA diagnosed according to the 1987 ACR criteria or the 2010 ACR/EULAR criteria and a RA duration of <10 years as of baseline; 2) inadequate responder to MTX continuously administered for ≥90 days prior to screening and receiving MTX at highest tolerable dose of ≥8 mg/week for ≥28 days (however, inadequate responder to MTX <8 mg/week is eligible if intolerance precludes dose increase); 3) at screening, ≥6 swollen joints, ≥6 tender joints, and CRP of >1.00 mg/dL; 4) bone erosion at the joint assessed in mTSS and positive for anti-CCP antibody

Peficitinib 100 or 150 mg or placebo was orally administered once daily after breakfast in combination with a stable dose of MTX[24] for 52 weeks. In the placebo group, patients categorized as inadequate responders at Week 12[25] were to receive peficitinib 100 or 150 mg from Week 12 onwards, and patients receiving placebo at Week 28 were to receive peficitinib 100 or 150 mg from Week 28 onwards[26]. The total treatment duration was 52 weeks.

Of 519 randomized patients, 1 patient was excluded[27] due to study protocol deviation, and the remaining 518 patients (174 in the peficitinib 100 mg group, 174 in the peficitinib 150 mg group, and 170 in the placebo group) were included in the FAS and the safety analysis set. The FAS was used for efficacy analyses.

The study drug was discontinued by Week 12 in 3.4% (6 of 175) of patients in the peficitinib 100 mg group, 4.6% (8 of 174) of patients in the peficitinib 150 mg group, and 5.3% (9 of 170) of patients in the placebo group. The main reasons for discontinuation included adverse events (1.7% [3 of 175] of patients in the peficitinib 100 mg group, 1.1% [2 of 174] of patients in the peficitinib 150 mg group, and 0.6% [1 of 170] of patients in the placebo group).

Over the entire study period (52 weeks), the study drug was discontinued in 15.4% (27 of 175) of patients in the peficitinib 100 mg group, 16.1% (28 of 174) of patients in the peficitinib 150 mg group, 21.2% (18 of 85) of patients in the placebo/ peficitinib 100 mg group, and 22.4% (19 of 85) of patients in the placebo/ peficitinib 150 mg group. Main reasons for discontinuation included adverse events (5.7% [10 of 175] of patients in the peficitinib 100 mg group, 6.9% [12 of 174] of patients in the peficitinib 150 mg group, 8.2% [7 of 85] of patients in the placebo/ peficitinib 100 mg group, and 3.5% [3 of 85] of patients in the placebo/peficitinib 150 mg group).

The co-primary efficacy endpoints were ACR20 responder index at Week 12 and changes from baseline in a modified total Sharp score (mTSS) at Week 28. The ACR20 responder index at Week 12 and the changes in mTSS at Week 28 are shown in Table 43 and Table **44**, respectively. Statistically significant differences in the co-primary endpoints were observed with a pair-comparison between the peficitinib 100 and 150 mg groups and the placebo group, showing the superiority of peficitinib over placebo. The cumulative probability distribution of the changes from baseline in mTSS at Week 28 is shown in Figure 2.

(≥4.5 U/mL) or rheumatoid factor (>15 IU/mL); 5) classified as Class I, II, or III according to the 1991 ACR Revised Criteria for the Classification of Global Functional Status in RA; 6) able to receive MTX with a stable dosing regimen; and 7) aged ≥20 years.

[24] Patients who continued to receive MTX for ≥90 days prior to screening and received MTX with a stable dosing regimen (a maximum of 16 mg/week) from ≥28 days prior to screening until the end of treatment

[25] Improvement by <20% from baseline in the number of tender joints and swollen joints

[26] In the placebo group, patients were to receive peficitinib at a dose randomly chosen at baseline (100 or 150 mg) at Week 12 or 28 in a blinded manner.

[27] At an unscheduled visit, the study drug was prescribed by a physician not involved in the clinical study in the absence of the investigator and the sub-investigators.

Table 43. ACR20 responder index at Week 12 (FAS, LOCF)

	Peficitinib 100 mg	Peficitinib 150 mg	Placebo
ACR20 responder index	58.6 (102/174)	64.4 (112/174)	21.8 (37/170)
Difference from placebo [95% CI] [a)] *p*-value [b)]	36.9 [26.7, 47.0] <0.001	42.6 [32. 6, 52.6] <0.001	—

% (number of subjects)
a) Based on normal approximation of binominal distribution (continuity correction).
b) A two-sided significance level of 5%, Fisher's exact test, and a closed testing procedure were used to consider multiplicity.

Table 44. Changes from baseline in mTSS at Week 28 (FAS, LEP)

	Peficitinib 100 mg (n = 164)	Peficitinib 150 mg (n = 164)	Placebo (n = 153)
Changes in mTSS	1.62 ± 4.23	1.03 ± 2.86	3.37 ± 5.46
Median (first quartile point, third quartile point)	0.00 (0.00, 1.50)	0.00 (0.00, 1.00)	1.17 (0.00, 5.50)
p-value [a)]	<0.001	<0.001	—

Mean ± standard deviation
a) A model of analysis of covariance with treatment as a factor for rank-transformed data and the rank-transformed mTSS at baseline as a covariate with a two-sided significance level of 5%. A closed testing procedure was used to consider multiplicity (each comparison for changes from baseline in mTSS at Week 28 was to be conducted with a closed testing procedure when statistically significant differences in the ACR20 responder index at Week 12 were observed both in the pair-comparison between the peficitinib 100 and 150 mg groups and the placebo group).

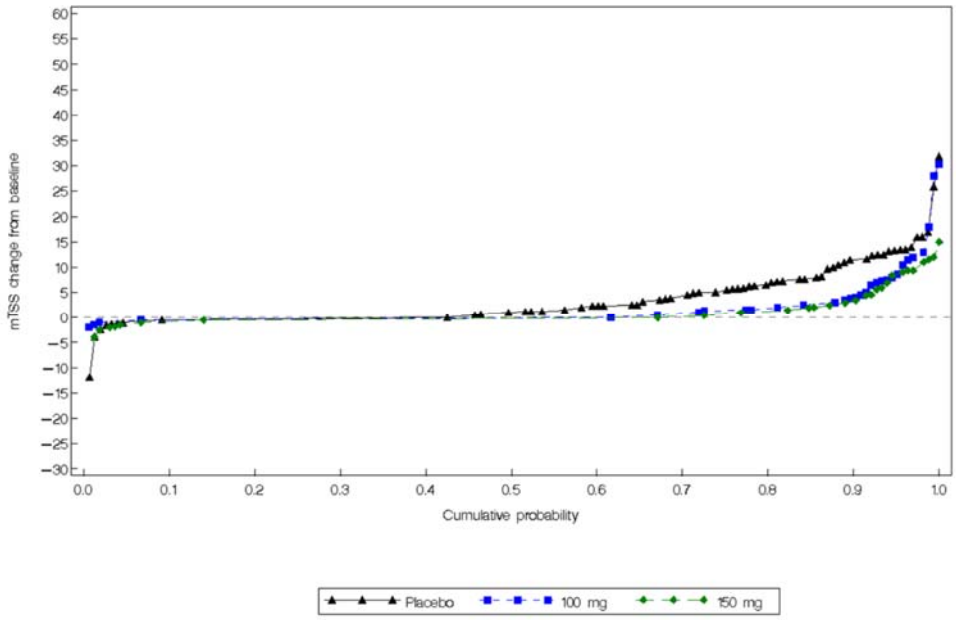


Figure 2. Cumulative probability distribution of changes from baseline in mTSS at Week 28 (FAS, LEP)

Adverse events occurred by Week 12 in 51.1% (89 of 174) of patients in the peficitinib 100 mg group, 59.8% (104 of 174) of patients in the peficitinib 150 mg group, and 49.4% (84 of 170) of patients in the placebo group. Main adverse events are shown in Table 45.

Table 45. Adverse events occurring at an incidence of ≥3% in any group (by Week 12, safety analysis set)

Event term	Peficitinib 100 mg (n = 174)	Peficitinib 150 mg (n = 174)	Placebo (n = 170)
Nasopharyngitis	19 (10.9)	16 (9.2)	14 (8.2)
Hepatic function abnormal	5 (2.9)	6 (3.4)	4 (2.4)
Rheumatoid arthritis	4 (2.3)	2 (1.1)	7 (4.1)
Pharyngitis	3 (1.7)	6 (3.4)	6 (3.5)

Number of subjects (%)

No deaths occurred.

Serious adverse events occurred in 2.9% (5 of 174 [retinal detachment, pneumonia, herpes zoster, osteoarthritis, and *Pneumocystis jirovecii* infection in 1 each]) of patients in the peficitinib 100 mg group, 1.7% (3 of 174 [lacunar infarction, pyelonephritis/nephrolithiasis, and drug eruption in 1 each]) of patients in the peficitinib 150 mg group, and 2.4% (4 of 170 [lacunar infarction, interstitial lung diseases, rheumatoid arthritis, and alveolitis allergic in 1 each]) of patients in the placebo group. Adverse events led to discontinuation of the study drug in 2.9% (5 of 174) of patients in the peficitinib 100 mg group, 2.9% (5 of 174) of patients in the peficitinib 150 mg group, and 4.1% (7 of 170) of patients in the placebo group. Adverse drug reactions occurred in 32.8% (57 of 174) of patients in the peficitinib 100 mg group, 46.0% (80 of 174) of patients in the peficitinib 150 mg group, and 27.6% (47 of 170) of patients in the placebo group.

Adverse events occurred between Weeks 12 and 28 in 56.9% (95 of 167) of patients in the peficitinib 100 mg group, 63.0% (104 of 165) of patients in the peficitinib 150 mg group, 56.8% (21 of 37) of patients in the placebo/peficitinib 100 mg at Week 12 group, 65.8% (25 of 38) of patients in the placebo/peficitinib 150 mg at Week 12 group, and 61.0% (50 of 82) of patients in the placebo group. The main adverse events are shown in Table 46.

Table 46. Adverse events occurring at an incidence of ≥3% in any group (between Weeks 12 and 28, safety analysis set)

Event term	Peficitinib 100 mg (n = 167)	Peficitinib 150 mg (n = 165)	Placebo/peficitinib 100 mg at Week 12 (n = 37)	Placebo/peficitinib 150 mg at Week 12 (n = 38)	Placebo (n = 82)
Nasopharyngitis	20 (12.0)	19 (11.5)	6 (16.2)	2 (5.3)	12 (14.6)
Upper respiratory tract inflammation	7 (4.2)	2 (1.2)	0	1 (2.6)	0
Pharyngitis	5 (3.0)	2 (1.2)	0	2 (5.3)	1 (1.2)
Back pain	5 (3.0)	1 (0.6)	0	1 (2.6)	3 (3.7)
Hepatic function abnormal	4 (2.4)	6 (3.6)	0	0	1 (1.2)
Upper respiratory tract infection	3 (1.8)	6 (3.6)	0	0	1 (1.2)
Cystitis	3 (1.8)	2 (1.2)	2 (5.4)	1 (2.6)	0
Rheumatoid arthritis	3 (1.8)	1 (0.6)	1 (2.7)	0	3 (3.7)
Blood creatine phosphokinase increased	1 (0.6)	7 (4.2)	1 (2.7)	1 (2.6)	0
Headache	1 (0.6)	5 (3.0)	1 (2.7)	1 (2.6)	1 (1.2)
Stomatitis	1 (0.6)	2 (1.2)	0	2 (5.3)	1 (1.2)
Hyperlipidemia	0	2 (1.2)	2 (5.4)	0	0
Vomiting	0	1 (0.6)	2 (5.4)	0	0
Dyspepsia	0	1 (0.6)	0	2 (5.3)	1 (1.2)

Number of subjects (%)

No deaths occurred.

Serious adverse events occurred in 3.0% (5 of 167 [spinal compression fracture in 2; acute cholecystitis, pneumonia, type 2 diabetes mellitus, and interstitial lung disease in 1 each]) of patients in the peficitinib 100 mg group, 1.8% (3 of 165 [hepatic function abnormal, cellulitis, and tendon disorder in 1 each]) of patients in the peficitinib 150 mg group, and 2.4% (2 of 82 [pleural effusion and squamous cell carcinoma in 1 each]) of patients in the placebo group. Adverse events led to discontinuation of the study drug in 2.4% (4 of 167) of patients in the peficitinib 100 mg group, 0.6% (1 of 165) of patients in the peficitinib 150 mg group, and 4.9% (4 of 82) of patients in the placebo group. Adverse drug reactions occurred in 37.7% (63 of 167) of patients in the peficitinib 100 mg group, 43.6% (72 of 165) of patients in the peficitinib 150 mg group, and 43.2% (16 of 37) of patients in the placebo/peficitinib 100 mg at Week 12 group, 28.9% (11 of 38) of patients in the placebo/peficitinib 150 mg at Week 12 group, and 32.9% (27 of 82) of patients in the placebo group.

Adverse events occurred between Weeks 28 and 52 in 72.2% (114 of 158) of patients in the peficitinib 100 mg group, 70.9% (112 of 158) of patients in the peficitinib 150 mg group, 61.1% (22 of 36) of patients in the placebo/peficitinib 100 mg at Week 12 group, 75.0% (27 of 36) of patients in the placebo/peficitinib 150 mg at Week 12 group, 64.1% (25 of 39) of patients in the placebo/peficitinib 100 mg at Week 28 group, and 76.5% (26 of 34) of patients in the placebo/peficitinib 150 mg at Week 28 group, and the main adverse events are shown in Table 47.

Table 47. Adverse events occurring at an incidence of ≥3% in any group (between Weeks 28 and 52, safety analysis set)

Event term	Peficitinib 100 mg (n = 158)	Peficitinib 150 mg (n = 158)	Placebo/peficitinib 100 mg at Week 12 (n = 36)	Placebo/peficitinib 150 mg at Week 12 (n = 36)	Placebo/peficitinib 100 mg at Week 28 (n = 39)	Placebo/peficitinib 150 mg at Week 28 (n = 34)
Nasopharyngitis	25 (15.8)	38 (24.1)	6 (16.7)	6 (16.7)	4 (10.3)	6 (17.6)
Dental caries	7 (4.4)	2 (1.3)	1 (2.8)	0	0	1 (2.9)
Blood creatine phosphokinase increased	6 (3.8)	9 (5.7)	2 (5.6)	3 (8.3)	2 (5.1)	3 (8.8)
Herpes zoster	6 (3.8)	1 (0.6)	1 (2.8)	1 (2.8)	1 (2.6)	1 (2.9)
Hypertension	5 (3.2)	6 (3.8)	0	0	1 (2.6)	3 (8.8)
Hepatic function abnormal	5 (3.2)	2 (1.3)	1 (2.8)	1 (2.8)	1 (2.6)	4 (11.8)
Constipation	5 (3.2)	2 (1.3)	0	0	0	0
Eczema	5 (3.2)	0	0	1 (2.8)	0	0
Pharyngitis	4 (2.5)	6 (3.8)	2 (5.6)	1 (2.8)	1 (2.6)	0
Upper respiratory tract infection	4 (2.5)	5 (3.2)	2 (5.6)	4 (11.1)	2 (5.1)	1 (2.9)
Gastroenteritis	4 (2.5)	3 (1.9)	3 (8.3)	1 (2.8)	1 (2.6)	0
Cystitis	3 (1.9)	4 (2.5)	0	2 (5.6)	0	0
Influenza	3 (1.9)	1 (0.6)	2 (5.6)	0	2 (5.1)	0
Bronchitis	2 (1.3)	5 (3.2)	1 (2.8)	4 (11.1)	0	3 (8.8)
Headache	2 (1.3)	5 (3.2)	1 (2.8)	0	0	0
Rheumatoid arthritis	2 (1.3)	3 (1.9)	1 (2.8)	2 (5.6)	1 (2.6)	0
Nausea	2 (1.3)	3 (1.9)	1 (2.8)	0	3 (7.7)	0
Vomiting	2 (1.3)	2 (1.3)	1 (2.8)	0	0	2 (5.9)
Rash	2 (1.3)	0	0	2 (5.6)	1 (2.6)	0
Back pain	1 (0.6)	4 (2.5)	0	0	0	4 (11.8)
Diarrhea	1 (0.6)	3 (1.9)	0	1 (2.8)	0	2 (5.9)
Upper respiratory tract inflammation	0	1 (0.6)	0	3 (8.3)	2 (5.1)	0
Dyslipidemia	0	1 (0.6)	0	0	0	2 (5.9)
Gastric ulcer	0	0	0	0	0	2 (5.9)

Number of subjects (%)

Death occurred in 1 patient (completed suicide) in the group of placebo/peficitinib 100 mg (at Week 28). A causal relationship with the study drug was ruled out for the death.

Serious adverse events occurred in 6.3% (10 of 158 [pyelonephritis, pneumonia, mania, spinal compression fracture, small cell lung cancer (stage unspecified), brachial plexus injury, vertigo positional/investigation, rheumatoid arthritis, pericarditis, and status asthmaticus in 1 each]) of patients in the peficitinib 100 mg group, 5.1% (8 of 158 [pneumonia in 2; spinal compression fracture, cerebellar hemorrhage, pneumonia cryptococcal, cellulitis, borderline ovarian tumour, and colonic polyp in 1 each]) of patients in the peficitinib 150 mg group, 5.6% (2/36 [organising pneumonia and gastroenteritis viral in 1 each]) of patients in the placebo/peficitinib 100 mg at Week 12 group, 2.8% (1 of 36 [gastroenteritis]) of patients in the placebo/peficitinib 150 mg at Week 12 group, 2.6% (1 of 39 [completed suicide]) of patients in the placebo/peficitinib 100 mg at Week 28 group, and 2.9% (1 of 34 [gastric ulcer]) of patients in the placebo/peficitinib 150 mg at Week 28 group. Adverse events led to discontinuation of the study drug in 2.5% (4 of 158) of patients in the peficitinib 100 mg group, 3.8% (6 of 158) of patients in the peficitinib 150 mg group, 8.3% (3 of 36) of patients in the placebo/peficitinib 100 mg at Week 12 group, 5.6% (2 of 36) of patients in the placebo/peficitinib 150 mg at Week 12 group, and 5.1% (2 of 39) of patients in the placebo/peficitinib 100 mg at Week 28 group. Adverse drug reactions occurred in 45.6% (72 of 158) of patients in the peficitinib 100 mg group, 46.8% (74 of 158) of patients in the peficitinib 150 mg group, 38.9% (14 of 36) of patients in the placebo/peficitinib 100 mg at Week 12 group, 50.0% (18 of 36) of patients in the placebo/peficitinib 150 mg at Week 12 group, 43.6% (17 of 39) of patients in the placebo/peficitinib 100 mg at Week 28 group, and50.0% (17 of 34) of patients in the placebo/peficitinib 150 mg at Week 28 group.

7.3 Extension study

7.3.1 Long-term treatment study in RA patients (5.3.5.2-1.1: Study CL-RAJ2 [June 2012 to May 31, 2018 (data cutoff date)])

An open-label, uncontrolled study was conducted in Japan, Korea, and Taiwan to evaluate the efficacy and safety of the long-term peficitinib treatment in RA patients who had completed the late phase II study (Study CL-RAJ1), the Global phase III study (Study CL-RAJ3) or the Japanese phase III study (Study CL-RAJ4) (target sample size, approximately 800).

Peficitinib 100 mg was orally administered once daily after breakfast to patients from Studies CL-RAJ3 and CL-RAJ4, and peficitinib 50 mg was orally administered once daily after breakfast to patients from Study CL-RAJ1. The dose could be increased to a maximum of 150 mg or be reduced by 50 mg from 100 or 150 mg at the discretion of the investigator. Treatment was to be continued until marketing approval was granted in Japan, Korea, or Taiwan. No patients in the ETN group in the global phase III study (Study CL-RAJ3) entered in this study.

All 843 patients receiving ≥1 dose of the study drug (201 patient from Study CL-RAJ1, 225 patients from Study CL-RAJ3, and 417 patients from Study CL-RAJ4) were included in the safety analysis set. A total of 6 patients with missing measurements of efficacy endpoints after administration were excluded, and the remaining 837 patients were included in the FAS, which was used for efficacy analyses.

The study drug was discontinued in 27.8% (234 of 843) of patients. Main reasons for discontinuation included adverse events (8.5% [72 of 843] of patients).

Changes over time in the ACR20 responder index in patients from individual studies are shown in Table 48. The ACR20 responder index was maintained throughout the study period in patients from Phase III studies (Studies CL-RAJ3 and CL-RAJ4). In patients from the late phase II (Study CL-RAJ1), the ACR20 responder index was 29.5% at Week 0 partially due to differences in study designs but subsequently improved and maintained throughout the study period.

Table 48. Changes in ACR20 responder index over time

	CL-RAJ1	CL-RAJ3	CL-RAJ4	Entire population
Week 0	29.5 (59/200)	82.5 (184/223)	86.2 (355/412)	71.6 (598/835)
Week 24	63.6 (119/187)	85.5 (177/207)	89.1 (351/394)	82.1 (647/788)
Week 48	76.1 (124/163)	84.7 (155/183)	91.9 (262/285)	85.7 (541/631)
Week 72	77.3 (116/150)	87.8 (115/131)	90.4 (161/178)	85.4 (392/459)
Week 96	78.1 (107/137)	84.7 (61/72)	91.4 (106/116)	84.3 (274/325)
Week 120	78.5 (102/130)	95.0 (19/20)	90.9 (40/44)	83.0 (161/194)
End of administration (LOCF)	64.7 (130/201)	76.8 (172/224)	86.9 (358/412)	78.9 (660/837)

% (number of subjects)

Adverse events occurred in 89.8% (757 of 843) of patients, and the main adverse events are shown in Table 49.

Table 49. Adverse events occurring at an incidence of ≥5% (safety analysis set)

Event term	Peficitinib (n = 843)	Event term	Peficitinib (n = 843)
Nasopharyngitis	335 (39.7)	Pharyngitis	56 (6.6)
Rheumatoid arthritis	105 (12.5)	Upper respiratory tract infection	51 (6.0)
Herpes zoster	99 (11.7)	Dental caries	51 (6.0)
Influenza	80 (9.5)	Constipation	49 (5.8)
Bronchitis	68 (8.1)	Gastroenteritis	47 (5.6)
Blood creatine phosphokinase increased	66 (7.8)	Cystitis	47 (5.6)
Contusion	59 (7.0)	Cough	42 (5.0)
Hypertension	57 (6.8)	Back pain	42 (5.0)

Number of subjects (%)

Death occurred in a patient (diffuse large B-cell lymphoma) and assessed as possibly related to the study drug. Serious adverse events occurred in 16.4% (138 of 843) of patients, and the main adverse events are shown in Table 50. Adverse events led to discontinuation of the study drug in 10.3% (87 of 843) of patients. Adverse drug reactions occurred in 69.5% (586 of 843) of patients.

Table 50. Serious adverse events occurring in ≥3 patients (safety analysis set)

Event term	Peficitinib (n = 843)	Event term	Peficitinib (n = 843)
Herpes zoster	7 (0.8)	Hepatic function abnormal	3 (0.4)
Tendon rupture	8 (0.9)	Anaphylactic shock	3 (0.4)
Pneumonia	6 (0.7)	Humerus fracture	3 (0.4)
Rheumatoid arthritis	4 (0.5)	Intervertebral disc protrusion	3 (0.4)
Gastric cancer	4 (0.5)		

Number of subjects (%)

7.R Outline of the review by PMDA

7.R.1 Development plan

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

In Japan, patients with RA are treated according to the JCR guidelines that comprise diagnostic criteria and treatment algorithms similar to those in the ACR and EULAR guidelines. Korea and Taiwan also follow the ACR and EULAR guidelines for RA treatment. Because of no clear differences in the pharmacokinetic profiles identified between Japanese and Asian subjects [see Section 6.R.1], the efficacy and safety of peficitinib in Japanese RA patients would be able to be evaluated based on clinical data package of the global phase III studies in Asia including Japan and the studies conducted in Japanese patients.

● Patients included in the phase III studies

The JCR, ACR, and EULAR clinical practice guidelines recommend to start antirheumatic drug therapy as soon as RA is confirmed, aiming to introduce and sustain clinical, structural, and functional remission. MTX is recommended as a first-line treatment of RA, and in general, treatment MTX alone or in combination with other cDMARDs is provided, except for patients intolerant to MTX. The use of biological products or JAK inhibitors is recommended for patients with inadequate response to cDMARDs including MTX (*the JCR Clinical Practice Guidelines for Rheumatoid Arthritis 2014*. *Ann Rheum Dis*. 2014;73:492-509; *Ann Rheum Dis*. 2017;0:1-18). In consideration of the above therapeutic system, the efficacy and safety of peficitinib were evaluated in RA patients with inadequate response to approved cDMARDs including MTX in the global phase III study (Study CL-RAJ3) and in RA patients with inadequate response to MTX in the Japanese phase III study (Study CL-RAJ4).

● Dosing regimen in phase III studies

In Study CL-RAJ1 conducted in RA patients, statistically significant differences in the ACR20 responder index at Week 12 as the primary endpoint were observed between the peficitinib (100 and 150 mg) and placebo, and a dose-dependent tendency was seen at the doses up to 150 mg (Table 35). No marked differences were observed for the safety among individual groups. In light of the above, it was considered appropriate to evaluate the dosing regimens of 100 and 150 mg once daily in the phase III studies.

PMDA's view:

The applicant's explanation is acceptable. The evaluation of the efficacy and safety of peficitinib in RA patients will be feasible by using the submitted clinical data package.

7.R.2 Efficacy

7.R.2.1 Efficacy for clinical symptoms of RA

The applicant's explanation about the efficacy of peficitinib for clinical symptoms of RA:

The ACR20 responder index at Week 12 was the primary efficacy endpoint in Study CL-RAJ3 in RA patients with inadequate response to cDMARDs and Study CL-RAJ4 in RA patients with inadequate response to MTX. In both studies, pairwise comparisons showed statistically significant differences in the primary efficacy

endpoint between peficitinib 100 and 150 mg and placebo, demonstrating the superiority of peficitinib 100 and 150 mg to placebo (Table 37 andTable **43**).

The efficacy of peficitinib in the Japanese subgroup in Study CL-RAJ3 is shown by ACR responder indices at Week 12 in Table 51. The results demonstrated a similar tendency between the peficitinib 100 and 150 mg groups and the entire study population.

Table 51. ACR responder indices Week 12 in individual groups in Study CL-RAJ3 (LOCF)

	ACR20 responder index		ACR50 responder index		ACR70 responder index	
	Entire population (FAS)	Japanese subgroup	Entire population (FAS)	Japanese subgroup	Entire population (FAS)	Japanese subgroup
100 mg	57.7 (60/104)	61.2 (52/85)	30.8 (32/104)	34.1 (29/85)	13.5 (14/104)	14.1 (12/85)
150 mg	74.5 (76/102)	74.7 (62/83)	42.2 (43/102)	43.4 (36/83)	27.5 (28/102)	28.9 (24/83)
Placebo	30.7 (31/101)	28.9 (24/83)	8.9 (9/101)	8.4 (7/83)	1.0 (1/101)	0 (0/83)
ETN	83.5 (167/200)	84.8 (139/164)	52.5 (105/200)	55.5 (91/164)	30.5 (61/200)	33.5 (55/164)

% (number of patients)

The changes in individual parameters of the ACR core set and results of the main secondary endpoints in Studies CL-RAJ3 and CL-RAJ4 are shown in Table 52. All endpoints in the peficitinib 100 mg and 150 mg groups tended to be superior to those in the placebo group, and the tendency continued until Week 52 (Table 53).

Table 52. Efficacy indices at Week 12 (FAS, LOCF)

Study	Study CL-RAJ3				Study CL-RAJ4		
Treatment group	Peficitinib 100 mg	Peficitinib 150 mg	Placebo	ETN	Peficitinib 100 mg	Peficitinib 150 mg	Placebo
Changes from baseline in parameters of ACR core set							
Number of swollen joints (66)	−6.0 ± 6.4 (102)	−8.4 ± 5.9 (101)	−3.2 ± 6.0 (99)	−8.3 ± 5.5 (200)	−5.9 ± 6.7 (172)	−7.6 ± 6.1 (171)	−2.2 ± 6.6 (168)
Number of painful joints (68)	−8.2 ± 8.8 (102)	−9.9 ± 8.0 (101)	−4.3 ± 9.2 (99)	−10.7 ± 7.8 (200)	−6.9 ± 8.6 (172)	−9.1 ± 8.0 (171)	−2.1 ± 8.2 (168)
Pain assessment	−23.8 ± 30.8 (102)	−30.7 ± 27.9 (101)	−6.6 ± 24.6 (99)	−30.8 ± 27.7 (200)	−21.1 ± 27.0 (172)	−26.9 ± 26.7 (171)	−6.6 ± 25.2 (168)
Patients' overall assessment	−23.7 ± 32.1 (102)	−31.6 ± 27.4 (101)	−7.9 ± 25.2 (99)	−32.4 ± 27.4 (200)	−21.1 ± 23.6 (172)	−26.6 ± 25.4 (171)	−7.1 ± 23.1 (168)
Physicians' overall assessment	−27.7 ± 25.4 (102)	−34.7 ± 21.2 (101)	−13.9 ± 24.9 (99)	−37.4 ± 20.7 (200)	−28.8 ± 22.2 (172)	−36.0 ± 25.0 (171)	−11.9 ± 21.5 (168)
HAQ−DI	−0.3 ± 0.6 (102)	−0.4 ± 0.5 (101)	0.0 ± 0.6 (99)	−0.4 ± 0.5 (200)	−0.2 ± 0.4 (172)	−0.4 ± 0.5 (171)	0.0 ± 0.5 (168)
CRP (mg/dL)	−1.1 ± 1.9 (101)	−1.7 ± 1.9 (101)	0.0 ± 1.5 (100)	−1.2 ± 2.7 (200)	−1.5 ± 1.9 (172)	−1.4 ± 2.2 (171)	−0.0 ± 2.0 (168)
ESR (mm/h)	−13.0 ± 21.5 (102)	−23.9 ± 21.3 (101)	−2.0 ± 17.8 (99)	−20.9 ± 21.7 (199)	−18.9 ± 19.9 (172)	−22.2 ± 22.8 (170)	−2.4 ± 19.7 (168)
Main combined endpoints and remission indices							
ACR20 responder index	57.7 (60/104)	74.5 (76/102)	30.7 (31/101)	83.5 (167/200)	58.6 (102/174)	64.4 (112/174)	21.8 (37/170)
ACR50 responder index	30.8 (32/104)	42.2 (43/102)	8.9 (9/101)	52.5 (105/200)	29.9 (52/174)	46.0 (80/174)	7.6 (13/170)
ACR70 responder index	13.5 (14/104)	27.5 (28/102)	1.0 (1/101)	30.5 (61/200)	12.1 (21/174)	23.6 (41/174)	2.4 (4/170)
Changes in DAS28-CRP	−1.62 ± 1.41 (101)	−2.17 ± 1.14 (101)	−0.64 ± 1.20 (99)	−2.42 ± 1.11 (200)	−1.70 ± 1.20 (172)	−2.09 ± 1.33 (171)	−0.51 ± 1.10 (168)
DAS28-CRP ≤3.2	40.2 (41/102)	53.5 (54/101)	11.0 (11/100)	68.0 (136/200)	47.1 (81/172)	57.9 (99/171)	12.4 (21/169)
DAS28-CRP <2.6	24.5 (25/102)	34.7 (35/101)	5.0 (5/100)	45.5 (91/200)	31.4 (54/172)	35.1 (60/171)	7.7 (13/169)
Changes in DAS28-ESR	−1.60 ± 1.39 (102)	−2.24 ± 1.23 (101)	−0.62 ± 1.17 (98)	−2.51 ± 1.27 (198)	−1.66 ± 1.22 (172)	−2.12 ± 1.36 (170)	−0.51 ± 1.11 (168)
DAS28-ESR ≤3.2	19.4 (20/103)	37.6 (38/101)	7.0 (7/100)	49.7 (99/199)	25.0 (43/172)	36.3 (62/171)	4.7 (8/169)
DAS28-ESR <2.6	11.7 (12/103)	17.8 (18/101)	1.0 (1/100)	31.7 (63/199)	12.8 (22/172)	19.3 (33/171)	2.4 (4/169)
Changes in SDAI	−16.08 ± 14.37 (101)	−20.93 ± 11.32 (101)	−7.22 ± 14.11 (99)	−21.94 ± 11.21 (200)	−15.66 ± 12.69 (172)	−19.57 ± 13.53 (171)	−4.90 ± 12.32 (168)
SDAI ≤3.3	8.8 (9/102)	8.9 (9/101)	0 (0/100)	18.5 (37/200)	7.0 (12/172)	14.0 (24/171)	0.6 (1/169)
ACR/EULAR remission	5.9 (6/102)	5.9 (6/101)	2.0 (2/100)	13.5 (27/200)	5.8 (10/172)	9.9 (17/171)	0.6 (1/169)

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

Table 53. Efficacy indices at Week 52 (FAS, LOCF)

Study	Study CL-RAJ3			Study CL-RAJ4	
Treatment group	Peficitinib 100 mg	Peficitinib 150 mg	ETN	Peficitinib 100 mg	Peficitinib 150 mg
Changes from baseline in parameters of ACR core set					
Number of swollen joints (66)	−7.7 ± 7.1 (102)	−10.0 ± 6.5 (101)	−9.7 ± 6.4 (200)	−8.8 ± 6.6 (172)	−10.3 ± 6.4 (171)
Number of painful joints (68)	−9.1 ± 9.7 (102)	−11.5 ± 9.9 (101)	−11.9 ± 8.8 (200)	−9.8 ± 7.8 (172)	−11.2 ± 8.8 (171)
Pain assessment	−28.5 ± 34.3 (102)	−38.0 ± 29.1 (101)	−35.5 ± 27.5 (200)	−28.9 ± 28.6 (172)	−32.7 ± 28.5 (171)
Patients' overall assessment	−28.5 ± 35.6 (102)	−38.8 ± 29.1 (101)	−37.1 ± 27.6 (200)	−29.3 ± 28.8 (172)	−34.1 ± 26.6 (171)
Physicians' overall assessment	−34.1 ± 25.9 (102)	−40.6 ± 22.9 (101)	−41.1 ± 22.7 (200)	−38.4 ± 25.1 (172)	−44.3 ± 24.3 (171)
HAQ-DI	−0.3 ± 0.6 (102)	−0.5 ± 0.6 (101)	−0.5 ± 0.5 (200)	−0.4 ± 0.6 (172)	−0.5 ± 0.6 (171)
CRP (mg/dL)	−1.0 ± 2.4 (102)	−1.8 ± 2.2 (101)	−1.3 ± 2.7 (200)	−1.6 ± 2.3 (172)	−1.6 ± 2.4 (171)
ESR (mm/h)	−14.9 ± 27.2 (102)	−26.2 ± 25.0 (101)	−20.8 ± 26.3 (200)	−24.0 ± 24.5 (172)	−26.1 ± 25.2 (171)
Main combined endpoints and remission indices					
ACR20 responder index	65.4 (68/104)	84.3 (86/102)	86.5 (173/200)	76.4 (133/174)	81.0 (141/174)
ACR50 responder index	43.3 (45/104)	66.7 (43/102)	69.0 (138/200)	60.3 (105/174)	62.6 (109/174)
ACR70 responder index	31.7 (33/104)	42.2 (43/102)	48.0 (96/200)	35.1 (61/174)	48.3 (84/174)
DAS28-CRP ≤3.2	54.9 (56/102)	77.2 (78/101)	81.5 (163/200)	66.9 (115/172)	71.3 (122/171)
DAS28-CRP <2.6	39.2 (40/102)	59.4 (60/101)	61.5 (123/200)	56.4 (97/172)	57.9 (99/171)
DAS28-ESR ≤3.2	38.8 (40/103)	61.4 (62/101)	58.0 (116/200)	50.6 (87/172)	57.3 (98/171)
DAS28-ESR <2.6	23.3 (24/103)	28.7 (29/101)	39.5 (79/200)	34.9 (60/172)	38.6 (66/171)
SDAI ≤3.3	17.6 (18/102)	25.7 (26/101)	33.5 (67/200)	28.5 (49/172)	35.1 (60/171)
ACR/EULAR remission	14.7 (15/102)	15.8 (16/101)	25.0 (50/200)	19.2 (33/172)	23.4 (40/171)

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

Results of a subgroup analysis in Studies CL-RAJ3 and Study CL-RAJ4 are shown in Table 54, showing no marked differences in the efficacy of peficitinib among subgroups.

Table 54. ACR20 responder index at Week 12 for each subgroup stratified by the patient characteristics at baseline (FAS, LOCF)

Study		Study CL-RAJ3			Study CL-RAJ4		
Patient characteristics		Peficitinib 100 mg	Peficitinib 150 mg	Placebo	Peficitinib 100 mg	Peficitinib 150 mg	Placebo
Age	<65 years	56.6 (47/83)	76.0 (57/75)	28.2 (20 /71)	51.7 (60/116)	66.4 (87/131)	22.4 (28/125)
	≥65 years	61.9 (13/21)	70.4 (19/27)	36.7 (11/30)	72.4 (42/58)	58.1 (25/43)	20.0 (9/45)
Sex	Male	63.0 (17/27)	83.3 (20/24)	35.7 (10/28)	53.6 (30/56)	53.1 (26/49)	28.6 (14/49)
	Female	55.8 (43/77)	71.8 (56/78)	28.8 (21/73)	61.0 (72/118)	68.8 (86/125)	19.0 (23/121)
Body weight	≤40 kg	0 (0/2)	0 (0/3)	50.0 (2/4)	80.0 (4/5)	33.3 (2/6)	0 (0/3)
	>40 kg and <60 kg	53.3 (32/60)	71.7 (43/60)	27.6 (16/58)	58.9 (63/107)	69.9 (72/103)	21.6 (21/97)
	>60 kg and <80 kg	68.6 (24/35)	86.1 (31/36)	33.3 (11/33)	53.8 (28/52)	60.4 (32/53)	26.7 (16/60)
	>80 kg	57.1 (4/7)	66.7 (2/3)	33.3 (2/6)	70.0 (7/10)	54.5 (6/11)	0 (0/10)
Disease duration	<5 years	62.2 (23/37)	90.9 (30/33)	28.0 (14/50)	62.5 (65/104)	70.2 (73/104)	23.0 (23/100)
	≥5 years	55.2 (37/67)	66.7 (46/69)	33.3 (17/51)	52.9 (37/70)	55.7 (39/70)	20.0 (14/70)
CRP	<1.0 mg/dL	63.9 (23/36)	83.9 (26/31)	25.7 (9/35)	68.9 (31/45)	64.3 (27/42)	39.3 (11/28)
	≥1.0 mg/dL	55.2 (37/67)	70.4 (50/71)	33.3 (22/66)	55.0 (71/129)	64.4 (85/132)	18.4 (26/141)
DAS28-CRP	≤3.2	0 (0/1)	0 (0/1)	0 (0/1)	0 (0/3)	66.7 (2/3)	0
	>3.2 and ≤5.1	58.7 (27/46)	76.3 (29/38)	28.9 (11/38)	63.2 (48/76)	57.6 (34/59)	34.9 (22/63)
	>5.1	58.9 (33/56)	74.6 (47/63)	32.8 (20/61)	56.8 (54/95)	67.9 (76/112)	14.2 (15/106)
DAS28-ESR	≤3.2	0	0	0 (0/1)	0 (0/1)	100 (1/1)	0
	>3.2 and ≤5.1	54.5 (12/22)	73.7 (14/19)	31.6 (6/19)	53.3 (16/30)	58.6 (17/29)	41.7 (10/24)
	>5.1	59.3 (48/81)	74.7 (62/83)	30.4 (24/79)	60.1 (86/143)	65.7 (94/143)	18.6 (27/145)
Previous biologic therapy	Used	57.1 (8/14)	84.6 (11/13)	27.3 (3/11)	63.6 (21/33)	51.9 (14/27)	21.1 (8/38)
	Not used	57.8 (52/90)	73.0 (65/89)	31.1 (28/90)	57.4 (81/141)	66.7 (98/147)	22.0 (29/132)
Concomitant cDMARDs	MTX	61.9 (39/63)	80.6 (50/62)	33.3 (19/57)	58.6 (102/174)	64.4 (112/174)	21.8 (37/170)
	Other than MTX	42.9 (12/28)	63.0 (17/27)	26.7 (8/30)	0	0	0
	Not used	69.2 (9/13)	69.2 (9/13)	28.6 (4/14)	0	0	0
Concomitant steroids	Used	58.8 (30/51)	65.2 (30/46)	19/57 (33.3)	54.8 (51/93)	66.3 (63/95)	16.7 (14/84)
	Not used	56.6 (30/53)	82.1 (46/56)	27.3 (12/44)	63.0 (51/81)	62.0 (49/79)	26.7 (23/86)

% (number of patients)

As shown above, peficitinib has been demonstrated to be effective for clinical symptoms in Japanese RA patients.

PMDA's view:

The primary efficacy endpoint of Studies CL-RAJ3 and CL-RAJ4 was ACR20 responder index at Week 12. Peficitinib 100 and 150 mg showed statistically significant difference from placebo. Secondary endpoints also demonstrated improvement in the peficitinib groups that was superior to the placebo group. In Study CL-RAJ3, the efficacy results in the Japanese subgroup were similar to those in the entire study population. These results have demonstrated the efficacy of peficitinib for clinical symptoms of RA in Japanese patients.

7.R.2.2 Preventive effects of peficitinib on structural joint damage

The applicant's explanation about the preventive effects of peficitinib on the progression of structural joint damage by RA:

In Study CL-RAJ4, preventive effects of peficitinib on structural joint damage was investigated based on changes from baseline in mTSS at Week 28, another the primary endpoint in addition to ACR20 responder index at Week 12.

As shown in Section 7.2.2, pairwise comparison showed statistically significant differences in the changes from baseline in mTSS at Week 28 between the peficitinib 100 and 150 mg groups and the placebo group. The cumulative probability distribution of changes from baseline in mTSS at Week 28 is shown in Figure 2.

Changes over time from baseline in mTSS are shown in Table 55. The preventive effects of peficitinib on joint damage were maintained at Week 52, as with Week 28.

Table 55. Changes over time from baseline in mTSS (FAS, LEP)

	Peficitinib 100 mg		Peficitinib 150 mg		Placebo	
	Measured value	Changes	Measured value	Changes	Measured value	Changes
Baseline	25.23 ± 35.50 (169)		25.00 ± 32.38 (173)		28.40 ± 36.28 (174)	
Week 28	27.11 ± 36.84 (164)	1.62 ± 4.23 (164)	26.01 ± 32.34 (164)	1.03 ± 2.86 (164)	33.14 ± 39.16 (153)	3.37 ± 5.46(153)
Week 52	27.62 ± 37.29 (164)	2.12 ± 5.83 (164)	26.52 ± 32.87 (164)	1.54 ± 4.11 (164)	36.04 ± 41.02 (153)	6.27 ± 10.18 (153)

Mean ± standard deviation (number of subjects)

The proportion of patients without progression of structural joint damage (0 or ≤0.5 for changes from baseline in mTSS) is shown in Table 56.

Table 56. Proportion of patients without progression of structural damage (FAS, LEP)

		Peficitinib 100 mg (n = 164)	Peficitinib 150 mg (n = 164)	Placebo (n = 153)
Week 28	Change in mTSS of ≤0.5	110 (67.1)	119 (72.6)	70 (45.8)
	Difference from placebo [95% CI] [a)]	21.3 [10.0, 32.6]	26.8 [15.7, 37.9]	
	Changes in mTSS of ≤0	101 (61.6)	110 (67.1)	65 (42.5)
	Difference from placebo [95% CI] [a)]	19.1 [7.7, 30.5]	24.6 [13.3, 35.9]	
Week 52	Changes in mTSS of ≤0.5	105 (64.0)	113 (68.9)	65 (42.5)
	Difference from placebo [95% CI] [a)]	21.5 [10.2, 32.9]	26.4 [15.2, 37.6]	
	Changes in mTSS of ≤0	91 (55.5)	101 (61.6)	65 (42.5)
	Difference from placebo [95% CI] [a)]	13.0 [1.5, 24.6]	19.1 [7.7, 30.5]	

Number of subjects (%)
a) Based on normal approximation of binominal distribution (continuity correction).

Results of the subgroup analysis for Studies CL-RAJ3 and CL-RAJ4 are shown in Table 57, revealing no marked differences in the efficacy of peficitinib among the subgroups.

Table 57 Changes from baseline in mTSS at Week 28 in subgroups classified according to baseline patient characteristics (FAS, LEP)

Patient characteristics		Peficitinib 100 mg	Peficitinib 150 mg	Placebo
Age	<65 years	1.88 ± 4.86 (109)	1.24 ± 3.11 (125)	3.73 ± 5.74 (117)
	≥65 years	1.08 ± 2.49 (55)	0.35 ± 1.74 (39)	2.17 ± 4.32 (36)
Sex	Male	0.88 ± 2.34 (53)	0.63 ± 1.79 (46)	2.50 ± 4.10 (43)
	Female	1.97 ± 4.85 (111)	1.18 ± 3.18 (118)	3.70 ± 5.89 (110)
Body weight	≤40 kg	3.00 ± 3.83 (4)	4.06 ± 6.55 (6)	11.47 ± 8.65 (3)
	>40 kg and <60 kg	2.22 ± 5.14 (101)	0.96 ± 2.82 (95)	4.03 ± 6.13 (87)
	>60 kg and <80 kg	0.44 ± 1.04 (49)	0.70 ± 2.05 (52)	1.95 ± 3.52 (54)
	>80 kg	0.78 ± 2.33 (10)	1.63 ± 3.21 (10)	2.80 ± 4.41 (9)
Disease duration	<5 years	2.05 ± 5.01 (100)	1.43 ± 3.16 (101)	4.21 ± 5.56 (89)
	≥5 years	0.94 ± 2.44 (64)	0.39 ± 2.18 (63)	2.20 ± 5.14 (64)
CRP	<1.0 mg/dL	0.38 ± 1.41 (42)	0.08 ± 0.80 (39)	1.63 ± 6.85 (27)
	≥1.0 mg/dL	2.04 ± 4.76 (122)	1.32 ± 3.19 (125)	3.74 ± 5.08 (126)
DAS28-CRP	≤3.2	1.67 ± 2.89 (3)	-0.83 ± 1.04 (3)	0
	>3.2 and ≤5.1	0.82 ± 2.26 (69)	0.34 ± 1.81 (57)	2.78 ± 5.32 (58)
	>5.1	2.21 ± 5.21 (92)	1.46 ± 3.26 (104)	3.72 ± 5.55 (95)
DAS28-ESR	≤3.2	5.00 (1)	0.00 (1)	0
	>3.2 and ≤5.1	0.98 ± 2.68 (25)	0.02 ± 1.20 (27)	3.19 ± 7.17 (22)
	>5.1	1.71 ± 4.45 (138)	1.25 ± 3.06 (135)	3.40 ± 5.16 (131)
mTSS	Median or lower	1.25 ± 3.74 (86)	1.04 ± 2.55 (87)	2.18 ± 3.74 (67)
	Above median	2.01 ± 4.69 (78)	1.02 ± 3.19 (77)	4.29 ± 6.37 (86)
Previous biologic therapy	Used	0.76 ± 1.64 (32)	0.67 ± 2.09 (26)	2.52 ± 5.87 (37)
	Not used	1.82 ± 4.62 (132)	1.10 ± 2.99 (138)	3.64 ± 5.33 (116)
Concomitant steroids	Used	1.98 ± 4.47 (87)	0.93 ± 2.42 (87)	2.29 ± 4.19 (75)
	Not used	1.21 ± 3.92 (77)	1.14 ± 3.30 (77)	4.40 ± 6.31 (78)

Mean ± standard deviation (number of subjects)

The above findings demonstrated the preventive effects of peficitinib on the progression of structural joint damage.

PMDA's view:

In Study CL-RAJ4, statistically significant differences in the changes from baseline in mTSS at Week 28 were observed between the peficitinib groups (100 and 150 mg) and the placebo group, and the tendency continued until Week 52. These results have demonstrated the preventive effects of peficitinib with MTX on structural joint damage. Meanwhile, the preventive effects of peficitinib alone on structural joint damage have not been studied and remain unknown. However, bone erosion in RA tends to occur at sites of active synovitis, and joint damages are closely related to clinical disease activities (*Arthritis Rheum*. 1998;41:1571-82). Further, as shown in Table 54 in Section 7.R.2.1, in light of no marked differences in the clinical efficacy between peficitinib alone and that with MTX, peficitinib, even alone, is expected to have preventive effects on structural joint damage to some extent when sufficient clinical remission is achieved.

TNF inhibitors and baricitinib, a similar drug are also known to have enhanced preventive effects on structural joint damage in use with MTX as compared with monotherapy (Lancet 2004;363:675-681; Arthritis Rheum 2011;63:1200-1210; Arthritis Rheumatol 2017;69:506-517). Accordingly, peficitinib should be used in combination with MTX as a rule to achieve clinical and structural remission particularly in RA patients with a high disease activity associated with a risk of progression of bone damage.

7.R.3 Safety

7.R.3.1 Outline of safety

The applicant's explanation about the safety of peficitinib based on pooled data from clinical studies conducted in Japanese and non-Japanese patients with RA shown in Table58.

Table58. Pooled data

Name	Studies included and scope
Pooled data from phase III studies	Safety data from a global phase III study (Study CL-RAJ3) and a Japanese phase III study (Study CL-RAJ4)
Pooled data from phase II/III studies	Data from a global phase III study (Study CL-RAJ3), a Japanese phase III study (Study CL-RAJ4), a phase II study (Study CL-RAJ1), and an extension study (Study CL-RAJ2 [data cutoff date of May 31, 2018])
Pooled data from phase II/III studies (including foreign phase II studies)	Data from a global phase III study (Study CL-RAJ3), a Japanese phase III study (Study CL-RAJ4), a phase II study (Study CL-RAJ1), an extension study (Study CL-RAJ2 [data cutoff date of May 31, 2018]), foreign phase II studies (Studies CL-RA21 and CL-RA22), and a foreign extension study (Study CL-RA25).

Summary of adverse events in individual pooled analyses are shown in Table 59.

Table 59. Summary of adverse events in the pooled analysis

	Pooled data from phase III studies (Weeks 0 to 12)				Pooled data from phase III studies (entire period)				Pooled data from phase II/III studies (including foreign phase II studies)
	Peficitinib 100 mg	Peficitinib 150 mg	Placebo	ETN	Peficitinib 100 mg	Peficitinib 150 mg	Total[a)]	ETN	All patients receiving peficitinib[a)]
Entire study population	n = 278	n = 276	n = 271	n = 200	n = 278	n = 276	n = 792	n = 200	n = 1712
Exposure (person-year)	62.8	63.4	61.1	46.4	250.5	255.7	660.0	197.3	3415.8
Adverse events	148 (53.2)	159 (57.6)	138 (50.9)	119 (59.5)	246 (88.5)	242 (87.7)	678 (85.6)	178 (89.0)	1517 (88.6)
Serious adverse events	8 (2.9)	5 (1.8)	8 (3.0)	4 (2.0)	26 (9.4)	21 (7.6)	61 (7.7)	18 (9.0)	286 (16.7)
Deaths	0	0	0	0	0	0	1 (0.1)	0	5 (0.3)
Adverse events leading to discontinuation of the study drug	11 (4.0)	8 (2.9)	11 (4.1)	5 (2.5)	26 (9.4)	18 (6.5)	57 (7.2)	13 (6.5)	228 (13.3)
Adverse drug reactions	90 (32.4)	118 (42.8)	76 (28.0)	75 (37.5)	181 (65.1)	186 (67.4)	499 (63.0)	122 (61.0)	1088 (63.6)
Japanese subgroup	n = 259	n = 257	n = 253	n = 164	n = 259	n = 257	n = 737	n = 164	n = 977
Exposure (person-year)	59.0	58.9	56.7	38.3	236.1	240.0	617.2	164.8	2221.3
Adverse events	139 (53.7)	152 (59.1)	130 (51.4)	101 (61.6)	231 (89.2)	229 (89.1)	638 (86.6)	146 (89.0)	948 (95.1)
Serious adverse events	7 (2.7)	5 (1.9)	7 (2.8)	3 (1.8)	24 (9.3)	20 (7.8)	57 (7.7)	15 (9.1)	193 (19.4)
Deaths	0	0	0	0	0	0	1 (0.1)	0	3 (0.3)
Adverse events leading to discontinuation of the study drug	9 (3.5)	8 (3.1)	11 (4.3)	4 (2.4)	22 (8.5)	17 (6.6)	52 (7.1)	11 (6.7)	165 (16.5)
Adverse drug reactions	88 (34.0)	114 (44.4)	74 (29.2)	68 (41.5)	174 (67.2)	179 (69.6)	480 (65.1)	109 (66.5)	788 (79.0)

Number of subjects (%), a) Including the occurrence after switching from placebo to peficitinib.

The pooled data from phase III studies (entire period) revealed a death of 1 patient (completed suicide) in the placebo/peficitinib 100 mg group. The pooled data from phase II/III studies (including foreign phase II studies) revealed deaths of 1 patient (completed suicide) in the placebo/peficitinib 100 mg group, 1 patient (cerebral hemorrhage) in the peficitinib 50 mg group, and 3 patients (diffuse large B-cell lymphoma, road traffic accident,

and cardiac arrest in 1 each) in the peficitinib 100 mg group during the study period. These patients except 2 in the peficitinib 100 mg group (road traffic accident and cardiac arrest) were Japanese.

Adverse events occurring at an incidence of ≥5% in any group in the pooled analysis are shown in Table 60.

Table 60. Adverse events occurring at an incidence of ≥5% in any group in the pooled analysis

Event term	Pooled data from phase III studies (entire period)				Pooled data from phase II/III studies (including foreign phase II studies)
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Total[a)] (n = 792)	ETN (n = 200)	All patients receiving peficitinib[a)] (n = 1712)
Nasopharyngitis	82 (29.5)	87 (31.5)	219 (27.7)	62 (31.0)	512 (29.9)
Blood creatine phosphokinase increased	20 (7.2)	31 (11.2)	69 (8.7)	5 (2.5)	166 (9.7)
Pharyngitis	18 (6.5)	15 (5.4)	42 (5.3)	10 (5.0)	114 (6.7)
Herpes zoster	17 (6.1)	10 (3.6)	36 (4.5)	5 (2.5)	153 (8.9)
Upper respiratory tract infection	16 (5.8)	19 (6.9)	53 (6.7)	6 (3.0)	185 (10.8)
Nausea	16 (5.8)	11 (4.0)	37 (4.7)	3 (1.5)	113 (6.6)
Bronchitis	15 (5.4)	12 (4.3)	42 (5.3)	8 (4.0)	151 (8.8)
Hepatic function abnormal	14 (5.0)	20 (7.2)	43 (5.4)	13 (6.5)	71 (4.1)
Rheumatoid arthritis	14 (5.0)	11 (4.0)	32 (4.0)	10 (5.0)	191 (11.2)
Dental caries	14 (5.0)	9 (3.3)	25 (3.2)	8 (4.0)	79 (4.6)
Upper respiratory tract inflammation	13 (4.7)	10 (3.6)	29 (3.7)	11 (5.5)	55 (3.2)
Cough	11 (4.0)	16 (5.8)	32 (4.0)	10 (5.0)	83 (4.8)
Influenza	11 (4.0)	10 (3.6)	29 (3.7)	10 (5.0)	136 (7.9)
Hypertension	10 (3.6)	16 (5.8)	36 (4.5)	10 (5.0)	124 (7.2)
Stomatitis	10 (3.6)	14 (5.1)	30 (3.8)	7 (3.5)	55 (3.2)
Headache	8 (2.9)	16 (5.8)	28 (3.5)	9 (4.5)	111 (6.5)
Diarrhea	8 (2.9)	11 (4.0)	24 (3.0)	5 (2.5)	107 (6.3)
Injection site reaction	0	0	0	26 (13.0)	0

Number of subjects (%), a) Including events occurring after switching from placebo to peficitinib.

Serious adverse events occurring at an incidence of ≥0.5% in any group in the pooled analysis are shown in Table 61.

Table 61. Serious adverse events occurring at an incidence of ≥0.5% in any peficitinib group in the pooled analysis

Event term	Pooled data from phase III studies (entire period)				Pooled data from phase II/III studies (including foreign phase II studies)
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Total[a)] (n = 792)	ETN (n = 200)	All patients receiving peficitinib[a)] (n = 1712)
Pneumonia	3 (1.1)	2 (0.7)	6 (0.8)	2 (1.0)	13 (0.8)
Spinal compression fracture	2 (0.7)	3 (1.1)	5 (0.6)	0	7 (0.4)
Rheumatoid arthritis	2 (0.7)	0	2 (0.3)	0	15 (0.9)
Herpes zoster	1 (0.4)	0	1 (0.1)	0	8 (0.5)
Cellulitis	0	2 (0.7)	2 (0.3)	0	3 (0.2)
Tendon rupture	0	0	0	0	8 (0.5)

Number of subjects (%), a) Including the occurrence after switching from placebo to peficitinib.

Adverse events leading to treatment discontinuation occurring at an incidence of ≥5% in any group in the pooled analysis are shown in Table 62.

Table 62. Adverse events leading to discontinuation of the study drug occurring at an incidence of ≥5% in any peficitinib group in the pooled analysis

Event term	Pooled data from phase III studies (entire period)				Pooled data from phase II/III studies (including foreign phase II studies)
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Total[a)] (n = 792)	ETN (n = 200)	All patients receiving peficitinib[a)] (n = 1712)
Rheumatoid arthritis	5 (1.8)	1 (0.4)	8 (1.0)	0	34 (2.0)
Lymphocyte count decreased	1 (0.4)	1 (0.4)	3 (0.4)	0	8 (0.5)

Number of subjects (%), a) Including the occurrence after switching from placebo to peficitinib.

Safety in the Japanese subgroup was analyzed based on the pooled data from phase III studies (entire period) and that from phase II/III studies. The incidences of adverse events in the Japanese subgroup were similar to those in the entire population, with no clear differences in the safety profiles affecting the tolerability.

A subset analysis of main intrinsic factors (e.g., sex, age, body weight, hepatic impairment, and eGFR) and extrinsic factors (previous biologic therapy, type of concomitant DMRADs, MTX dose, concomitant use of steroids and their doses s) was performed on the pooled data from phase III studies (entire period) and the data from the extension study (Study CL-RAJ2). Although the number of the evaluated subjects was limited, there was no subgroup which showed safety profiles markedly different from those for other subgroups.

7.R.3.2 Adverse events possibly related to treatment with peficitinib

In light of the occurrence of adverse events in the clinical studies and the pharmacological effects of peficitinib, the safety review was conducted with focuses on the events discussed below.

(a) Infections

(1) Serious infections

The applicant's explanation about the occurrence of serious infections (serious adverse events of those classified under the SOC of Infections and infestations):

Since peficitinib is an inhibitor of the JAK family, treatment with peficitinib may influence the host immunity to infections.

The occurrence of infections in individual pooled analyses is shown in Table 63.

Serious infections occurred only in the peficitinib group. Serious adverse events occurring in ≥2 patients in any peficitinib groups in the pooled data from phase III studies (entire period) included pneumonia (3 in the peficitinib 100 mg group [1.1%], 2 in the peficitinib 150 mg group [0.7%], 6 in the combined peficitinib group [0.8%], and 2 patients in the ETN group [1.0%]), cellulitis (0 in the peficitinib 100 mg group, 2 in the peficitinib150 mg group [0.7%], 2 in the combined peficitinib group [0.3%], and 0 in the ETN group). There were no obvious differences in the incidence of serious infections between the peficitinib and the ETN group as the control or no dose-dependent trend in the peficitinib 100 and 150 mg groups. According to published literature, etc., the incidence rate of serious infections in clinical studies of other medications in RA patients (pooled analyses) was 2.7 to 4.29 per 100 person-years and 2.9 to 4.11 per 100 person-years, respectively, for

tofacitinib and baricitinib, which are both JAK inhibitors (*Ann Rheum Dis*. 2017;76:1253-62; *J Rheumatol*. 2018. DOI: 10.3899/jrheum.171361) and 2.87 to 9.1 per 100 person-years for biologics (adalimumab, certolizumab pegol, tocilizumab, and abatacept) (*Ann Rheum Dis*. 2013;72:517-24; *J Rheumatol 2013;40:787-97; J Rheumaol*. 2015;42:1368-75), showing no marked differences from the incidence of serious infections with peficitinib.

Table 63. Occurrence of serious infections in the pooled analyses

	Pooled data from phase III studies (Weeks 0 to 12)				Pooled data from phase III studies (entire period)				Pooled data from phase II/III studies	Pooled data from phase II/III studies (including foreign phase II studies)
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Placebo (n = 271)	ETN (n = 200)	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Total[a)] (n = 792)	ETN (n = 200)	All patients receiving peficitinib[a)] (n = 1052)	All patients receiving peficitinib[a)] (n = 1712)
Serious infections and infestations (SOC)	3 (1.1) 4.8 [1.5, 14.9]	2 (0.7) 3.2 [0.8, 12.7]	0 0	1 (0.5) 2.2 [0.3, 15.3]	7 (2.5) 2.8 [1.3, 5.9]	8 (2.9) 3.2 [1.6, 6.3]	19 (2.4) 2.9 [1.9, 4.6]	4 (2.0) 2.0 [0.8, 5.5]	57 (5.4) 2.5 [1.9, 3.2]	76 (4.4) 2.2 [1.8, 2.8]
Opportunis-tic infection	2 (0.7) 3.2 [0.8, 12.8]	1 (0.4) 1.6 [0.2, 11.2]	0 0	0 0	3 (1.1) 1.2 [0.4, 3.7]	3 (1.1) 1.2 [0.4, 3.7]	6 (0.8) 0.9 [0.4, 2.0]	0 0	12 (1.1) 0.5 [0.3, 0.9]	14 (0.8) 0.4 [0.2, 0.7]

Upper row, number of subjects (%); lower row, incidence (per 100 person-years) [95% CI]
a) Including the occurrence after switching from placebo to peficitinib.

A subset analysis of main patient characteristics, previous medications, and concomitant drugs[28)] was conducted to investigate the incidence [95% confidence interval] of serious infections per exposure in the pooled data from phase II/III studies. The results of the subset analysis showed that the risk tended to be higher in patients aged ≥65 years (4.7 [3.1, 7.0] per 100 person-years) than in patients aged <65 years (1.9 [1.4, 2.6] per 100 person-years), but no marked differences in the incidence were observed for other factors among the subgroups.

Opportunistic infection[29)] occurred in 14 patients in the pooled data from phase II/III studies (including foreign phase II studies). Infections occurring in ≥2 patients were esophageal candidiasis in 3 patients, pneumonia cryptococcal in 3 patients, and pneumocystis jirovecii infection in 2 patients, with an incidence rate of 0.4 per 100 person-years. In clinical studies of approved anti-RA drugs, the incidence rate of opportunistic infections was reported to be 0.3 of 100 person-years for tofacitinib and baricitinib and <less than 0.1 to 0.5 of 100 person-years for biologics (adalimumab and abatacept) (*Ann Rheum Dis*. 2017;76:1253-62; *Ann Rheum Dis*. 2013;72:517-24). No marked differences in the incidence rate of opportunistic infections were observed between peficitinib and other anti-RA drugs.

In terms of virus reactivation, patients with active hepatitis B virus or with a risk of reactivation of hepatitis B virus were excluded from the phase III studies (Studies CL-RAJ3 and CL-RAJ4),[30)] and the influence of

[28)] The following patient characteristics were evaluated: Age, sex, body weight, previous use of biologics, concomitant use of cDMARDs at baseline (MTX, cDMARDs other than MTX, no concomitant use), use and dose of MTX at baseline, and use and dose of steroids at baseline.
[29)] The MedDRA preferred term for opportunistic infection defined in the published literature (Inflammatory Bowel Disease 2018 DOI: 10. 1093/ibd/izy153) was used.
[30)] Patients positive for any of HBs antigens, HBc antibodies, HBs antibodies, HBV-DNA titer, or HCV antibodies were excluded. However, patients negative for HBs antigens and HBV-DNA titers and positive for HBc and/or HBs antibodies were allowed to be enrolled under the condition that HBV-DNA levels were to be monitored by HBV-DNA quantification performed at the scheduled visits after the start of peficitinib or the reference drug.

peficitinib on the reactivation of hepatitis B virus thus remains unclear. Nevertheless, adverse events related to reactivation of viruses such as hepatitis B virus (HBV), cytomegalovirus, and Epstein-Barr virus (excluding herpes zoster) (defined as adverse events under a MedDRA high level term (HLT) of "Virus identification and serology") were hepatitis B DNA increased, hepatitis C antibody positive (1 patient each in Study CL-RAJ3), and influenza A virus test (1 patient in Study CL-RAJ2) in the peficitinib group and cytomegalovirus test positive (1 patient in Study CL-RAJ4) in the placebo group. All of the events were mild or moderate in severity, and viruses became undetectable during the study period in patients with hepatitis B DNA increased, influenza A virus test, or cytomegalovirus test positive. Also in the extension study (Study CL-RAJ2), hepatitis B reactivation was observed in 1 patient. At the time of this report, the number of evaluated subjects was very limited, and no evident dose-dependent trend was observed. Nevertheless, attention should be paid to the onset of viral reactivation, and therefore the package insert, etc. will give advice on the importance of pre-dose screening and post-dose monitoring for viral reactivation, as practiced in the use of with immunosuppressive anti-RA drugs.

Tuberculosis was not identified in the peficitinib group according to the pooled data from phase II/III studies (including foreign phase II studies). Patients with a medical history or concurrent condition of active tuberculosis were excluded from the clinical studies of peficitinib, and no tuberculosis was reported in the pooled data from phase II/III studies (including foreign phase II studies). In light of the pharmacological effects of peficitinib and the occurrence of tuberculosis in association with drugs of the same class, the package insert, etc. will advise that patients be checked for infection with tuberculosis prior to the use of peficitinib and that peficitinib not be administered to patients with active tuberculosis, as practiced for the use of the drugs of the same class.

PMDA's view:
Due to its action mechanism, the immunosuppressive effects of peficitinib may induce serious infections, opportunistic infection, tuberculosis, and reactivation of viruses such as hepatitis B virus. The incidence of serious infections following peficitinib therapy was similar to that with other JAK inhibitors for the treatment of RA. Therefore, the risk of serious infections associated with peficitinib should be highlighted as practiced for the approved products. Results of a subset analysis of the pooled data suggested that serious infections tended to occur frequently in patients aged ≥65 years. Attention should be paid to the onset of serious infections particularly when peficitinib is used in elderly patients. Until now, the possibility of increased risks associated with long-term treatment remains unclear. Therefore, post-marketing data should be collected on the occurrence of serious infections associated with peficitinib therapy, including long-term treatment. New findings should be communicated appropriately to healthcare professionals. No tendency of dose-depending increases in the risk of infections was observed in the peficitinib 100 or 150 mg groups.

(2) Herpes zoster

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

A high prevalence of herpes zoster has been reported in RA patients (*Rheumatology*. 2009;42:39-44; *Arthritis Rheum*. 2007;57:1431-8). The incidence of herpes zoster in association with treatment with tofacitinib or baricitinib is higher in Japanese and Asian patients as compared with Caucasians (*Mod Rheumatol*. 2017 doi;10.1080/14397595. 2017.1392057; *Arthritis Rheumatol*. 2014;66:2675-84).

The incidence rates of herpes zoster-related adverse events in the pooled analyses[31)] are shown in Table 64.

In the pooled data from phase III studies (Weeks 0 to 12), herpes zoster-related events occurred in 1.1% (3 of 278) of patients in the peficitinib 100 mg group, 1.1% (3 of 276) of patient in the peficitinib 150 mg group, 0% of patients in the placebo group, and 1.0% (2 of 200) of patient in the ETN group. In the pooled data from phase III studies (entire period), herpes zoster-related events occurred in 6.5% (18 of 278) of patients in the peficitinib 100 mg group, 3.6% (10 of 276) of patients in the in the peficitinib 150 mg group, and 2.5% (5 of 200) of patients in the ETN group. There was no tendency toward dose-dependent increases in the incidence of herpes zoster-related events in the peficitinib 100 mg and 150 mg groups, but the incidence tended to be higher in the peficitinib groups than in the placebo or ETN group.

In the pooled data from phase II/III studies (including foreign phase II studies), 156 patients treated with peficitinib experienced herpes zoster-related events. Serious adverse events occurred in 11 patients (herpes zoster in 8, herpes zoster oticus, herpes zoster disseminated, and ophthalmic herpes zoster in 1 each). All the patients but 1 experiencing ophthalmic herpes zoster were Japanese, and a causal relationship to the study drug was not ruled out in all 11 patients. The outcome was reported as “recovered” or “recovering” in all patients.

The incidence rate of herpes zoster-related events in the pooled data for Japanese or Asian patients from phase II/III studies was 6.5 of 100 person-years and was higher than the incidence rate (4.8 of 100 person-years) in the pooled data from phase II/III studies (including foreign phase II studies). The findings suggest that the risk of herpes zoster associated with peficitinib, as with other JAK inhibitors, is higher in Asian patients including Japanese patients.

The incidence rate of herpes zoster-related events with drugs of the same class was reported to be 8.1 of 100 person-years for tofacitinib (in Asian subjects) (*Ann Rheum Dis*. 2017;76:1253-62) and 6.5 of 100 person-years baricitinib (in Japanese subjects) (Review Report for Olumiant Tablets 2 mg and 4 mg, dated May 19, 2017). The reported incidence rates do not markedly differ from those in patients receiving peficitinib in the pooled data from phase II/III studies.

[31)] Herpes zoster-related adverse events included herpes zoster and varicella as well as the events falling under the following PTs:
Herpes zoster; herpes zoster, ophthalmic herpes zoster, herpes zoster cutaneous disseminated, herpes zoster infection neurological, herpes zoster oticus, and herpes zoster disseminated. Varicella; encephalitis post varicella, varicella, and varicella post vaccine.

Table 64. Occurrence of herpes zoster-related events in the pooled analysis

	Pooled data from phase III studies (Weeks 0 to 12)				Pooled data from phase III studies (entire period)				Pooled data from phase II/III studies	Pooled data from phase II/III studies (including foreign phase II studies)
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Placebo (n = 271)	ETN (n = 200	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Total[a)] (n = 792)	ETN (n = 200)	All patients receiving peficitinib[a)] (n = 1052)	All patients receiving peficitinib[a)] (n = 1712)
Number of patients with adverse events	3 (1.1)	3 (1.1)	0	2 (1.0)	18 (6.5)	10 (3.6)	37 (4.7)	5 (2.5)	140 (13.3)	156 (9.1)
Incidence rate	4.8 [1.5, 14.9]	4.7 [1.5, 14.7]	0	4.3 [1.1, 17.3]	7.4 [4.7, 11.8]	4.0 [2.1, 7.4]	5.7 [4.2, 7.9]	2.6 [1.1, 6.2]	6.5 [5.5, 7.7]	4.8 [4.1, 5.6]

Number of patients with adverse events, n (%). Incidence rate per 100 person-years [95% CI].
a) Including the occurrence after switching from placebo to peficitinib.

Subset analyses by main patient characteristics, previous medications, and concomitant drugs （エラー! ブックマークが定義されていません。） were conducted on the incidence rate of herpes zoster-related events per exposure in the pooled data from phase II/III studies. The results demonstrated incidence rates of 5.3 [4.3, 6.5] per 100 person-years in patients aged <65 years and 11.2 [8.5, 14.7] per 100 person-years in patients aged ≥65 years, showing a higher incidence rate in the subgroup of patients aged ≥65 years.

As shown above, the incidence rate of herpes zoster-related events associated with peficitinib did not markedly differ from that with approved JAK inhibitors. The package insert, etc. will call attention to the risk of herpes zoster, as practiced for approved JAK inhibitors.

PMDA's view:
Japanese and Western epidemiological studies revealed the risk of herpes zoster in RA patients 1.7 to 1.9 times higher than in non-RA patients, but with no marked differences in the odds ratio exist between Japan and the Western countries (*Arthritis Rheum*. 2007;57:1431-8; *Int J Rheum Dis*. 2018;21:1670-1677). Meanwhile, the risk of herpes zoster in patients receiving a JAK inhibitor (tofacitinib or baricitinib) is known to be higher in Asian countries including Japan and Korea than in the Western countries, suggesting that treatment with a JAK inhibitor may be a stronger risk factor of herpes zoster for Japanese patients (*Arthritis Rheum*. 2014;66:2675-84; *Arthritis Rheum*. 2016;68[Supple 10]; *Int J Rheum Dis.* 2018;21:1670-1677). Also, in the clinical studies of peficitinib, the incidence of herpes zoster-related events was higher in the peficitinib group than in the placebo or ETN group, as with other JAK inhibitors. In light of these findings, patients should be monitored for the signs or symptoms of reactivation of viruses such as herpes virus when peficitinib is used, and appropriate measures should be taken promptly against, if any, sign or symptoms occurs. This should be communicated to healthcare professionals. Further, post-marketing data should be collected on the occurrence of herpes zoster associated with peficitinib therapy, including long-term treatment. New findings should be communicated appropriately to healthcare professionals.

(b) Malignant tumors

The applicant's explanation about the occurrence of malignant tumors:
Treatment with a drug that may affect the immune system is suggested to increase the risk of malignant tumors in RA patients (*JAMA*. 2006;295:2275-85; *J Rheumatol*. 2010;37:2205-15). Accordingly, the risk of malignant tumors associated with peficitinib therapy was investigated.

The incidences of malignant tumors except nonmelanoma skin cancer (NMSC)[32)] and malignant lymphoma[33)] in pooled analyses are shown in Table 65. No clear differences were observed between the peficitinib group and the placebo or ETN (reference) group, or no dose-dependent increases in the incidences. The incidence rate of malignant tumors including NMSC in the pooled data from phase II/III studies and those from phase II/III studies (including foreign phase II studies) was 0.9 per 100 person-years and 0.8 per 100 person-years, respectively.

In the pooled data from phase II/III studies, malignant tumors (including NMSC) occurred in 22 patients receiving peficitinib: NMSC in 2 patients (carcinoma in situ and Bowen's disease in 1 each) and malignant lymphoma in 2 patients (lymphoma and diffuse large B-cell lymphoma in 1 each). After the termination of the studies, malignant tumors occurred in 2 patients receiving peficitinib (sarcoma uterus and diffuse large B-cell lymphoma in 1 each).

The standardized incidence ratio (SIR) [95% confidence interval] of malignant tumors (excluding NMSC), which was adjusted for age and sex based on the SEER[34)] in the pooled data from phase II/III studies and those from phase II/III studies (including foreign phase II studies), was 1.05 [0.68, 1.63] and 0.88 [0.59, 1.31], respectively, and did not markedly differ from the SIRs of malignant tumors (excluding NMSC) estimated by using data from the SEER database reported in pooled analyses of clinical studies of drugs of the same class (JAK inhibitors, 1.0-1.11 [*Ann Rheum Dis*. 2017;76:1253-62; *J Rheumatol*. 2018 doi:10.3899/jrheum. 171361]; biologics, 0.84-1.05 [*Ann Rheum Dis*. 2013;72:517-24; *J Rheumatol*. 2013;40:768-80; *J Rheumatol*. 2013;40:787-97]). For the pooled data from phase II/III studies conducted in Asian countries including Japan, the SIR [95% confidence interval] of malignant tumors was calculated by using the database of the Cancer Registry and Statistics, Center for Cancer Control and Information Services, National Cancer Center Japan (*Jpn J Clin Oncol*. 2015;45:884-91) and was 1.22 [0.79, 1.90] for malignant tumors excluding NMSC and 1.20 [0.79, 1.82] for malignant tumors including NMSC, which did not markedly differ from the SIR for malignant tumors (including NMSC) (0.745-1.18) reported in RA patients in the previous Japanese clinical studies (*Mod Rheumatol*. 2016;26:642-50; *J Rheumatol*. 2015;42:564-71; *Rheumatol Int*. 2011;31:1487-92).

[32)] Malignant tumor-related events were defined as events classified under the SMQ of Malignant tumors (Broad). Malignant tumors (except NMSC) were defined as events which were classified under the SMQ of Malignant tumors (Broad) and were those other than 3 NMSC events (carcinoma in situ, Bowen's disease, and Basal cell carcinoma) reported in Japanese and non-Japanese clinical studies of peficitinib.
[33)] Malignant lymphoma was defined as events classified under the SMQ of Malignant lymphomas (Broad).
[34)] The following were used as the SEER database:
Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2017 Sub (2000-2015), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2018, based on the November 2017 submission.

Similarly, an analysis of the SIR adjusted for age and sex based on the SEER[34)] was conducted also for malignant lymphoma. The SIR [95% confidence interval] in patients receiving peficitinib in the pooled data from phase II/III studies and those from phase II/III studies (including foreign phase II studies) was 2.55 [0.64, 10.18] and 1.79 [0.45, 7.17], respectively, and did not markedly differ from the SIRs of malignant lymphoma calculated by using data from the SEER database reported in pooled analyses of clinical studies of drugs of the same class (tofacitinib, 2.6 [*Ann Rheum Dis*. 2017;76:1253-62]; biologics used for RA treatment, 2.31-3.1 [*Ann Rheum Dis*. 2013;72:517-24; *J Rheumatol*. 2013;40:787-97]). For the pooled data from phase II/III studies, the SIR [95% confidence interval] of malignant lymphoma was calculated by using the database of the Cancer Registry and Statistics, Center for Cancer Control and Information Services, National Cancer Center Japan (*Jpn J Clin Oncol*. 2015;45:884-91) and was 4.11 [1.03, 16.43], showing no marked differences from the SIR (3.43-6.183) of malignant lymphoma reported in RA patients in the previous Japanese clinical studies (*Mod Rheumatol*. 2016;26:642-50; *J Rheumatol*. 2015;42:564-71; *Rheumatol Int*. 2011;31:1487-92).

Table 65. Occurrence of malignant tumors in the pooled analysis

	Pooled data from phase III studies (entire period)					Pooled data from phase II/III studies	Pooled data from phase II/III studies (including foreign phase II studies)
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Total[a)] (n = 792)	Placebo (n = 271)	ETN (n = 200)	All patients receiving peficitinib[a)] (n = 1052)	All patients receiving peficitinib[a)] (n = 1712)
Malignant tumors (except NMSC)							
Number of patients with adverse events	3 (1.1)	0	4 (0.5)	1 (0.4)	1 (0.5)	20 (1.9)	24 (1.4)
Incidence rate	1.2 [0.4, 3.7]	0	0.6 [0.2, 1.6]	1.2 [0.2, 8.3]	0.5 [0.1, 3.6]	0.9 [0.6, 1.3]	0.7 [0.5, 1.0]
Malignant lymphoma							
Number of patients with adverse events	0	0	0	0	0	2 (0.2)	2 (0.1)
Incidence rate	0	0	0	0	0	0.1 [0.0, 0.3]	0.1 [0.0, 0.2]

Number of patients with adverse events, n (%). Incidence rate per 100 person-years [95% CI].
a) Including onsets after switching from placebo to peficitinib.

As discussed above, no tendency toward dose-dependent increases were observed in the risk of malignant tumors (malignant tumors [except NMSC]) or malignant lymphoma associated with peficitinib therapy, and no marked differences in these incidences as compared to those reported for biologics used for the treatment of RA and other JAK inhibitors. This will be highlighted in the package insert of peficitinib, as practiced for the approved biologics and JAK inhibitors, and post-marketing data will continue to be collected on the occurrence of malignant tumors with the long-term treatment with peficitinib.

PMDA's view:

In light of the pharmacological effects of peficitinib, data from the rat carcinogenicity study [see Section 5.R.1], and cases of lymphoproliferative diseases including malignant lymphoma under the excessive immunosuppression, as well as the above applicant's discussion, cautionary advice on the risk of occurrence of malignant tumors associated with peficitinib therapy should be given in the "Warnings" section of the package insert of peficitinib, as practiced for the JAK inhibitors and approved biologics for the treatment of RA. In addition, the implementation of a long-term post-marketing study or survey should be considered so as to compare peficitinib with the approved drugs in the relation between the long-term treatment with peficitinib

and the occurrence of malignant tumors and lymphoproliferative diseases. The risk should be carefully monitored continuously.

(c) Gastrointestinal disorders and gastrointestinal perforation

The applicant's explanation about the occurrence of gastrointestinal disorders and gastrointestinal perforation:
Gastrointestinal disorders are a type of frequent adverse events in RA treatment. Among these, gastrointestinal perforation is a rare serious adverse event seen in RA patients and has been reported during treatment with tocilizumab, tofacitinib, or baricitinib (*Arthritis Rheumatol*. 2017;69 [Suppl 10]; *Arthritis Res Ther*. 2011;13:R141; *J Rheumatol*. 2014;41:837-52).

The incidences of gastrointestinal disorder-related adverse events (defined as events classified under the SMQ of gastrointestinal perforation, ulceration, haemorrhage or obstruction [Broad]) in the pooled analyses are shown in Table 66. In the pooled data from phase III studies (entire period), gastrointestinal perforation occurred more frequently in the peficitinib group than in the placebo or ETN group. The incidence of gastrointestinal perforation in the peficitinib group increased in a dose-dependent manner. In all patients receiving peficitinib in the pooled data from phase III studies, abdominal discomfort and gastric ulcers were most frequent (1.4%, 11 of 792 patients for both events), and the majority of these events were non-serious. In all serious cases, the outcome was reported as "recovered" or "recovering."

In the pooled data from phase II/III studies, the incidence rate [95% confidence interval] of gastrointestinal disorder-related events was highest in the early period of the treatment (before Month 6) with a value of 6.2 [4.3, 8.8] per 100 person-years and ranged from 1.5 to 4.3 per 100 person-years afterwards up to Month 60.

Subset analyses by main patient characteristics, previous medications, and concomitant drugs エラー! ブックマークが定義されていません。) were conducted to investigate the incidence of gastrointestinal disorder-related events by exposure in the pooled data from phase II/III studies. The results of the subset analysis showed that the incidence rate tended to be higher in patients with concomitant use of steroids at baseline (4.3 [3.3, 5.7] per 100 person-years) than in patients without concomitant use of steroids at baseline (2.3 [1.6, 3.4] per 100 person-years) and also to be higher in patients receiving concomitant steroids at a higher dose (>5 mg/day, 5.1 [2.8, 9.3] per 100 person-years) than in patients receiving concomitant steroids at a lower dose (0 to 5 mg/day, 4.1 [3.0, 5.7] per 100 person-years).

Table 66. Occurrence of gastrointestinal disorder-related adverse events in the pooled analysis

	Pooled data from phase III studies (Weeks 0 to 12)				Pooled data from phase III studies (entire period)				Pooled data from phase II/III studies	Pooled data from phase II/III studies (including foreign phase II studies)
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Placebo (n = 271)	ETN (n = 200)	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Total[a)] (n = 792)	ETN (n = 200)	All patients receiving peficitinib[a)] (n = 1052)	All patients receiving peficitinib[a)] (n = 1712)
Number of patients with adverse events	4 (1.4)	4 (1.4)	3 (1.1)	3 (1.5)	7 (2.5)	15 (5.4)	33 (4.2)	5 (2.5)	74 (7.0)	83 (4.8)
Incidence rate	6.4 [2.4, 17.1]	6.4 [2.4, 17.0]	4.9 [1.6, 15.3]	6.5 [2.1, 20.3]	2.8 [1.4, 5.9]	6.1 [3.7, 10.1]	5.1 [3.6, 7.2]	2.6 [1.1, 6.2]	3.3 [2.7, 4.2]	2.5 [2.0, 3.1]

Number of patients with adverse events, n (%). Incidence rate per 100 person-years [95% CI].
a) Including the occurrence after switching from placebo to peficitinib.

No gastrointestinal perforation-related events (defined as events classified under the SMQ of gastrointestinal perforation [Broad]) occurred during the study period of phase III studies (Studies CL-RAJ3 and CL-RAJ4), but adverse events related to gastrointestinal perforation occurred in 4 patients receiving peficitinib in the extension study (Study CL-RAJ2). After the final observation, 1 of these events in 1 patient was eliminated. The remaining 3 patients (large intestinal perforation/peritonitis, gastrointestinal perforation, and duodenal perforation in 1 patient each) had received long-term treatment with non-steroidal anti-inflammatory drugs (NSAIDs), which is a risk factor for gastrointestinal perforation, and 2 of them, except 1 with gastrointestinal perforation, had also received steroids concomitantly.

The incidence rate of gastrointestinal perforation-related events in the pooled data from phase II/III studies and those from phase II/III studies (including foreign phase II studies) was 0.2 per 100 person-years and 0.1 per 100 person-years, respectively, and did not markedly differ from the incidence rate of these events with other JAK inhibitors, i.e., tofacitinib and baricitinib (0.11 per 100 person-years and 0.05 per 100 person-years [*Ann Rheum Dis.* 2017;76:1253-62; *J Rheumatol*. 2018 doi:10.3899/jrheum. 171361], respectively) and tocilizumab (0.24 per 100 person-years [*J Rheumatol*. 2015;42:1368-75]).

As shown, the incidence of gastrointestinal disorders increased in a dose-dependent manner with peficitinib as compared with placebo or ETN. However, the majority of these events were non-serious and did not raise significant safety concerns. Peficitinib did not indicated marked differences in the risk for gastrointestinal perforation as compared with the drugs of the same class. As practiced for the other drugs of the same class, the package insert of peficitinib will call attention to the risk for gastrointestinal perforation associated with peficitinib therapy and patients at a higher risk of gastrointestinal perforation, e.g., those with a history of diverticulitis.

PMDA's view:

In light of clinical study data, etc., the package insert should call attention to the risk of gastrointestinal perforation associated with peficitinib therapy and indicate that patients with intestinal diverticulum, which is

considered a risk factor for gastrointestinal perforation, as being subject to careful administration. Many RA patients use concomitant drugs with known risks of gastrointestinal perforation, e.g., NSAIDs and steroids. Therefore, the post-marketing data including published literature should be collected further on the risk of gastrointestinal perforation in the use of peficitinib in combination with these drugs, along with the occurrence of relevant events associated with peficitinib therapy.

(d) Interstitial lung disease

The applicant's explanation about the occurrence of interstitial lung disease:
Interstitial lung disease is a pulmonary complication which frequently occurs in RA patients and may result in a fatal outcome.

Interstitial lung diseases-related events (defined as events classified under the SMQ of interstitial lung disease [Broad]) were reported in 7 patients (interstitial lung diseases in 3, organising pneumonia in 2, rheumatoid lung and lung infiltration in 1 each) in the pooled data from phase II/III studies. A causal relationship with peficitinib was not ruled out for all events except for lung infiltration in 1 patient. Serious events were interstitial lung diseases in 2 patients and organising pneumonia in 1 patient. A causal relationship with peficitinib was not ruled out for all, but the outcome of each event was "recovered" or "recovering."

The incidences of interstitial lung disease-related events in the pooled analysis are shown in Table 67.

No differences were observed in the incidence of interstitial lung disease-related events between the peficitinib 100 mg and 150 mg groups in the pooled data from phase III studies. No clear differences were identified between the peficitinib group and the placebo group or the ETN reference group. The incidence rate of interstitial lung disease-related events in the peficitinib groups in the pooled data from phase II/III studies and those from phase II/III studies (including foreign phase II studies) was 0.3 per 100 person-years and did not markedly differ from the incidence rates in the use of other anti-RA drugs (tofacitinib [long-term treatment study of tofacitinib 5 mg BID], 0.05 per 100 person-years [Review Report for Xeljanz Tablets 5 mg, dated February 28, 2013]; baricitinib, 0.19 per 100 person-years [Review Report for Olumiant Tablets 2 mg and 4 mg, dated May 19, 2017]; and abatacept, 0.11 per 100 person-years [*J Rheumatol*. 2013;40:787-97]).

Table 67. Occurrence of interstitial lung diseases in the pooled analysis

	Pooled data from phase III studies (entire period)					Pooled data from phase II/III studies	Pooled data from phase II/III studies (including foreign phase II studies)
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Total[a)] (n = 792)	Placebo (n = 271)	ETN (n = 200)	All patients receiving peficitinib[a)] (n = 1052)	All patients receiving peficitinib[a)] (n = 1712)
Number of patients with adverse events	1 (0.4)	0	3 (0.4)	2 (0.7)	4 (2.0)	7 (0. 7)	10 (0.6)
Incidence rate	0.4 [0.1, 2.8]	0	0.5 [0.1, 1.4]	2.3 [0.6, 9.4]	2.0 [0.8, 5.4]	0.3 [0.1, 0.6]	0.3 [0.2, 0.5]

Number of patients with adverse events, n (%). Incidence rate per 100 person-year [95% CI].
a) Including the occurrence after switching from placebo to peficitinib.

As shown, no marked differences were observed in the incidence rate of interstitial lung disease-related events among the peficitinib, placebo, and reference groups in the pooled data from phase III studies. The incidence rate did not markedly differ from those reported from clinical studies on the drugs of the same class. Interstitial lung diseases are events commonly observed in RA patients and require attentions in the use of peficitinib, as with the other drugs of the same class.

PMDA's view:
In light of clinical study data, etc., attention should be called to the possible occurrence of interstitial lung diseases associated with peficitinib therapy, while the importance of continuous data collection on the occurrence of interstitial lung diseases associated with peficitinib therapy, including that in long-term treatment, in the post-marketing setting and from published literature is communicated.

(e) Abnormal lipids and cardio- and cerebrovascular events

The applicant's explanation about the occurrence of abnormal lipids and cardio- or cerebrovascular adverse events:
Dyslipidemia is a known risk factor for ischemic heart diseases. Increased cholesterol and triglyceride levels during treatment were reported in patients with RA receiving tocilizumab, tofacitinib, or baricitinib (*Arthritis Rheum*. 2004;50:1761-9; *Arthritis Rheumatol*. 2015;67:117-27; *Ann Rheum Dis*. 2018;0:1-8).

The incidences of dyslipidemia (defined as events falling under the SMQ of dyslipidemia [Broad]) in the pooled analyses and dyslipidemia-related adverse events reported in ≥2 patients in any group of the pooled data from phase III studies are shown in Table 68 andTable **69**.

Although different observation periods, the incidence rate of dyslipidemia per 100 person-year in the pooled data from phase III studies (entire period) tended to be higher in the peficitinib groups than in the placebo group or the ETN reference group and in the peficitinib 150 mg group than in the peficitinib 100 mg group.

The incidence rate of dyslipidemia in the pooled data from phase II/III studies and those from phase II/III studies (including foreign phase II studies) was 5.6 per 100 person-years and 6.2 per 100 person-years, respectively,

and did not markedly differ from that in the use of baricitinib (8.8 per 100 person-years [Review Report for Olumiant Tablets 2 mg and 4 mg, dated May 19, 2017]).

A subset analysis was performed by main patient characteristics, previous medications and concomitant drugs, エラー! ブックマークが定義されていません。) to investigate the incidence of abnormal lipid-related events per exposure in the pooled data from phase II/III studies. The incidence rate of these events tended to be higher in patients aged ≥65 years (8.3 [6.0, 11.5] per 100 person-years) than in patients aged <65 years (4.8 [3.9, 6.0] per 100 person-years) and in patients using concomitant steroids at baseline (6.5 [5.2, 8.2] per 100 person-years) than in patients not using concomitant steroids at baseline (4.5 [3.4, 6.0] per 100 person-years). Particularly with steroids, the risk tended to increase in patients receiving higher doses of steroids (>5mg/day).

Table 68. Occurrence of dyslipidemia in the pooled analysis

	Pooled data from phase III studies (Weeks 0 to 12)				Pooled data from phase III studies (entire period)				Pooled data from phase II/III studies	Pooled data from phase II/III studies (including foreign phase II studies)
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Placebo (n = 271)	ETN (n = 200)	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg(n = 276)	Total[a)] (n = 792)	ETN (n = 200)	All patients receiving peficitinib[a)] (n = 1052)	All patients receiving peficitinib[a)] (n = 1712)
Number of patients with adverse events	7 (2.5)	6 (2.2)	2 (0.7)	1 (0.5)	14 (5.0)	24 (8.7)	54 (6.8)	5 (2.5)	118 (11.2)	196 (11.4)
Incidence rate	11.1 [5.3, 23.4]	9.5 [4.3, 21.1]	3.3 [0.8, 13.1]	2.2 [0.3, 15.3]	5.8 [3.4, 9.7]	9.8 [6.6, 14.7]	8.5 [6.5, 11.1]	2.6 [1.1, 6.2]	5.6 [4.6, 6.7]	6.2 [5.4, 7.2]

Number of patients with adverse events, n (%). Incidence rate per 100 person-year [95% CI].
a) Including the occurrence after switching from placebo to peficitinib.

Table 69. Adverse events related to dyslipidemia occurring in ≥2 patients in any group in the pooled data from phase III studies

	Pooled data from phase III studies (Weeks 0 to 12)					Pooled data from phase III studies (entire period)			
	Peficitinib 100 mg (n = 278)	Peficitinib 150 m (n = 276)	Peficitinib 100 mg + 150 mg (n = 554)	Placebo (n = 271)	ETN (n = 200)	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Peficitinib 100 mg + 150 mg (n = 554)	ETN (n = 200)
Dyslipidemia	5 (1.8)	3 (1.1)	8 (1.4)	0	0	7 (2.5)	5 (1.8)	12 (2.2)	2 (1.0)
Hypercholesterol-emia	1 (0.4)	0	1 (0.2)	1 (0.4)	0	3 (1.1)	6 (2.2)	9 (1.6)	1 (0.5)
Hyperlipidemia	0	2 (0.7)	2 (0.4)	0	0	1 (0.4)	6 (2.2)	7 (1.3)	0
Blood cholesterol increased	1 (0.4)	0	1 (0.2)	0	1 (0.5)	2 (0.7)	3 (1.1)	5 (0.9)	1 (0.5)
Hypertriglycerid-emia	0	1 (0.4)	1 (0.2)	0	0	0	2 (0.7)	2 (0.4)	0
Lipids abnormal	0	0	0	0	0	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.5)

Changes over time in the mean lipid parameters in the pooled data from phase III studies (entire period) were evaluated. In the peficitinib 100 mg and 150 mg groups, the levels of total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride increased, and the LDL/HDL ratio decreased. These changes were identified mainly by Week 12, and the parameters were maintained at around the levels afterward (Figure 3). In the phase III studies (Studies CL-RAJ3 and CL-RAJ4), 39 patients received statins for

dyslipidemia-related events, and the lipid control criteria were met for all lipid parameters in many of these patients (76.9% to 97.4%).[35)]

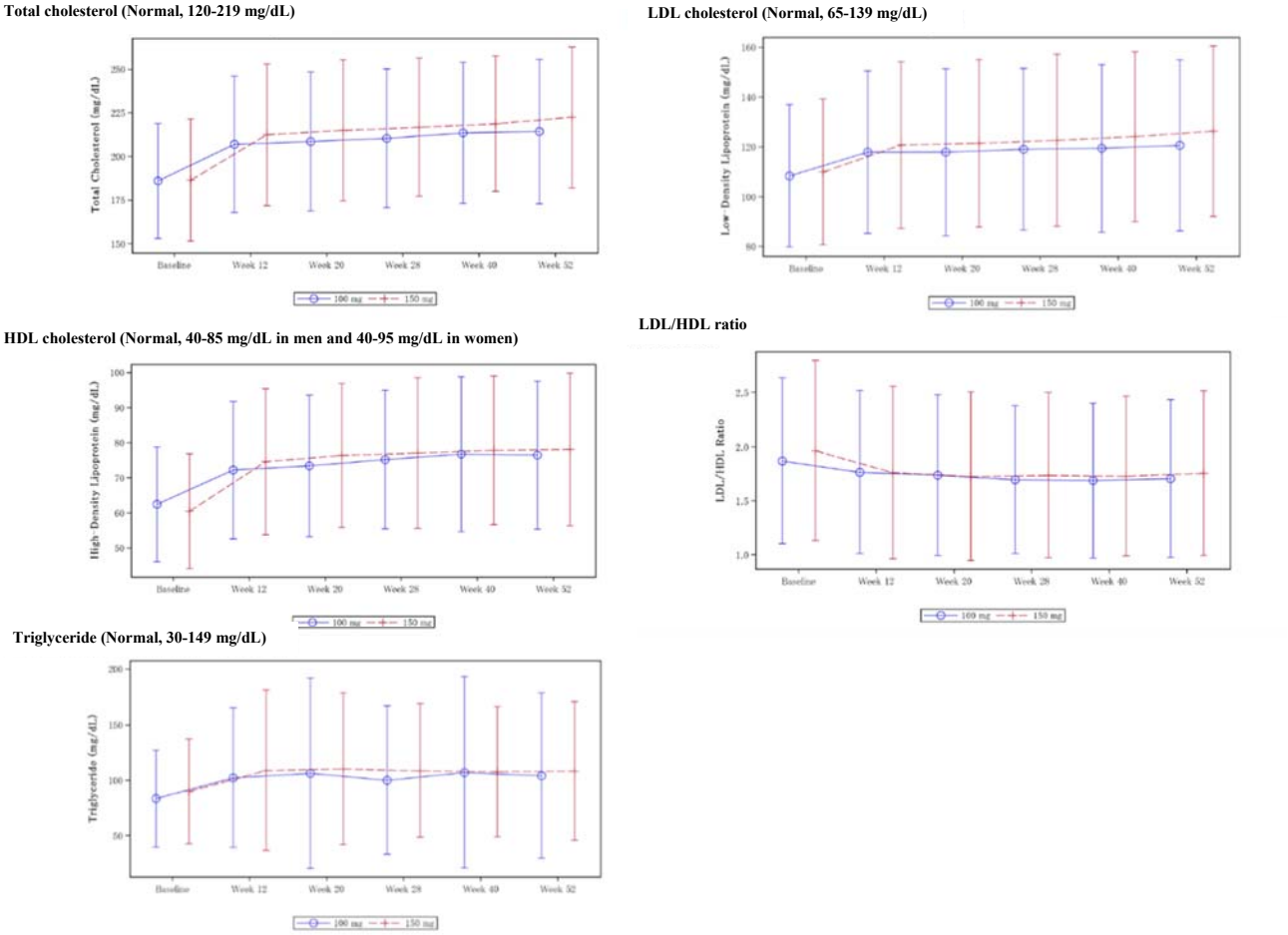


Figure 3. Changes over time in mean (standard deviation) lipid parameters in the pooled data from phase III studies (entire period)

The incidences of cardio- or cerebrovascular adverse events in the pooled analyses are shown in Table 70. Despite very limited number of subjects, no differences were seen in the incidence rate of cardio- or cerebrovascular adverse events in the phase III pooled analysis between the peficitinib 100 mg and 150 mg groups, or no clear differences were identified between the peficitinib group and the placebo group or the ETN reference group. The incidence rate of the events in the pooled data from phase II/III studies and those from phase II/III studies (including foreign phase II studies) was 0.5 per 100 person-years and 0.8 per 100 person-years, respectively, and did not significantly differ from the that of major adverse cardiovascular events (MACEs) in the use of other anti-RA drugs (tofacitinib, 0.4 per 100 person-years [*Ann Rheum Dis*. 2017;76:1253-62]; baricitinib, 0.5 per 100 person-years [*J Rheumatol*. 2018 doi: 10.3899/jrheum. 171361]; certolizumab pegol, 2.2 per 100 person-years [*Rheumatol Ther*. 2017;4:57-69]; and tocilizumab, 0.41 per 100 person-years [*J Rheumatol*. 2015;42:1368-75]).

[35)] Either of the following 2 criteria for ≥1 measurement after administration:
Criterion 1, equal to or lower than the upper limit of normal (equal to or higher than the lower limit of normal for HDL cholesterol); Criterion 2, equal to or higher than the upper limit of normal and equal to or lower than the baseline (equal to or lower than the lower limit of normal and equal to or higher than the baseline for HDL cholesterol)

Table 70. Occurrence of cardiovascular adverse events in the pooled analysis

	Pooled data from phase III studies (entire period)					Pooled data from phase II/III studies	Pooled data from phase II/III studies (including foreign phase II studies)
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Total[a)] (n = 792)	Placebo (n = 271)	ETN (n = 200)	All patients receiving peficitinib[a)] (n = 1052)	All patients receiving peficitinib[a)] (n = 1712)
Number of patients with adverse events	1 (0.4)	1 (0.4)	2 (0.3)	1 (0.4)	2 (1.0)	11 (1.0)	26 (1.5)
Incidence rate	0.4 [0.1, 2.8]	0.4 [0.1, 2.8]	0.3 [0.1, 1.2]	1.2 [0.2, 8.3]	1.0 [0.3, 4.1]	0.5 [0.3, 0.9]	0.8 [0.5, 1.1]

Number of patients with adverse events, n (%). Incidence rate per 100 person-year [95% CI].
a) Including the occurrence after switching from placebo to peficitinib.

As discussed, the incidence of dyslipidemia-related events was higher in peficitinib therapy than the placebo or ETN, and the risk of these events tended to increase in the peficitinib 150 mg group as compared with the peficitinib 100 mg group. Nevertheless, many of these events can be controlled by the use of statins, etc. Despite the limited number of subjects, the risk of cardio- and cerebrovascular events with peficitinib therapy did not seem to markedly differ from that with other anti-RA drugs. The package insert of peficitinib will call attention to abnormality in lipid test following peficitinib therapy, and will advise healthcare professionals to monitor lipid level on a regular basis after the start of peficitinib therapy and to take appropriate measures as clinically necessary.

PMDA's view:
In light of clinical study data, PMDA considers that the package insert of peficitinib should provide cautionary advice, i.e., because of abnormal lipid test data reported in association with peficitinib therapy, lipid test data should be monitored regularly during peficitinib therapy, and appropriate measures including additional pharmacotherapy should be taken as clinically necessary.

RA itself is suggested to be a risk factor for arteriosclerosis, and patients with RA are at higher risk for cardiovascular events. The possibility cannot be ruled out that an abnormal lipid level following peficitinib therapy increases the risk of cardiovascular events. Therefore, post-marketing data as well as published literature should be collected on the occurrence of cardiovascular events associated with peficitinib therapy, and obtained findings should be communicated appropriately to healthcare professionals in clinical practice.

(f) Venous embolism and thrombosis

The applicant's explanation about the occurrence of adverse events related to venous embolism and thrombosis:
The incidences of adverse events related to venous embolism and thrombosis (falling under the SMQ of embolic and thrombotic events, venous [Narrow]) in the pooled analyses are shown in Table 71.

Adverse events related to venous embolism and thrombosis occurred in a patient in the ETN group (thrombophlebitis) and did not occur in patients receiving peficitinib in the pooled data from phase III studies

(entire period). In the pooled data from phase II/III studies (including foreign phase II studies), adverse events occurred in 2 patients receiving peficitinib (deep vein thrombosis in 1 patient and retinal vein occlusion in 1 patient) in Study CL-RAJ2 and 4 patients receiving peficitinib (deep vein thrombosis and pulmonary embolism in 1 patient, deep vein thrombosis in 1 patient, pulmonary thrombosis in 1 patient, and thrombophlebitis in 1 patient) in the foreign extension study (Study CL-RA25). A relationship with peficitinib was ruled out for all events. The incidence rate of adverse events [95% confidence interval] in the pooled data from phase II/III studies and those from phase II/III studies (including foreign phase II studies) was 0.1 [0.0, 0.3] per 100 person-years and 0.2 [0.1, 0.4] per 100 person-years, respectively, and was not higher than the incidence rate of adverse events related to venous embolism and thrombosis reported in observational studies in RA patients (0.59 per 100 person-years [*JAMA*. 2012;308:1350-6] and 0.61 per 100 person-years [*Arthritis Care Res*. 2013;65:1600-7]) or of adverse events reported in a pooled analysis for baricitinib (0.5 per 100 person-years [*J Rheumatol*. 2018; DOI:10.3899/jrheum.171361]).

Table 71. Occurrence of adverse events related to venous embolism and thrombosis in the pooled analysis

	Pooled data from phase III studies (entire period)					Pooled data from phase II/III studies	Pooled data from phase II/III studies (including foreign phase II studies)
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Total[a)] (n = 792)	Placebo (n = 271)	ETN (n = 200)	All patients receiving peficitinib[a)] (n = 1052)	All patients receiving peficitinib[a)] (n = 1712)
Number of patients with adverse events	0	0	0	0	1 (0.5)	2 (0.2)	6 (0.4)
Incidence rate	0	0	0	0	0.5 [0.1, 3.6]	0.1 [0.0, 0.3]	0.2 [0.1, 0.4]

Number of patients with adverse events, n (%). Incidence rate per 100 person-year [95% CI].
a) Including the occurrence after switching from placebo to peficitinib.

Risk factors for adverse events related to venous embolism and thrombosis (advanced age [≥60 years], obesity [BMI >25], and a history of deep vein thrombosis) were investigated in patients experiencing these adverse events, and all patients were found to have ≥1 risk factor. One patient was a smoker, and the remaining 4 patients were non-smokers. No patient had a platelet count of >600 × 10^3/mm^3 before the onset of the events.

These clinical study data indicate no tendency toward an increased risk for events such as deep vein thrombosis in association with peficitinib therapy.

PMDA's view:
The occurrence of adverse events related to venous embolism and thrombosis was reported in the use of baricitinib, a JAK inhibitor of the same class. Related events, such as deep venous embolism, occurred in patients receiving peficitinib in clinical studies. In light of these findings, post-marketing data including published literature should be collected on the occurrence of events related to venous embolism and thrombosis associated with peficitinib therapy and that findings from these data should be communicated appropriately to healthcare professionals in clinical practice.

(g) Effects of peficitinib on QT intervals

The applicant's explanation about the effects of peficitinib on QT intervals:
Since a foreign TQT study in healthy adults (Study CL-QT01) showed a tendency toward shortened QT intervals in association with peficitinib therapy [see Section 6.2.4], the effects of peficitinib on QT intervals were evaluated also in phase III studies.

QTcB and QTcF in the phase III studies showed a tendency toward shortened QT intervals in the peficitinib groups as compared with the placebo group but demonstrated no clear differences in QT intervals between the peficitinib doses: QTcB, −7.7 ± 17.1 in the peficitinib 100 mg group, −5.8 ± 16.8 in the peficitinib 150 mg group, and −0.5 ± 15.8 in the placebo group in Study CL-RAJ3 and −6.8 ± 17.2 in the peficitinib 100 mg group, −8.6 ± 17.8 in the peficitinib 150 mg group, and 0.6 ± 21.2 in the placebo group in Study CL-RAJ4; and QTcF, −9.5 ± 13.3 in the peficitinib 100 mg group, −8.5 ± 13.0 in the peficitinib 150 mg group, and −2.7 ± 13.2 in the placebo group in Study CL-RAJ3 and −9.3 ± 14.0 in the peficitinib 100 mg group, −10.4 ± 14.7 in the peficitinib 150 mg group, and −2.6 ± 16.8 in the placebo group in Study CL-RAJ4.

No QTcB or QTcF intervals shortened to <360 milliseconds after administration of peficitinib. In one patient (in the peficitinib 100 mg group of Study CL-RAJ4), QTcB and QTcF intervals shortened by 60 milliseconds from baseline, but no QT interval-related adverse events occurred.

The incidences of QT interval-related adverse events in the pooled analyses[36)] are shown in Table 72. No evident differences in the incidence of these events were observed between the peficitinib 100 mg and 150 mg groups or between the peficitinib groups and the ETN group in the pooled data from phase III studies. In the pooled data from phase II/III studies, QT interval-related events occurred in 7 patients (ventricular extrasystoles in 2, atrial fibrillation, loss of consciousness, syncope, ventricular extrasystoles/ventricular tachycardia/atrial fibrillation/syncope, and electrocardiogram QT prolonged in 1 each) in the peficitinib 100 mg group and in 1 patient (loss of consciousness) in the peficitinib 150 mg group, and no event of shortened QT intervals was observed. Ventricular tachycardia observed during treatment with peficitinib 100 mg in the extension study (Study CL-RAJ2) was the only serious adverse event. A causal relationship with peficitinib was not ruled out for the serious event. However, the event did not lead to discontinuation of study treatment and resolved.

[36)] Events falling under the SMQ of torsade de pointes/QT prolongation (Broad), the HLT of ventricular arrhythmias and cardiac arrest, and the PTs of atrial fibrillation, atrial flutter, atrial tachycardia, or electrocardiogram QT shortened.

Table 72. Occurrence of QT interval-related adverse events in the pooled analysis

	Pooled data from phase III studies (Weeks 0 to 12)				Pooled data from phase III studies (entire period)				Pooled data from phase II/III studies	Pooled data from phase II/III studies (including foreign phase II studies)
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Placebo (n = 271)	ETN (n = 200)	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Total[a)] (n = 792)	ETN (n = 200)	All patients receiving peficitinib[a)] (n = 1052)	All patients receiving peficitinib[a)] (n = 1712)
Number of patients with adverse events	0	1 (0.4)	0	0	1 (0.4)	1 (0.4)	2 (0.3)	1 (0.5)	8 (0.8)	14 (0.8)
Incidence rate	0	1.6 [0.2, 11.2]	0	0	0.4 [0.1, 2.8]	0.4 [0.1, 2.8]	0.3 [0.1, 1.2]	0.5 [0.1, 3.6]	0.3 [0.2 0.7]	0.4 [0.2 0.7]

Number of patients with adverse events, n (%). Incidence rate per 100 person-year [95% CI].
a) Including the occurrence after switching from placebo to peficitinib.

As mentioned, QT intervals tended to be reduced by peficitinib. However, the change was not clinically significant, and there was no clear difference in the incidence rate of QT interval-related adverse events between the peficitinib and ETN groups. These findings suggest that the effects of peficitinib on QT intervals are of no clinically significant concern. Nevertheless, the package insert, etc. will highlight the possibility that peficitinib may reduce QT intervals and will advise caution about the careful administration of peficitinib in patients with congenital short QT syndrome.

PMDA's view:
The clinical studies revealed no clinically significant concerns. However, in light of the tendency toward reduced QT intervals by peficitinib, highlighting the possibility that peficitinib may reduce QT intervals and advising caution about peficitinib therapy in patients with congenital short QT syndrome via the package insert, etc. is appropriate. Data on the effects of peficitinib on QT intervals, including those from published literature, should continue to be collected in the post-marketing setting.

(h) Bone marrow depression

The applicant's explanation about the occurrence of events related to bone marrow depression:
Peficitinib pharmacologically inhibits the JAK-STAT pathway, thereby inhibiting the signal transduction of cytokines such as erythropoietin and GM-CSF, which may result in decreased production of erythrocytes, leukocytes, or platelets. A similar tendency was observed also in the clinical studies of JAK inhibitors of the same class (*Arthritis Rheumatol*. 2017;69:506-17; *Mod Rheumatol*. 2017;DOI:10.1080/14397595.2017.1392057; *J Rheumatol.* 2014;41:837-52). Therefore, a risk of events related to bone marrow depression with peficitinib was investigated.

In the clinical studies, hematological parameters were used for exclusion, interruption, or discontinuation criteria.[37)] The effect of peficitinib on platelet count is considered of no clinically significant concerns, due to the low incidence of thrombocytopenia-related adverse events associated with peficitinib and no marked

[37)] Exclusion criteria in Studies CL-RAJ3 and CL-RAJ4: hemoglobin <9.0 g/dL, absolute neutrophil count <1,000/μL, absolute lymphocyte count <800/μL, or platelet count <75,000/μL. Interruption or discontinuation criteria: hemoglobin <8.0 g/dL, absolute neutrophil count <500/μL, absolute lymphocyte count <500/μL, or platelet count <50,000/μL.

changes over time in platelet count after peficitinib therapy in the clinical studies. Accordingly, white blood cell count and hemoglobin level were evaluated.

(1) White blood cell count (neutrophil and lymphocyte counts)

The incidences of adverse events related to neutropenia or lymphopenia (defined as events falling under the SMQ of haematopoietic leukopenia [Broad]) in the pooled analyses and the details of adverse events related to neutropenia or lymphopenia in phase III studies are shown in Table 73 and 74, respectively.

In the pooled data from phase III studies, the incidence of events related to neutropenia or lymphopenia tended to be slightly higher in the peficitinib group than in the placebo group or the ETN reference group, but no tendency toward a dose-dependent increase in the risk was observed. The most frequent adverse event was lymphocytes decreased. The incidence of adverse events of neutropenia or lymphopenia in patients receiving peficitinib in the pooled data from phase II/III studies and those from phase II/III studies (including foreign phase II studies) was generally comparable to the incidence of these adverse events which were defined and evaluated in the same way in clinical studies of tofacitinib.

Table 73. Occurrence of neutropenia and lymphopenia in the pooled analysis

	Pooled data from phase III studies (Weeks 0 to 12)				Pooled data from phase III studies (entire period)				Pooled data from phase II/III studies	Pooled data from phase II/III studies (including foreign phase II studies)
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Placebo (n = 271)	ETN (n = 200)	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Total[a)] (n = 792)	ETN (n = 200)	All patients receiving peficitinib[a)] (n = 1052)	All patients receiving peficitinib[a)] (n = 1712)
Number of patients with adverse events	8 (2.9)	5 (1.8)	4 (1.5)	2 (1.0)	20 (7.2)	13 (4.7)	41 (5.2)	6 (3.0)	84 (8.0)	100 (5.8)
Incidence rate	12.9 [6.4, 25.7]	7.9 [3.3, 19.0]	6.6 [2.5, 17.6]	4.3 [1.1, 17.3]	8.3 [5.3, 12.9]	5.2 [3.0, 8.9]	6.4 [4.7, 8.7]	3.1 [1.4, 6.9]	3.7 [3.0, 4.6]	3.0 [2.5, 3.6]

Number of patients with adverse events, n (%). Incidence rate per 100 person-year [95% CI].
a) Including the occurrence after switching from placebo to peficitinib.

Table 74. Adverse events related to neutropenia or lymphopenia in phase III studies

	Pooled data from phase III studies (Weeks 0 to 12)					Pooled data from phase III studies (entire period)			
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Peficitinib 100 mg + 150 mg (n = 554)	Placebo (n = 271)	ETN (n = 200)	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Peficitinib 100 mg + 150 mg (n = 554)	ETN (n = 200)
Lymphocyte count decreased	7 (2.5)	3 (1.1)	10 (1.8)	0	0	13 (4.7)	8 (2.9)	21 (3.8)	0
Lymphopenia	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.4)	0	4 (1.4)	4 (1.4)	8 (1.4)	0
Leukopenia	0	0	0	0	1 (0.5)	2 (0.7)	0	2 (0.4)	3 (1.5)
White blood cell count decreased	0	1 (0.4)	1 (0.2)	2 (0.7)	1 (0.5)	1 (0.4)	1 (0.4)	2 (0.4)	2 (1.0)
Neutropenia	0	0	0	0	0	1 (0.4)	0	1 (0.2)	1 (0.5)

Number of subjects (%)

A subset analysis of main patient characteristics, previous medications, and concomitant drugs エラー! ブックマークが定義されていません。) was conducted to investigate the incidence of adverse events related to neutropenia or lymphopenia in the pooled data from phase II/III studies. The results of the subset analysis revealed that the

incidence rate tended to be higher in patients aged ≥65 years (4.8 [3.2, 7.2] per 100 person-years) than in patients aged <65 years (3.5 [2.7, 4.5] per 100 person-years) and in patients with concomitant use of MTX at baseline (5.4 [4.3, 6.9] per 100 person-years) than in patients without concomitant use of MTX at baseline (1.8 [1.1, 2.8] per 100 person-years) but showed no MTX dose-dependent increase in the incidence.

Changes over time from baseline in the neutrophil and lymphocyte counts in the Phase III studies (Studies CL-RAJ3 and CL-RAJ4) are shown in Table 75. The mean neutrophil count tended to decrease in the peficitinib groups, and the magnitude of the decrease was larger in the peficitinib 100 mg group than in the peficitinib 150 mg group. However, the changes were slight as assessed by the NCI-CTCAE Grade classification in many patients, and no patients had Grade 4 events (<500/μL) in any groups. Lymphocyte counts tended to decrease greater in the peficitinib than in the placebo group or the ETN group, but there was no consistent dose-related tendency. The percentage of patients with a decrease from baseline in lymphocyte count assessed as Grade 2 or higher according to the NCI-CTCAE Grade was as follows: in Study CL-RAJ3 (entire period), 19.2% (20 of 104) and 1.9% (2 of 104) of patients were assessed as Grade 2 (≥500/μL and <800/μL) and Grade 3 (≥200/μL and <500/μL), respectively, in the peficitinib 100 mg group, and 19.6% (20 of 102) and 1.0% (1 of 102) of patients were assessed as Grade 2 and Grade 3, respectively, in the peficitinib 150 mg group; and in Study CL-RAJ4 (entire period), 29.3% (51 of 174) and 4.0% (7 of 174) of patients were assessed as Grade 2 and 3, respectively, in the peficitinib 100 mg group, and 27.9% (48 of 172) and 3.5% (6 of 172) of patients were assessed as Grade 2 and 3, respectively, in the peficitinib 150 mg group. However, no patients had adverse events assessed as Grade 4 (<200/μL) in either group. An analysis of lymphocyte subsets suggested that the changes from baseline in the number of NK cells (positive for CD16 or CD56) at Week 12 or treatment discontinuation tended to decrease greater after the administration of peficitinib as compared with the placebo or ETN group in the phase III studies.

Table 75. Changes over time from baseline in neutrophil count and lymphocyte count in phase III studies

Study	Study CL-RAJ3				Study CL-RAJ4		
Study drug	Peficitinib 100 mg	Peficitinib 150 mg	Placebo	ETN	Peficitinib 100 mg	Peficitinib 150 mg	Placebo
Changes from baseline in neutrophil count (10^3/μL)							
Week 12	−0.10 ± 1.74 (102)	−0.94 ± 1.84 (101)	−0.47 ± 1.81 (100)	−1.36 ± 1.69 (200)	−0.58 ± 1.72 (172)	−0.72 ± 1.82 (171)	−0.04 ± 1.50 (169)
Week 52 or discontinuation	−0.29 ± 2.14 (102)	−1.16 ± 1.83 (101)		−1.46 ± 1.70 (200)	−0.70 ± 1.73 (172)	−0.74 ± 1.94 (171)	
Changes from baseline in lymphocyte count (/μL)							
Week 12	−55.9 ± 431.1 (102)	−48.5 ± 597.9 (101)	2.0 ± 398.2 (100)	238.5 ± 449.2 (200)	−89.0 ± 456.8 (172)	−28.7 ± 606.3 (171)	79.3 ± 400.0 (169)
Week 52 or discontinuation	−170.6 ± 449.1 (102)	−255.4 ± 436.2 (101)		251.5 ± 442.0 (200)	−250.0 ± 501.1 (172)	−198.2 ± 478.2 (171)	

Mean ± standard deviation (number of subjects)

The occurrence of infections (infections and infestations [SOC], serious infections) by lowest neutrophil count and lymphocyte count in the pooled data from phase III studies (entire period) is shown in Table 76. In the pooled data from phase III studies (entire period), neutrophil count decreased to <500/μL in no patients, but lymphocyte count decreased to <500/μL in some patients. However, no clear relationship was observed between the magnitude of decreases in blood cell counts and the incidence of infection.

Table 76. Occurrence of infections by the lowest lymphocyte count and neutrophil count (pooled data from phase III studies, entire period)

		Lowest count category	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Peficitinib 100 mg + 150 mg (n = 554)	ETN (n = 200)
Infections and infestations (SOC)	Neutrophil count (/μL)	≥1500 and <2000	6/13 (46.2)	2/13 (15.4)	8/26 (30.8)	14/30 (46.7)
		≥500 and <1500	0/2	1/1 (100.0)	1/3 (33.3)	5/12 (41.7)
		<500	-	-	-	-
		Other than above	158/263 (60.1)	160/262 (61.1)	318/525 (60.6)	93/158 (58.9)
	Lymphocyte count (/μL)	≥1500 and <2000	30/42 (71.4)	33/47 (70.2)	63/89 (70.8)	18/43 (41.9)
		≥500 and <1500	121/218 (55.5)	117/210 (55.7)	238/428 (55.6)	83/140 (59.3)
		<500	3/6 (50.0)	2/4 (50.0)	5/10 (50.0)	-
		Other than the above	10/12 (83.3)	11/15 (73.3)	21/27 (77.8)	11/17 (64.7)
Serious infections	Neutrophil count (/μL)	≥1500 and <2000	0/17	1/22 (4.5)	1/39 (2.6)	2/35 (5.7)
		≥500 and <1500	0/5	2/2 (100.0)	2/7 (28.6)	0/20
		<500	–	–	–	–
		Other than the above	7/256 (2.7)	5/252 (2.0)	12/508 (2.4)	2/145 (1.4)
	Lymphocyte count (/μL)	≥1500 and <2000	0/25	2/27 (7.4)	2/52 (3.8)	1/37 (2.7)
		≥500 and <1500	6/242 (2.5)	6/236 (2.5)	12/478 (2.5)	3/151 (2.0)
		<500	1/8 (12.5)	0/7	1/15 (6.7)	–
		Other than the above	0/3	0/6	0/9	0/12

Number of subjects (%)

As shown, neutrophil or lymphocyte count tended to decrease following peficitinib therapy, but the results do not show clear difference among the dose levels. The incidence of adverse events related to neutropenia or lymphopenia did not markedly differ from that with tofacitinib. Therefore, as practice for other drugs of the same class, the package insert, etc. will advise healthcare professionals to check neutrophil and lymphocyte counts in peripheral blood at baseline and during peficitinib therapy and to take appropriate measures such as interruption and discontinuation as needed.

PMDA's view:

The results of clinical studies revealed that events related to neutropenia or lymphopenia occurred slightly more frequently in the peficitinib group than in the placebo group or the ETN reference group, and that the changes from baseline in neutrophil and lymphocyte counts tended to decrease in the peficitinib group. As practiced for other drugs of the same class, the risk of decreases in neutrophil or lymphocyte count in association with peficitinib therapy should be communicated to healthcare professionals, and they should be advised not to administer peficitinib to patients whose neutrophil or lymphocyte count has severely decreased. Although no evident relationship has been established between decreased neutrophil or lymphocyte count and the onset of infections, the possibility cannot be ruled out that peficitinib increases the risk of infections associated with decreased neutrophil or lymphocyte count. NK cells, which play important roles in the prevention of viral infection and regulation of carcinogenesis (*Nat Immunol.* 2008;9:503-10), tended to decrease. Adverse events related to malignant tumors, in addition to those related to infections, should be monitored carefully. Post-marketing data relevant to these adverse events should be collected, and new findings should be communicated appropriately to healthcare professionals.

(2) Hemoglobin

The applicant's explanation about the effects of peficitinib on hemoglobin level:

The incidences of anemia-related events (the SMQ of haematopoietic erythropenia [Broad]) in the pooled analyses are shown in Table **77**.

In the pooled data from phase III studies, the incidence of anemia-related adverse events in the peficitinib group did not markedly differ from that in the placebo group or the ETN reference group, and no dose-dependent differences were observed.

The incidence rate of anemia-related events in patients receiving peficitinib in the pooled data from phase II/III studies and that from phase II/III studies (including foreign phase II studies) was 1.1 per 100 person-years and 1.4 per 100 person-years, respectively, and did not markedly differ from the reported incidence rate of these adverse events which were defined and evaluated in the same way in clinical studies of tofacitinib.

Table 77. Occurrence of anemia-related events in the pooled analysis

	Pooled data from phase III studies (Weeks 0 to 12)				Pooled data from phase III studies (entire period)				Pooled data from phase II/III studies	Phase II/III studies (including foreign phase II studies)
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Placebo (n = 271)	ETN (n = 200)	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Total[a)] (n = 792)	ETN (n = 200)	All patients receiving peficitinib[a)] (n = 1052)	All patients receiving peficitinib[a)] (n = 1712)
Number of patients with adverse events	1 (0.4)	2 (0.7)	1 (0.4)	1 (0.5)	5 (1.8)	4 (1.4)	11 (1.4)	5 (2.5)	26 (2.5)	49 (2.9)
Incidence rate	1.6 [0.2, 11.3]	3.2 [0.8, 12.6]	1.6 [0.2, 11.7]	2.2 [0.3, 15.3]	2.0 [0.8, 4.8]	1.6 [0.6, 4.2]	1.7 [0.9, 3.0]	2.6 [1.1, 6.2]	1.1 [0.8, 1.7]	1.4 [1.1, 1.9]

Number of patients with adverse events, n (%). Incidence rate per 100 person-year [95% CI].
a) Including the occurrence after switching from placebo to peficitinib.

Changes over time from baseline in hemoglobin levels in phase III studies are shown in Table 78. Hemoglobin levels tended to increase in association with peficitinib therapy.

Table 78. Changes over time from baseline in hemoglobin (g/L) in phase III studies

Study	Study CL-RAJ3				Study CL-RAJ4		
Study drug	Peficitinib 100 mg	Peficitinib 150 mg	Placebo	ETN	Peficitinib 100 mg	Peficitinib 150 mg	Placebo
Week 12	1.4 ± 7.5 (102)	4.1 ± 8.4 (101)	−0.4 ± 8.5 (100)	4.5 ± 8.0 (200)	4.5 ± 8.4 (172)	5.0 ± 7.7 (171)	0.2 ± 7.4 (169)
Week 52 or discontinuation	2.3 ± 10.8 (102)	5.5 ± 11.6 (101)		5.2 ± 10.1 (200)	4.7 ± 10.5 (172)	4.4 ± 10.2 (171)	

Mean ± standard deviation (number of subjects)

Among patients with a baseline hemoglobin level within the normal range, the percentage of patients in whom hemoglobin level decreased below the normal range during the study period was as follows: in Study CL-RAJ3 (Weeks 0 to 12), 13.3% (8 of 60) of patients in the peficitinib 100 mg group and 11.5% (7 of 61) of patients in the peficitinib 150 mg group; in Study CL-RAJ4 (Weeks 0 to 12), 19.5% (17 of 87) of patients in the peficitinib 100 mg group and 10.1% (10 of 99) of patients in the peficitinib 150 mg group; in Study CL-RAJ3 (entire period), 30.0% (18 of 60) of patients in the peficitinib 100 mg group and 26.2% (16 of 61) of patients in the peficitinib 150 mg group; and in Study CL-RAJ4 (entire period), 31.8% (28 of 88) of patients in the peficitinib

100 mg group and 28.7% (29 of 101) of patients in the peficitinib 150 mg group. The percentage of patients with a hemoglobin level of <8.0 g/dL during the study period was 1.9% (2 of 104) of patients in the peficitinib 100 mg group and 2.0% (2 of 102) of patients in the peficitinib 150 mg group in Study CL-RAJ3 (entire period) and 0.6% (1 of 174) of patients in the peficitinib 100 mg group and 1.7% (3 of 173) of patients in the peficitinib 150 mg group in Study CL-RAJ4 (entire period). The percentage of patients in whom a hemoglobin level decreased >2.0 g/dL from baseline was 4.8% (5 of 104) of patients in the peficitinib 100 mg group and 2.9% (3 of 102) of patients in the peficitinib 150 mg group in Study CL-RAJ3 (entire period) and 2.9% (5 of 174) of patients in the peficitinib 100 mg group and 4.6% (8 of 173) of patients in the peficitinib 150 mg group in Study CL-RAJ4 (entire period), and only a few patients presented with a severely decreased hemoglobin level after administration of peficitinib.

As shown, there was no clear tendency toward decreased hemoglobin level with peficitinib therapy or no differences between the dose levels. At the same time, anemia-related adverse events and relatively severe decrease in hemoglobin level occurred. The package insert will also advise healthcare professionals to check hemoglobin level at baseline and during peficitinib therapy so that appropriate measures such as interruption and discontinuation are taken accordingly.

PMDA's view:
Results of the clinical studies revealed no marked difference in the incidence rate of anemia-related adverse events between peficitinib and other drugs of the same class. However, anemia is an expected adverse event from the pharmacological effects of peficitinib. The prevalence of comorbid anemia is high in RA patients. In light of these facts, a current or previous history of anemia should be checked before the start of peficitinib therapy, and due care should be taken for the occurrence or worsening of anemia during peficitinib therapy, in addition to the confirmation of hemoglobin levels and discontinuation/interruption of peficitinib therapy as proposed by the applicant. Therefore, post-marketing data relevant to the risk and the occurrence of decreased hemoglobin levels and anemia, including those from published literature, should continue to be collected.

(i) Muscle disorder-related events

The applicant's explanation about muscle disorder-related events:
The incidences of muscle disorder-related adverse events (falling under the SMQ of rhabdomyolysis/myopathy [Broad]) in the pooled analyses are shown in Table 79.

The incidence of muscle disorder-related adverse events in the pooled data from phase III studies tended to be higher in the peficitinib groups than in the placebo group or the ETN reference group and was higher in the peficitinib 100 mg group than in the peficitinib 150 mg group.

Table 79. Occurrence of muscle disorder-related adverse events in the pooled analysis

	Pooled data from phase III studies (Weeks 0 to 12)				Pooled data from phase III studies (entire period)				Pooled data from phase II/III studies	Pooled data from phase II/III studies (including foreign phase II studies)
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Placebo (n = 271)	ETN (n = 200)	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Total[a)] (n = 792)	ETN (n = 200)	All patients receiving peficitinib[a)] (n = 1052)	All patients receiving peficitinib[a)] (n = 1712)
Number of patients with adverse events	9 (3.2)	12 (4.3)	2 (0.7)	4 (2.0)	31 (11.2)	37 (13.4)	90 (11.4)	14 (7.0)	174 (16.5)	231 (13.5)
Incidence rate	14.5 [7.6, 27.9]	19.2 [10.9, 33.8]	3.3 [0.8, 13.1]	8.7 [3.3, 23.2]	13.1 [9.2, 18.7]	15.7 [11.4, 21.6]	14.5 [11.8, 17.8]	7.4 [4.4, 12.5]	8.5 [7.3, 9.9]	7.5 [6.6, 8.5]

Number of patients with adverse events, n (%). Incidence rate, per 100 person-year [95% CI].
a) Including the occurrence after switching from placebo to peficitinib.

The muscle disorder-related adverse events occurring in ≥ 2 patients in any group in the pooled data from phase III studies are shown in Table 80. The most frequent event was blood creatine phosphokinase increased, while no rhabdomyolysis or myopathy was reported. Among muscle disorder-related adverse events observed in the pooled data from phase II/III studies (including foreign phase II studies), the most frequent event was blood creatine phosphokinase increased in 166 of 1712 patients (9.7%). Other adverse events occurring at an incidence of ≥1% included myalgia in 29 patients (1.7%), musculoskeletal pain in 19 patients (1.1%), and blood creatinine increased in 18 patients (1.1%). Among muscle disorder-related adverse events in patients receiving peficitinib in the pooled data from phase II/III studies (including foreign phase II studies), a serious adverse event occurred in a patient (blood creatine phosphokinase increased, the peficitinib 25/100 mg group of Study CL-RA25 conducted outside Japan). A causal relationship with peficitinib was ruled out for the event, and the outcome of the event was reported as "resolved." Muscle disorder-related adverse events led to discontinuation of peficitinib in 9 patients (blood creatine phosphokinase increased in 6 patients, blood creatine phosphokinase increased and myopathy in 1 patient, myalgia in 1 patient, and musculoskeletal pain in 1 patient). A causal relationship with peficitinib could not be ruled out for all these events except myalgia in 1 patient. Except myalgia in 1 patient (in the peficitinib 150 mg/100 mg group of Study CL-RA25 conducted outside Japan) and blood creatine phosphokinase increased and myopathy in 1 patient (in the placebo/peficitinib 100 mg group of Study CL-RA25 conducted outside Japan), all events were resolving or resolved.

Table 80. Adverse events related to muscle disorders occurring in ≥2 patients in any group in the pooled data from phase III studies

	Pooled data from phase III studies (Weeks 0 to 12)					Pooled data from phase III studies (entire period)			
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Peficitinib 100 mg + 150 mg (n = 554)	Placebo (n = 271)	ETN (n = 200)	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Peficitinib 100 mg + 150 mg (n = 554)	ETN (n = 200)
Blood CPK increased	7 (2.5)	9 (3.3)	16 (2.9)	1 (0.4)	1 (0.5)	20 (7.2)	31 (11.2)	51 (9.2)	5 (2.5)
Myalgia	0	1 (0.4)	1 (0.2)	0	0	5 (1.8)	3 (1.1)	8 (1.4)	3 (1.5)
Renal dysfunction	1 (0.4)	0	1 (0.2)	0	0	3 (1.1)	2 (0.7)	5 (0.9)	1 (0.5)
Blood creatinine increased	1 (0.4)	0	1 (0.2)	1 (0.4)	1 (0.5)	3 (1.1)	0	3 (0.5)	1 (0.5)

Number of subjects (%)

Changes over time from baseline in CPK level in the phase III studies are shown in Table 81 and tended to be higher in the peficitinib groups than in the placebo group.

Table 81. Changes over time from baseline in CPK level (U/L) in phase III studies

	Study CL-RAJ3				Study CL-RAJ4		
	Peficitinib 100 mg	Peficitinib 150 mg	Placebo	ETN	Peficitinib 100 mg	Peficitinib 150 mg	Placebo
Week 12	55.5 ± 118.6 (102)	67.7 ± 61.1 (101)	0.6 ± 22.3 (100)	79.5 ± 1117.7 (200)	49.0 ± 46.1 (172)	61.9 ± 93.3 (171)	−1.7 ± 26.6 (169)
Week 52 or discontinuation	91.9 ± 213.9 (102)	102.2 ± 105.4 (101)		86.4 ± 1117.8 (200)	74.0 ± 72.3 (172)	80.1 ± 79.2 (171)	

Mean ± standard deviation (number of subjects)

The occurrence of increased blood CPK level in each category in the phase III studies is shown in Table 82. A slight increase was observed in many patients, while a limited number of patients experienced an increase of >5 times the upper limit of the normal range.

Table 82. Occurrence of increased CPK level by category in phase III studies (entire period)

		Peficitinib 100 mg	Peficitinib 150 mg	100 mg + 150 mg	ETN
Study CL-RAJ3					
CPK (maximum)	>2 × ULN and ≤5 × ULN	12/104 (11.5)	19/102 (18.6)	31/206 (15.0)	5/200 (2.5)
	>5 × ULN and ≤10 × ULN	3/104 (2.9)	3/102 (2.9)	6/206 (2.9)	0/200
	>10 × ULN	1/104 (1.0)	2/102 (2.0)	3/206 (1.5)	1/200 (0.5)
Study CL-RAJ4					
CPK (maximum)	>2 × ULN and ≤5 × ULN	18/174 (10.3)	27/173 (15.6)	45/347 (13.0)	−
	>5 × ULN and ≤10 × ULN	0/174	4/173 (2.3)	4/347 (1.2)	−
	>10 × ULN	0/174	0/173	0/347	−

Number of subjects meeting the criteria /number of subjects evaluated (%); ULN, the upper limit of the normal range (270 U/L for men and 150 U/L for women)

The incidence rate of blood creatine phosphokinase increased in the pooled data from phase II/III studies and those from phase II/III studies (including foreign phase II studies) was 6.3 per 100 person-years and 5.2 per 100 person-years, respectively, and tended to be higher than that of blood creatine phosphokinase increased reported in the use of for tofacitinib and baricitinib, drugs of the same class (1.21 per 100 person-years and 3.3 per 100 person-years, respectively [Review Report for Xeljanz Tablets 5 mg, dated February 28, 2013], J Rheumatol 2018 doi:10.3899/jrheum.171361]).

As shown, the onset of muscle disorder-related events tended to increase dose-dependently in patients receiving peficitinib. These events, however, were mostly abnormality in laboratory tests, and only a limited number of patients had increased blood CPK level of >5 times the upper limit of the normal range. No muscular symptoms accompanied the abnormality in most patients. Accordingly, increased CPK following peficitinib therapy is clinically insignificant.

PMDA's view:

While not many muscle symptom-related events were serious or led to discontinuation of treatment, high blood CPK was observed in many patients, CPK increased in a dose-dependent manner. A long-term effect of peficitinib remain unknown in patients with persistent high CPK. Therefore, in the post-marketing setting,

including published literature, data should continue to be collected on the occurrence of muscle disorder-related events such as high CPK levels, rhabdomyolysis, and myopathy in association with peficitinib therapy.

(j) Effects of peficitinib on hepatic function

The applicant's explanation about the effects of peficitinib on hepatic function:

Adverse events related to increased transaminase or hepatic function have been reported in the use of tofacitinib and baricitinib, which are drugs of similar type to peficitinib (*Arthritis Rheumatol*. 2017;69:506-17; *J Rheumatol*. 2014;41:837-52; *Mod Rheumtol*. 2017 DOI:10.1080/14397595.2017.1392057).

The incidences of hepatic dysfunction-related adverse events in the pooled analyses are shown in Table 83.

There was an exclusion criterion related to hepatic function[38)] in the pooled data from phase III studies. The incidence of hepatic dysfunction-related events (under the SMQ of hepatic disorders [Broad]) tended to be higher in the peficitinib 150 mg group than in the peficitinib 100 mg group, while they did not markedly differ between the peficitinib group and the placebo or ETN reference group.

The incidence rate of these events in the pooled data from phase II/III studies and that from phase II/III studies (including foreign phase II studies) was 7.3 per 100 person-years and 5.7 per 100 person-years, respectively, and did not markedly differ from that reported for baricitinib in its clinical studies (5.7 per 100 person-years, Review Report for Olumiant Tablets 2 mg and 4 mg, dated May 19, 2017).

Table 83. Occurrence of hepatic dysfunction in the pooled analysis

	Pooled data from phase III studies (Weeks 0 to 12)				Pooled data from phase III studies (entire period)				Pooled data from phase II/III studies	Pooled data from phase II/III studies (including foreign phase II studies)
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Placebo (n = 271)	ETN (n = 200)	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Total[a)] (n = 792)	ETN (n = 200)	All patients receiving peficitinib[a)] (n = 1052)	All patients receiving peficitinib[a)] (n = 1712)
Number of patients with adverse events	11 (4.0)	22 (8.0)	16 (5.9)	12 (6.0)	27 (9.7)	43 (15.6)	91 (11.5)	26 (13.0)	153 (14.5)	182 (10.6)
Incidence rate	17.9 [9.9, 32.2]	36.0 [23.7, 54.6]	26.8 [16.4, 43.8]	26.5 [15.1, 46.7]	11.4 [7.8, 16.7]	18.7 [13.9, 25.2]	14.8 [12.1, 18.2]	14.1 [9.6, 20.8]	7.3 [6.2, 8.5]	5.7 [4.9, 6.6]

Number of patients with adverse events, n (%). Incidence rate, per 100 person-year [95% CI].
a) Including the occurrence after switching from placebo to peficitinib.

Subset analyses based on main patient characteristics, previous medications, and concomitant drugs エラー! ブックマークが定義されていません。) were performed on the incidence rate of hepatic dysfunction-related adverse events by exposure The results in Table 84 show a tendency toward higher risk in patients with high body weight and those treated with concomitant MTX, and the incidence of adverse events tended to be higher in a dose-dependent manner particularly in patients on concomitant MTX.

38) Exclusion criteria: during the screening period, AST or ALT of ≥2 times the upper limit of the normal range or total bilirubin of ≥1.5 times the upper limit of the normal range.

Table 84. Subset analyses of the incidence rate of hepatic dysfunction-related adverse events per exposure (safety analysis set)

		Pooled data from phase III studies (entire period)					Pooled data from phase II/III studies
		Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Total (n = 792)	ETN (n = 200)	Placebo (n = 271)	All patients receiving peficitinib (n = 1712)
Age	<65 years	20/168.5 11.9 [7.7, 18.4]	33/170.9 19.3 [13.7, 27.2]	67/450.0 14.9 [11.7, 18.9]	22/141.6 15.5 [10.2, 23.6]	13/57.7 22.5 [13.1, 38.8]	114/1647.5 6.9 [5.8, 8.3]
	≥65 years	7/67.6 10.4 [4.9, 21.7]	10/58.8 17.0 [9.1, 31.6]	24/162.8 14.7 [9.9, 22.0]	4/42.3 9.5 [3.6, 25.2]	5/24.5 20.4 [8.5, 49.0]	39/453.1 8.6 [6.3, 11.8]
Body weight	≤40.0 kg	0/5.6 0.0	0/8.8 0.0	0/18.4 0.0	0/8.6 0.0	0/1.8 0.0	1/50.9 2.0 [0.3, 13.9]
	40.0< ≤60.0 kg	11/146.7 7.5 [4.2, 13.5]	20/137.4 14.6 [9.4, 22.6]	42/363.4 11.6 [8.5, 15.6]	10/114.2 8.8 [4.7, 16.3]	11/46.5 23.6 [13.1, 42.7]	68/1275.3 5.3 [4.2, 6.8]
	60.0< ≤80.0 kg	12/70.2 17.1 [9.7, 30.1]	18/72.8 24.7 [15.6, 39.2]	35/198.0 17.7 [12.7, 24.6]	15/54.7 27.4 [16.5, 45.5]	5/29.3 17.1 [7.1, 41.0]	66/676.8 9.8 [7.7, 12.4]
	80.0 kg<	4/13.7 29.2 [11.0,77.9]	5/10.0 49.8 [20.7,119.7]	14/32.3 43.4 [25.7,73.3]	1/6.3 15.9 [2.2,113.1]	2/4.6 44.0 [11.0,175.7]	18/96.7 18.6 [11.7,29.5]
	Unknown	–	0/0.8 0.0	0/0.8 0.0	–	–	0/0.8 0.0
Concomitant use of MTX at the start	No	2/35.7 5.6 [1.4, 22.4]	4/36.3 11.0 [4.1, 29.3]	7/100.8 6.9 [3.3, 14.6]	8/80.0 10.0 [5.0, 20.0]	1/10.0 10.0 [1.4, 71.1]	36/973.9 3.7 [2.7, 5.1]
	Yes	25/200.4 12.5 [8.4, 18.5]	39/193.4 20.2 [14.7, 27.6]	84/512.0 16.4 [13.2, 20.3]	18/103.9 17.3 [10.9, 27.5]	17/72.2 23.5 [14.6, 37.9]	117/1126.6 10.4 [8.7, 12.4]

Upper row, number of patients with the event/exposure (person-year); lower row, incidence rate (per 100 person-year) [95% CI]

The changes over time from baseline in ALT and AST levels in phase III studies are shown in Table 85. The mean ALT and AST levels tended to increase slightly in the peficitinib groups but remained within their normal range.

Table 85. Changes over time from baseline in ALT and AST in phase III studies

Study	Study CL-RAJ3				Study CL-RAJ4		
Study drug	Peficitinib 100 mg	Peficitinib 150 mg	Placebo	ETN	Peficitinib 100 mg	Peficitinib 150 mg	Placebo
Changes from baseline in ALT (U/L)							
Week 12	2.3 ± 8.9 (102)	6.9 ± 17.4 (101)	2.0 ± 12.4 (100)	4.6 ± 15.9 (200)	3.8 ± 16.7 (172)	6.9 ± 19.6 (171)	−0.2 ± 12.8 (169)
Week 52 or discontinuation	3.8 ± 12.2 (102)	5.9 ± 22.9 (101)		3.2 ± 15.0 (200)	3.2 ± 16.5 (172)	7.5 ± 19.9 (171)	
Changes from baseline in AST(U/L)							
Week 12	2.7 ± 7.1 (102)	4.9 ± 14.6 (101)	0.8 ± 7.9 (100)	4.3 ± 18.6 (200)	3.6 ± 11.9 (172)	5.6 ± 14.4 (171)	−0.1 ± 10.8 (169)
Week 52 or discontinuation	4.3 ± 10.3 (102)	5.1 ± 16.4 (101)		3.8 ± 19.0 (200)	4.2 ± 12.4 (172)	7.0 ± 16.0 (171)	

Mean ± standard deviation (number of subjects)

Of patients with baseline ALT within the normal range, those who had an ALT level exceeding the normal range during the study period between Weeks 0 and 12 was 6.1% (6 of 98) in the peficitinib 100 mg group, 15.4% (14 of 91) in the peficitinib 150 mg group, 6.4% (6 of 94) in the placebo group, and 11.5% (22 of 192) in the ETN group in Study CL-RAJ3 and 11.0% (18 of 164) in the peficitinib 100 mg group, 14.3% (23 of 161) in the peficitinib 150 mg group, and 7.0% (11 of 157) in the placebo group in Study CL-RAJ4. The corresponding percentage in the entire study period was 16.0% (16 of 100) in the peficitinib 100 mg group, 25.0% (23 of 92) in the peficitinib 150 mg group, and 23.4% (45 of 192) in the ETN group in Study CL-RAJ3 and 22.3% (37 of 166) in the peficitinib 100 mg group and 30.2% (49 of 162) in the peficitinib 150 mg group in Study CL-RAJ4. Of patients with baseline AST within the normal range, those who had an AST level exceeding the normal range during the study period between Weeks 0 and 12 accounted for 11.5 % (11 of 96)

in the peficitinib 100 mg group, 14.4% (13 of 90) in the peficitinib 150 mg group, 7.6 % (7 of 92) in the placebo group, 12.9% (24 of 186) in the ETN group in Study CL-RAJ3 and 11.9% (19 of 160) in the peficitinib 100 mg group, 16.7% (26 of 156) in the peficitinib 150 mg group, and 9.3% (15 of 162) in the placebo group in Study CL-RAJ4. The percentage of corresponding patients during the entire study entire period was 25.5% (25 of 98) in the peficitinib 100 mg group, 34.1% (31 of 91) in the peficitinib 150 mg group, and 28.0 % (52 of 186) in the ETN group in Study CL-RAJ3 and 29.0% (47 of 162) in the peficitinib 100 mg group and 37.3% (59 of 158) in the peficitinib 150 mg group in Study CL-RAJ4. AST and ALT levels were both higher in the peficitinib group than in the placebo group and were higher in the peficitinib 100 mg group than in the peficitinib 150 mg group but did not markedly differ between the peficitinib group and the ETN group.

The incidences of abnormal liver function test in each category in the phase III studies (entire period) are shown in Table 86. Only few patients had abnormal liver function test assessed as NCI-CTCAE Grade 2 (>3 × ULN and ≤5 × ULN) or Grade 3 (>5 × ULN and ≤20 × ULN), and no patient had Grade 4 (>20 × ULN) abnormalities.

Table 86. Occurrence of abnormal laboratory data related to hepatic dysfunction by category in phase III studies

		Peficitinib 100 mg	Peficitinib 150 mg	Peficitinib 100 mg + 150 mg	ETN
Study CL-RAJ3					
ALT	≥1 × ULN and <2 × ULN	16/104 (15.4)	24/102 (23.5)	40/206 (19.4)	36/200 (18.0)
	≥2 × ULN and <3 × ULN	3/104 (2.9)	6/102 (5.9)	9/206 (4.4)	9/200 (4.5)
	≥3 × ULN	0/104	3/102 (2.9)	3/206 (1.5)	7/200 (3.5)
AST	≥1 × ULN and <2 × ULN	24/104 (23.1)	31/102 (30.4)	55/206 (26.7)	50/200 (25.0)
	≥2 × ULN and <3 × ULN	4/104 (3.8)	8/102 (7.8)	12/206 (5.8)	6/200 (3.0)
	≥3 × ULN	1/104 (1.0)	1/102 (1.0)	2/206 (1.0)	8/200 (4.0)
Total bilirubin	>1.5 × ULN	3/104 (2.9)	1/102 (1.0)	4/206 (1.9)	6/200 (3.0)
ALT or AST of >3 × ULN or total bilirubin of >2 × ULN		1/104 (1.0)	3/102 (2.9)	4/206 (1.9)	12/200 (6.0)
ALT or AST of >3 × ULN and total bilirubin of >2 × ULN		0	0	0	0
Study CL-RAJ4					
ALT	≥1 × ULN and <2 × ULN	36/174 (20.7)	44/173 (25.4)	80/347 (23.1)	–
	≥2 × ULN and <3 × ULN	5/174 (2.9)	5/173 (2.9)	10/347 (2.9)	–
	≥3 × ULN	3/174 (1.7)	10/173 (5.8)	13/347 (3.7)	–
AST	≥1 × ULN and <2 × ULN	51/174 (29.3)	57/173 (32.9)	108/347 (31.1)	–
	≥2 × ULN and <3 × ULN	5/174 (2.9)	10/173 (5.8)	15/347 (4.3)	–
	≥3 × ULN	2/174 (1.1)	6/173 (3.5)	8/347 (2.3)	–
Total bilirubin	>1.5× ULN	1/174 (0.6)	11/173 (6.4)	12/347 (3.5)	–
ALT and/or AST of >3× ULN or total bilirubin >2× ULN		4/174 (2.3)	11/173 (6.4)	15/347 (4.3)	–
ALT and/or AST of >3 × ULN and total bilirubin of >2 × ULN		0	0	0	–

Number of patients meeting the criterion/number of subjects evaluated (%)

As shown, hepatic dysfunction with increased transaminase occurred following peficitinib therapy. The package insert, etc. will inform healthcare professionals of elevated hepatic function test values and advise to monitor patients' condition including hepatic function closely, administer peficitinib carefully to patients with hepatic impairment, and to use extra caution when administering peficitinib in combination with MTX or other drugs potentially causing hepatic dysfunction.

PMDA's review:
In light of more frequent hepatic disorder-related events in the peficitinib group as compared with the placebo group and the tendency of the incidence to increase dose-dependently, healthcare professionals should be informed of the risk of hepatic dysfunction associated with peficitinib and careful administration of peficitinib required for patients with hepatic impairment. Besides, because peficitinib may be used with MTX, a NSAID or other that may pose a risk of hepatic dysfunction in RA patients, the possibility could not be ruled out that peficitinib or concomitant drugs may increase the risk of hepatic dysfunction. Therefore, post-marketing data including those from published literature, on the effects of peficitinib on hepatic function should continue to be collected.

(k) Effects of peficitinib on renal function

The applicant's explanation about the effects of peficitinib on renal function:
The incidences of renal dysfunction-related events (under the SMQ of acute renal failure [Broad]) in the pooled analyses and renal dysfunction-related events occurring in ≥2 patients in any group in the pooled data from phase III studies are shown in Table 87 and Table 88, respectively.

In the pooled data from phase III studies, the incidence rate of renal dysfunction-related events in the peficitinib group did not markedly differ from that in the placebo group or the ETN reference group and showed no tendency to dose-dependent increase in the incidence. The most frequent adverse event at Week 12 and during the entire period was protein urine present and renal dysfunction, respectively. In the pooled data from phase II/III studies (including foreign phase II studies), the most frequent adverse event was blood creatinine increased with an incidence of 1.1% (18 of 1712 patients).

The incidence rate of renal dysfunction-related events in patients receiving peficitinib in the pooled data from phase II/III studies and those from phase II/III studies (including foreign phase II studies) was 1.4 per 100 person-years and 1.5 per 100 person-years, respectively, and did not markedly differ from that of these events with tofacitinib reported in clinical studies (tofacitinib [long-term treatment study of tofacitinib 5 mg BID], which was 1.72 per 100 person-years [Review Report for Xeljanz Tablets 5 mg, dated February 28, 2013]). A subset analysis of the pooled data from phase II/III studies showed that the incidence rate tended to be higher in patients aged ≥65 years (3.3 [2.0, 5.4] per 100 person-years) than in patients aged <65 years (0.8 [0.5, 1.4] per 100 person-years).

Table 87. Occurrence of renal dysfunction-related events in the pooled analysis

	Pooled data from phase III studies (Weeks 0 to 12)				Pooled data from phase III studies (entire period)				Pooled data from phase II/III studies	Pooled data from phase II/III studies (including foreign phase II studies)
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Placebo (n = 271)	ETN (n = 200)	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Total[a)] (n = 792)	ETN (n = 200)	All patients receiving peficitinib[a)] (n = 1052)	All patients receiving peficitinib[a)] (n = 1712)
Number of patients with adverse events	4 (1.4)	1 (0.4)	2 (0.7)	3 (1.5)	9 (3.2)	3 (1.1)	17 (2.1)	4 (2.0)	31 (2.9)	51 (3.0)
Incidence rate	6.4 [2.4, 17.1]	1.6 [0.2, 11.2]	3.3 [0.8, 13.1]	6.5 [2.1, 20.2]	3.7 [1.9, 7.0]	1.2 [0.4, 3.7]	2.6 [1.6, 4.2]	2.0 [0.8, 5.5]	1.4 [1.0, 1.9]	1.5 [1.1, 2.0]

Number of patients with adverse events, n (%). Incidence rate, per 100 person-year [95% CI].
a) Including the occurrence after switching from placebo to peficitinib.

Table 88. Renal dysfunction-related events occurring in ≥2 patients in any groups in the pooled data from phase III studies

	Pooled data from phase III studies (Weeks 0 to 12)					Pooled data from phase III studies (entire period)			
	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Peficitinib 100 mg + 150 mg (n = 554)	Placebo (n = 271)	ETN (n = 200)	Peficitinib 100 mg (n = 278)	Peficitinib 150 mg (n = 276)	Peficitinib 100 mg + 150 mg (n = 554)	ETN (n = 200)
Renal dysfunction	1 (0.4)	0	1 (0.2)	0	0	3 (1.1)	2 (0.7)	5 (0.9)	1 (0.5)
Blood creatinine increased	1 (0.4)	0	1 (0.2)	1 (0.4)	1 (0.5)	3 (1.1)	0	3 (0.5)	1 (0.5)
Proteinuria	1 (0.4)	0	1 (0.2)	1 (0.4)	0	2 (0.7)	0	2 (0.4)	0
Protein urine present	1 (0.4)	1 (0.4)	2 (0.4)	0	2 (1.0)	1 (0.4)	1 (0.4)	2 (0.4)	2 (1.0)

Number of subjects (%)

Changes over time from baseline in serum creatinine levels in the phase III studies are shown in Table 89. Changes in serum creatinine levels tended to be greater in the peficitinib groups than in the placebo group.

Table 89. Changes over time from baseline in serum creatinine levels (μmol/L) in phase III studies

Study	Study CL-RAJ3				Study CL-RAJ4		
Study drug	Peficitinib 100 mg	Peficitinib 150 mg	Placebo	ETN	Peficitinib 100 mg	Peficitinib 150 mg	Placebo
Week 12	3.90 ± 6.26 (102)	5.40 ± 6.60 (101)	−0.25 ± 5.32 (100)	3.54 ± 7.18 (200)	4.73 ± 4.61 (172)	5.24 ± 6.61 (171)	−0.13 ± 5.19 (169)
Week 52 or discontinuation	4.47 ± 7.57 (102)	8.39 ± 6.54 (101)		4.24 ± 7.46 (200)	7.31 ± 5.46 (172)	9.13 ± 7.93 (171)	

Mean ± standard deviation (number of subjects). Normal range of serum creatinine: 53.9 to 91.9 μmol/L in men and 41.5 to 69.8 μmol/L in women.

The incidence of increased serum creatinine in each category in the phase III studies (entire period) is shown in Table 90. Extremely few patients experienced increased serum creatinine levels to >3 times the upper limit of the normal range.

Table 90. Occurrence of blood creatinine (maximum) by category in phase III studies (entire period)

		Peficitinib 100 mg	Peficitinib 150 mg	Peficitinib 100 mg + 150 mg	ETN
Study CL-RAJ3					
Creatinine	>1.5 × BL and ≤3.0 × BL	2/104 (1.9)	1/102 (1.0)	3/206 (1.5)	5/200 (2.5)
	>3.0 × BL	0/104	0/102	0/206	0/200
Study CL-RAJ4					
Creatinine	>1.5 × BL and ≤3.0 × BL	8/174 (4.6)	13/173 (7.5)	21/347 (6.1)	−
	>3.0 × BL	1/174 (0.6)	1/173 (0.6)	2/347 (0.6)	−

Number of patients meeting the criteria/number of subjects evaluated (%)

As discussed, despite the tendency for gradual elevation in the mean serum creatinine level in patients receiving peficitinib, an increase to >3 times the baseline was seen in few patients. The incidence of renal disorder-related adverse events in the peficitinib group did not markedly differ from that in the placebo or ETN group in the clinical studies. Increased serum creatinine in association with peficitinib therapy is thus clinically insignificant.

PMDA's view:
The applicant's explanation is generally acceptable. However, the clinical studies had with renal function test-based exclusion or interruption/discontinuation criteria t.[39)] Patients with RA may receive peficitinib with concomitant MTX or an NSAID, which may pose a risk of renal dysfunction, and it cannot be ruled out that the risk of renal dysfunction is increased by peficitinib therapy in these patients. Therefore, relevant data including those from published literature should continue to be collected in the post-marketing setting.

PMDA's view on the safety of peficitinib based on the review in the sections 7.R.3.1 and 7.R.3.2:
In light of submitted clinical study data and the pharmacological effects of peficitinib, the use of peficitinib in patients with RA requires close attention to the possible serious infections including opportunistic infection, tuberculosis, and herpes zoster, malignant tumors, gastrointestinal perforation, interstitial lung diseases, cytopenia, lipids abnormal, and hepatic dysfunction. Peficitinib is accompanied by adverse events which are observed in the use of JAK inhibitors (tofacitinib and baricitinib) of the same class. Accordingly, adverse events can be managed during peficitinib therapy when it is used by physicians with adequate knowledge about peficitinib and knowledge and experience in pharmacotherapy for RA, with the same cautionary advice given for the use of the JAK inhibitors of similar type.

The above conclusion by PMDA on the safety profiles of peficitinib will be discussed at the Expert Discussion.

7.R.4 Clinical positioning

The applicant's explanation about the expected clinical positioning of peficitinib:
With the advance in diagnosis and treatment of RA, treat-to-target (T2T) principles, which aim to achieve not only clinical remission but also structural and functional remission by sufficiently inhibiting joint damage at an early stage, are recommended as the core therapeutic strategies in the Japanese, US, and European guidelines. The positioning of JAK inhibitors in the T2T-based treatment algorithm has changed since the market launch of tofacitinib as the first JAK inhibitor in Japan in 2013. In the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis (*Ann Rheum Dis*. 2014;73:510-5) and the Clinical Practice Guidelines for Rheumatoid Arthritis of the Japan College of Rheumatology published in 2014, JAK inhibitors were described as an option for inadequate responders to ≥1 biologics. With the accumulation of evidence for JAK inhibitors including long-term data, the 2015 ACR Guideline for the Treatment of Rheumatoid Arthritis (*Arthritis Care Res*. 2016;68:1-25) and the 2016 update of the EULAR recommendations (*Ann Rheum Dis*. 2017;0:1-18) basically recognize JAK inhibitors as equivalent to biologics, recommending them as an option

[39)] Studies CL-RAJ3 and CL-RAJ4: exclusion criteria, estimated glomerular filtration rate (estimated by MDRD method) of ≤40 mL/min; interruption or discontinuation criteria, serum creatinine levels of >150% of baseline at 2 consecutive measurements at scheduled visits.

for inadequate responders to cDMARDs with poor prognostic factors such as high autoantibodies or high disease activity or inadequate responders to ≥2 cDMARDs.

Based on these RA clinical practice guidelines, the efficacy and safety of peficitinib were evaluated mainly with data from the phase III studies (Studies CL-RAJ3 and CL-RAJ4) conducted in RA patients with inadequate response to cDMARDs including MTX, who are eligible for treatment with JAK inhibitors. As shown in Sections 7.R.2 and 7.R.3, peficitinib 100 and 150 mg were effective as compared to placebo and was acceptably tolerated. Although no confirmatory clinical study was performed in RA patients with inadequate response to biologics, results of a subset analysis in the phase III studies [see Section 7.R.2.1] suggest a certain degree of efficacy of peficitinib regardless of previous biologic therapies, with no marked differences in the safety profiles. Another subset analysis was conducted in phase III studies (Studies CL-RAJ3 and CL-RAJ4) by concomitant drug [see Section 7.R.2.1], and the results suggest that peficitinib has a certain degree of efficacy by itself or in combination with cDMARDs other than MTX or with oral steroids. As shown in Section 7.R.3, lymphopenia, neutropenia, and hepatic dysfunction-related adverse events tended to occur more frequently in the use of peficitinib with MTX. However, patients who experienced other events showed no marked differences in the safety profiles regardless of whether or what type of concomitant drug was used.

As discussed above, peficitinib is expected to offer a therapeutic option for RA patients with inadequate response to conventional therapies when used alone or in combination with cDMARDs including MTX, as with approved biologics and JAK inhibitors. The use of peficitinib with biologics or other JAK inhibitors was not allowed in the clinical studies, and thus no data are referable for the concomitant use of peficitinib and these medications. Therefore, the package insert, etc. of peficitinib will advise that its concomitant use with biologics or other JAK inhibitors be avoided.

PMDA's view:
In view of currently available data on the study population and the efficacy and safety profiles of peficitinib, it is reasonable to recognize peficitinib as a therapeutic option for RA patients with inadequate response to cDMARDs such as MTX, as with approved biologics and JAK inhibitors.

Peficitinib is considered to have risks similar to those of JAK inhibitors and biologics for the treatment of RA, and there is no experience in the concomitant use of peficitinib with biologics or JAK inhibitors in the clinical studies. As practiced for the approved biologics and JAK inhibitors, the package insert, etc. of peficitinib should advise that its concomitant use with biologics or JAK inhibitors be avoided. Peficitinib should not be used casually just because being an oral agent, and it should be used only at medical institutions capable of coping with serious infections and only at the decision of physicians with adequate knowledge and experience in pharmacotherapy for RA. Physicians should decide the suitability of peficitinib therapy with due consideration of the benefit-risk balance both in peficitinib and conventional therapies, and according to the treatment history, poor prognostic factors, and other characteristics of individual patients. This should be communicated to healthcare professionals.

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

7.R.5 Indications

PMDA's view:

On the basis of the reviews of the submitted data and the consideration described in the sections 7.R.2, 7.R.3, and 7.R.4, the proposed indication of "rheumatoid arthritis (including prevention of structural joint damage) in patients who have an inadequate response to conventional therapies" is acceptable. The "Precautions for Indications" section of the package insert should warn that peficitinib be used for patients who have obvious residual symptoms attributable to RA despite previous appropriate treatment with antirheumatics.

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

7.R.6 Dosage and administration

Initially, the proposed dosing regimen was "The usual adult dosage is 100 to 150 mg of peficitinib administered orally once daily after a meal. The dose can be reduced to 50 mg per dose according to the patient's condition." Later, the applicant explained that the description in the "Dosage and Administration" section should be revised to "The usual adult dosage is 150 mg of peficitinib administered orally once daily after a meal. A 100-mg dose may be administered once daily according to the patient's condition." because of the reasons shown below.

The superior efficacy of peficitinib 100 and 150 mg over placebo was proven in the phase III studies (Studies CL-RAJ3 and CL-RAJ4), as discussed in 7.R.1. Generally, peficitinib 150 mg tended to be more effective than peficitinib 100 mg for the primary and other endpoints at all evaluation time points.

As discussed in 7.R.3.2, available safety data demonstrate a tendency toward a dose-dependent increase in the risk of some adverse events related to abnormal test values for blood cells, hepatic function, renal function, lipid, and muscle enzymes. However, the safety profiles of peficitinib 100 and 150 mg are acceptable in RA patients, suggesting no obvious clinically significant risks.

In recent years, the recommended RA treatment strategy focuses on the achievement of remission or low disease activity as soon as possible (*Ann Rheum Dis*. 2010; 69: 964-75). In view of this, the dose of 150 mg is the appropriate recommended dose of peficitinib. However, in light of a dose-dependent tendency in the incidences of abnormality in hepatic function test, hepatic disorder-related adverse events, and decreased peripheral neutrophil count, the dose of 100 mg should also be made available for patients at a higher risk of hepatic dysfunction or elderly ones at a higher risk of infections, etc., to be selected according to the condition of patients.

Meanwhile, in a long-term treatment study (Study CL-RAJ2), the initial dose was 50 mg for patients from Study CL-RAJ1 and 100 mg for patients from Studies CL-RAJ3 or CL-RAJ4, and the dose could be increased up to 150 mg for inadequate responders who had no safety concerns or decreased to 50 mg for those with safety

concerns. Among 843 patients who continued with Study CL-RAJ2, the percentage of patients classified by highest dose and previous study was 4.6% for 50 mg (39 patients from Study CL-RAJ1), 66.5% for 100 mg (561 patients; 104 from Study CL-RAJ1, 160 from Study CL-RAJ3, and 297 from Study CL-RAJ4;), and 28.8% for 150 mg (243 patients; 58 from Study CL-RAJ1, 65 from Study CL-RAJ3, and 120 from Study CL-RAJ4).

The ACR20 responder index (FAS) at baseline and the last administration by highest dose (with last observation carried forward: LOCF) was 38.5% (15 of 39 patients) and 71.8% (28 of 39 patients), respectively, for 50 mg, 77.4% (428 of 553 of patients) and 83.6% (464 of 555 patients), respectively, for 100 mg, and 63.8% (155 of 243 patients) and 69.1% (168 of 243 patients), respectively, for 150 mg. The long-term efficacy of peficitinib was maintained in many patients receiving the drug at 100 mg, suggesting the efficacy tended to be enhanced by a dose increase in patients requiring it to 150 mg. Meanwhile, 4.7% (40 of 843) of patients required a dose reduction to 50 mg. Of the 40 patients, 8 discontinued peficitinib after dose reduction, 21 had their dose increased back to 100 or 150 mg, and 19 continued to receive the 50 mg dose until the cutoff point or the discontinuation. In view of the fact that peficitinib could be continued and was still effective after a dose reduction to 50 mg in some patients, it could be a therapeutic option to continue peficitinib at a reduced dose to 50 mg in patients with problems with tolerability.

The exposure after administration of peficitinib 50 mg in RA patients with moderate hepatic impairment is estimated to be similar to that after administration of peficitinib 100 mg in RA patients with normal hepatic impairment. Therefore, it was decided that the package insert of peficitinib would include precautionary advice that RA patients with moderate hepatic impairment should be treated with peficitinib 50 mg once daily [see Section 6.R.2].

Accordingly, the following dosing regimen was proposed: “The usual adult dosage is 150 mg of peficitinib administered orally once daily after a meal. A dose of 100 mg can be administered once daily depending on the patient’s condition.” Furthermore, the “Precautions for Dosage and Administration” section of the package insert should advise that a dose reduction to 50 mg once daily or any appropriate measures be taken for patients with intolerance to the dose given.

PMDA’s view:
As shown in the sections 7.R.2 and 7.R.3, peficitinib was demonstrated to be superior both at 100 and 150 mg to placebo in the primary endpoint, and peficitinib tended to be more effective at 150 mg than at 100 mg in other efficacy endpoints at all evaluation time points. The currently available data show that the safety profiles of peficitinib 100 and 150 mg are acceptable in RA patients. The current RA treatment strategy recommends to relieve arthritis symptoms as soon as possible to induce remission, and to achieve long-term sustained remission (*Clinical Practice Guidelines for Rheumatoid Arthritis 2014*), aiming to achieve remission or low disease activity as soon as possible (*Ann Rheum Dis*. 2010;69:964-75). In light of this situation, peficitinib 150 mg can be selected as the recommended clinical dose for RA patients with inadequate response to conventional therapies.

Meanwhile, dose-dependent changes in laboratory data were observed in the pooled data from phase III studies, although the incidence of these changes did not exceed that in the conventional therapies. Therefore, the possibility cannot be ruled out that the risk of adverse events including serious infections may increase in a dose-dependent manner. In addition, because of the limited data on long-term treatment, it cannot be ruled out that the risk of adverse drug reactions may potentially increase with the long-term administration of peficitinib.

Because the efficacy of peficitinib was markedly lower at 50 mg than at 150 or 100 mg in Study CL-RAJ1, the continuation of peficitinib therapy at the reduced dose of 50 mg is not an appropriate option for patients with safety concerns, and an alternative therapeutic option without using peficitinib should be considered.

Accordingly, the administration of peficitinib 100 mg is acceptable depending on the condition of patients, such as the condition and disease activities of patients at a higher risk of adverse drug reactions or those who may have higher systemic exposure [see Section 7.R.3]. Based on the discussion in Section 6.R.2, the administration of peficitinib 50 mg once daily is acceptable for RA patients with moderate hepatic impairment.

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

7.R.7 Post-marketing safety measures

The applicant plans to conduct post-marketing surveillance to confirm the safety profiles of peficitinib including long-term safety in all patients treated with peficitinib in the post-marketing setting. Through the surveillance, data on the occurrence of malignant tumors and serious infections will be collected so as to further evaluate the safety of peficitinib in a way that allows comparison with appropriate external controls.

PMDA's view:

As discussed in Section 7.R.3, the available clinical study data show acceptable safety of peficitinib. However, in light of its action mechanism and safety profiles observed in clinical studies, serious infections or serious events such as malignant tumors may occur in long-term use of peficitinib, as with other JAK inhibitors. Peficitinib is expected to be used in long-term treatment, and a relationship between the risk of infections and malignant tumors and long-term inhibition of JAK signal transduction has not been clarified. Therefore, as with the approved JAK inhibitors, post-marketing surveillance should be performed involving all patients treated with peficitinib to evaluate the long-term safety profiles of peficitinib so that the safety profiles of peficitinib including unknown adverse events should be elucidated early. It is important that the safety of peficitinib be further carefully evaluated in a way that allows comparison with appropriate external controls.

The use of peficitinib involves safety measures that have been taken for approved JAK inhibitors and biologics as well, including clear communication of the following cautionary advice: peficitinib must be used under the supervision of physicians with adequate knowledge about the drug and have knowledge and experience in treatment of RA; serious infections or malignant tumors may occur in association with peficitinib; and screening for infection with tuberculosis and hepatitis B virus should precede peficitinib therapy.

Furthermore, because of its effects on embryos and fetuses observed in its toxicity studies, peficitinib should be contraindicated in pregnant women or possibly pregnant women. Women of childbearing potential should be advised to use effective contraception during the treatment with peficitinib and a certain period after the completion of the treatment [see Section 5.R.2].

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

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

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

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

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

The new drug application data (CTDs 5.3.5.1-1, 5.3.5.1-2, 5.3.5.1-3, and 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. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following room for improvement at some study sites, although no significant impact on the overall assessment of the studies. The heads of the medical institutions were notified of this matter.

Findings requiring corrective action

Study sites

・Misconduct in the study drug management (Study drugs were stored at an unspecified temperature and used without checking whether they were usable.)

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

On the basis of the data submitted, PMDA has concluded that peficitinib is proven to have efficacy in RA patients with inadequate response to conventional therapies and that peficitinib has acceptable safety in view of its benefits. However, in light of the efficacy and safety profiles observed in the clinical studies and the potential risks related to its pharmacological activity, any of other options than peficitinib should be chosen for RA patients who are expected to respond to the conventional therapies. Peficitinib provides a new therapeutic option for RA patients with inadequate response to the conventional therapies, which is of clinical significance.

Because of the concerns of possible serious adverse drug reactions such as infections and malignant tumors, the applicant should take similar safety measures to those taken for biologics for RA or drugs of the same class (e.g., tofacitinib and baricitinib). The safety and efficacy of peficitinib, including those in a long-term, should be further investigated via the post-marketing surveillance.

PMDA has concluded that peficitinib may be approved if peficitinib is not considered to have any particular problems based on comments from the Expert Discussion, on the premise that the above safety measures are followed.

10. Other

The main efficacy evaluation parameters used in the Japanese phase III study (Study CL-RAJ4) and the global phase III study (Study CL-RAJ3) are tabulated below.

Items	Definition
ACR20, 50, or 70 responder index	ACR20, 50, or 70 responder index is a percentage of patients who have achieved a decrease by ≥20%, 50%, or 70% in (1) and (2) and with an improvement by ≥20%, 50%, or 70% in ≥3 items of (3) to (7) in the seven-item core data set of the ACR: (1) tender joint count (TJC) in 68 joints; (2) swollen joint count (SJC) in 66 joints, assessed with the 0 to 100 mm VAS; (3) subject's pain assessment; (4) subject's global assessment (SGA); (5) physician's global assessment (PGA); (6) assessment of daily living activities (HAQ-DI: a questionnaire for evaluation of RA specific health); and (7) acute phase reactants (C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR]).
DAS28	The disease activity score (DAS) 28 consists of components of TJC and SJC in 28 joints, SGA assessed with the 0 to 100 mm VAS, and inflammatory phase reactants (either CRP [mg/L] or ESR [mm/h]) and is calculated by the following equation to evaluate the disease activity. DAS28-CRP = $0.56\sqrt{\mathrm{TJC}} + 0.28\sqrt{\mathrm{SJC}} + 0.36\{\ln(\mathrm{CRP}+1)\} + 0.014 \times \mathrm{SGA} + 0.96$ DAS28-ESR = $0.56\sqrt{\mathrm{TJC}} + 0.28\sqrt{\mathrm{SJC}} + 0.70\{\ln(\mathrm{ESR})\} + 0.014 \times \mathrm{SGA}$ The disease activity assessed by the DAS28 score is defined as follows: >5.1, high disease activity; >3.2 and ≤5.1, moderate disease activity; ≥2.6 and ≤3.2, low disease activity; and <2.6, remission.
HAQ-DI	The health assessment questionnaire disability index (HAQ-DI) is a questionnaire for the assessment of physical function concerning 8 categories relevant to daily activities of RA patients (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities) and is calculated from patient's assessment on the degree of difficulty (0 to 3). The higher is the score, the more severe is the physical dysfunction.
mTSS	The modified total Sharp score (mTSS) is the sum of the bone erosion score and the joint space narrowing score to evaluate structural joint damage. The degrees of bone erosion in 44 joints and the joint space narrowing in 42 joints are assessed and quantified based on hand/wrist and feet radiograms. The higher the score is, the more severe the joint damage is.
SDAI	The simplified disease activity index (SDAI) score consists of components of TJC and SJC in 28 joints, global assessment converted to the 10 cm VAS (SGA and PGA), and CRP levels (mg/dL) and is calculated by the formula shown below to evaluate the disease activity. SDAI = TJC + SJC + SGA + PGA + CRP

	The disease activity assessed by SDAI is defined as follows: >26, high disease activity; >11 and ≤26, moderate disease activity; >3.3 and ≤11, low disease activity; and ≤3.3, remission.
ACR/EULAR remission	Meeting all of the following: TJC ≤1, SJC ≤1, CRP (mg/dL) ≤1, and SGA ≤10 mm.

VAS: Visual analog scale

Review Report (2)

February 14, 2019

Product Submitted for Approval

Brand Name	Smyraf Tablets 50 mg, Smyraf Tablets 100 mg
Non-proprietary Name	Peficitinib Hydrobromide
Applicant	Astellas Pharma Inc.
Date of Application	May 31, 2018

List of Abbreviations

See Appendix

1. Content of the Review

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

1.1 Efficacy, clinical positioning, and indication

At the Expert Discussion, the expert advisors supported PMDA's conclusion on the efficacy, clinical positioning, and indication of the product presented in the Review Report (1).

1.2 Dosage and administration

At the Expert Discussion, the expert advisors generally supported PMDA's conclusion on the dosage and administration of the product presented in the Review Report (1). The following comments were raised from the expert advisors.

- Data from Studies CL-RAJ3 and CL-RAJ4 and other studies suggest that peficitinib is more effective at 150 mg than at 100 mg. In light of the current treatment strategies for RA, the usual dose of peficitinib should be 150 mg once daily.
- Since peficitinib 100 mg is expected to be effective in some patients, it is meaningful that a once-daily dose of peficitinib 100 mg be made available for patients with a certain condition, including concurrent diseases such as hepatic impairment, age, and disease activities.

  Following treatment with peficitinib 150 or 100 mg, the incidence of adverse events such as serious infections including herpes zoster showed no evident dose-dependency. However, given a dose-dependent tendency suggested in the incidence of hepatic dysfunction or changes in laboratory test

data, a dose reduction to 100 mg for patients who responding to peficitinib 150 mg may be an option to consider.

The exposure to peficitinib in subjects with moderate hepatic impairment receiving peficitinib 50 mg was similar to that in subjects with normal hepatic function receiving peficitinib 100 mg. The results indicate that a once-daily dose of peficitinib 50 mg can be recommended for RA patients with moderate hepatic impairment.

At the same time, the efficacy and safety of peficitinib 50 mg have not been evaluated in RA patients with moderate hepatic impairment. In these patients, an exposure level equivalent to that in RA patients with normal hepatic function receiving peficitinib 150 mg is expected to be achieved at the dose of 75 mg, but such formulation is not available for administration. In the current situation where there are other therapeutic options recognized as clinically comparable to peficitinib, advising the use of other options is an alternative to consider for RA patients with moderate hepatic impairment.

PMDA's view:

The usual dose of peficitinib for patients with normal hepatic function should be 150 mg. The option of 100 mg-dose should also be made available according to the patient's condition.

In response to the comments from the expert advisors, the "Precautions for Dosage and Administration" section of the package insert should give the following cautionary advice on the use of peficitinib in RA patients with moderate hepatic impairment: peficitinib may be administered to RA patients with moderate hepatic impairment at a dose of 50 mg, which is considered equivalent to 100 mg for RA patients with normal hepatic function. However, the need of peficitinib therapy should be carefully examined and determined with due understanding of the pharmacokinetics, efficacy, and safety of peficitinib based on the data from the clinical studies, etc.

Since no data on the efficacy and safety of peficitinib in RA patients with moderate hepatic impairment are available, the efficacy and safety data of these patients should be collected via a specified drug use-results survey planned to be conducted in all patients receiving peficitinib in the post-marketing setting.

The above PMDA's view was communicated to the applicant, and the applicant agreed to take actions accordingly.

1.3 Safety and risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusion on the safety and post-marketing safety measures for the product presented in the Review Report (1), and the following comments were raised from the expert advisors.

- Currently available data indicate that the safety profiles of peficitinib are similar to those of approved biologics and JAK inhibitors of the same class. However, in its clinical use, peficitinib is expected to inhibit not only JAK1, JAK2, and JAK3 activities but also TYK2 activity, the long-term safety of

peficitinib should be carefully investigated further via post-marketing surveillance encompassing all patients treated with peficitinib.

- Increased CPK level, although known in the use of the JAK inhibitors of the same class, exceeded >10 times the upper limit of the normal range in some patients in the clinical studies. Therefore, the occurrence of rhabdomyolysis and myopathy should be further investigated via post-marketing surveillance.

In view of the review presented in the section "7.R.7 Post-marketing safety measures" in the Review Report (1) and comments from the expert advisors at the Expert Discussion, PMDA has concluded that the current risk management plan (draft) for peficitinib should include the safety and efficacy specifications presented in Table 91 and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in the Table 92. PMDA instructed the applicant to conduct post-marketing surveillance, etc. so that these specifications and activities are investigated.

Table 91. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
·Decreased neutrophils, decreased lymphocytes, and decreased hemoglobin ·Serious infections (including tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, and opportunistic infection) ·Herpes zoster ·Gastrointestinal perforation ·Interstitial pneumonia ·Reactivation of hepatitis B virus ·Hepatic dysfunction	·Malignant tumors ·Cardiovascular events ·Rhabdomyolysis, Myopathy	None
Efficacy specification		
None		

Table 92. Summary of additional pharmacovigilance activities, survey/study on efficacy, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Survey/study on efficacy	Additional risk minimization activities
·Early post-marketing phase vigilance ·Specified drug use-results survey (all-case surveillance) ·Post-marketing database surveillance (serious infections) ·Post-marketing database surveillance (malignant tumors) ·Post-marketing clinical study [a)]	None	·Information provision by the early post-marketing phase vigilance ·Preparation and distribution of materials for healthcare professionals. ·Preparation and distribution of materials for patients ·Secure provision of information on the proper use of peficitinib before delivery

a) An extension study (Study CL-RAJ2) is planned to be conducted as a post-marketing clinical study after marketing approval of peficitinib.

The applicant's explanation:

As shown in Table 93, a specified drug use-results survey will be conducted with observation of up to 3 years in all patients receiving peficitinib until data on the specified number of peficitinib-treated patients (a target sample size of 3000) are collected, to confirm the safety and efficacy of peficitinib in routine use. Malignant tumors and adverse events resulting in death will be followed up to 3 years after the start of peficitinib therapy, regardless of the continuation or discontinuation of the therapy, to further evaluate long-term safety. The risk

of malignant tumors and serious infections associated with peficitinib therapy will be evaluated and compared by using the Medical Information Database.

Table 93. Outline of the plan of specified drug use-results survey (draft)

Objective	To confirm the safety and efficacy of peficitinib in routine use.
Survey method	All-case surveillance
Population	RA patients with inadequate response to conventional therapies
Observation period	Up to 3 years
Planned sample size	3,000 patients
Main survey items	·Safety specification: Decreased neutrophils, decreased lymphocytes, decreased hemoglobin, herpes zoster, serious infections (including tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, opportunistic infection), gastrointestinal perforation, interstitial pneumonia, reactivation of hepatitis B virus, hepatic dysfunction, malignant tumors, cardiovascular events, rhabdomyolysis, and myopathy. ·Patient characteristics (including body weight, age, severity, disease duration, medical history ·concurrent diseases) ·Status of treatment with peficitinib ·Prior treatment of RA ·Concomitant drugs and therapies ·Laboratory tests ·Adverse events ·Efficacy evaluation

PMDA accepted the applicant's response. PMDA considers that updated safety information including the occurrence of malignant tumors and serious infections should be provided by the applicant whenever available, through written materials and their website so that healthcare professionals and patients are informed promptly and appropriately. The methodology of information gathering in the Medical Information Database-based survey should be discussed further in detail, and the survey should be conducted on a basis of an appropriate plan.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and the dosage and administration shown below that are modified from the proposed ones, and with the following conditions.

The product is a drug with a new active ingredient, thus the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

Treatment of rheumatoid arthritis (including prevention of structural joint damage) in patients who have an inadequate response to conventional therapies.

Dosage and Administration

The usual adult dosage is ~~100 to~~ 150 mg of peficitinib administered orally once daily after a meal. A 100-mg dose may be administered once daily~~The dose can be reduced to 50 mg per dose~~ according to the patient's condition.

(Underline denote addition and strikethrough deletions.)

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a drug use-results survey covering all patients treated with the product after its market launch until data from a certain number of patients have been accumulated, to early collect the safety and efficacy data on the product and to take necessary measures to facilitate the proper use of the product.

Appendix

List of Abbreviations

abatacept	abatacept (genetical recombination)
ACR	American College of Rheumatology
ACRxx% Responder Index xx: 20, 50, 70	American College of Rheumatology 20, 50, 70 responder index
adalimumab	adalimumab (genetical recombination)
A/G ratio	albumin/globulin ratio
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
AUC_{inf}	AUC up to infinity
AUC_{last}	AUC up to the last time point with a measurable concentration after dosing
AUC_t	AUC up to the final sampling time
BCRP	breast cancer resistance protein
BID	twice daily
cDMARDs	conventional disease modifying anti-rheumatic drugs
certolizumab pegol	certolizumab pegol (genetical recombination)
CL	clearance
CL/F	apparent total body clearance
CL_{tot}	total body clearance
C_{max}	maximum plasma concentration
CRP	C-reactive protein
CYP	cytochrome P450
GM-CSF	granulocyte macrophage colony -stimulating factor
CPK	creatine phosphokinase
DDI	drug-drug interaction
eGFR	estimated glomerular filtration rate
ETN	etanercept
EULAR	European League Against Rheumatism
FAS	full analysis set
HBV	hepatitis B virus
HDL	high density lipoprotein
HPLC	high performance liquid chromatography
IC_{50}	half maximal inhibitory concentration
IFN	interferon
IL	interleukin
IR	infrared absorption spectrum
JAK	Janus kinase
JCR	Japan College of Rheumatology
JP	Japanese Pharmacopoeia
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LEP	linear Extrapolation
LIF	leukemia inhibitory factor
LOCF	last observation carried forward
MMF	mycophenolate mofetil
MRP	multidrug resistance-associated protein
mTSS	modified total sharp score
MTX	methotrexate
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Event
NK cell	natural killer cell
NMR	nuclear magnetic resonance spectrum

NMSC	nonmelanoma skin cancer
NMT	N-methyltransferase
NNMT	nicotinamide N-methyltransferase
NSAIDs	non-steroidal anti-inflammatory drugs
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PBMC	peripheral blood mononuclear cell
peficitinib	peficitinib hydrobromide
P-gp	p-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
QbD	quality by design
QD	once daily
SEER	surveillance epidemiology and end result
SIR	standardized incidence rate
SMQ	standard MedDRA Queries
STAT	signal transducer and activator of transcription
SULT	sulfotransferase
t_{max}	time to reach maximum plasma concentration
TNF	tumor necrosis factor
tofacitinib	tofacitinib citrate
TYK2	tyrosine kinase 2
$t_{1/2}$	elimination half-life
RA	rheumatoid arthritis
RH	relative humidity
RTRT	real time release testing
V_{ss}	steady-state distribution volume
Vz/F	apparent volume of distribution during the terminal phase