Report on the Deliberation Results

September 10, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Cibinqo Tablets 50 mg, Cibinqo Tablets 100 mg, Cibinqo Tablets 200 mg
Non-proprietary Name	Abrocitinib (JAN*)
Applicant	Pfizer Japan Inc.
Date of Application	December 9, 2020

Results of Deliberation

In its meeting held on September 6, 2021, 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.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

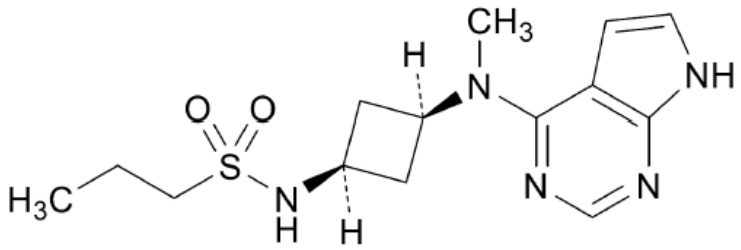
Review Report

August 26, 2021
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Cibinqo Tablets 50 mg, Cibinqo Tablets 100 mg, Cibinqo Tablets 200 mg
Non-proprietary Name	Abrocitinib
Applicant	Pfizer Japan Inc.
Date of Application	December 9, 2020
Dosage Form/Strength	Tablets each containing 50, 100, or 200 mg of Abrocitinib
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{14}H_{21}N_5O_2S$

Molecular weight: 323.41

Chemical name: *N*-{*cis*-3-[methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]cyclobutyl}propane-1-sulfonamide

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 atopic dermatitis in patients with an inadequate response to conventional treatments, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. Adequate safety measures should be taken to address possible serious adverse drug reactions such as serious infections and malignancies in the clinical use

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of the product, as practiced with existing oral Janus kinase inhibitors for atopic dermatitis. The safety and efficacy of the product should be further investigated in clinical practice via post-marketing surveillance etc.

Indication

Atopic dermatitis in patients who have had an inadequate response to conventional treatments

Dosage and Administration

The usual dosage for adults and adolescents aged 12 years and older is 100 mg of abrocitinib administered orally once daily. A dose of 200 mg once daily may be given according to the patient's condition.

Approval Condition

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

Attachment

Review Report (1)

August 13, 2021

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

Product Submitted for Approval

Brand Name	Cibinqo Tablets 50 mg, Cibinqo Tablets 100 mg, Cibinqo Tablets 200 mg
Non-proprietary Name	Abrocitinib
Applicant	Pfizer Japan Inc.
Date of Application	December 9, 2020
Dosage Form/Strength	Tablets each containing 50, 100, or 200 mg of Abrocitinib

Proposed Indication

Atopic dermatitis in patients who have had an inadequate response to conventional treatments (including improvement in itch)

Proposed Dosage and Administration

The usual dosage for adults and adolescents aged 12 years and older is 100 or 200 mg of abrocitinib administered orally once daily.

Table of Contents

List of Abbreviations

See Appendix.

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

Cibinqo Tablets 50 mg, Cibinqo Tablets 100 mg, and Cibinqo Tablets 200 mg (the product) contain the active substance Abrocitinib (abrocitinib). Abrocitinib is a Janus kinase (JAK) inhibitor discovered by Pfizer Inc. (the US).

Atopic dermatitis (AD) is a disease characterized by relapsing eczema with pruritus as a primary lesion. Treatment of AD basically consists of drug therapy, topical therapy/skin care for physiological abnormalities in the skin, and investigations/elimination of exacerbating factors, based on the symptoms and characteristics of individual patients, etc. (AD clinical practice guidelines 2018). Drug therapy for AD is basically the management with topical anti-inflammatory agents such as topical corticosteroids (TCS) and tacrolimus (a topical calcineurin inhibitor [TCI]) under continuous use of emollients. If patients have responded inadequately to these topical therapies, intermittent oral cyclosporin, and the use of oral corticosteroids to induce the remission of acute exacerbation or severe/the most severe conditions will also be considered. In recent years, a monoclonal antibody to the interleukin (IL)-4 receptor α subunit, dupilumab (genetical recombination), and a JAK inhibitor, baricitinib, have been approved for the indication of atopic dermatitis in patients who have had an inadequate response to conventional treatments and have become new systemic therapy options.

Multiple cytokines are involved in the pathophysiology of AD, including IL-4, IL-13, IL-22, IL-31, and thymic stromal lymphopoietin (TSLP). Since abrocitinib inhibits the Janus kinase–signal transducers and activators of transcription (JAK-STAT) pathway, which is involved in the transduction of signals mediated by these cytokines, abrocitinib was developed with an expectation of its therapeutic effects for AD.

The clinical development of abrocitinib began in [redacted] 20[redacted], and a marketing application has been submitted based on the results from global studies involving Japan, etc. Outside Japan, US and EU applications are under review as of [redacted] 20[redacted].

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

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to pale-purple or pale pink powder. Its appearance, solubility, hygroscopicity, thermal analysis (differential scanning calorimetry, thermogravimetric analysis), dissociation constant, partition coefficient, and crystalline form (X-ray powder diffraction) have been determined.

Its chemical structure has been elucidated by ultraviolet-visible spectroscopy, infrared spectrophotometry (IR), nuclear magnetic resonance spectrometry (NMR) (^{1}H- and ^{13}C-NMR), mass spectrometry, single crystal X-ray crystallography, and X-ray powder diffraction.

2.1.2 Manufacturing process

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

A Quality by Design (QbD) approach was used. A quality control strategy was established based on the following etc. (Table 1).

● Identification of critical quality attributes (CQAs)

● Identification of critical process parameters (CPPs) through quality risk assessment and design of experiments

Table 1. Overview of drug substance control strategy

CQA	Method of control
Identity	Specification
Content	Manufacturing process, Specification
[redacted]	Manufacturing process, Specification
Organic impurities (related substances, residual solvents)	Manufacturing process, Specification
Residue on ignition	Manufacturing process, Specification
[redacted]	Manufacturing process

[redacted] has been defined as a critical step. [redacted] and [redacted] are controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance consist of content, appearance, identity (IR), purity [related substances (high performance liquid chromatography [HPLC]), residual solvents (gas chromatography [GC])], residue on ignition, [redacted], and assay (HPLC).

2.1.4 Stability of drug substance

The primary stability studies on the drug substance are shown in Table 2. The stability results indicated that the drug substance is stable. Photostability data showed that the drug substance is photostable.

Table 2. Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 pilot-scale batches	30℃	75%RH	double polyethylene bags + high-density polyethylene drum	12 months
Accelerated	3 pilot-scale batches	40℃	75%RH		6 months

Based on the above, a re-test period of 24 months was proposed for the drug substance when stored in double polyethylene bags within a high-density polyethylene drum at room temperature, in accordance with "Guideline on Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3, 2003). The long-term testing will be continued up to 36 months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is immediate-release film-coated tablets containing 50, 100, or 200 mg of abrocitinib and the following excipients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, magnesium stearate, and Opadry II Pink ([redacted]).

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of material feeding, mixing, tablet compression, film-coating, and packaging/labeling. The material feeding, mixing, and tablet compression steps are performed in a continuous manufacturing process, and the subsequent film-coating process is performed as a batch process. [redacted], [redacted], and [redacted] have been defined as critical steps, and process control items and values have been established.

A QbD approach was used. A quality control strategy was established based on the following etc. (Table 3).

- Identification of CQAs
- Identification of CPPs through quality risk assessment and design of experiments
- Real-time monitoring using a hybrid near infrared spectroscopy (NIR)-soft sensor (SS) method

Table 3. Overview of drug product control strategy

CQA	Method of control
Appearance	Specification
Identity	Specification
Strength	Manufacturing process, Specification
Degradation products	Manufacturing process, Specification
Uniformity of dosage units	Manufacturing process, Specification
Dissolution	Manufacturing process, Specification

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, appearance, identity (HPLC, ultraviolet-visible spectrum), purity [degradation products (HPLC)], uniformity of dosage units (mass variation test), dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

The primary stability studies on the drug product are shown in Table 4. The stability results indicated that the drug product is stable. Photostability data showed that the drug product is photostable.

Table 4. Stability studies on drug product

Study	Strength of the drug product	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	50 mg	3 commercial-scale batches	25℃	60%RH	Blister pack	12 months
	100 mg					
	200 mg					
Accelerated	50 mg	3 commercial-scale batches	40℃	75%RH		6 months
	100 mg					
	200 mg					

Based on the above, a shelf-life of 24 months was proposed for the drug product when packaged in blister packs (films made from polyvinyl chloride and polyvinylidene chloride/aluminum foils) and stored at room temperature, in accordance with "Guideline on Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3, 2003). The long-term testing will be continued up to 36 months.

2.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations etc., PMDA concluded that the quality of the drug substance and the drug product is adequately controlled. Based on Section 5.R.5, the permissible daily exposure (PDE) for a mutagenic impurity, PF-07216658, has been re-established at the threshold of toxicological concern (TTC) value, and then PF-07216658 is controlled based on the removal capability of the manufacturing process.

2.R.1 Manufacturing control of drug product

The applicant explained that a control strategy for the homogeneous production of the drug product, including a continuous manufacturing process, consists of the following elements:

(1) Confirming that the tablet composition is not vulnerable to variations during manufacture and identifying the allowable variations associated with the target drug product quality by evaluating the impact of [redacted] on the quality of the drug product

(2) Controlling the rate of [redacted] to the continuous blender and the proportion of [redacted] by monitoring [redacted] of [redacted] feeder by raw material (Real-time)

(3) Ensuring the blend uniformity based on [redacted] control of the powder blend in the continuous blender (Real-time)

(4) Controlling [redacted] concentration in the powder blend discharged from the blender by [redacted] model [Estimate [redacted] concentration based on the [redacted] rate in (2) and the [redacted] setpoint in (3)] (Real-time)

(5) Real-time monitoring of the drug substance content in [redacted] powder blend by a hybrid NIR-SS method and the exclusion of non-conforming tablets (If the NIR cannot be used, check the drug substance content and the uniformity of dosage units by off-line testing of tablet cores sampled periodically over the entire run time)

(6) Confirming that [redacted] and [redacted] of tablet cores sampled periodically over the entire run time are within the specified ranges (Off-line)

(7) Release testing of film-coated tablets (Off-line)

PMDA considers that the control strategy policy proposed by the applicant is acceptable, but requested the applicant to also provide the following information concerning this policy in the application form. The applicant responded accordingly.

● Although [redacted] is controlled by [redacted] and [redacted] in the blender, this parameter is considered to depend on the characteristics of the manufacturing equipment, [redacted] information should be clearly provided.

● Because the method to estimate [redacted] or [redacted] content in the powder blend by [redacted] model and a softsensor depends on [redacted] model used, the model should be indicated as well.

2.R.2 Use of a hybrid NIR-SS method

For the monitoring of [redacted] content in [redacted] to control the homogeneity in drug product production, a hybrid method with content estimation by SS based on [redacted] model with input variables of process parameters, such as [redacted] of the feeder and [redacted] of the blender, has been utilized, instead of using the NIR [redacted] model alone.

The applicant's explanation about the use of the hybrid NIR-SS method:
The reasons for combining the NIR and SS are as follows: In the NIR [redacted] model, batches of raw materials, etc., affect the robustness of the model, which may result in deviated estimated values. Meanwhile, the SS employed is a [redacted] model with input variables and is not affected by factors that can deviate estimated values in the NIR procedure. The hybrid NIR-SS method is considered to provide more robust estimation.

In the NIR-SS method for the drug product, as a method of combining the SS, the [redacted] value for 1 tablet in the NIR [redacted] model is corrected for the difference between the [redacted] in the NIR [redacted] model and the [redacted] in the SS. Although [redacted] range used for calibration, testing, and validation of this hybrid NIR-SS method is narrower than the drug substance specification range, the method is not affected by [redacted] of the drug substance and can be utilized for process control, for the following reasons.
● The NIR [redacted] model is 1 element of the hybrid NIR-SS method. The [redacted] range used for establishing the NIR [redacted] model is very close to the specification range for the [redacted] of the drug substance.
● Scattering effects on NIR spectra based on differences in the [redacted] of drug substance have not been identified. The scattering effects are considered to be minimized by pretreatment of spectral data that are used in the NIR [redacted] model.
● As the anomaly scores from the Hotelling T^2 analysis are comparable over the [redacted] range investigated, there should be no correlation between [redacted] range and Hotelling T^2.

PMDA accepted the applicant's explanation.

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

The applicant submitted primary pharmacodynamic data, in the form of the results from studies on inhibition of the JAK family and STAT phosphorylation etc., a study in the adjuvant-induced arthritis rat model, etc. The applicant submitted the results from secondary pharmacodynamic studies that evaluated inhibition of various enzymes and receptors, etc. and the results from safety pharmacology studies that assessed the effects of abrocitinib on the central nervous, cardiovascular, and respiratory systems.

Pharmacologic parameters are expressed as the mean.

3.1 Primary pharmacodynamics

3.1.1 Inhibition of JAK family of kinases and a panel of kinases (CTD 4.2.1.1-1 to 4.2.1.1-3)

In the assays using human recombinant JAK1, JAK2, JAK3, and tyrosine-kinase 2 (TYK2), the IC_{50} values of abrocitinib and its main metabolites [see Section 4.3], M1, M2, and M4 for JAK1, JAK2, JAK3, and TYK2 are shown in Table 5.

Table 5. Inhibitory activities of abrocitinib, M1, M2, and M4 against JAK family of kinases (IC_{50}: nmol/L)

	Abrocitinib	Metabolites		
		M1	M2	M4
JAK1 [a)]	29.2	43.4	17.9	>10,000
JAK2 [a)]	803	1,140	886	>10,000
JAK3 [a)]	>10,000	>10,000	>10,000	>10,000
TYK2 [a)]	1,250	3,190	1,210	>10,000

a) In the presence of 1 mmol/L ATP

In the assays against a panel of 40 kinases including JAK3, in the presence of the apparent K_m for adenosine triphosphate (ATP) (5-400 µmol/L), abrocitinib (1,000 nmol/L) showed ≥50% inhibition of JAK3 only (60.6% inhibition).

3.1.2 Effect on STAT phosphorylation etc. in human whole blood and various cell types (CTD 4.2.1.1-5 to 4.2.1.1-7, 4.2.1.1-9, 4.2.1.1-12, 4.2.1.1-13)

Table 6 shows the IC_{50} values of abrocitinib, M1, and M2 for STAT phosphorylation in lymphocytes in human whole blood and various cell types.

Table 6. Inhibitory activities of abrocitinib, M1, and M2 against cytokine-induced STAT phosphorylation

JAK involved	STAT phosphorylation	Stimulation	IC_{50} (nmol/L)			Cell type
			Abrocitinib	M1	M2	
JAK1/JAK2	STAT1	IFNγ (500 ng/mL)	1,690	-	-	Human $CD14^+$ monocytes
		IFNγ (100 ng/mL)	-	1,950	2,160	
		IFNγ (500 ng/mL)	161	-	-	Human lymphocytes
	STAT3	IL-31 (1 μg/mL)	40.0	79.6	56.0	THP-1 cell line[a)]
	STAT5	TSLP (50 ng/mL)	1,021	785	271	Human $CD3^+$T cells
JAK1/JAK2/TYK2	STAT1	IL-6 (100 ng/mL)	354	-	-	
		IL-6 (50 ng/mL)	-	171	136	
		IL-6 (100 ng/mL)	167	-	-	Human $CD14^+$ monocytes
	STAT3	IL-6 (50 ng/mL)	-	2,770	2,260	Human $CD3^+$T cells
		IL-6 (100 ng/mL)	83.7	-	-	Human megakaryocyte precursor cells
		IL-27 (1,200 ng/mL)	234	382	234	Human lymphocytes
	STAT6	IL-4 (4 ng/mL)	77.0	-	-	Human keratinocytes
		IL-4 (2 ng/mL)	-	433	134	
		IL-4 (0.3 ng/mL)	185-503	-	-	Human $CD20^+$B cells, human $CD3^+$T cells, human $CD14^+$ monocytes
		IL-13 (40 ng/mL)	81.9	-	-	Human keratinocytes
		IL-13 (20 ng/mL)	-	236	84.1	
		IL-13 (1 ng/mL)	285, 351	-	-	Human $CD20^+$B cells, human $CD14^+$ monocytes
JAK1/JAK3	STAT3	IL-21 (50 ng/mL)	525	844	487	Human lymphocytes
	STAT5	IL-15 (30 ng/mL)	537	558	353	
JAK1/TYK2	STAT3	IL-22 (100 ng/mL)	420	703	198	Human keratinocytes
		IL-10 (30 ng/mL)	576	675	233	Human lymphocytes
		IFNα (6,000 U/mL)	183	-	-	
		IFNα (5,000 U/mL)	-	296	90.5	
JAK2/TYK2	STAT3	IL-23 (100 ng/mL)	>16,300	26,200	6,210	
	STAT4	IL-12 (30 ng/mL)	9,730	-	-	
		IL-12 (5 ng/mL)	-	33,400	5,170	
JAK2/JAK2	STAT5	EPO (2 U/mL)	7,780	9,750	9,470	Human $CD34^+$ progenitor cells
		TPO (100 ng/mL)	1,060	-	-	Human megakaryocyte precursor cells

[a)] Primed with IFNγ (20 ng/mL)

3.1.3 Effect on differentiation and expansion using human megakaryocyte precursor cells (CTD4.2.1.1-9)

The IC_{50} of abrocitinib for IL-6-mediated differentiation and expansion of human CD34+ progenitor cells to megakaryocyte precursor cells was 5,670 nmol/L.

3.1.4 Effect in the adjuvant-induced arthritis rat model (CTD 4.2.1.1-14)

Female rats were immunized with complete Freund's adjuvant to induce arthritis. After arthritis of the hind paw was confirmed by plethysmography, abrocitinib 0 (vehicle), 5, 15, or 50 mg/kg was administered orally once daily for 7 days. Abrocitinib at ≥5 mg/kg resulted in a dose-dependent inhibition of hind paw swelling. At 15 minutes after the last dose of abrocitinib, rat whole blood samples showed dose-dependent inhibition of IL-6, IFNγ, and IFNα (100 ng/mL each) stimulated STAT1 phosphorylation, IL-21 and IL-10 (100 ng/mL each) stimulated STAT3 phosphorylation, and GM-CSF (60 ng/mL) stimulated STAT5 phosphorylation.

In addition, in order to determine the minimum effective dose of abrocitinib, abrocitinib 0.5, 1, 5, or 15 mg/kg was administered orally once daily for 7 days. Abrocitinib at ≥1 mg/kg resulted in a dose-dependent inhibition of hind paw swelling. At 15 minutes after the last dose of abrocitinib, whole blood samples showed dose-dependent inhibition of each cytokine-dependent STAT phosphorylation.

3.2 Secondary pharmacodynamics

3.2.1 Inhibition of a panel of enzymes, receptors, etc. (CTD 4.2.1.2-1, 4.2.1.2-2)

In a broad ligand binding assay, the binding potency of abrocitinib against 61 receptors, transporters, ion channels, and enzymes was evaluated. Abrocitinib (10 μmol/L) caused ≥50% inhibition of monoamine oxidase A (MAO-A) and vascular endothelial growth factor receptor-2 (VEGFR2) only, with IC_{50} values of 6.0 μmol/L and 1.2 μmol/L, respectively (3.4-fold and 0.7-fold the human exposure [unbound C_{max} (569 ng/mL)[1)]], respectively).

In the assay at a physiological concentration of ATP (1,000 μmol/L), abrocitinib (≤30 μmol/L [17-fold the human exposure (unbound C_{max} [569 ng/mL])[1)]]) did not inhibit VEGFR2.

3.2.2 Inhibition of monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B) and reversibility (CTD 4.2.1.2-3, 4.2.1.2-4)

Among MAO-A and MAO-B, abrocitinib (0.1-100 μmol/L) caused ≥50% inhibition of MAO-A only, with an IC_{50} of 7.67 μmol/L (4.4-fold the human exposure [unbound C_{max} (569 ng/mL)][1)]).

MAO-A inhibition by the IC_{80} concentration of abrocitinib (10 μmol/L) was reversible upon 24-hour dialysis.

3.3 Safety pharmacology (CTD 4.2.1.3)

Table 7 shows the results of safety pharmacology studies of abrocitinib, M1, M2, and M4.

[1)] Unbound C_{max} calculated by multiplying the estimated C_{max} at steady state following once daily administration of abrocitinib 200 mg in Japanese AD patients (1,581 ng/mL [see Section 6.3]) by the fraction unbound (fu) 0.36 [see Section 4.2.2]

Table 7. Overview of safety pharmacology studies

Organ systems evaluated	Test system	Endpoints/Method of assessment, etc.	Dose	Route of administration	Findings	Exposure margin[a)]	Attached document CTD
CNS	Wistar Han rat (6 males/group)	Body temperature, functional observation battery (FOB), locomotor activity (Conscious)	Abrocitinib 75, 200, 600 mg/kg	Oral gavage	· A decrease in mean body temperature at ≥200 mg/kg: −0.6℃ · Decreased locomotor activity at ≥75 mg/kg: horizontal movement, −40% to −49% vertical movement, −46% to −59%	LOEL 75 mg/kg: 7-fold	4.2.1.3.4
Cardiovascular	hERG-transfected HEK293 cells	hERG current (Patch-clamp technique)	Abrocitinib 10, 30, 100, 300 µmol/L	*In vitro*	11% to 77.9% inhibition at 10-300 µmol/L IC_{50} was 94.7 µmol/L.	IC_{50}: 54-fold	4.2.1.3.3
			M1, M2 30, 300 µmol/L M4 30, 100, 300 µmol/L		IC_{50} was all >300 µmol/L.	IC_{50}: >170-fold	4.2.3.7.5. 4-6
	Cynomolgus monkey (8 males)	ECG, blood pressure, heart rate, physical activity (Telemetry, Conscious)	Abrocitinib 15, 40, 80, 150 mg/kg	Oral gavage	· 15-150 mg/kg A dose-dependent increase in heart rate at 0.5-3.5 hours post-dose: 9-30 bpm · 15 and 150 mg/kg Increased heart rate at 5-7.75 hours post-dose: 6 and 15 bpm · 15-150 mg/kg Decreases in RR and PR intervals at 0.5-3.5 hours post-dose: −20 to −82 msec and −3 to −8 msec, respectively · 15-150 mg/kg Decreased QT interval at 0.5-3.5 hours post-dose:−8 to −26 msec Decreased QT interval at 5-7.75 hours post-dose: −15 msec · 150 mg/kg Increased diastolic blood pressure (+4 mmHg on average at 0.5-3.5 hours post-dose)	LOEL 15 mg/kg: 0.7-fold	4.2.1.3.6
Respiratory	Wistar Han rat (6 males/group)	Respiratory rate, tidal volume, minute volume (Conscious)	Abrocitinib 75, 200, 600 mg/kg	Oral gavage	No effects	600 mg/kg: 24-fold	4.2.1.3.4

[a)] Calculated based on the unbound C_{max} (569 ng/mL) obtained by multiplying the estimated C_{max} at steady state following once daily administration of abrocitinib 200 mg in Japanese AD patients (1,581 ng/mL) [see Section 6.3] by the fraction unbound (fu) 0.36 [see Section 4.2.2].

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological effects of abrocitinib on AD

PMDA's view:

The submitted data show that abrocitinib inhibits the JAK/STAT signaling pathway, and the effect of abrocitinib on AD is expected from a pharmacological standpoint because the JAK/STAT signaling pathway is considered to be involved in the pathogenesis of AD. Given that abrocitinib and its metabolites can potentially inhibit other JAK family members (other than JAK1) to a certain extent, according to the results in Sections 3.1.1 and 3.1.2, attention should be paid to the possible effects on the immune and hematopoietic systems during treatment with abrocitinib, as with other JAK inhibitors [For safety, see Section 7.R.3].

3.R.2 Inhibition of VEGFR2 and MAO-A

The applicant's explanation about inhibition of VEGFR2 and MAO-A by abrocitinib observed in a pharmacology study:

In a biochemical assay at a physiological concentration of ATP, abrocitinib did not inhibit VEGFR2, and safety pharmacology, toxicity, and clinical studies showed no effects on the bones, kidneys, ovaries, or uterine that were considered associated with VEGFR2 inhibition. Given the human exposure in clinical use, increased blood pressure observed in some animals in a safety pharmacology study is not considered to be mediated by VEGFR2, etc. Thus, VEGFR2 inhibition by abrocitinib is unlikely to cause safety issues.

MAO-A inhibition is known to block the metabolism of noradrenaline and serotonin and cause increases in blood pressure and heart rate and serotonin syndrome (metal symptoms, extrapyramidal symptoms, autonomic symptoms, etc.). Although increases in heart rate and blood pressure, etc., were observed in a safety pharmacology study, the distribution of abrocitinib to the brain is limited, MAO-A inhibition is reversible, abrocitinib does not inhibit MAO-B, which has some overlapping effects with MAO-A, and no increases in heart rate and blood pressure or no effects suggestive of serotonin syndrome were observed in clinical studies. Given these findings etc., MAO-A inhibition by abrocitinib is unlikely to cause safety issues.

PMDA's view on the secondary pharmacodynamic effects of abrocitinib:

PMDA accepted the applicant's explanation about inhibition of VEGFR2 by abrocitinib. With regard to MAO-A inhibition, given that increased heart rate etc. were observed at exposure levels less than the human exposure in the safety pharmacology study, etc., the risk of these events during treatment with abrocitinib in clinical use needs to be assessed carefully, taking account of clinical study results [see Section 7.R.3].

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

The applicant submitted the data on the absorption, distribution, metabolism, and excretion of abrocitinib, in the form of the results from oral and intravenous studies in mice, rats, monkeys, and minipigs. Plasma concentrations of abrocitinib and its metabolites were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Lower limit of quantitation [LLOQ], 5 ng/mL in mouse plasma, 1 or 5 ng/mL in rat plasma, 1 ng/mL in monkey and minipig plasma), and radioactivity concentrations in samples were determined by quantitative whole-body autoradiography. Unless otherwise specified, doses are expressed in terms of abrocitinib, and pharmacokinetic parameters are expressed as the mean or the mean ± standard deviation (SD).

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2.1, 4.2.2.2.2, 4.2.3.1.2)

Table 8 shows the pharmacokinetic parameters following a single oral or intravenous dose of abrocitinib in rats, monkeys, and minipigs. The absolute oral bioavailability of abrocitinib was 95.6% in rats and 9.6% to 10% in monkeys.

Table 8. Pharmacokinetic parameters following a single dose of abrocitinib

Species	Route of administration/ Feeding condition		Dose (mg/kg)	No. of animals	C_{max} (μg/mL)	AUC_{last} (μg·h/mL)	t_{max} (h)	CL (mL/min/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)
Rat	Fasted	Oral	3	M2	0.849	1.79	0.50	－	－	1.1
	Fed	IV	1	M2	－	0.628	－	26.6	1.04	0.82
Monkey	Fed	IV	1	M1	－	0.570	－	29.2	0.650	0.457
				F1	－	0.515	－	32.4	0.984	0.580
		Oral	3	M1	0.137	0.161	0.500	－	16.9	0.540
				F1	0.0947	0.158	0.500	－	22.9	1.11
Minipig	Fed	IV	0.5	M3	－	1.12 ± 0.216	－	7.37 ± 1.79	0.793 ± 0.0440	1.65 ± 0.314

Mean or Mean ± SD; Median or Median [Range] for t_{max}; －, Not applicable or not calculated

4.1.2 Repeated-dose studies (CTD 4.2.2.2.3, 4.2.3.2.2, 4.2.3.2.5)

Table 9 shows the pharmacokinetic parameters of abrocitinib and its metabolites following repeated oral doses of abrocitinib in rats and monkeys. With respect to the pharmacokinetics of abrocitinib, abrocitinib exposure increased in an approximately dose-proportional manner in both animal species tested, and there were no evident gender differences or accumulation.

Table 9. Pharmacokinetic parameters following repeated oral doses of abrocitinib

Species	Analyte	No. of animals	Sampling time point	Dose (mg/kg/day)	C_{max} (μg/mL)		$AUC_{0\text{-}24\ h}$ (μg·h/mL)		t_{max} (h)	
					M	F	M	F	M	F
Rat	Abrocitinib	4M4F	Day 1	25	4.05 ± 0.806	5.17 ± 0.887	19.6 ± 5.19	36.3 ± 7.25	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]
				75	9.77 ± 3.16	11.6 ± 3.35	124 ± 21.3	135 ± 32.6	2.0 [1.0, 7.0]	1.0 [1.0, 7.0]
				200	14.0 ± 1.34	21.2 ± 7.93	236 ± 18.9	305 ± 57.4	7.0 [1.0, 7.0]	2.0 [1.0, 3.0]
			Day 29	25	5.25 ± 1.14	6.28 ± 0.784	28.4 ± 6.13	40.6 ± 15.2	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]
				75	11.5 ± 3.37	11.3 ± 2.36	124 ± 23.8	135 ± 33.6	1.0 [1.0, 3.0]	1.0 [1.0, 1.0]
				200	23.6 ± 3.73	23.1 ± 2.31	326 ± 27.3	295 ± 40.7	2.0 [1.0, 7.0]	1.0 [1.0, 3.0]
	Abrocitinib	5M5F	Day 5	M: 45 F: 70	4.64 ± 0.648	14.4 ± 3.93	48.5 ± 3.50	164 ± 20.9	0.50 [0.25, 2.0]	1.0 [0.50, 1.0]
	M1※				8.89 ± 2.76	BLQ	22.7 ± 6.67	BLQ	0.25 [0.25, 0.5]	－
	M2				0.122 ± 0.0394	0.0502 ± 0.0119	1.37 ± 0.228	0.662 ± 0.0795	2.0 [0.25, 2.0]	1.0 [0.50, 1.0]
	M4				0.917 ± 0.145	1.69 ± 0.411	9.72 ± 0.401	20.5 ± 1.98	0.50 [0.50, 2.0]	1.0 [1.0, 1.0]
Monkey	Abrocitinib	3M3F	Day 8	40	2.72 ± 1.60	0.888 ± 0.262	16.0 ± 8.23	4.33 ± 1.14	3.0 [1.0, 3.0]	1.0 [1.0, 1.0]
				80	6.75 ± 3.10	2.92 ± 1.03	57.5 ± 40.7	23.9 ± 0.913	1.0 [1.0, 3.0]	3.0 [3.0, 3.0]
				150	14.8 ± 12.9	17.0 ± 7.42	179 ± 152	213 ± 88.0	3.0 [3.0, 7.0]	3.0 [3.0, 7.0]
			Day 29	40	2.90 ± 1.37	1.96 ± 0.987	18.7 ± 0.823	8.90 ± 5.04	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]
				80	5.44 ± 4.90	2.12 ± 1.11	74.9 ± 69.3	18.8 ± 5.88	3.0 [3.0, 7.0]	1.0 [1.0, 1.0]
				150	16.6 ± 1.22	11.5 ± 6.95	187 ± 62.6	154 ± 102	7.0 [3.0, 7.0]	7.0 [3.0, 7.0]

Mean ± SD; Median [Range] for t_{max}; BLQ = below limit of quantitation; －, Not calculated; ※ ng/mL for C_{max}, ng·h/mL for AUC

4.1.3 *In vitro* cell permeability (CTD 4.2.2.6.21)

The cell permeability of abrocitinib was evaluated in Madin-Darby canine kidney (MDCK) cells expressing breast cancer resistance protein (BCRP). In the presence of Ko143, a BCRP inhibitor, the apparent apical-to-basolateral permeability coefficient ($P_{app\ A\rightarrow B}$) was 5.0×10^{-6}cm/s (the concentration tested was 0.5 μmol/L). The $P_{app\ A\rightarrow B}$ values of a poorly permeable control compound (10 μmol/L atenolol) and a highly permeable control compound (10 μmol/L propranolol) were 0.05×10^{-6} and 13.5×10^{-6} cm/s, respectively.

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.3.10)

The tissue distribution of radioactivity[2)] in male Long Evans rats following a single oral dose of ^{14}C-abrocitinib 10 mg/kg was evaluated up to 672 hours post-dose by quantitative whole-body autoradiography.

Following administration of ^{14}C-abrocitinib, radioactivity was distributed into systemic tissues rapidly with the highest levels occurring at 0.25 hours post-dose in most tissues. While radioactivity concentrations were higher in the uveal tract, liver, kidney, adrenal glands, and salivary glands than in blood, radioactivity distribution to the lens (eye), non-circumventricular CNS tissues, bone, abdominal fat, turbinate, and testes was low. At 168 hours post-dose, radioactivity was below the detection limit in tissues other than the arterial walls, intervertebral ligament(s), uveal tract, whole eyes, liver, turbinate, and thyroid glands. Also in these tissues, radioactivity was below the detection limit or declined to approximately 1% to 4% of the maximum level at 672 hours post-dose.

The applicant's explanation:
Although abrocitinib showed an affinity for melanin-containing tissues including the uveal tract and pigmented skin, as an *in vivo* phototoxicity study in rats showed no ocular toxicity, there is little safety concern about abrocitinib accumulation in melanin-containing tissues.

4.2.2 Plasma protein binding and distribution in blood cells (CTD 4.2.2.3.1 to 4.2.2.3.9)

Plasma protein binding as determined by an equilibrium dialysis method (the concentration tested was 2 μmol/L) and the blood to plasma ratio (the concentration tested was 1 μmol/L) of abrocitinib, M1, M2, and M4 in mice, rats, rabbits, monkeys, and humans are shown in Table 10.

Table 10. Plasma protein binding and blood to plasma ratio of abrocitinib and its metabolites

Plasma protein binding						Blood to plasma ratio					
	Mouse	Rat	Rabbit	Monkey	Human		Mouse	Rat	Rabbit	Monkey	Human
Abrocitinib	45%	62%	81%	63%	64%	Abrocitinib	1.00	0.92	0.59	1.01	1.07
M1	37%	45%	63%	36%	37%	M1	1.03	0.95	0.80	1.03	1.13
M2	40%	45%	54%	34%	29%	M2	1.05	1.00	0.90	1.12	1.27
M4	5%	24%	41%	6%	17%	M4	0.92	0.83	0.73	0.89	0.87

4.2.3 Placental transfer

Although placental transfer of abrocitinib and its metabolites has not been studied, an embryo-fetal development study in rats showed developmental toxicity, and a prenatal and postnatal development study showed decreases in postnatal survival and birth weight [see Section 5.5], suggesting that abrocitinib or its metabolites may cross the placenta.

[2)] The adrenal glands, arterial walls, bile, blood, bone, bone marrow, brain, cerebellum, cerebrum, choroid plexus in the brain, brain medulla, brain olfactory lobe, bulbourethral gland, cecum, diaphragm, epididymis, esophagus, exorbital lacrimal gland, lens (eye), uveal tract (eye), vitreous fluid (eye), whole eyes, abdominal fat, brown fat, harderian gland, intervertebral ligaments, intraorbital lacrimal gland, renal cortex, renal medulla, kidneys, large intestine, liver, lungs, lymph nodes, muscles, cardiac muscle, turbinate, pancreas, pituitary gland, preputial gland, prostate gland, salivary glands, seminal vesicle, non-pigmented skin, pigmented skin, small intestine, spinal cord, spleen, stomach, testes, thymus, thyroid gland, bladder, and urine were evaluated.

4.3 Metabolism

4.3.1 *In vitro* studies (CTD 4.2.2.4.4 to 4.2.2.4.7)

When abrocitinib (10 μmol/L) was incubated with rat, monkey, or human liver microsomes or hepatocytes, the major metabolic pathway of abrocitinib was oxidation, and various metabolites formed via hydroxylation, N-demethylation, or glutathione conjugation presented in Figure 1 were detected. A study using human hepatocytes and selective inhibitors of P450 isoforms[3)] suggested that abrocitinib is metabolized by CYP2C19, CYP2C9, CYP3A4, and CYP2B6 (The fraction metabolized [f_m] was 0.53, 0.30, 0.11, and 0.07, respectively). No metabolites unique to humans were identified.

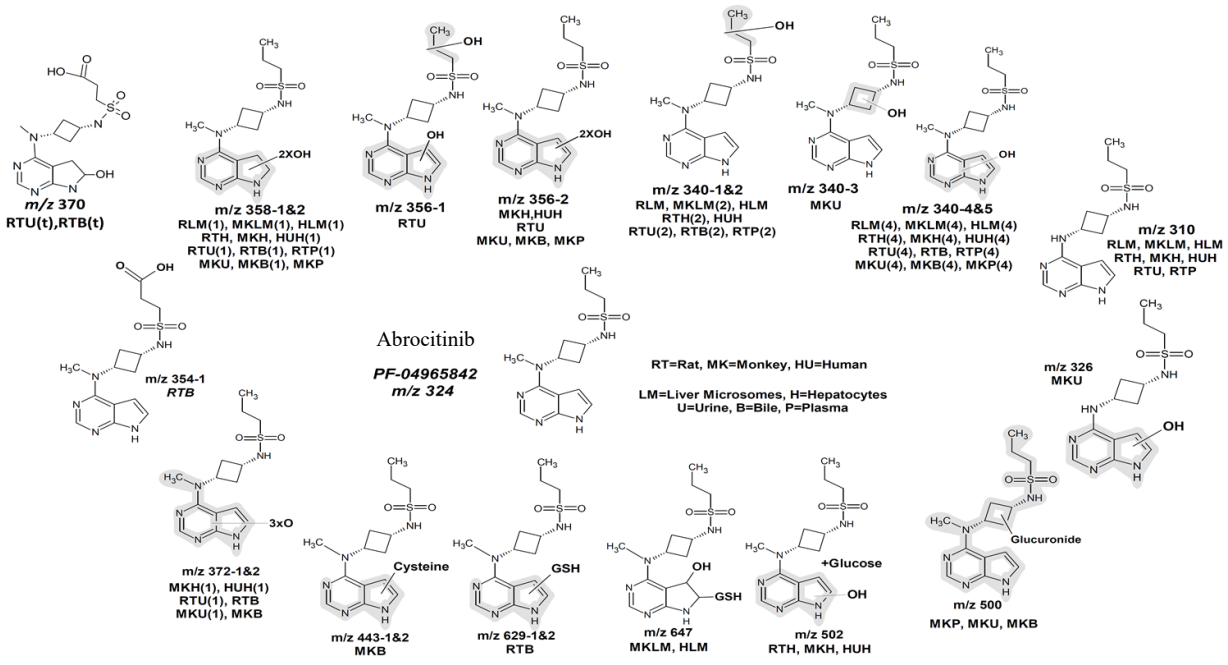


Figure 1. Metabolites of abrocitinib detected in incubations with rat, monkey, or human liver microsomes or hepatocytes

When M1, M2, and M4 (10 μmol/L) were incubated with human liver microsomes or human hepatocytes, M1 was metabolized to M6, M7, M8, and its glucuronide conjugate, M2 was metabolized to 2 oxidized metabolites (m/z 340-5, 356-1a), and M4 was metabolized to 1 oxidized metabolite (m/z 372-1). Studies using human recombinant P450, or human hepatocytes and selective inhibitors of P450 isoforms suggested that CYP2D6, CYP1A1, and CYP1B1 mainly contribute to the metabolism from M1 to M8, and that CYP2C9 mainly contributes to the metabolism from M1 to M7.

4.3.2 *In vivo* studies (CTD 4.2.2.4.1 and 4.2.2.4.4)

Table 11 shows metabolites in samples following a single oral dose or multiple oral doses of abrocitinib in mice, rats, and monkeys. In a foreign mass balance study [see Section 6.1.1], no metabolites unique to humans were identified.

[3)] As selective inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5, furafylline, 2-phenyl-2-(1-piperdinyl)propane, gemfibrozil glucuronide, tienilic acid, esomeprazole, quinidine, and troleandomycin were used, respectively.

Table 11. Metabolite profiles in different animal species

Species	Method of administration	Plasma	Bile	Urine	Attached document CTD
Mouse	300 mg/kg/day Repeated oral doses	Unchanged drug, M1, M2/M3, M4, M5, m/z 326, 342, 356-2, 358-1, 358-2, 358-3, 372-1			4.2.2.4.1
	75 mg/kg/day Repeated oral doses			Unchanged drug, M2/M3, M4, m/z 326, 342, 358-1, 358-3, 372-1	
	150 mg/kg/day Repeated oral doses	Unchanged drug, M2/M3, M4, m/z 326, 342, 358-1, 358-3, 372-1		Unchanged drug, M2/M3, M4, m/z 326, 342, 358-1, 358-3, 372-1	
	450 mg/kg/day Repeated oral doses			Unchanged drug, M2/M3, M4, m/z 326, 342, 358-1, 358-3, 372-1	
Rat	120 mg/kg Single oral dose	Unchanged drug, M2/M3, M4, M5, m/z 340-5, 358-1	Unchanged drug, M2/M3, M4, M5, M6, M7, M8, m/z 340-5, 356-2, 358-1, 358-2, 372-1, 372-2, 629-1, 629-2, 647	Unchanged drug, M1, M2/M3, M4, M5, M6, M7, M8, m/z 340-3, 356-2, 358-1, 358-2, 372-1, 372-2	4.2.2.4.4
Monkey	100 mg/kg/day Repeated oral doses	Unchanged drug, M4, M5, m/z 340-3, 356-2, 358-1, 358-2, 372-1, 500	Unchanged drug, M4, M7, m/z 500, 356-2, 358-1, 358-2, 372-1, 372-2, 443-1, 443-2, 629-2	Unchanged drug, M4, M5, m/z 326, 500, 340-3, 356-2, 358-1, 358-2, 372-1, 372-2	

Based on the above metabolism studies, the proposed metabolic pathway of abrocitinib is shown in Figure 2.

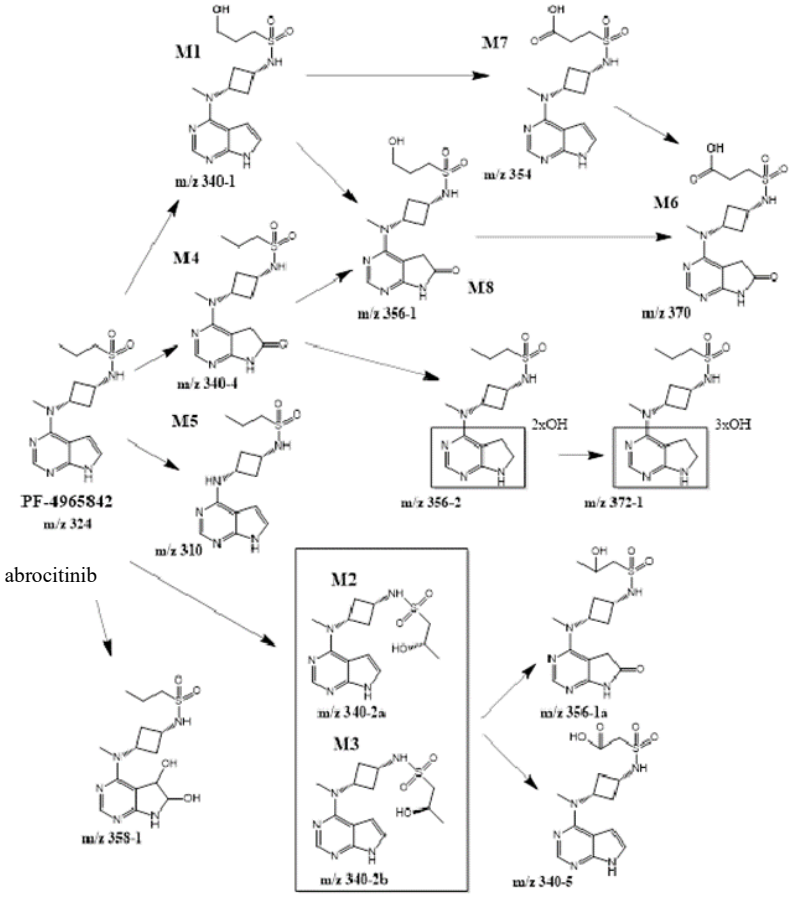


Figure 2. Proposed metabolic pathway of abrocitinib in humans

4.4 Excretion

4.4.1 Urinary and biliary excretion (CTD 4.2.2.2.1 and 4.2.2.4.1)

When male and female rasH2 (wt/wt) mice were dosed orally with abrocitinib 150 mg/kg/day once daily for 28 days, M4 was mainly detected in the urine and urinary sediment, and unchanged drug was a minor component.

Following a single intravenous dose of abrocitinib 1 or 3 mg/kg in intact rats or bile duct cannulated rats, 6.8% of the dose was excreted as unchanged drug in the urine and 0.12% of the dose was excreted as unchanged drug in the bile, up to 24 hours post-dose.

4.4.2 Excretion into milk (CTD 4.2.2.5.1)

Table 12 shows plasma and milk concentrations of abrocitinib following a single oral dose of abrocitinib 10 mg/kg in lactating female rats. Abrocitinib was secreted in milk.

Table 12. Plasma and milk concentrations of abrocitinib
following a single dose of abrocitinib 10 mg/kg in lactating female rats (ng/mL)

Matrix	Time after administration (h)			
	1	3	8	24
Plasma	1,710 ± 200	556 ± 165	26.7 ± 12.0	BLQ
Milk	8,050 ± 1,650	3,000 ± 426	153 ± 49.6	0.278 ± 0.555

Mean ± SD, 4 females/time point, BLQ = below limit of quantitation

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition or induction (CTD 4.2.2.6.1 to 4.2.2.6.19)

Using human liver microsomes, abrocitinib, M1, M2, and M4 were evaluated for their potential as inhibitors of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5).[4)] Abrocitinib, M1, M2, or M4 was not a reversible inhibitor of any of the isoforms (IC_{50} >99.5 μmol/L). Meanwhile, the results suggested that following once daily administration of abrocitinib 200 mg,[5)] abrocitinib has the potential for time-dependent inhibition of CYP2C19, CYP2D6, and CYP3A4/5, and M4 has the potential for time-dependent inhibition of CYP2D6.

Using human hepatocytes, the potential of abrocitinib (1-100 μmol/L) to induce CYP1A2, CYP2B6, CYP3A4, CYP2C8, CYP2C9, and CYP2C19 and the potential of M1, M2, and M4 (0.3-300 μmol/L) to induce CYP1A2, CYP2B6, and CYP3A4 were evaluated. Abrocitinib induced increases in the mRNA expression of CYP3A4, CYP2B6, CYP2C8, and CYP2C19. M1 and M2 induced increases in the mRNA expression of CYP2B6 and CYP1A2. M4 induced an increase in CYP1A2 mRNA expression.

Using human liver microsomes, abrocitinib, M1, M2, and M4 were evaluated for their potential as inhibitors

[4)] The following compounds were used as substrates of CYP isoforms: phenacetin for CYP1A2, bupropion for CYP2B6, paclitaxel and amodiaquine for CYP2C8, diclofenac for CYP2C9, *S*-mephenytoin for CYP2C19, dextromethorphan for CYP2D6, testosterone, midazolam, and nifedipine for CYP3A4/5

[5)] Based on the unbound C_{max} of abrocitinib, M1, M2, and M4 at steady state following once daily administration of abrocitinib 200 mg (1.3, 0.36, 0.35, and 0.95 μmol/L, respectively).

of uridine diphosphate glucronosyl transferase (UGT) isoforms (UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7, UGT2B15 [M1, M2, and M4 only for UGT2B15]).[6] The IC_{50} values of abrocitinib, M1, M2, and M4 were >100 μmol/L for all isoforms tested.

Using human liver cytosol, the potential of abrocitinib to inhibit sulfotransferase (SULT) isoforms (SULT1E1, SULT1A1, SULT2A1) was evaluated.[7] The IC_{50} was >100 μmol/L for all isoforms tested.

4.5.2 Transporter substrate assessment (CTD 4.2.2.6.20 to 4.2.2.6.23)

Studies using MDCK cells expressing human P-glycoprotein (P-gp) or BCRP or human embryonic kidney cells (HEK293 cells) expressing organic anion-transporting polypeptide 1B1 (OATP1B1) or OATP1B3[8] suggested that abrocitinib may be a substrate for P-gp and BCRP.

A study using HEK293 cells expressing human organic cation transporter 2 (OCT2), organic anion transporter 1 (OAT1), OAT3, multidrug and toxin extrusion protein 1 (MATE1), or MATE2K[9] suggested that M1, M2, and M4 may be substrates of OAT3.

4.5.3 Transporter inhibition (CTD 4.2.2.6.24 to 4.2.2.6.28)

Using MDCKII cells expressing human P-gp, HEK293 cells expressing human BCRP, bile salt export pump (BSEP), OATP1B1, OATP1B3, OCT1, OAT1, OAT3, OCT2, MATE1, or MATE2K, and *Trichoplusia ni* ovarian (Hi5) cells expressing human BSEP, abrocitinib, M1, M2, and M4 were evaluated for their potential as inhibitors of these drug transporters.[10] The results are shown in Table 13.

[6] The following compounds were used as substrates of UGT isoforms: β-estradiol for UGT1A1, trifluoperazine for UGT1A4, 5-hydroxytryptophol for UGT1A6, propofol for UGT1A9, zidovudine for UGT2B7, oxazepam for UGT2B15

[7] Ethinylestradiol was used as a substrate of SULT isoforms.

[8] As inhibitors of P-gp and BCRP, PSC833 and Ko143 were used, respectively.

[9] The following compounds were used as inhibitors of transporters: quinidine for OCT2, probenecid for OAT1 and OAT3, cimetidine for MATE1 and MATE2K

[10] The following compounds were used as substrates of transporters: digoxin for P-gp, rosuvastatin for BCRP, [^{3}H]-taurocholic acid for BSEP, rosuvastatin for OATP1B1, rosuvastatin for OATP1B3, [^{14}C]-metformin for OCT1, *p*-aminohippuric acid for OAT1, estrone-3-sulfate for OAT3, metformin for OCT2, metformin for MATE1, metformin for MATE2K

Table 13. Inhibition of drug transporters by abrocitinib and its metabolites

Transporter	Test article	Concentrations tested (μmol/L)	IC_{50} (μmol/L) (% inhibition at highest concentration tested)	Transporter	Test article	Concentrations tested (μmol/L)	IC_{50} (μmol/L) (% inhibition at highest concentration tested)
P-gp	Abrocitinib	0.6-400	100.3 (86%)	OCT2	Abrocitinib	0.073-300	>300 (30%)
	M1	0.018-300	>300 (1%)		M1	0.14-300	>300 (0%)
	M2	0.018-300	>300 (0%)		M2	0.14-300	>300 (0%)
	M4	0.018-300	>300 (0%)		M4	0.14-300	>300 (0%)
BCRP	Abrocitinib	0.095-300	9.8 (97%)	OAT1	Abrocitinib	0.073-300	>300 (25%)
	M1	0.018-300	44.9 (85%)		M1	0.14-300	>300 (0%)
	M2	0.018-300	79.0 (87%)		M2	0.14-300	>300 (31%)
	M4	0.018-300	61.6 (87%)		M4	0.14-300	>300 (0%)
OATP1B1	Abrocitinib	0.1-300	>300 (52%)	OAT3	Abrocitinib	0.073-300	26.0 (86%)
	M1	0.018-300	208.9 (61%)		M1	0.14-300	56.2 (83%)
	M2	0.018-300	>300 (42%)		M2	0.14-300	44.6 (87%)
	M4	0.018-300	>300 (0%)		M4	0.14-300	61.3 (76%)
OATP1B3	Abrocitinib	0.1-300	>300 (0%)	MATE1	Abrocitinib	0.073-300	5.5 (93%)
	M1	0.018-300	279.5 (50%)		M1	0.14-300	55.1 (79%)
	M2	0.018-300	>300 (27%)		M2	0.14-300	54.4 (71%)
	M4	0.018-300	>300 (0%)		M4	0.14-300	111.3 (61%)
OCT1	Abrocitinib	0.095-300	44.2 (92%)	MATE2K	Abrocitinib	0.07-300	10.7 (88%)
	M1	0.018-300	223.2 (65%)		M1	0.14-300	121.2 (79%)
	M2	0.018-300	149.4 (72%)		M2	0.14-300	121.4 (66%)
	M4	0.018-300	130.4 (74%)		M4	0.14-300	50.8 (83%)
BSEP	Abrocitinib	0.82-200	>200 (42%)				

4.R Outline of the review conducted by PMDA

PMDA concluded that the submitted study results gave a grasp of the body's handling of abrocitinib to a certain extent. Since abrocitinib or its metabolites were suggested to inhibit or induce CYP isoforms and inhibit drug transporters, etc., the potential of abrocitinib to cause relevant drug interactions in clinical use needs to be assessed, taking also account of the clinical study results [see Section 6.R.4].

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the results from the following toxicity studies of abrocitinib: single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, and reproductive and developmental toxicity studies, studies in juvenile animals, and other toxicity studies (a phototoxicity study, an immunotoxicity study, mechanistic investigations/studies on metabolites/impurities). Unless otherwise specified, 0.5% (w/v) methylcellulose/0.1% (v/v) Polysorbate 80 in deionized water was used as vehicle in studies in mice, rats, and rabbits. In cynomolgus monkey studies, abrocitinib formulated as a spray dried dispersion (SDD) containing a constant mix-ratio of abrocitinib and hydroxypropyl methylcellulose acetate succinate-medium granular (HPMCAS-MG) as test article, and 45 or 67.5 mg/mL hydroxypropyl methylcellulose acetate succinate-high fine (HPMCAS-HF)-containing 0.5% methylcellulose/0.5% HPMCAS-HF in 20 mmoL/L tris buffer in purified water or reverse osmosis water (pH7.4) as vehicle were used.

5.1 Single-dose toxicity

In single-dose studies of oral abrocitinib in rats and monkeys, the approximate lethal dose and acute toxicity of abrocitinib were assessed (Table 14). The approximate lethal dose in rats was determined to be 1,000 mg/kg. No acute symptoms were noted in rats and cynomolgus monkeys.

Table 14. Overview of single-dose toxicity studies

Test system	Route of administration	Doses (mg/kg)	Noteworthy findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male rat (SD)	Oral gavage	0, 250, 500, 1,000	1,000: Mortality (3 of 3 rats), decreased activity, chromodacryorrhea	1,000	4.2.3.1.1
Male and female cynomolgus monkeys	Oral gavage or IV bolus	Oral gavage Arm 1 and Arm 2[a)]: 150 Arm 3: 50, 150 Arm 5: 3 IV bolus Arm 4: 1	Arm 2: Emesis/vomitus (7-10 hours post-dose)	Oral gavage > 150 IV bolus > 1	4.2.3.1.2

Arm 3: Test article, Abrocitinib nanosuspension; Vehicle, 1.25% HPC-SL/0.05% dioctyl sodium sulfosuccinate in deionized water
Arm 4: Test article, Abrocitinib; Vehicle, 10% SBECD in sterile water for injection
Arm 5: Test article, Abrocitinib; Vehicle, 0.5% (w/v) methylcellulose/0.1% (v/v) Polysorbate 80 in deionized water
a) 75 mg/kg BID 4 hours apart

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies of oral abrocitinib were conducted in rats (Table 15). The noteworthy systemic toxicities or abnormal findings were decreases in white blood cell/lymphocyte parameters, decreased lymphoid cellularity in lymphoid organs, decreases in red blood cell parameters, increases in blood hepatobiliary function markers, increased extramedullary hematopoiesis in the spleen, urinary crystals, bone dystrophy with increased alkaline phosphatase (ALP) activity, increased coarse vacuolation in brown adipose tissue, prostate inflammation/intranuclear inclusions in epithelial cells due to viral opportunistic infection, and skin ulcer/erosion due to bacterial infection. Increased coarse vacuolation in brown adipose tissue was considered less adverse because findings such as necrosis/inflammation were not observed.

The no-observed-adverse-effect levels (NOAELs) in a 6-month repeated-dose toxicity study in rats were determined to be 45 mg/kg/day in males and 70 mg/kg/day in females. The $AUC_{0\text{-}24h}$ values of unbound abrocitinib (free abrocitinib) at the NOAELs at Week 26 were 37,200 ng·h/mL (males) and 53,200 ng·h/mL (females), which were approximately 12-fold (males) and approximately 18-fold (females) the human exposure (unbound AUC_{tau} [2,980 ng·h/mL]).[11)]

[11)] Unbound AUC_{tau} calculated by multiplying the estimated AUC_{tau} at steady state following once daily oral administration of abrocitinib 200 mg in Japanese AD patients (8,275 ng·h/mL [see Section 6.3]) by the fraction unbound (fu) 0.36 [see Section 4.2.2].

Table 15. Overview of repeated-dose toxicity studies in rats

Test system	Route of adminis-tration	Duration of dosing	Doses (mg/kg)	Noteworthy findings	NOAEL (mg/kg)	Attached document CTD
Male and female rats (Wistar)	Oral gavage	1 month (QD)	0, 25, 75, 200	≥25: decreases in white blood cell count/lymphocyte count/eosinophil count, decreased weights of the thymus/spleen, decreased cellularity of lymphoid follicles in the thymus/spleen/mesenteric lymph nodes (male and female), decreases in reticulocyte count/monocyte count, skin ulcer/crust/scabs/erosion (male), increased mean red cell distribution width, increases in blood AST/ALP/total bilirubin (female) ≥75: decreased cellularity of lymphoid follicles in the inguinofemoral lymph nodes, physis dystrophy in the stifle joint at the interface of the growth plate and the primary spongiosum (male and female), decreased platelet count, increases in blood AST/total protein/globulin (male), increased blood ALT, small thymus, increased coarse vacuolation in brown adipose tissue (female) 200: increases in blood cholesterol/HDL, increased liver weight, decreased cellularity of lymphoid follicles in GALT, periportal hepatocyte hypertrophy, hyperkeratosis of the epidermis (male and female), increases in blood ALT and A/G ratio (male), decreases in red blood cell count/hemoglobin/hematocrit/neutrophil count, increases in MCH/MCHC/reticulocyte count, increases in blood total protein/globulin, skin ulcer/crust/scabs/erosion, increased extramedullary hematopoiesis in the spleen (female)	25	4.2.3.2.2
Male and female rats (Wistar)	Oral gavage	6 months (QD) + 12-week recovery period	0, 30, 45, 70	≥30: crust formation, decreases in platelet count[1)]/white blood cell count/lymphocyte count/eosinophil count, decreased weights of the spleen/thymus, small spleen,[2)] decreased cellularity of lymphoid follicles in the thymus/spleen/mesenteric lymph nodes/inguinal lymph nodes, increased extramedullary hematopoiesis in the spleen, decreased mononuclear infiltrates in the liver (male and female), decreases in reticulocyte count[1)]/neutrophil count/monocyte count, increased blood AST, decreased cellularity of lymphoid follicles in GALT (male), increased mean red cell distribution width, decreases in blood albumin[1)] and A/G ratio,[1)] increased blood ALP (female) ≥45: decreased red blood cell count, abnormal urinary crystals (male and female), decreased hemoglobin, increases in mean red cell distribution width/blood ALT (male), decreases in hematocrit/blood calcium, skin crust/erosion/ulcer, decreased cellularity of lymphoid follicles in GALT (female) 70: decreased hematocrit, prostate inflammation/intranuclear inclusions in epithelial cells (male) These findings were reversible.	Males: 45 Females: 70	4.2.3.2.3

1) Including a decreasing trend. The findings were considered of little toxicological significance because these were minimal without associated changes.
2) Excluding males in the 45 mg/kg group

Repeated-dose toxicity studies of oral abrocitinib were conducted in cynomolgus monkeys (Table 16).

The noteworthy abnormal findings were decreases in blood white blood cell/lymphocyte parameters, decreased immune or hematopoietic cellularity in lymphoid and bone marrow organs, increases in blood liver function markers, cytomegalovirus infection-related lesions associated with immunosuppressive effects, decreases in red blood cell parameters, and decreased antibody response. Decreased immune cellularity in blood and lymphoid organs and abnormal findings related to immunosuppression were considered reflective of the JAK inhibitory effect of abrocitinib and were not considered adverse. Increased blood interferon inducible protein-10 (IP-10) was related to abrocitinib, but was considered of little toxicological significance because no associated inflammatory lesions were noted.

The NOAEL in a 9-month repeated dose toxicity study in cynomolgus monkeys was 75 mg/kg/day for both males and females. The $AUC_{0\text{-}24h}$ of free abrocitinib at the NOAEL at Week 39 was 20,400 ng·h/mL (the mean of males and females), which was approximately 6.8-fold the human exposure (unbound AUC_{tau} [2,980

ng·h/mL]).[11)]

Table 16. Overview of repeated-dose toxicity studies in cynomolgus monkeys

Test system	Route of adminis-tration	Duration of dosing	Doses (mg/kg)	Noteworthy findings	NOAEL (mg/kg)	Attached document CTD
Male and female cynomolgus monkeys	Oral gavage	1 month (QD)	0, 40, 80, 150	≥40: decreased body weight, increases in blood ALT/AST, increased liver weight, decreased cellularity of the bone marrow (erythroid/granulocytes/megakaryocytes), decreased cellularity of lymphoid follicles in the spleen (male), decreased reticulocyte count, increased blood interferon inducible protein-10 (female) ≥80: decreases in hemoglobin/hematocrit, decreased cellularity of lymphoid follicles in the thymus (male and female), decreases in red blood cell count/reticulocyte count (male), decreased lymphocyte count, decreased cellularity of the bone marrow (erythroid/granulocytes/megakaryocytes), decreased thymus weight, decreased cellularity of lymphoid follicles in the spleen (female) 150: decreases in lymphocyte count/monocyte count, increased blood IP-10, cytomegalovirus infection (male) Immunophenotyping ≥40: decreases in T cells[1)]/NK cells (male and female) ≥80: decreases in helper T cells/cytotoxic T cells[1)]/plasma cells (female) 150: decreases in cytotoxic T cells/plasma cells (male)	80	4.2.3.2.5
Male and female cynomolgus monkeys	Oral gavage	9 months (QD) + 12-week recovery period	0, 15, 35, 75	≥15: decreased lymphocyte count, decreased weights of the spleen[1)]/thymus,[1)] decreased cellularity of lymphoid follicles in the thymus/spleen (female) ≥35: decreased lymphocyte count,[1)] decreased cellularity of lymphoid follicles in the thymus (male) 75: decreased serum IgA (male and female), decreases in red blood cell count/hemoglobin,[1)] decreased blood inorganic phosphate,[2)] decreased thymus weight,[1)] decreased cellularity of lymphoid follicles in the spleen (male) Immunophenotyping ≥15: decreased NK cells[1)] (male and female) TDAR evaluation ≥15: reduced anti-KLH IgM/IgG titers[1)] (female) ≥35: reduced anti-KLH IgM/IgG titers[1)] (male) These findings were reversible.	75	4.2.3.2.6

1) Including a decreased value/a decreasing trend.
2) The finding was considered of little toxicological significance because no associated changes were noted.

5.3 Genotoxicity

An *in vitro* bacterial reverse mutation assay (Ames assay), an *in vitro* micronucleus assay in TK6 cells/a fluorescent in situ hybridization (FISH) assay with a pan-centromeric DNA probe, and a rat bone marrow micronucleus assay were conducted (Table 17). Although abrocitinib increased micronucleated cells without metabolic activation in the *in vitro* micronucleus assay, micronuclei were not induced at the maximum feasible dose[12)] in the rat bone marrow micronucleus assay. Thus, abrocitinib was considered negative for genotoxicity.

[12)] Abrocitinib exposure following oral administration of 600 mg/kg (C_{max} = 13,500 ng/mL) was approximately 24-fold the human exposure (free abrocitinib) following repeated oral administration at the recommended clinical dose (200 mg/day) in Japanese AD patients (C_{max} = 569 ng/mL).

Table 17. Overview of genotoxicity studies

Type of study		Test system	Metabolic activation (Treatment time)	Concentrations or doses	Test result	Attached document CTD
In vitro	Ames assay	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2uvrA pKM101	S9−/+	0,[1)] 100, 250, 500, 1,000, 2,500, 5,000 µg/plate	Negative	4.2.3.3.1.1
	Micronucleus assay in TK6 cells	TK6 human lymphoblastoid cells	S9− (27 hours)	0,[1)] 10.4, 12.2, 14.4, 16.9, 19.9, 23.4, 27.5, 32.0, 37.4, 43.6, 50.9, 59.3, 69.2, 80.8, 94.2, 110 µg/mL	Positive	4.2.3.3.1.2
			S9− (4 hours)	0,[1)] 59.3, 69.2, 80.8, 94.2, 110, 128, 150, 175, 204, 238, 277, 323 µg/mL	Negative	
			S9+ (4 hours)			
	FISH assay with pan-centromeric DNA probe in TK6 cells	TK6 human lymphoblastoid cells	S9− (27 hours)	0,[1)] 121, 166 µmol/L	Aneugenic	4.2.3.3.1.3
In vivo	Rat micronucleus assay	Male and female rats (Wistar) Bone marrow		0, 100, 300, 600 mg/kg/day (oral gavage, 2 consecutive days)	Negative	4.2.3.3.2.1

1) Vehicle: DMSO

5.4 Carcinogenicity

A 6-month carcinogenicity study of oral abrocitinib was conducted in Tg rasH2 hemizygous (tg/wt) mice (Tg rasH2) (Table 18). Abrocitinib did not increase the incidence of neoplastic lesions. Hemangiosarcoma and bronchiolo-alveolar adenoma/carcinoma in the lung that were not observed in the vehicle group or tended to be observed more frequently in animals dosed with abrocitinib, are considered unlikely related to abrocitinib because the incidences fell within the historical control ranges of the test facility. As abrocitinib-related non-neoplastic lesions, hyperplasia of the thymic epithelium and obstructive nephropathy with associated abnormal findings were observed. The kidney findings were related to crystalline precipitates of a metabolite M4, which is excreted in the urine, and are considered changes specific to mice due to their highly concentrated urine.

Based on the above, the no-observed-effect level (NOEL) for carcinogenicity was determined to be 60/75 mg/kg/day (male/female). The $AUC_{0\text{-}24h}$ values of free abrocitinib at the NOELs at Week 26 were 743 ng·h/mL (male) and 1,760 ng·h/mL (female), which were approximately 0.2-fold (male) and approximately 0.6-fold (female) the human exposure (unbound AUC_{tau} [2,980 ng·h/mL]).[11)]

Table 18. Overview of carcinogenicity study in Tg rasH2 mice

Test system	Route of administration	Duration of dosing	Major lesions	Sex	Doses (mg/kg/day)				NOEL for carcinogenicity (mg/kg/day)	Attached document CTD
					Vehicle	Abrocitinib				
					Male: 0 Female: 0	Male: 10 Female: 10	Male: 20 Female: 25	Male: 60 Female: 75		
				N	25/sex	25/sex	25/sex	25/sex		
Male and female mice (Tg rasH2)	Oral gavage	26 weeks	Neoplastic lesions						Males: 60 Females: 75	4.2.3.4.2.4
			Malignant lymphoma	M	0	0	0	0		
				F	1	0	1	0		
			Whole body[1)]/Hemangiosarcoma	M	1	2	0	0		
				F	1	0	3	0		
			Lung/ Bronchiolo-alveolar adenoma/carcinoma	M	1	4	2	3		
				F	2	2	1	3		
			Hemolymphoreticular tumor	M	0	0	0	0		
				F	2	0	2	0		
			Hyperplastic lesions							
			Thymus/ Hyperplasia of the thymic epithelium	M	0	0	2	0		
				F	0	1	10	7		
			Other findings							
			Survival rate (%)	M	100	92	96	92		
				F	96	100	100	71		
			20/25: decreased cellularity of lymphoid follicles in the thymus (male and female) 60/75: thin appearance, piloerection, kidney cyst/abnormal shape/small/discolored, obstructive nephropathy, renal pelvis dilatation (male and female), rough surface of the kidney (male), large kidney/abnormal contents (female)							

1) The sum of mice with hemangiosarcoma in any organ/tissue in the whole body

A 2-year carcinogenicity study of oral abrocitinib was conducted in rats (Table 19). As the major abrocitinib-related neoplastic lesions, an increased incidence of thymoma derived from the thymic epithelium was observed in females at ≥10 mg/kg. The increased incidence of benign thymoma is considered to result from a non-genotoxic mechanism. The applicant explained that the thymus of female Wistar rats, compared to that of males, exhibits delayed physiologic involution (*Toxicol Pathol*. 2019; 47: 129-137), which may lead to a higher sensitivity for spontaneous thymoma formation in the female Wistar rat following administration of an immunosuppressive drug. As hyperplastic lesions, hyperplasia of the thymic epithelium was observed in females in the 30 mg/kg group. Although the incidences of pancreatic adenoma, skin lipoma, and mammary gland carcinoma tended to increase in animals dosed with abrocitinib, these findings are considered unlikely related to abrocitinib, based on the historical control ranges. As non-hyperplastic lesions related to abrocitinib, increased extramedullary hematopoiesis in the spleen, malocclusion of the incisors, and white teeth were noted. The abnormal findings in the incisors are considered less adverse in patients in the target age group for abrocitinib, given that no abnormal findings in the tooth tissue were noted, and taking account of the age of permanent teeth eruption in humans.

Based on the above, the NOEL for carcinogenicity was determined to be 3 mg/kg/day. The $AUC_{0\text{-}24h}$ of free abrocitinib at the NOEL at Day178 was 1,200 ng·h/mL, which was approximately 0.4-fold the human exposure (unbound AUC_{tau} [2,980 ng·h/mL]).[11)]

Table 19. Overview of carcinogenicity study in rats

Test system	Route of administration	Duration of dosing	Major lesions	Sex	Doses (mg/kg/day)				NOEL for carcinogenicity (mg/kg/day)	Attached document CTD
					Vehicle	Abrocitinib				
					0	3	10	30		
				N	60/sex	60/sex	60/sex	60/sex		
Male and female rats (Wistar)	Oral gavage	104 weeks	Neoplastic lesions						3	4.2.3.4.1.1
			Thymus/Thymoma (derived from thymic epithelium)	M	1	2	7	5		
				F	2	10	20*	15*		
			Malignant lymphoma[1)]	M	1	0	0	0		
				F	0	0	1	0		
			Hemolymphoreticular tumor[1)]	M	0	0	0	2		
				F	1	0	0	0		
			Pancreas/Islet cell adenoma	M	1	2	4	2		
				F	2	0	3	0		
			Skin/Lipoma	M	0	0	2	0		
				F	0	1	0	1		
			Mammary gland/Carcinoma	M	0	0	0	0		
				F	6	8	10	11		
			Hyperplastic lesions							
			Thymus/ Hyperplasia of the thymic epithelium	M	5	2	5	5		
				F	3	6	4	17*		
			Other findings							
			Survival rate (%)	M	75	65	62	47*		
				F	42	53	67	52		
			30: malocclusion of the incisors, white teeth (male and female), decreased body weight, increased extramedullary hematopoiesis in the spleen (male), large thymus/mass (female)							

* Considered related to abrocitinib.
1) The sum of rats with malignant lymphoma or hemolymphoreticular tumor in any organ/tissue in the whole body

5.5 Reproductive and developmental toxicity

An oral study of fertility and early embryonic development to implantation was conducted in male and female rats (Table 20). Abrocitinib had effects on fertility and early embryonic development. The NOAEL for male and female reproductive toxicity was determined to be 70 mg/kg/day, and the $AUC_{0\text{-}24h}$ of free abrocitinib at 70 mg/kg/day at Week 26 in a repeated-dose toxicity study[13)] (54,000 ng·h/mL in males, 53,200 ng·h/mL in females) was approximately 18-fold (males and females) the human exposure (unbound AUC_{tau} [2,980 ng·h/mL]).[11)] The NOAEL for female fertility and early embryonic development was determined to be 10 mg/kg/day, and the $AUC_{0\text{-}24h}$ of free abrocitinib at 10 mg/kg/day (4,180 ng·h/mL) was approximately 1.4-fold the human exposure (unbound AUC_{tau} [2,980 ng·h/mL]).[11)]

[13)] A 6-month repeated-dose toxicity study in rats [CTD 4.2.3.2.3, see Section 5.2]

Table 20. Overview of fertility and early embryonic development study

Type of study	Test system	Route of administration	Duration of dosing	Doses (mg/kg)	Noteworthy findings	NOAEL (mg/kg)	Attached document CTD
Fertility and early embryonic development to implantation	Male and female rats (Wistar)	Oral gavage	Males: 28 days prior to mating to the day before necropsy Females: 14 days prior to mating to gestation day 7 (QD)	0, 30, 45, 70	Parental animals 70: decreases in fertility index/conception index/mean number of corpora lutea/mean number of implantation sites Early embryonic development ≥30: decreased number of viable embryos per litter ≥45: increases in mean percent of post-implantation loss/early resorptions	Parental animals (General toxicity): 70 Parental animals (Reproductive toxicity): 70 Fertility and early embryonic development: <30	4.2.3.5.1.1
	Female rat (Wistar)	Oral gavage	Females: 14 days prior to mating to gestation day 7 (QD)	0, 3, 10, 70	Parental animals 70: decreases in fertility index/fecundity index/mean number of implantation sites Early embryonic development 70: total litter loss, increases in mean percent of post-implantation loss/early resorptions	Parental animals (General toxicity): 70 Parental animals (Reproductive toxicity): 10 Early embryonic development: 10	4.2.3.5.1.2

Embryo-fetal development studies of oral abrocitinib were conducted in rats and New Zealand white (NZW) rabbits (Table 21). As effects on embryo-fetal development, external malformations were observed in 1 rat fetus, there were skeletal variations and effects on post-implantation embryonic development in rats and rabbits, and dead fetuses were noted in rats. An increased incidence of unossified forelimb phalanges in rabbits dosed with abrocitinib is considered less adverse in humans because such finding has been reported to resolve postnatally (*Dev Reprod Toxicol*. 2007; 80: 473-496), and no other indications of skeletal dysmorphogenesis were noted. The $AUC_{0\text{-}24h}$ values of free abrocitinib at the NOAELs for embryo-fetal development (10 mg/kg/day in rats, 75 mg/kg/day in rabbits) were 4,900 ng·h/mL (in rats on gestation day 17) and 8,170 ng·h/mL (in rabbits on gestation day 19), which were approximately 1.6-fold (rats) and approximately 2.7-fold (rabbits) the human exposure (unbound AUC_{tau} [2,980 ng·h/mL]).[11)]

Table 21. Overview of embryo-fetal development studies

Type of study	Test system	Route of adminis-tration	Duration of dosing	Doses (mg/kg)	Noteworthy findings	NOAEL (mg/kg)	Attached document CTD
Embryo-fetal development	Female rat (SD)	Oral gavage	Gestation days 6-17 (QD) Cesarean Section: Gestation day 21	0, 75, 200, 400	Dams ≥75: decreases in body weight/food consumption ≥200: All died or euthanized (before necropsy), decreased motor activity, ptosis, red substance (perivagina), pale forepaws/hind paws or ears, ungroomed coat, dehydration, thin body, hunched posture, cold to touch, scant feces, hyperpnea, vaginal bleeding 200: pale body, red substance (abdomen) 400: ataxia, lacrimation, urine-stained abdominal fur, chromodacryorrhea, low carriage, bradypnea, red substance (tail), piloerection, dark concentrated urine, red substance (abdomen) 75: decreased uterine weight Embryo-fetal development 75: increases in late resorptions/post-implantation loss/resorbed or dead conceptuses per litter, dead fetuses (including total litter loss), decreased fetal weight, decreased litter size, external malformations (whole body edema, umbilical hernia, and medially rotated forelimbs in 1 fetus) 200: increases in early resorptions or dead fetuses 400: total litter loss	—	4.2.3.5.2.1
				0, 10, 30, 60	Dams None Embryo-fetal development ≥10: increased incidence of unossified metatarsals [1)] ≥30: increased incidence of short ribs (13th)[1)] 60: increases in mean number of dead fetuses/resorbed or dead conceptuses per litter/incidence of thickened ribs[1)]/incidence of cervical arches with reduced ventral processes[1)]	Dams (General toxicity/Reproductive toxicity): 60 Embryo-fetal development:10	4.2.3.5.2.2
	Female rabbit (NZW)	Oral gavage	Gestation days 7-19 (QD) Cesarean Section: Gestation day 29	0, 30, 75, 150, 300	Dams ≥30: ungroomed coat, scant feces/decreased food consumption ≥75: soft or liquid feces, thin body ≥150: no feces, decreased body weight 300: All died or euthanized, scant or no feces, thin body, decreased motor activity, impaired righting reflex, ptosis, ataxia, splayed hindlimbs, salivation, dyspnea 30: decreased body weight gain 150: abortion, decreased body weight gain Embryo-fetal development 30: increases in late resorptions/post-implantation loss/resorbed or dead conceptuses per litter/females with any resorptions 150: increases in early and late resorptions/post-implantation loss/resorbed or dead conceptuses per litter/females with any resorptions, decreased fetal body weight, open eyelid (1 fetus) 300: early resorptions	—	4.2.3.5.2.3
				0, 10, 30, 75	Dams None Embryo-fetal development 75: increased fetal or litter incidence of unossified forelimb phalanges	Dams (General toxicity/Reproductive toxicity): 75 Embryo-fetal development: 75	4.2.3.5.2.4

1) Variations

An oral study for effects on pre- and postnatal development, including maternal function, was conducted in rats (Table 22). The major effects on maternal reproductive function were prolonged parturition and dystocia, and effects on the F_1 generation were decreased survival during suckling associated with pup deaths and decreased body weight after weaning. Postweaning parameters were not evaluated in the 60 mg/kg group due to a marked decrease in postnatal survival. The applicant explained about prolonged parturition and dystocia observed in rats dosed with abrocitinib as follows: Since similar findings are not consistently observed in reproductive and developmental toxicity studies of other JAK inhibitors, and parturition is not affected in JAK knockout mice (*Genome Biology*. 2004; 5: 253), the findings are unlikely related to JAK inhibition, and its mechanism is unknown. The NOAEL for dams and pups was determined to be 10 mg/kg/day. The $AUC_{0\text{-}24h}$ of

free abrocitinib at the NOAEL (repeated dosing) in dams was 4,900 ng·h/mL, which was approximately 1.6-fold the human exposure (unbound AUC_{tau} [2,980 ng·h/mL]).[11)]

Table 22. Overview of study for effects on pre- and postnatal development, including maternal function

Type of study	Test system	Route of adminis -tration	Duration of dosing	Doses (mg/kg)	Noteworthy findings	NOAEL (mg/kg)	Attached document CTD
Pre- and postnatal development, including maternal function	Female rat (SD)	Oral gavage	Dams: gestation day 6 to lactation day 20 (QD)	0, 10, 30, 60	Dams ≥30: dystocia 60: prolonged parturition F_1 generation 30[1)]: decreased body weight (before and after weaning) 60: reduced postnatal survival/pup viability (total litter loss, 13 of 20 females), pale/cool body, milk not present in stomach	Dams (General toxicity): 10 Dams (Reproductive toxicity): 10 F_1 pups (General toxicity): 10	4.2.3.5.3.1

1) 60 mg/kg: not evaluated due to reduced pup viability

5.6 Studies in juvenile animals

A repeated oral dose toxicity study of abrocitinib was conducted in juvenile rats (Table 23). Toxicology findings specific to juvenile animals dosed with abrocitinib included abnormal bone development or formation, and similar changes were present also after a recovery period. Abnormal values/findings in while blood cell/lymphocyte parameters and lymphoid tissue are considered reflective of the JAK inhibitory effect of abrocitinib.

Table 23. Overview of repeated-dose toxicity study in juvenile animals

Test system	Route of adminis-tration	Duration of dosing	Doses (mg/kg)	Noteworthy findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female juvenile rats (Wistar)	Oral gavage	Postnatal days 10-63 (QD) + 2-month recovery period	0 , 5, 25, 75	Deaths (25: 1 male and 1 female; 75: 3 males and 2 females) Malrotation/impaired use of forelimbs or hindlimbs, malrotated/swollen hind paw, short radius/ulna, dark red femur/tibia, mass/mineralization/granulomatous inflammation in quadriceps femoris muscle, paw joint inflammation, tibia fracture, adhesion of the liver and kidney, kidney inflammation, bone tissue necrosis Surviving animals ≥5: decreased weights of the spleen/thymus, decreased primary spongiosa in metaphysis of femur/tibia (male and female), decreases in blood white blood cell count/lymphocyte count, small/abnormal morphology of femoral head (female) ≥25: malrotation of forelimbs or hindlimbs, bent tibia[1)] (male and female), decreases in body weight/body weight gain/food consumption, impaired use of forelimbs or hindlimbs, decreases in blood white blood cell count/lymphocyte count, decreases in femur length/width, small/abnormal morphology of femoral head (male), hind paw malrotation, erythrocytosis in sinus of mesenteric lymph node (female) 75: chronic hind paw fracture, decreased cellularity of lymphoid follicles in the thymic cortex (male and female), misshapen femoral head, hind paw malrotation, mass/mineralization in quadriceps femoris muscle, erythrocytosis in sinus of mesenteric lymph node (male), decreases in body weight/body weight gain, impaired use of forelimbs or hindlimbs, decreases in femur length/width, hind paw bone degeneration (female)	<5	4.2.3.5.4.2
				Recovery period ≥5: small femoral head (male) ≥25: hindlimb malrotation, soft femoral head (male and female), small/abnormal morphology of femoral head, hind paw malrotation (female) 75: decreased femur length (male and female), hind paw malrotation, abnormal morphology of femur (male) Except for the above bone effects observed during dosing period, all findings were reversible.		

1) Excluding males in the 75 mg/kg group

5.7 Other studies

5.7.1 Phototoxicity

Since abrocitinib absorbs UVB and visible light (the wavelengths of maximum absorbance are 217 nm and 288 nm) and is distributed into the uveal tract of pigmented rats [see Section 4.2.1], a phototoxicity study of abrocitinib was conducted in pigmented rats. There were no abrocitinib-related abnormal findings in the eyes or skin, and abrocitinib was considered negative for phototoxicity (Table 24).

Table 24. Overview of phototoxicity study

Type of study	Test system	Test method	Noteworthy findings	Attached document CTD
Phototoxicity	Female pigmented rat (Long-Evans)	Rats were dosed with abrocitinib 0, 50, 150, or 300 mg/kg by oral gavage once daily for 7 days. The eyes and skin of the rats were exposed to UV-A (10.3 J/cm^2) and UV-B (145 mJ/cm^2) for 42 minutes at 150 minutes after administration.	None	4.2.3.7.7.1

5.7.2 Immunotoxicity

Abrocitinib and tofacitinib were compared in *in vitro* assays of human cellular immune function (Table 25). Both abrocitinib and tofacitinib inhibited IFN-γ production by peripheral blood mononuclear cells (PBMCs) following viral antigen-specific T cell activation. Also in assays for assessment of type I or II IFN response in human PBMCs or dermal fibroblasts, inhibitory effects were observed. Abrocitinib is considered to have no unique activities on human cellular immune function.

The effects of abrocitinib on the immune/lymphohematopoietic systems observed in repeated-dose toxicity studies in rats and monkeys (Table 15 and Table 16) were reflective of the JAK signaling inhibitory pharmacological action of abrocitinib and were reversible after a recovery period. The NOAELs for effects on the immune system were determined to be 75 mg/kg/day in a 9-month repeated-dose toxicity study in monkeys and 45 mg/kg/day (males) and 70 mg/kg/day (females) in a 6-month repeated-dose toxicity study in rats.

Table 25. Overview of study to assess the effects of abrocitinib on human immune function

Test system	Test method	Test results (IC_{50})	Attached document CTD
Human NK cell killing of K562 erythroleukaemic cells	Human PBMCs containing NK cells were treated with 0.0073-30 µmoL/L of abrocitinib or tofacitinib. CFSE-labeled K562 cells were added, and NK cell killing activity was assessed.	Abrocitinib: 11.69 µmoL/L Tofacitinib: 15.78 µmoL/L Abrocitinib did not affect NK cell killing activity at human exposures.	4.2.3.7.2.1
Degranulation of activated T cells/intracellular IFN-γ accumulation	Human PBMCs containing T cells were treated with 0.001-30 µmoL/L of abrocitinib or tofacitinib. Granules of CD8+T cells activated by CD3/CD28 co-stimulatory signal and intracellular IFNγ accumulation were assessed.	Degranulation of activated T cells Abrocitinib: >30 µmoL/L Tofacitinib: 21.12 µmoL/L Intracellular IFN-γ accumulation Abrocitinib: >30 µmoL/L Tofacitinib: 26.26 µmoL/L Abrocitinib had no effect on cytolytic T cell function.	
IFN-γ production following CMV or VZV antigen-specific T cell activation	Human PBMCs containing T cells were treated with 0.0003-1 µmoL/L of abrocitinib or tofacitinib. Granules of CMV or VZV antigen-activated T cells and IFN-γ production by PBMCs were assessed.	CMV antigen stimulation Abrocitinib: 0.164 µmoL/L Tofacitinib: 0.022 µmoL/L VZV antigen stimulation Abrocitinib: 0.214 µmoL/L Tofacitinib: 0.01 µmoL/L Abrocitinib inhibited IFN-γ production following viral antigen-specific T cell activation.	
IP-10 secretion from IFN-α or IFN-γ stimulated PBMCs	PBMCs were treated with 0.00152-30 µmoL/L of abrocitinib or tofacitinib. IP-10 secretion from IFN-α or IFN-γ stimulated PBMCs was assessed.	IFN-α stimulation Abrocitinib: 0.292 µmoL/L Tofacitinib: 0.064 µmoL/L IFN-γ stimulation Abrocitinib: 1.06 µmoL/L Tofacitinib: 0.41 µmoL/L Abrocitinib inhibited IP-10 secretion from IFN-α or IFN-γ stimulated PBMCs.	
HSV-1 replication in IFN-β treated HDF cells	HDF cells were treated with 0.0098-10 µmoL/L of abrocitinib or tofacitinib. The cells were treated with IFN-β and then infected with HSV-1. Effect on IFN-β activity was assessed based on HSV-1 replication.	Abrocitinib: 0.380 µmoL/L Tofacitinib: 0.121 µmoL/L Abrocitinib inhibited IFN-β activity as measured by HSV-1 replication.	

CFSE: carboxyfluorescein succinimidyl ester
HDF: human dermal fibroblasts
CMV: cytomegalovirus
VZV: varicella zoster virus
HSV: herpes simplex virus

5.7.3 Toxicologic evaluation of metabolites

Following repeated administration of abrocitinib in humans, M2 and M4 were identified as metabolites that were observed at exposures >10% of total drug-related exposure [see Section 6.1.1]. The non-clinical safety of M2 and M4 was characterized by a 6-month repeated-dose toxicity study, an *in vivo* micronucleus assay, a carcinogenicity study, and an embryo-fetal development study in rats whose rat to human ratios for the AUC of M2 and M4 were >0.5. Metabolites M1, M2, and M4 were evaluated for their inhibitory effects on the Nav1.5 sodium channel, the Cav1.2 calcium channel, and the hERG potassium channel. M1, M2, and M4 had no inhibitory activity against these ion channels (Table 26).

Table 26. Overview of study to assess the effects of metabolites on ion channels

Test system	Test method	Test results (IC_{50})	Attached document CTD
Inhibition of Nav1.5 channel	CHO cells stably expressing human Nav1.5 sodium channel were treated with 0.001-100 µmol/L of M1, M2, or M4 to assess their inhibitory activities against Nav1.5 sodium channel current.	M1, M2, and M4: >100 µmoL/L No inhibitory activity	4.2.3.7.5.1 to 4.2.3.7.5.3
Inhibition of Cav1.2 channel	CHO cells stably expressing human Cav1.2 calcium channel were treated with 0.001-100 µmol/L of M1, M2, or M4 to assess their inhibitory activities against Cav1.2 calcium channel current.	M1, M2, and M4: >100 µmoL/L No inhibitory activity	
Inhibition of hERG channel	HEK293 cells stably expressing hERG were treated with 30 and 300 µmol/L of M1 or M2 or 30, 100 and 300 µmol/L of M4 to assess their inhibitory activities against hERG potassium channel current.	M1, M2, and M4: >300 µmoL/L No inhibitory activity	4.2.3.7.5.4 to 4.2.3.7.5.6

5.7.4 Toxicologic evaluation of impurities

Impurities detected in the proposed manufacturing process for the drug substance, PF-01323624, PF-03817968-09, PF-06238566, PF-07094402, PF-07097547-24, PF-07297478, and PF-07103166 (CTD 4.2.3.7.6.1 to 4.2.3.7.6.3, 4.2.3.7.6.5, 4.2.3.7.6.6, 4.2.3.7.6.7, 4.2.3.7.6.9) were not mutagenic in the Ames assays. PF-07085579, PF-07275639, and PF-07216658 were mutagenic in the Ames assays (Table 27). PF-07216658 was further evaluated in an *in vivo* mutation assay in transgenic mice and was considered a mutagenic substance (Table 27). PF-07085579 and PF-07275639 are classified as Class 2 impurities and considered of little safety concern because the levels of these impurities in the drug substance are individually controlled below the threshold of toxicological concern (TTC). The lowest genotoxic dose of PF-07216658 was 100 mg/kg, i.e., the lowest dose in the *in vivo* mutation assay, and following dose response assessment using the 50% benchmark response value, the permissible daily exposure (PDE) to PF-07216658 was established at 1.36 µg/kg/day based on the lower confidence bound of the benchmark dose (BMDL), 16.3 mg/kg/day.

Table 27. Overview of genotoxicity studies on impurities

Type of study		Test system	Metabolic activation (Treatment time)	Name and concentrations or doses of impurity	Test result	Attached document CTD
In vitro	Ames assay	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP 2*uvrA*	S9−/+	PF-07085579 0,[a] 1.7, 5.4, 17, 52, 164, 512, 1,600, 5,000 µg/plate	Positive	4.2.3.7.6.4
		Salmonella typhimurium: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP 2*uvrA*	S9−/+	PF-07275639 0,[a] 313, 625, 1,250, 2,500, 5,000 µg/plate	Positive	4.2.3.7.6.8
		Salmonella typhimurium: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP 2*uvrA*	S9−/+	PF-07216658 0,[a] 15, 50, 150, 500, 1,500, 5,000 µg/plate	Positive	4.2.3.7.6.10
		Salmonella typhimurium: TA1535	S9+	PF-07216658 0,[a] 250, 750, 1,500, 3,000, 5,000 µg/plate	Positive	
		Salmonella typhimurium: TA1535	S9+	PF-07216658 0,[a] 262, 790, 1,570, 3,140, 5240 µg/plate	Positive	
In vivo	Mutation assay in Tg mice	Male Big Blue® Tg mouse Liver/Duodenum		PF-07216658 0, 100, 300, 600 mg/kg/day (oral, 28 days)	Liver: Positive Duodenum: Positive	4.2.3.7.6.12

a) DMSO
Tg: Transgenic

In order to qualify impurities PF-07103164, PF-07216658, and PF-07103166, a 13-week repeated oral dose

toxicity study with the drug substance spiked with these 3 impurities was conducted in rats (Table 28). The occurrence of abnormal findings was similar between spiked and unspiked samples, and there was also no difference in the NOAEL.

Table 28. Overview of repeated oral dose toxicity study with the drug substance spiked with impurities

Test system	Route of adminis-tration	Duration of dosing	Doses (mg/kg)	Noteworthy findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (Wistar)	Oral gavage	13 weeks (QD)	Drug substance: 30 Drug substance spiked with impurities[a]: 30 Vehicle: 0	[Drug substance] 30: decreases in blood white blood cell count/lymphocyte count/large unstained cells/eosinophil count, decreased weights of the spleen/thymus, decreased lymphocyte cellularity of the spleen/thymus/mesenteric lymph node (male and female), decreased blood neutrophil count, decreased incidence/severity of mononuclear cell infiltration of the prostate gland (male) [Drug substance spiked with impurities] 30: decreases in blood white blood cell count/lymphocyte count/large unstained cells/eosinophil count, decreased weights of the spleen/thymus, decreased lymphocyte cellularity of the spleen/thymus/mesenteric lymph node (male and female), decreased blood neutrophil count, small thymus, decreased incidence/severity of mononuclear cell infiltration of the prostate gland (male)	Drug substance spiked with impurities: 30 Drug substance: 30	4.2.3.7.6.13

a) Drug substance contains 0.44% PF-07103164, 0.44% PF-07216658, and 0.43% PF-07103166.

5.R Outline of the review conducted by PMDA

5.R.1 Systemic toxicity

5.R.1.1 Effects on immune system

PMDA's view:

As findings suggestive of immunosuppression reflective of the JAK inhibitory effect of abrocitinib, an increased susceptibility to viral infection in cynomolgus monkeys, findings suggestive of viral opportunistic infection in rats, etc., were observed. Thus, the safety of abrocitinib in humans at risk of or with infectious disease needs to be discussed, taking account of clinical study results [see Section 7.R.3].

5.R.1.2 Effects on red blood cell parameters

PMDA's view:

With respect to the effects of abrocitinib on red blood cell parameters, similar changes have been observed also with the currently approved other JAK inhibitors (tofacitinib, baricitinib, upadacitinib, filgotinib, etc.) (Review Report on Xeljanz Tablets 5 mg as of February 28, 2013, Review Report on Olumiant tablets 2 mg and 4 mg as of May 19, 2017, Review Report on Rinvoq Tablets 7.5 mg and 15 mg as of November 14, 2019, Review Report on Jyseleca Tablets 100 mg and 200 mg as of August 26, 2020). Since these changes are considered abnormal findings related to JAK inhibition, the safety of abrocitinib in humans needs to be discussed, taking account of clinical study results [see Section 7.R.3].

5.R.1.3 Effects on hepatic function

PMDA's view:

Although toxicity studies of abrocitinib showed no histological findings suggestive of serious liver injury such as hepatocyte necrosis, as abnormalities in blood liver function markers were noted in both rats and cynomolgus monkeys, the safety of abrocitinib in humans needs to be discussed, taking account of clinical study results [see Section 7.R.3].

5.R.2 Carcinogenicity

PMDA's view:

Given the following points, the possibility that immunosuppression due to chronic administration of abrocitinib is associated with an increased risk of malignancy in humans cannot be ruled out. This risk of malignancy needs to be managed carefully, taking account of discussion on the risks and benefits of abrocitinib in patients in clinical practice in Section 7.R.3.

● Abrocitinib tended to increase spontaneous tumor development at exposures less than the human exposure in a rat carcinogenicity study. Immunosuppression such as decreased NK cells following administration of abrocitinib generally increases the risk of malignancy, and it has been reported that patients who receive immunosuppressive drugs are susceptible to developing a lymphoproliferative disorder (*Int J Toxicol*. 2010; 29: 435-66).

● Other JAK inhibitors, tofacitinib and peficitinib, also increased spontaneous tumor development associated with immunosuppression in rat carcinogenicity studies, and the development of malignancies has been reported in clinical studies (Review Report on Xeljanz Tablets 5 mg as of February 28, 2013, Review Report on Smyraf Tablets 50 mg and 100 mg as of February 14, 2019).

5.R.3 Effects on embryos/fetuses/parturition/pups

PMDA's view:

Only in rat and rabbit preliminary embryo-fetal studies, external malformations were observed in a few animals dosed with abrocitinib and were possibly related to abrocitinib, whereas the results of these studies showed no clear teratogenic risk of abrocitinib. However, since evident skeletal or visceral malformations have been observed with other JAK inhibitors (Review Report on Xeljanz Tablets 5 mg as of February 28, 2013, Review Report on Olumiant tablets 2 mg and 4 mg as of May 19, 2017, Review Report on Rinvoq Tablets 7.5 mg and 15 mg as of November 14, 2019, Review Report on Jyseleca Tablets 100 mg and 200 mg as of August 26, 2020), abrocitinib should also be considered to have potential teratogenic risk as a class effect of JAK inhibitors. Taking also into account that abrocitinib has been shown to affect fetal development and parturition and potentially cause fetal lethality and dystocia, abrocitinib should be contraindicated in pregnant women or women who may be pregnant.

The applicant's explanation:

As the risk of abrocitinib when used in women during early pregnancy cannot be ruled out, the package insert will include the information on the specific toxicological findings and effects of abrocitinib.

5.R.4 Bone effects

PMDA's view:

Based on the results of non-clinical evaluation of bone toxicity, bone toxicity considered related to JAK inhibition observed in juvenile rats following repeated administration of abrocitinib was not noted in young cynomolgus monkeys with open epiphyses. Thus, it is likely that there are species differences. Bone physiology and bone development are similar for cynomolgus monkeys and humans. Based on evaluation in cynomolgus monkeys, abrocitinib is unlikely to affect bone development and bone fragility during secondary sexual characteristics in humans. The effects of abrocitinib on bone development and bone fragility during secondary sexual characteristics in humans will be discussed in Section 7.R.3.3, taking also account of assessment of the height standard deviation scores and the incidences of adverse events such as fractures in clinical studies.

5.R.5 Safety assessment of mutagenic impurities

PMDA considers that the PDE for a mutagen should be established based on the results from a carcinogenicity study of the relevant substance. Thus, PMDA concluded that concerning a mutagenic impurity present in the drug substance, PF-07216658, it is not appropriate to establish the PDE based on the BMDL after dose response assessment using the benchmark response value of the data from the *in vivo* mutation assay. PMDA instructed the applicant to control the impurity levels in the drug substance at the TTC-based limit, and the applicant agreed to follow the instruction.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

The applicant submitted the following biopharmaceutic studies as reference data: an absolute bioavailability study, a relative bioavailability study, and a bioequivalence study.

In the clinical development of abrocitinib, 3 types of formulations (Formulation 1 [oral solution/suspension], Formulation 2 [the 10-, 50-, and 100-mg film-coated tablets], Formulation 3 [the 100-mg film-coated tablet]) were mainly used.[14)] Study B7451032 demonstrated the bioequivalence between Formulation 3 and the commercial 200-mg tablet. An *in vitro* dissolution testing demonstrated the bioequivalence among the commercial 50-mg, 100-mg, and 200-mg tablets.

Concentrations of abrocitinib, M1, M2, and M4 in human plasma or urine were determined by LC-MS/MS (LLOQ, plasma [1 ng/mL for abrocitinib, M1, and M4, 5 ng/mL for M2], urine [10 ng/mL for abrocitinib]). Unless otherwise specified, doses are expressed in terms of abrocitinib, and pharmacokinetic parameters and the data are expressed as the mean ± SD.

[14)] Formulation 1 was used in phase I studies (Studies B7451001, B7451004, and B7451008). Formulation 2 was used in a phase I study (Study B7451004) and phase II studies (Studies B7451005 and B7451006). Formulation 3 was used in phase I studies (Studies B7451017, B7451019, B7451026, B7451028, B7451032, B7451043, B7451020, B7451021, B7451027, B7451016, B7451022, B7451033, and B7451034) and phase III studies (Studies B7451012, B7451013, B7451014, B7451015, B7451029, and B7451036).

6.1.1 Absolute bioavailability study (CTD 5.3.1.1.1, Study B7451008 [July 2017 to September 2017])

Non-Japanese healthy subjects (N = 6) received a single oral dose of unlabeled abrocitinib 200 mg under fasting conditions followed by an oral dose (Part A) or an intravenous dose (Part B) of ^{14}C-abrocitinib 80 μg, and the fraction absorbed and absolute bioavailability of abrocitinib were determined.

In Part A and Part B, 85.0 ± 6.0% (at 240 hours after oral administration) and 93.8 ± 0.7% (at 144 hours after intravenous administration) of the radioactivity were recovered in urine, and the fraction absorbed after oral administration was estimated at 91%. The dose-normalized AUC_{inf} values following oral administration of unlabeled abrocitinib 200 mg and following intravenous administration of ^{14}C-abrocitinib 80 μg were 9.78 ± 3.76 and 15.7 ± 2.17 (ng·hr/mL/mg), respectively, and the absolute bioavailability [90% confidence interval (CI)] was estimated at 60% [46%, 78%]. As metabolites of abrocitinib, M1, M2, M3, M4, M6, M7, m/z 340-5, 372-1, 358-1, 356-1a, and 356-2 were detected in the pooled plasma, urine, and feces from all subjects, and M5 and M8 (356-1) were also found in the pooled plasma and urine.

6.1.2 Relative bioavailability study (CTD 5.3.1.2.1, Study B7451004 [June 2014 to August 2014])

A randomized, open-label, 3-treatment, 3-period, crossover study was conducted in non-Japanese healthy subjects (N = 12) to evaluate the bioavailability of Formulation 2 relative to Formulation 1 after a single oral dose under fasting conditions and the effect of food on the bioavailability of Formulation 2. The results are shown in Table 29.

Table 29. Pharmacokinetic parameters of a single oral dose of abrocitinib

Formulation (Dosing condition)	N	C_{max} (μg/mL)	AUC_{last} (μg·h/mL)	AUC_{inf} (μg·h/mL)	t_{max} (h)	Geometric least-squares mean ratio [a] [90% CI]		
						C_{max}	AUC_{last}	AUC_{inf}
Formulation 1/400 mg (Fasted)	11	2.34 ± 0.995	11.0 ± 4.08	11.1 ± 4.04	0.517 [0.500, 4.02]			
Formulation 2/100-mg tablet × 4 (Fasted)	12	1.88 ± 0.906	10.9 ± 4.24	11.0 ± 4.16	2.00 [0.533, 6.00]	0.795 [0.629, 1.00]	0.965 [0.895, 1.04]	0.965 [0.903, 1.03]
Formulation 2/100-mg tablet × 4 (Fed)	12	1.62 ± 0.326	11.1 ± 3.85	11.1 ± 3.85	4.00 [2.00, 8.00]	0.956 [0.762, 1.20]	1.02 [0.948, 1.10]	1.01 [0.944, 1.07]

Mean ± SD, Median [Range] for t_{max}

a) Ratio of fasted Formulation 2 to fasted Formulation 1/Ratio of fed Formulation 2 to fasted Formulation 2

6.1.3 Bioequivalence study (CTD 5.3.1.2.2, Study B7451032 [July 2019 to December 2019])

The study consisted of Part A and Part B.

In Part A, a randomized, open-label, 4-treatment, 4-period, crossover study was conducted in non-Japanese healthy subjects to estimate the relative bioavailability of the commercial tablet formulation or the variant tablet formulation with slow dissolution rate (200-mg tablet × 1) compared to Formulation 3 (100-mg tablet × 2) under fasting conditions and the effect of food on the bioavailability of the commercial tablet formulation.[15)] The results are shown in Table 30.

[15)] Food effect was evaluated using a high-fat meal (approximately 800-1,000 kcal and approximately 50% fat).

Table 30. Pharmacokinetic parameters of a single oral dose of abrocitinib

Formulation (Dosing condition)	N	C_{max} (μg/mL)	AUC_{last} (μg·h/mL)	AUC_{inf} (μg·h/mL)	t_{max} (h)	Geometric least-squares mean ratio[a] [90% CI]		
						C_{max}	AUC_{last}	AUC_{inf}
Formulation 3/100-mg tablet × 2 (Fasted)	16	1.02 ± 0.478	4.47 ± 2.44	4.49 ± 2.45	1.00 [0.500, 6.00]			
Commercial formulation/200-mg tablet × 1 (Fasted)	15	1.01 ± 0.850	4.02 ± 2.35	4.06 ± 2.34	1.00 [0.500, 6.02]	0.900 [0.690, 1.17]	0.950 [0.865, 1.04]	0.956 [0.875, 1.04]
Variant tablet/200-mg tablet × 1 (Fasted)	15	1.18 ± 0.519	4.70 ± 2.58	4.71 ± 2.58	1.00 [0.500, 6.05]	1.20 [0.983, 1.48]	1.14 [1.05, 1.22]	1.13 [1.05, 1.22]
Commercial formulation/200-mg tablet × 1 (Fed)	15	1.10 ± 0.402	4.95 ± 2.55	4.96 ± 2.55	3.00 [1.00, 6.02]	1.29 [1.05, 1.58]	1.27 [1.18, 1.37]	1.26 [1.17, 1.36]

Mean ± SD, Median [Range] for t_{max}
a) Ratio of fasted commercial formulation/fasted variant tablet formulation to fasted Formulation 3
Ratio of fed commercial formulation to fasted commercial formulation

In Part B, a randomized, open-label, 2-treatment, 4-period, crossover study was conducted in non-Japanese healthy subjects to estimate the bioequivalence of the commercial formulation (200-mg tablet × 1) relative to Formulation 3 (100-mg tablet × 2) under fasting conditions. The results are shown in Table 31. The 90% confidence intervals for the geometric least-squares mean ratios of C_{max}, AUC_{last}, and AUC_{inf} for the commercial formulation vs. Formulation 3 met the predefined bioequivalence criteria (0.80-1.25).

Table 31. Pharmacokinetic parameters of a single oral dose of abrocitinib

Formulation (Dosing condition)	N	C_{max} (μg/mL)	AUC_{last} (μg·h/mL)	AUC_{inf} (μg·h/mL)	t_{max} (h)	Geometric least-squares mean ratio[a] [90% CI]		
						C_{max}	AUC_{last}	AUC_{inf}
Formulation 3/100 mg × 2 (Fasted)	57	1.05 ± 0.472	4.12 ± 2.06	4.27 ± 2.03	1.00 [0.500, 4.02]			
Commercial formulation/200 mg × 1 (Fasted)	60	1.09 ± 0.557	4.24 ± 2.30	4.27 ± 2.30	1.00 [0.500, 4.00]	1.01 [0.901, 1.14]	1.01 [0.961, 1.06]	0.999 [0.955, 1.05]

Mean ± SD, Median [Range] for t_{max}
a) Ratio vs. fasted Formulation 3

6.2 Clinical pharmacology

The applicant submitted clinical pharmacology data, in the form of the results from studies in healthy subjects and subjects with hepatic or renal impairment and pharmacokinetic interaction studies, the results of a population pharmacokinetic analysis, etc. *In vitro* studies using human biomaterials are described in Sections 4.1, 4.2, 4.3, and 4.5. Unless otherwise specified, doses are expressed in terms of abrocitinib, and pharmacokinetic parameters and the data are expressed as the mean ± SD.

6.2.1 Studies in healthy subjects

6.2.1.1 Phase I study (CTD 5.3.3.1.1, Study B7451001 [May 2013 to June 2014])

The pharmacokinetics following a single oral dose or multiple oral doses of abrocitinib or placebo in Japanese and non-Japanese healthy adult subjects were evaluated. The pharmacokinetic parameters of abrocitinib are shown in Table 32. The C_{max} was dose-proportional over the dose range tested, and the AUC_{inf} was more than dose-proportional between 400 and 800 mg.

Table 32. Pharmacokinetic parameters of abrocitinib following a single oral dose or multiple oral doses

Subjects	Regimen[a)]	Dose	N	C_{max} (μg/mL)	$AUC^{b)}$ (μg·h/mL)	$t_{1/2}$ (h)	t_{max} (h)	CL/F (L/h)	V_z/F (L)
Non-Japanese	Single dose	3 mg	6	0.0175 ± 0.0040	0.0547 ± 0.0241[c)]	2.09 ± 0.87[c)]	0.634 [0.517, 1.27]	72.2 ± 52.9[c)]	177 ± 48[c)]
		10 mg	6	0.0479 ± 0.0115	0.154 ± 0.074[c)]	1.94 ± 0.54[c)]	0.750 [0.500, 1.00]	74.6 ± 26.4[c)]	192 ± 31[c)]
		30 mg	6	0.154 ± 0.057	0.419 ± 0.152	2.53 ± 1.32	0.792 [0.500, 1.08]	82.3 ± 37.4	300 ± 205
		100 mg	7	0.503 ± 0.198	1.56 ± 0.63[c)]	3.59 ± 2.08[c)]	0.550 [0.500, 1.03]	72.5 ± 26.2[c)]	376 ± 277[c)]
		200 mg	6	1.12 ± 0.34	2.99 ± 0.92	3.89 ± 2.20	0.767 [0.500, 1.17]	71.5 ± 18.5	375 ± 194
		400 mg	6	2.46 ± 1.05	10.5 ± 2.7	3.55 ± 1.11	1.50 [0.517, 4.03]	40.6 ± 11.2	207 ± 96
		800 mg	6	3.91 ± 0.94[c)]	28.8 ± 9.2[c)]	5.27 ± 2.92[c)]	4.03 [2.00, 4.30][c)]	30.4 ± 10.6[c)]	246 ± 212[c)]
Japanese		800 mg	10	3.98 ± 1.59	23.4 ± 8.5[d)]	4.67 ± 1.57[d)]	2.02 [1.00, 4.00]	39.6 ± 18.1[d)]	273 ± 156[d)]
Non-Japanese	QD	30 mg	6	0.175 ± 0.074[c)]	0.526 ± 0.172[c)]	2.76 ± 1.11[c)]	0.550 [0.500, 1.03][c)]	63.5 ± 25.8[c)]	240 ± 117[c)]
		100 mg	5	0.726 ± 0.219	2.14 ± 0.97	2.99 ± 0.76	0.550 [0.500, 2.02]	54.4 ± 21.8	227 ± 89
		200 mg	6	1.23 ± 0.30	4.49 ± 1.64	3.06 ± 0.24	1.05 [1.02, 1.05]	48.9 ± 15.2	213 ± 55
		400 mg	8	3.38 ± 0.60[e)]	18.7 ± 4.4[e)]	4.85 ± 1.86[e)]	0.767 [0.500, 2.05][e)]	22.5 ± 5.2[e)]	152 ± 50[e)]
	BID	100 mg	6	0.813 ± 0.279	3.23 ± 0.97	5.03 ± 2.34	0.759 [0.500, 1.02]	33.5 ± 10.6	252 ± 189
	BID	200 mg	5	2.70 ± 0.21	14.1 ± 3.6	5.17 ± 1.60	1.02 [0.500, 1.07]	15.0 ± 4.1	112 ± 48
Japanese	BID	200 mg	9	2.37 ± 0.69[e)]	9.06 ± 2.60[e)]	3.64 ± 0.83[e)]	0.500 [0.500, 1.00][e)]	23.7 ± 6.8[e)]	123 ± 38[e)]

Mean ± SD, Median [Range] for t_{max}

a) Oral administration, b) AUC_{inf} after a single dose, AUC_{tau} after multiple doses, c) N = 5, d) N = 9, e) N = 6

6.2.2 Intrinsic factor pharmacokinetic studies

6.2.2.1 Study in subjects with hepatic impairment (CTD 5.3.3.3.1, Study B7451020 [October 2018 to April 2019])

The pharmacokinetics of abrocitinib following a single oral dose of abrocitinib 200 mg under fasting conditions were determined in 16 non-Japanese subjects with hepatic impairment (8 subjects with mild [Child-Pugh A] hepatic impairment and 8 subjects with moderate [Child-Pugh B] hepatic impairment) and 8 non-Japanese subjects with normal hepatic function. Table 33 shows the pharmacokinetic parameters of abrocitinib, M1, and M2. Although the AUC_{inf} of abrocitinib increased and the metabolite-to-parent exposure ratios decreased with increasing severity of hepatic impairment, there was no clinically relevant effect on the AUC_{inf} of the active moiety.

Table 33. Effect of hepatic function on pharmacokinetic parameters of abrocitinib and its metabolites

Analyte	Degree of hepatic impairment	N	C_{max} (μg/mL)[a)]	AUC_{inf} (μg·h/mL)[b)]	$t_{1/2}$ (h)	Geometric least-squares mean ratio [90% CI] (Hepatic impairment/Normal hepatic function)	
						C_{max}	AUC_{inf}
Abrocitinib	Normal	8	1.44 ± 0.48	6.63 ± 3.84	4.66 ± 2.72	—	—
	Mild	8	1.36 ± 0.50	7.69 ± 1.88	5.09 ± 2.23	0.94 [0.63, 1.42]	1.33 [0.86, 2.06]
	Moderate	8	1.59 ± 0.61	9.41 ± 3.44	7.25 ± 2.92	1.06 [0.70, 1.58]	1.54 [1.00, 2.38]
M1	Normal	8	0.263 ± 0.107	1.16 ± 0.30	5.17 ± 2.76	—	—
	Mild	8	0.0635 ± 0.0360	0.397 ± 0.219	4.99 ± 2.16	0.23 [0.15, 0.36]	0.32 [0.22, 0.46]
	Moderate	8	0.0780 ± 0.0442	0.619 ± 0.362	6.78 ± 2.37	0.29 [0.18, 0.44]	0.49 [0.34, 0.71]
M2	Normal	8	0.268 ± 0.081	1.59 ± 0.503[d)]	4.24 ± 2.63[d)]	—	—
	Mild	8	0.145 ± 0.040	1.20 ± 0.271	5.31 ± 2.39	0.55 [0.40, 0.76]	0.78 [0.59, 1.03]
	Moderate	8	0.127 ± 0.042	1.38 ± 0.471	6.36 ± 1.93	0.47 [0.34, 0.64]	0.86 [0.65, 1.14]
Active moiety[c)]	Normal	8	2.43 ± 0.47	12.7 ± 4.3[d)]	—	—	—
	Mild	8	1.91 ± 0.63	11.8 ± 2.5	—	0.76 [0.57, 1.00]	0.96 [0.73, 1.26]
	Moderate	8	2.13 ± 0.68	14.3 ± 3.7	—	0.84 [0.64, 1.11]	1.15 [0.87, 1.51]

Mean ± SD

a) μmol/L for active moiety, b) μmol·h/L for active moiety, c) The sum of unbound exposures of abrocitinib, M1, and M2 (each expressed in molar units and adjusted for relative potencies), d) N = 7

6.2.2.2 Study in subjects with renal impairment (CTD 5.3.3.3.2, Study B7451021 [October 2018 to November 2019])

The pharmacokinetics of abrocitinib following a single oral dose of abrocitinib 200 mg under fasting conditions were determined in 15 non-Japanese subjects with renal impairment (7 subjects with moderate [eGFR 30-

59 mL/min] renal impairment and 8 subjects with severe [eGFR <30 mL/min] renal impairment) and 8 non-Japanese subjects with normal renal function (eGFR ≥90 mL/min). Table 34 shows the pharmacokinetic parameters of abrocitinib, M1, and M2. The AUC_{inf} values of the metabolites and active moiety increased with increasing severity of renal impairment, suggesting the need for dose adjustment in patients with moderate or severe renal impairment [see Section 6.R.3].

Table 34. Effect of renal function on pharmacokinetic parameters of abrocitinib and its metabolites

Analyte	Degree of renal impairment	N	C_{max} (μg/mL)[a)]	AUC_{inf} (μg·h/mL)[b)]	$t_{1/2}$ (h)	Geometric least-squares mean ratio [90% CI] (Renal impairment/Normal renal function)	
						C_{max}	AUC_{inf}
Abrocitinib	Normal	8	1.31 ± 0.62	5.66 ± 3.57	4.86 ± 2.28	—	—
	Moderate	7	1.69 ± 0.51	9.39 ± 3.94	4.74 ± 1.64	1.38 [0.94, 2.05]	1.83 [1.17, 2.86]
	Severe	8	1.37 ± 0.65	6.92 ± 4.07[d)]	4.45 ± 3.96[d)]	0.99 [0.57, 1.71]	1.21 [0.68, 2.15]
M1	Normal	8	0.214 ± 0.091	0.934 ± 0.321	4.68 ± 2.33	—	—
	Moderate	7	0.226 ± 0.147	1.44 ± 0.53	5.92 ± 2.38	1.00 [0.60, 1.66]	1.54 [1.05, 2.26]
	Severe	8	0.393 ± 0.228	2.70 ± 1.01	6.39 ± 2.90	1.68 [0.97, 2.90]	2.87 [1.97, 4.19]
M2	Normal	8	0.253 ± 0.080	1.54 ± 0.46	4.87 ± 2.99	—	—
	Moderate	7	0.338 ± 0.072	4.20 ± 1.40	6.73 ± 1.19	1.37 [1.07, 1.77]	2.70 [1.97, 3.70]
	Severe	8	0.443 ± 0.112	8.67 ± 2.30	13.0 ± 5.13	1.78 [1.36, 2.33]	5.71 [4.47, 7.30]
Active moiety[c)]	Normal	8	2.22 ± 0.75	10.7 ± 4.4	—	—	—
	Moderate	7	2.86 ± 0.58	21.6 ± 6.2	—	1.34 [1.02, 1.75]	2.10 [1.55, 2.86]
	Severe	8	2.87 ± 0.81	29.7 ± 7.7[d)]	—	1.29 [0.93, 1.81]	2.91 [2.17, 3.89]

Mean ± SD
a) μmol/L for active moiety, b) μmol·h/L for active moiety, c) The sum of unbound exposures of abrocitinib, M1, and M2 (each expressed in molar units and adjusted for relative potencies), d) N = 7

6.2.3 Pharmacokinetic interaction studies[16)]

A total of 8 studies were conducted to evaluate the drug-drug interaction potential of abrocitinib. The geometric least-squares mean ratios of pharmacokinetic parameters of abrocitinib or concomitant drugs administered in combination to those administered alone are shown in Table 35 and Table 36. Although coadministration with CYP2C19/CYP2C9 inhibitors increased the AUC_{inf} of the active moiety, and coadministration with a CYP2C19/CYP2C9 inducer reduced the AUC_{inf} of the active moiety, coadministration with an OAT3 inhibitor did not result in a clinically significant increase in the AUC_{inf} of the active moiety. Abrocitinib had no effects on the pharmacokinetics of oral contraceptives and the substrates of CYP3A4/5, BCRP, OAT3, and MATE1/2K, but was suggested to increase the exposure of a P-gp substrate.

16) CTD 5.3.3.4.1, Study B7451016 [September 2018 to January 2019]; CTD 5.3.3.4.2, Study B7451017 [September to December 2018]; CTD 5.3.3.4.3, Study B7451019 [September to December 2018]; CTD 5.3.3.4.4, Study B7451022 [July to October 2018]; CTD 5.3.3.4.5, Study B7451026 [November 2018 to December 2019]; CTD 5.3.3.4.6, Study B7451033 [January to April 2019]; CTD 5.3.3.4.7, Study B7451034 [January to March 2019]; CTD 5.3.3.4.8, Study B7451043 [May to July 2019]

Table 35. Effect of concomitant drugs on pharmacokinetic parameters of abrocitinib and its metabolites

Dosing regimen (Oral administration)		N	Analyte	Geometric least-squares mean ratio [90% CI] (Coadministration/Alone)	
Concomitant drug	Abrocitinib			C_{max}	AUC_{inf}
Fluvoxamine 50 mg QD	100 mg single dose	12	Abrocitinib	1.84 [1.33, 2.55]	2.75 [2.39, 3.17]
			M1	0.42 [0.32, 0.54]	0.79 [0.73, 0.86]
			M2	0.71 [0.59, 0.87]	1.13 [1.06, 1.20]
			Active moiety[a)]	1.33 [1.00, 1.78]	1.91 [1.74, 2.10]
Fluconazole 200 mg QD	100 mg single dose	12	Abrocitinib	1.92 [1.54, 2.39]	4.83 [3.84, 6.07]
			M1	0.095 [0.078, 0.12]	0.26 [0.23, 0.29]
			M2	0.24 [0.20, 0.28]	0.61 [0.38, 1.00]
			Active moiety[a)]	1.23 [1.08, 1.42]	2.55 [2.42, 2.69]
Rifampicin 600 mg QD	200 mg single dose	12	Abrocitinib	0.21 [0.14, 0.30]	0.12 [0.093, 0.17]
			M1	1.68 [1.16, 2.45]	0.95 [0.80, 1.12]
			M2	1.45 [1.03, 2.05]	0.73 [0.68, 0.78]
			Active moiety[a)]	0.69 [0.50, 0.94]	0.44 [0.41, 0.47]
Probenecid 1000 mg BID	200 mg single dose	12	Abrocitinib	1.21 [0.93, 1.59]	1.28 [1.15, 1.42]
			M1	1.37 [1.16, 1.61]	1.77 [1.64, 1.91]
			M2	1.35 [1.15, 1.57]	2.25 [2.08, 2.43]
			Active moiety[a)]	1.30 [1.04, 1.63]	1.66 [1.52, 1.80]

a) The sum of unbound exposures of abrocitinib, M1, and M2 (each expressed in molar units and adjusted for relative potencies)

Table 36. Effect of abrocitinib on pharmacokinetic parameters of concomitant drugs

Dosing regimen (Oral administration)		N	Geometric least-squares mean ratio [90% CI] (Coadministration/Alone)	
Abrocitinib	Concomitant drug (single dose)		C_{max}	AUC[a)]
200 mg QD	Ethinylestradiol 30 μg	15	1.07 [0.99, 1.16]	1.19 [1.12, 1.26]
200 mg QD	Levonorgestrel 150 μg	15	0.86 [0.76, 0.98]	0.98 [0.87, 1.10]
200 mg QD (Day 2)	Midazolam 2 mg	25	0.86 [0.77, 0.96]	0.84 [0.79, 0.90]
200 mg QD (Day 7)	Midazolam 2 mg	25	0.94 [0.84, 1.04]	0.92 [0.86, 0.99]
200 mg single dose	Dabigatran 75 mg	20	1.40 [0.92, 2.13]	1.53 [1.09, 2.15]
200 mg QD	Rosuvastatin 10 mg	12	0.99 [0.86, 1.14]	1.02 [0.93, 1.12]
200 mg QD	Metformin 500 mg	12	0.88 [0.81, 0.96]	0.94 [0.88, 1.01]

a) AUC_{inf} for ethinylestradiol, midazolam, dabigatran, and rosuvastatin, AUC_{last} for levonorgestrel and metformin

6.2.4 QT/QTc study (CTD 5.3.4.1.1, Study B7451027 [July 2018 to October 2018])

A 3-treatment, 3-period, placebo- and positive-controlled, crossover study was conducted in non-Japanese healthy subjects (N = 36) to determine the effect of a single oral dose of abrocitinib 600 mg on the QT interval. Moxifloxacin (a single oral dose of 400 mg) was used as a positive control.

The relationship between the plasma abrocitinib concentration and the change from baseline in the QT interval corrected using the Fridericia formula was analyzed using a pre-specified linear mixed-effects model. In the worst case scenario (the expected highest exposure after administration of a clinical dose of abrocitinib), i.e., the predicted abrocitinib exposure after abrocitinib 200 mg QD dosing in combination with fluconazole in patients with moderate to severe AD (C_{max} 2,757[17)] or 2,156[18)] ng/mL), the upper bound of the 90% confidence interval for the predicted placebo-corrected change from baseline in the QT interval (9.52 and 7.49 ms, respectively) was estimated to be below 10 msec. Thus, the risk of QT interval prolongation associated with abrocitinib should be low.

The largest difference between moxifloxacin and placebo [90% CI] was 14.83 [12.58, 17.08] msec (at 2 hours post-dose).

[17)] Predicted from clinical pharmacology studies and a preliminary population pharmacokinetic analysis.
[18)] Predicted from the final updated population pharmacokinetic model including phase III data

6.3 Population pharmacokinetic analysis (CTD 5.3.3.5.1)

Using plasma abrocitinib concentrations obtained from 11 Japanese and foreign clinical studies in healthy adult subjects or patients with psoriasis or AD [19)] (995 subjects [7,795 sampling points]), a population pharmacokinetic analysis (NONMEM version 7.4.3) was performed.

The pharmacokinetics of abrocitinib were described by a 2-compartment model with parallel zero- and first-order absorption, time-dependent F, and decreasing CL with increasing time and dose, and the base model included the effects of concomitant medications (rifampicin, fluconazole, fluvoxamine) on CL and F and food and formulation effects on absorption parameters. Based on the results of covariate exploration,[20)] race, patient type, hepatic impairment, age, dose, and sex for F and body weight for CL, Q, V_c, and V_p were selected as covariates in the final model.

The final model-predicted pharmacokinetic parameters after abrocitinib 200 mg QD dosing in Japanese and non-Japanese AD patients are shown in Table 37. Among the incorporated covariates, concomitant medications (rifampicin, fluconazole, fluvoxamine) and hepatic impairment had clinically relevant effects on the pharmacokinetic of abrocitinib.

Table 37. Final model-predicted pharmacokinetic parameters at steady state after abrocitinib 200 mg QD dosing

Race	Body weight (kg)	C_{max} (μg/mL)	AUC_{tau} (μg·h/mL)
Japanese	67.8	1.581	8.275
Non-Japanese Asian	66	1.602	8.371
Others	71.6	1.538	8.071
Western (White, Black, unknown)	76	1.153	5.795

6.R Outline of the review conducted by PMDA

6.R.1 Ethnic differences in pharmacokinetics of abrocitinib

The applicant's explanation about the impact of ethnic factors on the pharmacokinetics of abrocitinib:

In Study B7451001 [see Section 6.2.1.1], following 10-day administration of abrocitinib 200 mg BID, the C_{max} was similar in Japanese and non-Japanese healthy subjects, and the AUC_{tau} was approximately 36% lower in Japanese subjects than in non-Japanese subjects. The number of subjects was limited, and inter-individual variability was large. On the other hand, the population pharmacokinetic analysis [see Section 6.3] predicted approximately 37% higher C_{max} and 43% higher AUC_{tau} in Japanese AD patients than in non-Japanese patients, whereas the distributions of the predicted C_{max} and AUC_{tau} values of abrocitinib in Japanese and non-Japanese patients overlapped (Figure 3).

Based on the above, it was concluded that there are no marked differences in the pharmacokinetics of

[19)] Studies B7451001, B7451004, B7451017, B7451019, B7451020, B7451027, and B7451043 in healthy subjects, Study B7451005 in patients with moderate to severe psoriasis, Studies B7451006, B7451012, and B7451013 in patients with moderate to severe AD

[20)] The potential covariates evaluated were sex, age (continuous or adolescent vs. adult), race, patient type (healthy subject, AD, psoriasis), hepatic impairment (normal, mild, moderate), and concomitant medications for CL, sex, age (continuous or adolescent vs. adult), race, and patient type (healthy subject, AD, psoriasis) for V_c, food (fasted or fed), formulation (oral suspension, tablets), and dose for absorption parameters (k_a, k_0, Tk_0, Ak_1, ALAG1), and food (fasted, high-fat meal, food not controlled), formulation (oral suspension, tablets), concomitant medications, and dose for bioavailability. In addition, visual assessment of diagnostic plots was made.

abrocitinib between Japanese and non-Japanese populations.

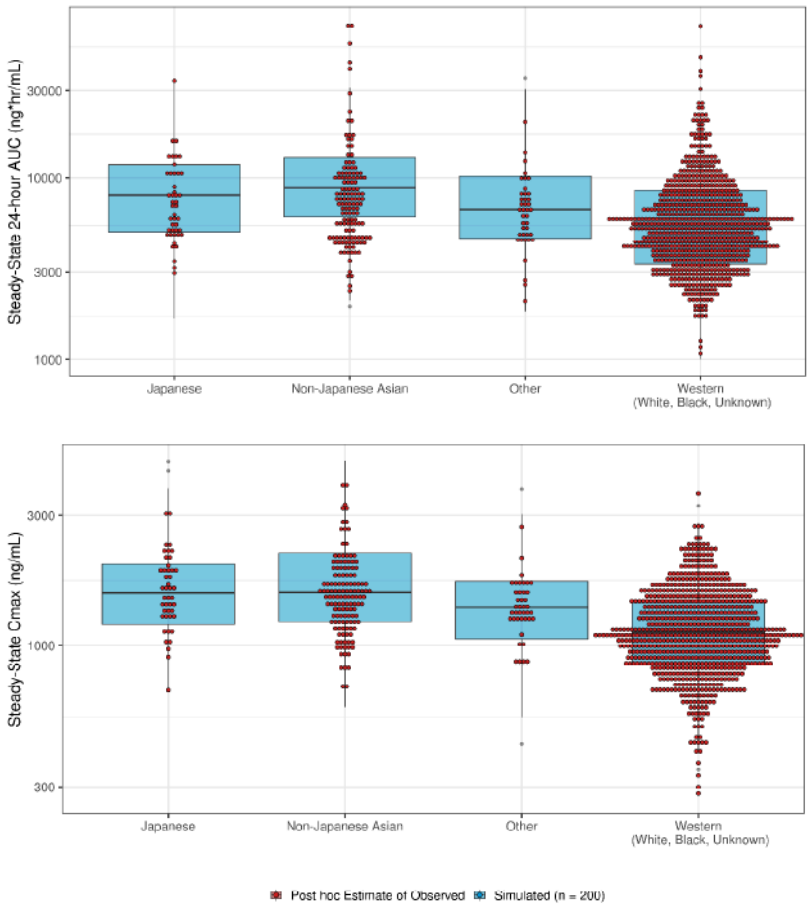


Figure 3. Steady-state C_{max} and AUC by race predicted by population pharmacokinetic analysis

PMDA accepted the above explanation.

6.R.2 Effects of CYP2C19 and CYP2C9 polymorphisms on pharmacokinetics of abrocitinib

The applicant's explanation about the effects of CYP2C19 and CYP2C9 polymorphisms on the pharmacokinetics of abrocitinib:

Using the data from phase I studies,[21)] the effects of CYP2C19 and CYP2C9 genotypes on the AUC or C_{max} of abrocitinib and its active moiety were analyzed by a linear model. The results are shown in Table 38. It was concluded that there are no clinically relevant phenotype-related differences in the exposures of abrocitinib and its active moiety.

[21)] Studies B7451001, B7451004, B7451008, B7451017, B7451019, B7451020, B7451021, B7451027, B7451028, B7451032, and B7451043

Table 38. Effects of CYP2C19 and CYP2C9 genotypes on pharmacokinetic parameters of abrocitinib

Overall Phenotype	Phenotype Combinations (CYP2C19[a)]/CYP2C9 [b)])	N (%)	Abrocitinib		Active moiety
			AUC	C_{max}	AUC
Wild type	EM/EM	76 (26)	—	—	—
Elevated	RM/EM or UM/EM	63 (22)	0.810 [0.689, 0.953]	0.809 [0.703, 0.931]	0.990 [0.801, 1.224]
Mixed	RM/IM	13 (4)	1.150 [0.871, 1.519]	0.983 [0.764, 1.265]	1.264 [0.939, 1.703]
Reduced	Others	121 (41)	1.333 [1.159, 1.534]	1.071 [0.946, 1.213]	1.114 [0.956, 1.296]

Ratio vs. wild type [90% CI]
a) UM: *17/*17; RM: *1/*17; EM: *1/*1; IM: *1 or *17/* (2,3,4); PM: * (2,3,4)/* (2,3,4)
b) EM: *1/*1; IM: *1/*(2/3); PM: *(2/3)/*(2/3)

PMDA accepted the above explanation.

6.R.3 Dose adjustment of abrocitinib in patients with hepatic or renal impairment

The applicant's explanation about the need for dose adjustment of abrocitinib in patients with hepatic or renal impairment:

In a clinical pharmacology study in subjects with hepatic impairment [see Section 6.2.2.1], although the metabolite-to-parent exposure ratios decreased in subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function, the AUC_{inf} of the active moiety was almost comparable. Thus, no dose adjustment of abrocitinib should be required in patients with mild or moderate hepatic impairment. Abrocitinib will be contraindicated in patients with severe hepatic impairment because there is not clinical experience with abrocitinib in these patients, and liver disease in addition to the immunosuppressive effects of abrocitinib, may further increase the risk of infections.

Table 39 shows the active moiety exposure ratio for subjects with renal impairment vs. subjects with normal renal function, based on the results of a clinical pharmacology study in subjects with renal impairment [see Section 6.2.2.2] and the results of an analysis of the correlation between the AUC_{inf} of the active moiety and eGFR in this study (Figure 4). Although abrocitinib exposure increases with increasing severity of renal impairment, no clinically meaningful increases are expected in patients with mild renal impairment, and no dose adjustment is required. On the other hand, the dose of abrocitinib should be reduced by half in patients with moderate renal impairment, taking account of the extent of increase in exposure. Also in patients with severe renal impairment including patients with end-stage renal disease (eGFR <15 mL/min/1.73 m^2), abrocitinib may be used at half the dose.

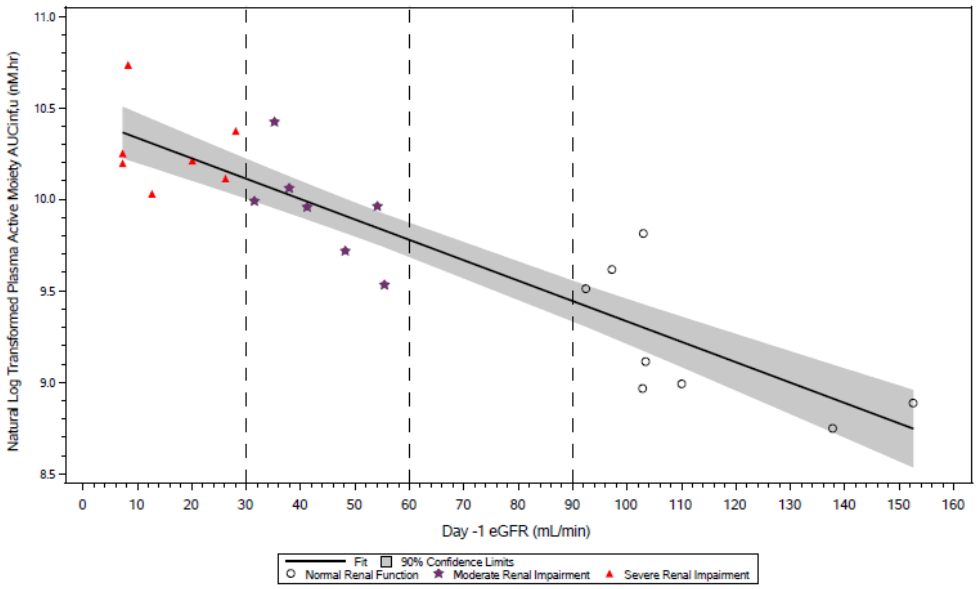


Figure 4. Correlation between active moiety AUC_{inf} and eGFR in Study B7451021

Table 39. Ratio of active moiety AUC after a single dose of abrocitinib for subjects with renal impairment vs. subjects with normal renal function

Degree of renal impairment	N	eGFR (mL/min)[a)]	Ratio of active moiety AUC (Renal impairment/Normal renal function)
Normal	8	112.39 [92.4, 152.6][b)]	—
Mild	—	75	1.44
		60	1.70
Moderate	7	43.36 [31.5, 55.4] [b)]	2.10
Severe	8	15.61 [7.3, 28.1] [b)]	2.91
End-stage renal disease	—	15	2.79
		5	3.12
		1	3.26

a) Mean [Range], b) Subject characteristic data from Study B7451021

PMDA accepted the applicant's explanation, except for the issue of patients with renal impairment. The need for dose adjustment in patients with renal impairment will be described in Section 7.R.6.2.

6.R.4 Drug interactions

The applicant's explanation about potential drug interactions in clinical use of abrocitinib, based on non-clinical pharmacokinetic data [see Sections 4.3 and 4.5] and the results from clinical pharmacokinetic interaction studies [see Section 6.2.3]:

Since coadministration of abrocitinib with strong CYP2C19 inhibitors, fluconazole or fluvoxamine, increased the AUC of abrocitinib active moiety by 2.55-fold or 1.91-fold, respectively [see Section 6.2.3], the package insert should advise that the dose of abrocitinib should be reduced by half in patients receiving strong CYP2C19 inhibitors. Coadministration with a strong CYP2C19 or CYP2C9 inducer, rifampicin, results in reduction of abrocitinib exposure, and the effectiveness of abrocitinib may be reduced. Thus, coadministration with such drugs should be avoided wherever possible, and the package insert will advise that switching to other drugs that do not induce or weakly induce CYP2C19 or CYP2C9 should be considered. As coadministration with abrocitinib may increase the blood concentrations of dabigatran via P-gp inhibition, a relevant precautionary statement will be included in the package insert etc.

PMDA accepted the above explanation.

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

The applicant submitted the main efficacy and safety evaluation data, in the form of the results from 6 studies presented in Table 40.

Table 40. Listing of main efficacy and safety clinical studies

Geographical location	Study ID	Phase	Study population	Number of subjects enrolled	Dosing regimen	Main endpoints
Foreign	B7451006 (Monotherapy)	IIb	Adult patients with moderate to severe AD who had a documented history of inadequate response to treatment with topical medications, or for whom topical treatments were otherwise medically inadvisable (eg, because of important side effects or safety risks)	(1) 49 (2) 51 (3) 56 (4) 55 (5) 56	(1) Abrocitinib 10 mg QD (2) Abrocitinib 30 mg QD (3) Abrocitinib 100 mg QD (4) Abrocitinib 200 mg QD (5) Placebo QD	Efficacy Safety
Foreign	B7451012 (Monotherapy)	III	Patients with moderate to severe AD who had a documented recent history of inadequate response to treatment with topical medications, or for whom topical treatments were otherwise medically inadvisable (eg, because of important side effects or safety risks), or who had required systemic therapies for control of their disease (≥12 years of age)	(1) 156 (2) 154 (3) 77	(1) Abrocitinib 100 mg QD (2) Abrocitinib 200 mg QD (3) Placebo QD	Efficacy Safety
Global	B7451013 (Monotherapy)	III	Patients with moderate to severe AD who had a documented recent history of inadequate response to treatment with topical medications, or for whom topical treatments were otherwise medically inadvisable (eg, because of important side effects or safety risks), or who had required systemic therapies for control of their disease (≥12 years of age)	(1) 158 (2) 155 (3) 78	(1) Abrocitinib 100 mg QD (2) Abrocitinib 200 mg QD (3) Placebo QD	Efficacy Safety
Global	B7451029 (TCS combination)	III	Adult patients with moderate to severe AD who had a documented recent history of inadequate response to treatment with medicated topical therapy for AD, or who had required systemic therapies for control of their disease	(1) 238 (2) 226 (3) 242 (4) 131	(1) Abrocitinib 100 mg QD (2) Abrocitinib 200 mg QD (3) Dupixent (4) Placebo	Efficacy Safety
Global	B7451036 (TCS combination)	III	Adolescent patients with moderate to severe AD who had a documented history of inadequate response to treatment with medicated topical therapy for AD, or who had been treated with systemic therapy for AD (12 to <18 years of age)	(1) 95 (2) 94 (3) 96	(1) Abrocitinib 100 mg QD (2) Abrocitinib 200 mg QD (3) Placebo QD	Efficacy Safety
Global	B7451015 (Long-term extension)	III	Patients who had completed the full treatment period of a qualifying parent phase III study (Study B7451012, Study B7451013, Study B7451029) OR had completed the full rescue treatment period of Study B7451014 OR had completed the full open-label run-in period of Study B7451014[a)]	(1) 725 (2) 865	(1) Abrocitinib 100 mg QD (2) Abrocitinib 200 mg QD	Efficacy Safety

a) An interim report submitted at filing (April 2020 Data Cutoff) contained unblinded subject data only because parent phase III studies were ongoing.

7.1 Phase IIb study

7.1.1 Foreign clinical study (Monotherapy, CTD 5.3.5.1.1, Study B7451006 [April 2016 to April 2017])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 5 countries or regions including the US, Canada, and Australia to characterize the dose-response relationship and safety of abrocitinib in AD patients who had a documented history of inadequate response to treatment with topical medications, such as topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI), or for whom topical treatments

were otherwise medically inadvisable (e.g., because of important side effects or safety risks) (target sample size, 250 subjects [50 per group]). Table 41 shows key inclusion criteria for the study.

Table 41. Key inclusion criteria

1. A clinical diagnosis of AD for at least 1 year and confirmed AD (Hanifin and Rajka criteria of AD) at the screening visit
2. Inadequate response to treatment with topical medications given for at least 4 weeks, or for whom topical treatments were otherwise medically inadvisable (e.g., because of important side effects or safety risks) within 12 months of the first dose of study drug
3. EASI score ≥12
4. Affected body surface area (BSA) ≥10%
5. IGA score ≥3
6. 18-75 years of age

Abrocitinib 10, 30, 100, or 200 mg or placebo was to be administered orally once daily for 12 weeks. Subjects were to start the emollient ≥7 days prior to baseline through to the end of study visit. Except for oral antihistamines, all concomitant medications for AD were prohibited throughout the study period.

Two hundred sixty-seven subjects who were randomized and received at least 1 dose of study drug (49 in the 10 mg group, 51 in the 30 mg group, 56 in the 100 mg group, 55 in the 200 mg group, 56 in the placebo group) were included in the safety analysis set. Among the safety analysis set, 263 subjects after excluding all subjects from 1 study site due to major protocol deviations (1 in the 30 mg group, 1 in the 100 mg group, 1 in the 200 mg group, 1 in the placebo group) were included in the full analysis set (FAS), which was used as the efficacy analysis population.

The discontinuation rates were 44.9% (22 of 49 subjects) in the 10 mg group, 47.1% (24 of 51 subjects) in the 30 mg group, 33.9% (19 of 56 subjects) in the 100 mg group, 30.9% (17 of 55 subjects) in the 200 mg group, and 50.0% (28 of 56 subjects) in the placebo group. The main reasons for discontinuations were adverse events not related to study drug (12.2% [6 of 49 subjects] in the 10 mg group, 11.8% [6 of 51 subjects] in the 30 mg group, 16.1% [9 of 56 subjects] in the 100 mg group, 12.7% [7 of 55 subjects] in the 200 mg group, 8.9% [5 of 56 subjects] in the placebo group), consent withdrawal (8.2% [4 of 49 subjects] in the 10 mg group, 7.8% [4 of 51 subjects] in the 30 mg group, 5.4% [3 of 56 subjects] in the 100 mg group, 7.3% [4 of 55 subjects] in the 200 mg group, 10.7% [6 of 56 subjects] in the placebo group), etc.

The primary efficacy endpoint of the Investigator's Global Assessment (IGA) (0/1) response rate at Week 12 is shown in Table 42.

Table 42. IGA (0/1) response rate at Week 12 (FAS, NRI)

	10 mg	30 mg	100 mg	200 mg	Placebo
IGA (0/1) response rate [% (n)]	10.9 (5/46)	8.9 (4/45)	29.6 (16/54)	43.8 (21/48)	5.8 (3/52)
Difference from placebo [95% CI][a)]	1.8 [-0.7, 4.4]	6.0 [-1.8, 13.8]	21.5 [5.5, 37.6]	38.2 [19.7, 56.6]	

Subjects who did not discontinue from the study, but had missing IGA data at Week 12 were excluded from the FAS.
a) Estimated using a 3-parameter Emax model.

The incidences of adverse events were 69.4% (34 of 49 subjects) in the 10 mg group, 66.7% (34 of 51 subjects) in the 30 mg group, 76.8% (43 of 56 subjects) in the 100 mg group, 74.5% (41 of 55 subjects) in the 200 mg

group, and 57.1% (32 of 56 subjects) in the placebo group. The main events are shown in Table 43.

No deaths were reported.

The incidences of serious adverse events were 4.1% (2 of 49 subjects) in the 10 mg group (asthma and condition aggravated; and malignant melanoma [1 subject each]), 5.4% (3 of 56 subjects) in the 100 mg group (atopic dermatitis and condition aggravated; eczema herpeticum; and asthma [1 subject each]), 3.6% (2 of 55 subjects) in the 200 mg group (pneumonia; and pulmonary embolism [1 subject each]), and 3.6% (2 of 56 subjects) in the placebo group (dermatitis and condition aggravated; and atopic dermatitis [1 subject each]). A causal relationship to study drug could not be ruled out for 1 case in the 100 mg group (eczema herpeticum) and 1 case in the 200 mg group (pneumonia).

The incidences of adverse events leading to discontinuation were 16.3% (8 of 49 subjects) in the 10 mg group, 13.7% (7 of 51 subjects) in the 30 mg group, 21.4% (12 of 56 subjects) in the 100 mg group, 14.5% (8 of 55 subjects) in the 200 mg group, and 16.1% (9 of 56 subjects) in the placebo group.

The incidences of adverse drug reactions were 16.3% (8 of 49 subjects) in the 10 mg group, 25.5% (13 of 51 subjects) in the 30 mg group, 26.8% (15 of 56 subjects) in the 100 mg group, 30.9% (17 of 55 subjects) in the 200 mg group, and 19.6% (11 of 56 subjects) in the placebo group.

Table 43. Adverse events reported by ≥5% of subjects in any group (Safety analysis set)

Event term	10 mg (N = 49)	30 mg (N = 51)	100 mg (N = 56)	200 mg (N = 55)	Placebo (N = 56)
Atopic dermatitis	8 (16.3)	9 (17.6)	7 (12.5)	7 (12.7)	7 (12.5)
Viral upper respiratory tract infection	5 (10.2)	6 (11.8)	10 (17.9)	7 (12.7)	5 (8.9)
Upper respiratory tract infection	3 (6.1)	5 (9.8)	3 (5.4)	5 (9.1)	5 (8.9)
Nausea	3 (6.1)	3 (5.9)	1 (1.8)	8 (14.5)	1 (1.8)
Diarrhoea	3 (6.1)	1 (2.0)	1 (1.8)	5 (9.1)	1 (1.8)
Headache	2 (4.1)	5 (9.8)	5 (8.9)	4 (7.3)	2 (3.6)
Dizziness	0	1 (2.0)	0	3 (5.5)	0
Contact dermatitis	0	0	3 (5.4)	0	0

n (%)

7.2 Phase III studies

7.2.1 Foreign clinical study (Monotherapy, CTD 5.3.5.1.2, Study B7451012 [December 2017 to March 2019])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 8 countries or regions including the US, Canada, and Germany to evaluate the superiority of abrocitinib monotherapy to placebo and its safety in AD patients who had a documented recent history of inadequate response to treatment with topical medications, such as TCS or TCI, or for whom topical treatments were otherwise medically inadvisable (e.g., because of important side effects or safety risks), or who had required systemic therapies for control of their disease (target sample size, 375 subjects [150 in the 100 mg group, 150 in the 200 mg group, 75 in the placebo

group][22]). Table 44 shows key inclusion criteria for the study.

Table 44. Key inclusion criteria

1. A clinical diagnosis of AD for at least 1 year and confirmed AD (Hanifin and Rajka criteria for AD) at the screening and baseline visits
2. Documented recent history within 6 months before the screening visit of inadequate response to treatment with topical medications for at least 4 weeks, or for whom topical treatments were otherwise medically inadvisable (eg, because of important side effects or safety risks), or who had required systemic therapies for control of their disease
3. EASI score ≥16
4. Affected BSA ≥10%
5. IGA score ≥3
6. Pruritus NRS score ≥4
7. 12 years of age or older and body weight ≥40kg

Abrocitinib 100 or 200 mg or placebo was to be administered orally once daily for 12 weeks.

Subjects were permitted to use emollients and oral antihistamines throughout the study period, and other concomitant medications for AD were prohibited throughout the study period. Patients completing the 12-week treatment period of the study had the option to enter a long-term extension study B7451015.

Three hundred eighty-seven subjects who were randomized[23] and received at least 1 dose of study drug (156 in the 100 mg group, 154 in the 200 mg group, 77 in the placebo group) were included in the FAS and in the safety analysis set, and the FAS was used as the efficacy analysis population.

The discontinuation rates were 13.5% (21 of 156 subjects) in the 100 mg group, 11.0% (17 of 154 subjects) in the 200 mg group, and 20.8% (16 of 77 subjects) in the placebo group. The main reasons for discontinuations were adverse events (5.8% [9 of 156 subjects] in the 100 mg group, 5.8% [9 of 154 subjects] in the 200 mg group, 9.1% [7 of 77 subjects] in the placebo group), subject's consent withdrawal (3.2% [5 of 156 subjects] in the 100 mg group, 1.9% [3 of 154 subjects] in the 200 mg group, 5.2% [4 of 77 subjects] in the placebo group), etc.

The co-primary efficacy endpoints were the IGA (0/1) response rate and Eczema Area and Severity Index (EASI)-75 response rate at Week 12. As shown in Table 45, pairwise comparisons between abrocitinib 100 mg and placebo and between abrocitinib 200 mg and placebo showed statistically significant differences in both endpoints, demonstrating the superiority of abrocitinib 100 mg and 200 mg to placebo.

[22] A sample of 150 subjects randomized to abrocitinib 200 mg QD, 150 subjects randomized to abrocitinib 100 mg QD, and 75 subjects randomized to placebo was expected to provide at least 95% power to detect a difference in IGA (0/1) response rate between abrocitinib 200 mg QD (or abrocitinib 100 mg QD) and placebo, assuming 100 mg, 200 mg, and placebo response rates of 26%, 26%, and 6%, respectively, at Week 12 and a two-sided significance level of 5%. This was also to provide at least 99% power to detect a difference in EASI-75 response rate between abrocitinib 200 mg QD (or abrocitinib 100 mg QD) and placebo, assuming 100 mg, 200 mg, and placebo response rates of 45%, 45%, and 15%, respectively, at Week 12 and a two-sided significance level of 5%.

[23] Randomization was stratified by baseline disease severity (IGA score 3 vs. 4) and age (<18 years vs. ≥18 years).

Table 45. Results of co-primary efficacy endpoints (FAS, NRI)

	100 mg	200 mg	Placebo
IGA (0/1) response rate at Week 12	23.7 (37/156)	43.8 (67/153)	7.9 (6/76)
Difference from placebo [95% CI][a)] Adjusted *P*-value[a), b)]	15.8 [6.8, 24.8] 0.0037	36.0 [26.2, 45.7] <0.0001	
EASI-75 response rate at Week 12	39.7 (62/156)	62.7 (96/153)	11.8 (9/76)
Difference from placebo [95% CI][a)] Adjusted *P*-value[a), b)]	27.9 [17.4, 38.3] <0.0001	51.0 [40.5, 61.5] <0.0001	

% (n), Subjects who did not discontinue from the study, but had missing data at Week 12 were excluded from the FAS.
a) Cochran-Mantel-Haenszel test adjusted by randomization strata of baseline AD severity and age
b) A two-sided significance level of 5%. Graphical approach was used to adjust for multiplicity in hypothesis testing [For details, see Section 10].

The incidences of adverse events were 69.2% (108 of 156 subjects) in the 100 mg group, 77.9% (120 of 154 subjects) in the 200 mg group, and 57.1% (44 of 77 subjects) in the placebo group, and the main events are shown in Table 46.

No deaths were reported.

The incidences of serious adverse events were 3.2% (5 of 156 subjects) in the 100 mg group (retinal detachment; acute pancreatitis; appendicitis; dizziness; and seizure [1 subject each]), 3.2% (5 of 154 subjects) in the 200 mg group (asthma [2 subjects]; inflammatory bowel disease; peritonsillitis; and dehydration [1 subject each]), and 3.9% (3 of 77 subjects) in the placebo group (appendicitis; condition aggravated and meniscal degeneration; and atopic dermatitis [1 subject each]). A causal relationship to study drug could not be ruled out for 1 case in the 100 mg group (acute pancreatitis) and 1 case in the 200 mg group (inflammatory bowel disease).

The incidences of adverse events leading to discontinuation were 5.8% (9 of 156 subjects) in the 100 mg group, 5.8% (9 of 154 subjects) in the 200 mg group, and 9.1% (7 of 77 subjects) in the placebo group.

The incidences of adverse drug reactions were 25.6% (40 of 156 subjects) in the 100 mg group, 38.3% (59 of 154 subjects) in the 200 mg group, and 14.3% (11 of 77 subjects) in the placebo group.

Table 46. Adverse events reported by ≥2% of subjects in any group (Safety analysis set)

Event term	100 mg (N = 156)	200 mg (N = 154)	Placebo (N = 77)
Nasopharyngitis	23 (14.7)	18 (11.7)	8 (10.4)
Atopic dermatitis	22 (14.1)	8 (5.2)	13 (16.9)
Nausea	14 (9.0)	31 (20.1)	2 (2.6)
Headache	12 (7.7)	15 (9.7)	2 (2.6)
Upper respiratory tract infection	11 (7.1)	11 (7.1)	5 (6.5)
Fatigue	6 (3.8)	2 (1.3)	0
Dizziness	5 (3.2)	6 (3.9)	1 (1.3)
Oropharyngeal pain	5 (3.2)	6 (3.9)	0
Gastroenteritis	5 (3.2)	3 (1.9)	0
Vomiting	4 (2.6)	6 (3.9)	1 (1.3)
Conjunctivitis	4 (2.6)	4 (2.6)	0
Eczema infected	4 (2.6)	0	2 (2.6)
Blood creatine phosphokinase increased	3 (1.9)	5 (3.2)	0
Diarrhoea	3 (1.9)	4 (2.6)	2 (2.6)
Acne	1 (0.6)	4 (2.6)	0
Respiratory tract infection	0	4 (2.6)	0

n (%)

7.2.2 Global study (Monotherapy, CTD 5.3.5.1.3, Study B7451013 [June 2018 to August 2019])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 13 countries or regions including Japan, the US, and Poland to evaluate the superiority of abrocitinib monotherapy to placebo and its safety in AD patients who had a documented recent history of inadequate response to treatment with topical medications, such as TCS or TCI, or for whom topical treatments were otherwise medically inadvisable (e.g., because of important side effects or safety risks), or who had required systemic therapies for control of their disease (target sample size, 375 subjects [150 in the 100 mg group, 150 in the 200 mg group, 75 in the placebo group][24]). Table 47 shows key inclusion criteria for the study.

Table 47. Key inclusion criteria

1. A clinical diagnosis of AD for at least 1 year and confirmed AD (Hanifin and Rajka criteria for AD) at the screening and baseline visits
2. Documented recent history within 6 months before the screening visit of inadequate response to treatment with topical medications for at least 4 weeks, or for whom topical treatments were otherwise medically inadvisable (eg, because of important side effects or safety risks), or who had required systemic therapies for control of their disease
3. EASI score ≥16
4. Affected BSA ≥10%
5. IGA score ≥3
6. Pruritus NRS score ≥4
7. 12 years of age or older and body weight ≥40kg

Abrocitinib 100 or 200 mg or placebo was to be administered orally once daily for 12 weeks.

Except for oral antihistamines, all concomitant medications for AD were prohibited throughout the study period. Patients were permitted to use emollients during the study. Patients completing the 12-week treatment period of the study had the option to enter a long-term extension study B7451015.

Three hundred ninety-one subjects who were randomized[23] and received at least 1 dose of study drug (158 in the 100 mg group, 155 in the 200 mg group, 78 in the placebo group) were included in the FAS and in the

[24] A sample of 150 subjects randomized to abrocitinib 200 mg QD, 150 subjects randomized to abrocitinib 100 mg QD, and 75 subjects randomized to placebo was expected to provide at least 95% power to detect a difference in IGA (0/1) response rate between abrocitinib 200 mg QD (or abrocitinib 100 mg QD) and placebo, assuming 100 mg, 200 mg, and placebo response rates of 26%, 26%, and 6%, respectively, at Week 12 and a two-sided significance level of 5%. This was also to provide at least 99% power to detect a difference in EASI-75 response rate between abrocitinib 200 mg QD (or abrocitinib 100 mg QD) and placebo, assuming 100 mg, 200 mg, and placebo response rates of 45%, 45%, and 15%, respectively, at Week 12 and a two-sided significance level of 5%.

safety analysis set, and the FAS was used as the efficacy analysis population.

The discontinuation rates were 13.3% (21 of 158 subjects) in the 100 mg group, 9.0% (14 of 155 subjects) in the 200 mg group, and 33.3% (26 of 78 subjects) in the placebo group. The main reasons for discontinuations were subject's consent withdrawal (3.8% [6 of 158 subjects] in the 100 mg group, 0.6% [1 of 155 subjects] in the 200 mg group, 11.5% [9 of 78 subjects] in the placebo group), adverse events (3.2% [5 of 158 subjects] in the 100 mg group, 3.2% [5 of 155 subjects] in the 200 mg group, 10.3% [8 of 78 subjects] in the placebo group), etc.

Among the FAS, there were 44 subjects in the Japanese subgroup (15 in the 100 mg group, 22 in the 200 mg group, 7 in the placebo group). The discontinuation rates in the Japanese subgroup were 13.3% (2 of 15 subjects) in the 100 mg group, 13.6% (3 of 22 subjects) in the 200 mg group, and 57.1% (4 of 7 subjects) in the placebo group. The reasons for discontinuations were lack of efficacy (13.3% [2 of 15 subjects] in the 100 mg group, 9.1% [2 of 22 subjects] in the 200 mg group, 57.1% [4 of 7 subjects] in the placebo group) and an adverse event (4.5% [1 of 22 subjects] in the 200 mg group).

The co-primary efficacy endpoints were the IGA (0/1) response rate and the EASI-75 response rate at Week 12. As shown in Table 48, pairwise comparisons between abrocitinib 100 mg and placebo and between abrocitinib 200 mg and placebo showed statistically significant differences in both endpoints, demonstrating the superiority of abrocitinib 100 mg and 200 mg to placebo. The results in the Japanese subgroup are shown in Table 48.

Table 48. Results of primary efficacy endpoints (FAS, NRI)

		100 mg	200 mg	Placebo
Overall population	IGA (0/1) response rate at Week 12	28.4 (44/155)	38.1 (59/155)	9.1 (7/77)
	Difference from placebo [95% CI][a)] Adjusted *P*-value[a), b)]	19.3 [9.6, 29.0] 0.0008	28.7 [18.6, 38.8] <0.0001	
	EASI-75 response rate at Week 12	44.5 (69/155)	61.0 (94/154)	10.4 (8/77)
	Difference from placebo [95% CI][a)] Adjusted *P*-value[a), b)]	33.9 [23.3, 44.4] <0.0001	50.5 [40.0, 60.9] <0.0001	
Japanese subgroup	IGA (0/1) response rate at Week 12	13.3 (2/15)	9.1 (2/22)	14.3 (1/7)
	Difference from placebo [95% CI]	-1.0 [-32.1, 30.2]	-5.2 [-33.8, 23.4]	
	EASI-75 response rate at Week 12	26.7 (4/15)	45.5 (10/22)	0 (0/7)
	Difference from placebo [95% CI]	26.7 [-2.0, 55.3]	45.5 [18.0, 72.9]	

% (n), Subjects who did not discontinue from the study, but had missing data at Week 12 were excluded from the FAS.
a) Cochran-Mantel-Haenszel test adjusted by randomization strata of baseline AD severity and age
b) A two-sided significance level of 5%. Graphical approach was used to adjust for multiplicity in hypothesis testing [For details, see Section 10].

The incidences of adverse events were 62.7% (99 of 158 subjects) in the 100 mg group, 65.8% (102 of 155 subjects) in the 200 mg group, and 53.8% (42 of 78 subjects) in the placebo group, and the main events are shown in Table 49.

Death occurred in 0.6% (1 of 158) of subjects in the 100 mg group (sudden death), but its causal relationship to study drug was denied.

The incidences of serious adverse events were 3.2% (5 of 158 subjects) in the 100 mg group (sudden death; herpangina; bacterial osteomyelitis and staphylococcal bacteraemia; pneumonia; and atopic dermatitis [1 subject each]), 1.3% (2 of 155 subjects) in the 200 mg group (anaphylactic shock; and femoral neck fracture [1 subject each]), and 1.3% (1 of 78 subjects) in the placebo group (eczema herpeticum and staphylococcal infection]). A causal relationship to study drug could not be ruled out for 2 cases in the 100 mg group (herpangina; and pneumonia) and 1 case in the placebo group (eczema herpeticum and staphylococcal infection).

The incidences of adverse events leading to discontinuation were 3.8% (6 of 158 subjects) in the 100 mg group, 3.2% (5 of 155 subjects) in the 200 mg group, and 12.8% (10 of 78 subjects) in the placebo group.

The incidences of adverse drug reactions were 22.2% (35 of 158 subjects) in the 100 mg group, 36.1% (56 of 155 subjects) in the 200 mg group, and 21.8% (17 of 78 subjects) in the placebo group.

Table 49. Adverse events reported by ≥2% of subjects in any group (Safety analysis set)

Event term	100 mg (N = 158)	200 mg (N = 155)	Placebo (N = 78)
Nasopharyngitis	20 (12.7)	12 (7.7)	5 (6.4)
Upper respiratory tract infection	14 (8.9)	5 (3.2)	3 (3.8)
Nausea	12 (7.6)	22 (14.2)	2 (2.6)
Atopic dermatitis	9 (5.7)	6 (3.9)	12 (15.4)
Headache	9 (5.7)	12 (7.7)	2 (2.6)
Cough	4 (2.5)	1 (0.6)	2 (2.6)
Pyrexia	4 (2.5)	1 (0.6)	0
Herpes simplex	3 (1.9)	6 (3.9)	1 (1.3)
Blood creatine phosphokinase increased	3 (1.9)	5 (3.2)	2 (2.6)
Sinusitis	3 (1.9)	0	2 (2.6)
Acne	2 (1.3)	9 (5.8)	0
Vomiting	2 (1.3)	8 (5.2)	1 (1.3)
Abdominal pain upper	2 (1.3)	6 (3.9)	0
Diarrhoea	2 (1.3)	3 (1.9)	3 (3.8)
Oral herpes	2 (1.3)	2 (1.3)	2 (2.6)
Urticaria	1 (0.6)	1 (0.6)	2 (2.6)
Folliculitis	0	5 (3.2)	2 (2.6)
Thrombocytopenia	0	5 (3.2)	0

n (%)

In the Japanese subgroup, the incidences of adverse events were 60.0% (9 of 15 subjects) in the 100 mg group, 50.0% (11 of 22 subjects) in the 200 mg group, and 14.3% (1 of 7 subjects) in the placebo group, and the main events are shown in Table 50. There were no deaths or serious adverse events. Adverse events leading to discontinuation occurred in 4.5% (1 of 52) of subjects in the 200 mg group (palpitations, nausea, chills, and headache), and a causal relationship to study drug could not be ruled out for all those events. The incidences of adverse drug reactions were 6.7% (1 of 15 subjects) in the 100 mg group and 13.6% (3 of 22 subjects) in the 200 mg group.

Table 50. Adverse events reported by ≥2 subjects in any group (Japanese subgroup, Safety analysis set)

Event term	100 mg (N = 15)	200 mg (N = 22)	Placebo (N = 7)
Nasopharyngitis	3 (20.0)	1 (4.5)	0
Herpes simplex	2 (13.3)	2 (9.1)	0
Pyrexia	2 (13.3)	0	0
Nausea	1 (6.7)	2 (9.1)	0
Acne	0	3 (13.6)	0
Headache	0	2 (9.1)	0

n (%)

7.2.3 Global study (TCS combination, CTD 5.3.5.1.4, Study B7451029 [August 2018 to March 2020])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 18 countries or regions including Japan, the US, and Poland to evaluate the superiority of abrocitinib to placebo and its safety in combination with background TCS in AD patients who had a documented recent history of inadequate response to treatment with medicated topical therapy for AD, such as TCS or TCI, or who had required systemic therapies for control of their disease (target sample size, 700 subjects [200 each in the 100 mg, 200 mg, and dupilumab groups, 100 in the placebo group][25]). Table 51 shows key inclusion criteria for the study.

Table 51. Key inclusion criteria

1. A clinical diagnosis of AD for at least 1 year and confirmed AD (Hanifin and Rajka criteria for AD) at the screening and baseline visits
2. Documented recent history within 6 months before the screening visit of inadequate response to treatment with medicated topical therapy for AD for at least 4 weeks, or who had required systemic therapies for control of their disease
3. EASI score ≥16
4. Affected BSA ≥10%
5. IGA score ≥3
6. Pruritus NRS score ≥4
7. During the last 7 days prior to baseline, the subject must have used only emollient at least twice daily, with response to treatment remaining inadequate at baseline.
8. 18 years of age or older

The total treatment period of the study was 20 weeks. Abrocitinib 100 or 200 mg or placebo was to be administered orally once daily, or dupilumab 300 mg[26] was to be administered subcutaneously every other week for 16 weeks. Following Week 16, subjects previously receiving placebo were to receive abrocitinib 100 or 200 mg orally once daily as per their randomized allocation. Subjects previously receiving abrocitinib 100 or 200 mg were to continue on their respective dose, and subjects previously receiving dupilumab were to take oral placebo once daily. These alterations to study treatment was conducted while maintaining the blind. Patients completing the entire 20-week treatment period of the study had the option to enter a long-term extension study B7451015. Emollients were to be used at least twice daily, starting at least 7 days before baseline and continued throughout the study, and TCS therapy was to be started at baseline and then stopped upon lesion resolution.[27] Concomitant use of oral antihistamines was permitted during the study.

[25] A sample of 200 subjects randomized to abrocitinib 200 mg QD, 200 subjects randomized to abrocitinib 100 mg QD, and 100 subjects randomized to placebo was expected to provide at least 96% power to detect a difference in IGA (0/1) response rate between either dose of abrocitinib and placebo, assuming 100 mg, 200 mg, and placebo response rates of 32%, 32%, and 12%, respectively, at Week 12 and a two-sided significance level of 5%. This was also to provide at least 99% power to detect a difference in EASI-75 response rate between either dose of abrocitinib and placebo, assuming 100 mg, 200 mg, and placebo response rates of 53%, 53%, and 23%, respectively, at Week 12 and a two-sided significance level of 5%.

[26] With a loading dose of 600 mg at baseline

[27] Medium potency TCS (e.g., triamcinolone acetonide 0.1% cream or fluocinolone acetonide 0.025% ointment [equivalent to strong class TCS in the Japanese classification]) were to be applied once daily to body areas with active lesions. After lesions were under control ("clear" or "almost clear"), treat once daily for a further 7 days, and then stop. If lesions returned, then resume treatment with medium potency TCS. Low potency TCS (i.e., hydrocortisone 1% cream) or TCI were to be applied to body areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.) with active lesions or to body areas where continued treatment with medium potency TCS was considered unsafe.

Eight hundred thirty-seven subjects who were randomized[28] and received at least 1 dose of study drug (238 in the 100 mg group, 226 in the 200 mg group, 242 in the Dupixent group, 131 in the placebo group) were included in the FAS and in the safety analysis set, and the FAS was used as the efficacy analysis population.

The discontinuation rates through Week 16 were 8.8% (21 of 238 subjects) in the 100 mg group, 8.0% (18 of 226 subjects) in the 200 mg group, 7.9% (19 of 242 subjects) in the Dupixent group, and 10.7% (14 of 131 subjects) in the placebo group. The main reasons for discontinuations were adverse events (2.1% [5 of 238 subjects] in the 100 mg group, 3.5% [8 of 226 subjects] in the 200 mg group, 2.5% [6 of 242 subjects] in the Dupixent group, 3.8% [5 of 131 subjects] in the placebo group), subject's consent withdrawal (3.8% [9 of 238 subjects] in the 100 mg group, 1.3% [3 of 226 subjects] in the 200 mg group, 2.5% [6 of 242 subjects] in the Dupixent group, 3.8% [5 of 131 subjects] in the placebo group), etc.

Among the FAS, there were 76 subjects in the Japanese subgroup (19 in the 100 mg group, 25 in the 200 mg group, 21 in the Dupixent group, 11 in the placebo group). The discontinuation rates through Week 16 were 16.0% (4 of 25 subjects) in the 200 mg group and 9.5% (2 of 21 subjects) in the Dupixent group. The main reasons for discontinuations were adverse events (12.0% [3 of 25 subjects] in the 200 mg group, 4.8% [1 of 21 subjects] in the Dupixent group), etc.

The co-primary efficacy endpoints were the IGA (0/1) response rate and the EASI-75 response rate at Week 12. As shown in Table 52, pairwise comparisons between abrocitinib 100 mg and placebo and between abrocitinib 200 mg and placebo showed statistically significant differences in both endpoints, demonstrating the superiority of abrocitinib 100 mg and 200 mg to placebo. The results in the Japanese subgroup are shown in Table 52.

Table 52. Results of primary efficacy endpoints (FAS, NRI)

		100 mg	200 mg	Dupixent	Placebo
Overall population	IGA (0/1) response rate at Week 12	36.6 (86/235)	48.4 (106/219)	36.5 (88/241)	14.0 (18/129)
	Difference from placebo [95% CI][a)] Adjusted *P*-value[a), b)]	23.1 [14.7, 31.4] <0.0001	34.8 [26.1, 43.5] <0.0001	22.5 [14.2, 30.9]	
	EASI-75 response rate at Week 12	58.7 (138/235)	70.3 (154/219)	58.1 (140/241)	27.1 (35/129)
	Difference from placebo [95% CI][a)] Adjusted p-value[a), b)]	31.9 [22.2, 41.6) <0.0001	43.2 [33.7, 52.7] <0.0001	30.9 [21.2, 40.6]	
Japanese subgroup	IGA (0/1) response rate at Week 12	42.1 (8/19)	48.0 (12/25)	47.6 (10/21)	18.2 (2/11)
	Difference from placebo [95% CI]	23.9 [-7.9, 55.7]	29.8 [-0.2, 59.9]	29.4 [-1.8, 60.7]	
	EASI-75 response rate at Week 12	63.2 (12/19)	68.0 (17/25)	66.7 (14/21)	27.3 (3/11)
	Difference from placebo [95% CI]	35.9 [1.8, 70.0]	40.7 [8.7, 72.8]	39.4 [6.2, 72.5]	

% (n), Subjects who did not discontinue from the study, but had missing data at Week 12 were excluded from the FAS.
a) Cochran-Mantel-Haenszel test adjusted by baseline AD severity
b) A two-sided significance level of 5%. Graphical approach was used to adjust for multiplicity in hypothesis testing [For details, see Section 10].

The incidences of adverse events were 50.8% (121 of 238 subjects) in the 100 mg group, 61.9% (140 of 226 subjects) in the 200 mg group, 50.0% (121 of 242 subjects) in the Dupixent group, and 53.4% (70 of 131 subjects) in the placebo group, and the main events are shown in Table 53.

[28] Randomization was administered using center-based permuted blocks with a block size of 14.

No deaths were reported.

The incidences of serious adverse events were 2.5% (6 of 238 subjects) in the 100 mg group (pancytopenia; drug-induced liver injury; infectious diarrhoea; pneumonia, oral herpes, and interstitial lung disease; ankle fracture; and muscle injury and tendon injury [1 subject each]), 0.9% (2 of 226 subjects) in the 200 mg group (intervertebral disc protrusion; and uterine haemorrhage [1 subject each]), 0.8% (2 of 242 subjects) in the Dupixent group (meniscus injury; and invasive ductal breast carcinoma [1 subject each]), and 3.8% (5 of 131 subjects) in the placebo group (anaphylactic reaction; aspartate aminotransferase increased; breast mass, abdominal pain, pyrexia, night sweats, and chills; dyspnoea; and atopic dermatitis [1 subject each]). A causal relationship to study drug could not be ruled out for the events reported by 3 subjects in the 100 mg group (pancytopenia; drug-induced liver injury; and pneumonia, oral herpes, and interstitial lung disease) and the events reported by 2 subjects in the placebo group (aspartate aminotransferase increased; and atopic dermatitis).

The incidences of adverse events leading to discontinuation were 2.5% (6 of 238 subjects) in the 100 mg group, 4.4% (10 of 226 subjects) in the 200 mg group, 3.3% (8 of 242 subjects) in the Dupixent group, and 3.8% (5 of 131 subjects) in the placebo group.

The incidences of adverse drug reactions were 21.8% (52 of 238 subjects) in the 100 mg group, 30.5% (69 of 226 subjects) in the 200 mg group, 18.6% (45 of 242 subjects) in the Dupixent group, and 18.3% (24 of 131 subjects) in the placebo group.

Table 53. Adverse events reported by ≥2% of subjects in any group (Safety analysis set)

Event term	100 mg (N = 238)	200 mg (N = 226)	Dupixent (N = 242)	Placebo (N = 131)
Nasopharyngitis	22 (9.2)	15 (6.6)	23 (9.5)	9 (6.9)
Upper respiratory tract infection	12 (5.0)	9 (4.0)	9 (3.7)	6 (4.6)
Nausea	10 (4.2)	25 (11.1)	7 (2.9)	2 (1.5)
Headache	10 (4.2)	15 (6.6)	13 (5.4)	6 (4.6)
Acne	7 (2.9)	15 (6.6)	3 (1.2)	0
Blood creatine phosphokinase increased	7 (2.9)	6 (2.7)	2 (0.8)	3 (2.3)
Atopic dermatitis	7 (2.9)	3 (1.3)	2 (0.8)	5 (3.8)
Herpes simplex	5 (2.1)	8 (3.5)	2 (0.8)	1 (0.8)
Impetigo	5 (2.1)	0	0	0
Urinary tract infection	4 (1.7)	7 (3.1)	4 (1.7)	2 (1.5)
Dizziness	4 (1.7)	7 (3.1)	0	2 (1.5)
Diarrhoea	4 (1.7)	4 (1.8)	3 (1.2)	4 (3.1)
Folliculitis	4 (1.7)	4 (1.8)	2 (0.8)	4 (3.1)
Oral herpes	4 (1.7)	2 (0.9)	5 (2.1)	1 (0.8)
Conjunctivitis	2 (0.8)	3 (1.3)	15 (6.2)	3 (2.3)
Back pain	0	1 (0.4)	7 (2.9)	5 (3.8)

n (%)

In the Japanese subgroup, the incidences of adverse events were 63.2% (12 of 19 subjects) in the 100 mg group, 84.0% (21 of 25 subjects) in the 200 mg group, 57.1% (12 of 21 subjects) in the Dupixent group, and 45.4% (5 of 11 subjects) in the placebo group, and the main events are shown in Table 54.

No deaths or serious adverse events were reported.

The incidences of adverse events leading to discontinuation were 12.0% (3 of 25 subjects) in the 200 mg group (ALT increased and AST increased; nausea; and schizophrenia [1 subject each]) and 4.8% (1 of 21 subjects) in the Dupixent group (hepatic function abnormal]). A causal relationship to study drug could not be ruled out for 1 case in the 200 mg group (nausea).

The incidences of adverse drug reactions were 15.8% (3 of 19 subjects) in the 100 mg group, 36.0% (9 of 25 subjects) in the 200 mg group, and 28.6% (6 of 21 subjects) in the Dupixent group.

Table 54. Adverse events reported by ≥2 subjects in any group (Japanese subgroup, Safety analysis set)

Event term	100 mg (N = 19)	200 mg (N = 25)	Dupixent (N = 21)	Placebo (N = 11)
Nasopharyngitis	2 (10.5)	4 (16.0)	6 (28.6)	1 (9.1)
Folliculitis	2 (10.5)	1 (4.0)	0	0
Acne	1 (5.3)	6 (24.0)	2 (9.5)	0
Nausea	1 (5.3)	5 (20.0)	0	0
Herpes simplex	1 (5.3)	3 (12.0)	0	0
Headache	0	3 (12.0)	0	1 (9.1)
Herpes zoster	0	2 (8.0)	0	0
Musculoskeletal pain	0	0	0	2 (18.2)

n (%)

7.2.4 Global study (TCS combination, CTD 5.3.5.1.5, Study B7451036 [February 2019 to April 2020])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 13 countries or regions including Japan, the US, and Poland to evaluate the superiority of abrocitinib to placebo and its safety in combination with background TCS in AD patients who had a documented history of inadequate response to treatment with medicated topical therapy for AD, such as TCS or TCI, or a need for systemic therapy for AD (target sample size, 225 subjects [75 each in the 100 mg, 200 mg, and placebo groups][29]). Table 55 shows key inclusion criteria for the study.

Table 55. Key inclusion criteria

1. A clinical diagnosis of AD and confirmed AD (Hanifin and Rajka criteria for AD) at the screening and baseline visits
2. Documentation of any of the following:
a: Inadequate response to treatment with medicated topical therapy for AD for at least 4 consecutive weeks, within 6 months before the screening visit
b: Treatment with systemic therapy for AD within 6 months before the screening visit
c: A candidate for systemic therapy for AD
3. EASI score ≥16
4. Affected BSA ≥10%
5. IGA score ≥3
6. Pruritus NRS score ≥4
7. During the last 7 days prior to baseline, the subject must have used only emollient at least twice daily, with response to treatment remaining inadequate at baseline
8. 12 to <18 years of age and body weight ≥25 kg

Abrocitinib 100 or 200 mg or placebo was to be administered orally once daily for 12 weeks. Emollients were to be used at least twice daily, starting at least 7 days before baseline and continued throughout the study, and TCS therapy was to be started at baseline and then stopped upon lesion resolution.[30] Concomitant use of oral antihistamines was permitted during the study. Patients completing the 12-week treatment period of the study had the option to enter a long-term extension study B7451015.

Two hundred eighty-five subjects who were randomized[31] and received at least 1 dose of study drug (95 in the 100 mg group, 94 in the 200 mg group, 96 in the placebo group) were included in the FAS and in the safety analysis set, and the FAS was used as the efficacy analysis population.

The discontinuation rates were 3.2% (3 of 95 subjects) in the 100 mg group, 3.2% (3 of 94 subjects) in the 200 mg group, and 6.3% (6 of 96 subjects) in the placebo group. The main reasons for discontinuations were adverse events (1.1% [1 of 95 subjects] in the 100 mg group, 2.1% [2 of 94 subjects] in the 200 mg group, 2.1% [2 of 96 subjects] in the placebo group), etc.

Among the FAS, there were 26 subjects in the Japanese subgroup (9 in the 100 mg group, 9 in the 200 mg

[29] A sample of 75 subjects randomized to abrocitinib 200 mg QD, 75 subjects randomized to abrocitinib 100 mg QD, and 75 subjects randomized to placebo was expected to provide at least 80% power to detect a difference in IGA (0/1) response rate between either dose of abrocitinib and placebo, assuming 100 mg, 200 mg, and placebo response rates of 32%, 32%, and 12%, respectively, at Week 12 and a two-sided significance level of 5%. This was also to provide at least 96% power to detect a difference in EASI-75 response rate between either dose of abrocitinib and placebo, assuming 100 mg, 200 mg, and placebo response rates of 53%, 53%, and 23%, respectively, at Week 12 and a two-sided significance level of 5%.

[30] Medium potency TCS (e.g., triamcinolone acetonide 0.1% cream or fluocinolone acetonide 0.025% ointment [equivalent to strong class TCS in the Japanese classification]) were to be applied once daily to body areas with active lesions. After lesions were under control ("clear" or "almost clear"), treat once daily for a further 7 days, and then stop. If lesions returned, then resume treatment with medium potency TCS. Low potency TCS (i.e., hydrocortisone 1% cream) or TCI were to be applied to body areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.) with active lesions or to body areas where continued treatment with medium potency TCS was considered unsafe.

[31] Randomization was stratified by baseline disease severity (IGA score 3 vs. 4).

group, 8 in the placebo group). Study discontinuation occurred in 12.5% (1 of 8) of subjects in the placebo group, and the reason for discontinuation was an adverse event.

The co-primary efficacy endpoints were the IGA (0/1) response rate and the EASI-75 response rate at Week 12. As shown in Table 56, pairwise comparisons between abrocitinib 100 mg and placebo and between abrocitinib 200 mg and placebo showed statistically significant differences in both endpoints, demonstrating the superiority of abrocitinib 100 mg and 200 mg to placebo. The results in the Japanese subgroup are shown in Table 56.

Table 56. Results of primary efficacy endpoints (FAS, NRI)

		100 mg	200 mg	Placebo
Overall population	IGA (0/1) response rate at Week 12	41.6 (37/89)	46.2 (43/93)	24.5 (23/94)
	Difference from placebo [95% CI][a)] Adjusted *P*-value[a), b)]	16.7 [3.5, 29.9] 0.0147	20.6 [7.3, 33.9] 0.0030	
	EASI-75 response rate at Week 12	68.5 (61/89)	72.0 (67/93)	41.5 (39/94)
	Difference from placebo [95% CI][a)] Adjusted *P*-value[a) b)]	26.5 [13.1, 39.8] 0.0002	29.4 [16.3, 42.5] <0.0001	
Japanese subgroup	IGA (0/1) response rate at Week 12	55.6 (5/9)	33.3 (3/9)	62.5 (5/8)
	Difference from placebo [95% CI]	-6.9 [-53.6, 39.7]	-29.2 [-74.7, 16.4]	
	EASI-75 response rate at Week 12	77.8 (7/9)	100.0 (9/9)	75.0 (6/8)
	Difference from placebo [95% CI]	2.8 [-37.7, 43.3]	25.0 [-5.0, 55.0]	

% (n), Subjects who did not discontinue from the study, but had missing data at Week 12 were excluded from the FAS.
a) Cochran-Mantel-Haenszel test adjusted by baseline AD severity
b) A two-sided significance level of 5%. Graphical approach was used to adjust for multiplicity in hypothesis testing [For details, see Section 10].

The incidences of adverse events were 56.8% (54 of 95 subjects) in the 100 mg group, 62.8% (59 of 94 subjects) in the 200 mg group, and 52.1% (50 of 96 subjects) in the placebo group, and the main events are shown in Table 57.

No deaths were reported.

Serious adverse events occurred in 1.1% (1 of 94) of subjects in the 200 mg group (anxiety) and 2.1% (2 of 96) of subjects in the placebo group (angioedema; and atopic dermatitis [1 subject each]), but a causal relationship to study drug was denied for all those events.

The incidences of adverse events leading to discontinuation were 1.1% (1 of 95 subjects) in the 100 mg group, 2.1% (2 of 94 subjects) in the 200 mg group, and 2.1% (2 of 96 subjects) in the placebo group.

The incidences of adverse drug reactions were 21.1% (20 of 95 subjects) in the 100 mg group, 33.0% (31 of 94 subjects) in the 200 mg group, and 16.7% (16 of 96 subjects) in the placebo group.

Table 57. Adverse events reported by ≥2% of subjects in any group (Safety analysis set)

Event term	100 mg (N = 95)	200 mg (N = 94)	Placebo (N = 96)
Upper respiratory tract infection	9 (9.5)	10 (10.6)	10 (10.4)
Nasopharyngitis	8 (8.4)	8 (8.5)	9 (9.4)
Nausea	7 (7.4)	17 (18.1)	1 (1.0)
Folliculitis	7 (7.4)	2 (2.1)	1 (1.0)
Headache	5 (5.3)	8 (8.5)	7 (7.3)
Pharyngitis	5 (5.3)	3 (3.2)	3 (3.1)
Vomiting	4 (4.2)	5 (5.3)	0
Blood creatine phosphokinase increased	4 (4.2)	4 (4.3)	0
Influenza	4 (4.2)	2 (2.1)	1 (1.0)
Cough	4 (4.2)	1 (1.1)	2 (2.1)
Acne	3 (3.2)	5 (5.3)	1 (1.0)
Pyrexia	3 (3.2)	1 (1.1)	4 (4.2)
Gastroenteritis	2 (2.1)	2 (2.1)	1 (1.0)
Atopic dermatitis	2 (2.1)	1 (1.1)	3 (3.1)
Diarrhoea	2 (2.1)	1 (1.1)	0
Fatigue	2 (2.1)	0	1 (1.0)
Hordeolum	2 (2.1)	0	0
Contusion	2 (2.1)	0	0
Abdominal pain	1 (1.1)	3 (3.2)	1 (1.0)
Oral herpes	1 (1.1)	2 (2.1)	0
Blood lactate dehydrogenase increased	1 (1.1)	2 (2.1)	0
Asthma	1 (1.1)	1 (1.1)	2 (2.1)
Rhinorrhoea	1 (1.1)	0	3 (3.1)
Blood uric acid increased	1 (1.1)	0	2 (2.1)
Protein urine	1 (1.1)	0	2 (2.1)
Dizziness	0	6 (6.4)	1 (1.0)
Abdominal pain upper	0	4 (4.3)	0
Sinusitis	0	3 (3.2)	0
Somnolence	0	2 (2.1)	2 (2.1)
Haemoglobin decreased	0	2 (2.1)	0
Eosinophilia	0	0	2 (2.1)
Lip swelling	0	0	2 (2.1)
Pharyngitis streptococcal	0	0	2 (2.1)

n (%)

In the Japanese subgroup, the incidences of adverse events were 77.8% (7 of 9 subjects) in the 100 mg group, 66.7% (6 of 9 subjects) in the 200 mg group, and 50.0% (4 of 8 subjects) in the placebo group, and the main events are shown in Table 58.

No deaths or serious adverse events were reported.

An adverse event leading to discontinuation occurred in 12.5% (1 of 8) of subjects in the placebo group (wound abscess), but its causal relationship to study drug was denied.

The incidences of adverse drug reactions were 33.3% (3 of 9 subjects) in the 100 mg group, 44.4% (4 of 9 subjects) in the 200 mg group, and 12.5% (1 of 8 subjects) in the placebo group.

Table 58. Adverse events reported by ≥2 subjects in any group (Japanese subgroup, Safety analysis set)

Event term	100 mg (N = 9)	200 mg (N = 9)	Placebo (N = 8)
Nausea	3 (33.3)	4 (44.4)	0
Acne	2 (22.2)	1 (11.1)	0

n (%)

7.2.5 Long-term extension study[32] (CTD 5.3.5.2.1, Study B7451015 [ongoing since March 2018 (April 2020 Data Cutoff)])

A long-term extension study was conducted in 28 countries or regions including Japan, the US, and Poland to evaluate the long-term safety and efficacy of abrocitinib in patients who had completed the full treatment period of a qualifying parent study (Study B7451012, Study B7451013, or Study B7451029) OR had completed the full rescue treatment period of Study B7451014[33] OR had completed the full open-label run-in period of Study B7451014 and failed to meet the protocol defined response criteria at Week 12[34] (target sample size, ≥3,000 subjects).

The study consisted of a double-blind phase[35] (92 weeks) and an open-label phase (beyond Week 92). In the double-blind phase, patients were to continue dosing at the same abrocitinib dose they were randomized to in the qualifying parent study, and the blind was maintained. If randomized to active comparator or placebo in the qualifying study, the patient was to be randomized to oral abrocitinib 100 or 200 mg QD in a double-blind fashion. Patients were to continue oral abrocitinib 200 mg QD if entering directly from the open-label run-in period of Study B7451014. Concomitant use of emollients and topical medications for AD was permitted at the discretion of the physician throughout the treatment period.

Among 1,591 subjects who entered from a parent study and were allocated to study drug, 1590 subjects (725 in the 100 mg group, 865 in the 200 mg group) after excluding 1 subject who did not receive study drug were included in the FAS and in the safety analysis set. The discontinuation rates were 20.3% (147 of 725 subjects) in the 100 mg group and 21.6% (187 of 865 subjects) in the 200 mg group. The main reasons for discontinuations were subject's consent withdrawal (6.8% [49 of 725 subjects] in the 100 mg group, 6.1% [53 of 865 subjects] in the 200 mg group), adverse events (5.2% [38 of 725 subjects] in the 100 mg group, 8.0% [69 of 865 subjects] in the 200 mg group), etc.

Ninety Japanese patients who had completed Study B7451013 or B7451029 (42 in the 100 mg group, 48 in the 200 mg group) entered Study B7451015. The discontinuation rates were 2.4% (1 of 42 subjects) in the 100 mg group and 2.1% (1 of 48 subjects) in the 200 mg group. The reasons for discontinuations were all adverse events.

The incidences of adverse events were 57.4% (416 of 725 subjects) in the 100 mg group and 65.7% (568 of 865 subjects) in the 200 mg group, and the main events are shown in Table 59. Death occurred in 0.1% (1 of 865) of subjects in the 200 mg group (COVID-19), but its causal relationship to study drug was denied. The incidences of serious adverse events were 3.9% (28 of 725 subjects) in the 100 mg group (atopic dermatitis;

[32] An interim report submitted at filing (April 2020 Data Cutoff) contained unblinded subject data only because parent phase III studies were ongoing.
[33] A phase III, randomized withdrawal, double-blind, comparative study to compare the time to flare requiring rescue treatment in patients aged 12 years and over, with moderate to severe AD [The study consisted of a 12-week open-label induction treatment period and a double-blind treatment period of up to 52 weeks] (ongoing at the time of filing). Patients meeting the definition of flare were to enter an open-label rescue treatment with abrocitinib 200 mg QD plus topical therapy for 12 weeks.
[34] A loss of at least 50% of the EASI response from randomization and an IGA score of 2 or higher
[35] Subjects entering from the open-label run-in period of Study B7451014 were not blinded to treatment group because they were to continue abrocitinib 200 mg QD in this study.

and eczema herpeticum [3 subjects each]; anaphylactic reaction; and intervertebral disc protrusion [2 subjects each], etc.) and 5.1% (44 of 865 subjects) in the 200 mg group (atopic dermatitis [4 subjects]; herpes zoster [3 subjects]; myocardial infarction; herpes simplex; suicidal ideation; asthma; and pulmonary embolism [2 subjects each], etc.). A causal relationship to study drug could not be ruled out for the events reported by 7 subjects in the 100 mg group (eczema herpeticum [2 subjects]; depression, atopic dermatitis, and skin infection; bacterial pneumonia; duodenal ulcer haemorrhage; osteomyelitis; and eczema herpeticum and impetigo [1 subject each]) and the events reported by 20 subjects in the 200 mg group (atopic dermatitis; and herpes zoster [3 subjects each]; pulmonary embolism; myositis, osteomyelitis, muscle abscess, bacterial arthritis, and staphylococcal sepsis; herpes simplex; prostate cancer; dermatitis; pulmonary imaging procedure abnormal; ophthalmic herpes simplex; alanine aminotransferase increased and aspartate aminotransferase increased; chronic hepatitis; corneal abscess; drug-induced liver injury; cellulitis; skin candida; and bacterial keratitis [1 subject each]). The incidences of adverse events leading to discontinuation were 5.8% (42 of 725 subjects) in the 100 mg group and 7.5% (65 of 865 subjects) in the 200 mg group. The incidences of adverse drug reactions were 20.8% (151 of 725 subjects) in the 100 mg group and 28.2% (244 of 865 subjects) in the 200 mg group.

Table 59. Adverse events reported by ≥2% of subjects in either group (Safety analysis set)

Event term	100 mg (N = 725)	200 mg (N = 865)
Atopic dermatitis	85 (11.7)	96 (11.1)
Nasopharyngitis	76 (10.5)	83 (9.6)
Upper respiratory tract infection	41 (5.7)	72 (8.3)
Oral herpes	18 (2.5)	25 (2.9)
Asthma	18 (2.5)	11 (1.3)
Blood creatine phosphokinase increased	17 (2.3)	23 (2.7)
Urinary tract infection	16 (2.2)	24 (2.8)
Nausea	13 (1.8)	30 (3.5)
Headache	12 (1.7)	27 (3.1)
Herpes simplex	12 (1.7)	25 (2.9)
Acne	10 (1.4)	31 (3.6)
Herpes zoster	10 (1.4)	23 (2.7)
Influenza	10 (1.4)	21 (2.4)
Folliculitis	9 (1.2)	20 (2.3)

n (%)

In the Japanese subgroup, the incidences of adverse events were 69.0% (29 of 42 subjects) in the 100 mg group and 60.4% (29 of 48 subjects) in the 200 mg group, and the main events are shown in Table 60.

No deaths were reported. A serious adverse event occurred in 2.4% (1 of 42) of subjects in the 100 mg group (anal abscess), but its causal relationship to study drug was denied.

The incidences of adverse events leading to discontinuation were 2.4% (1 of 42 subjects) in the 100 mg group and 2.1% (1 of 48 subjects) in the 200 mg group.

The incidences of adverse drug reactions were 11.9% (5 of 42 subjects) in the 100 mg group and 10.4% (5 of 48 subjects) in the 200 mg group.

Table 60. Adverse events reported by ≥2 subjects in either group (Japanese subgroup, Safety analysis set)

Event term	100 mg (N = 42)	200 mg (N = 48)
Nasopharyngitis	6 (14.3)	9 (18.8)
Acne	2 (4.8)	3 (6.3)
Oral herpes	2 (4.8)	3 (6.3)
Atopic dermatitis	2 (4.8)	2 (4.2)
Herpes simplex	2 (4.8)	2 (4.2)
Liver function test increased	2 (4.8)	1 (2.1)
Acute sinusitis	2 (4.8)	0
Headache	2 (4.8)	0
Tenosynovitis	2 (4.8)	0
Gastroenteritis	0	2 (4.2)
Otitis externa	0	2 (4.2)

n (%)

7.R Outline of the review conducted by PMDA

7.R.1 Development plan

The applicant's explanation about the development plan of abrocitinib:

For diagnosing of AD, the diagnostic criteria of the Japanese Dermatological Association are used in Japan, while the Hanifin and Rajka criteria for AD are most commonly used internationally. However, no major differences between these diagnostic criteria are seen, and there are no substantial differences in the diagnostic criteria for AD between Japan and overseas (AD clinical practice guidelines 2018, *Acta Derm-Venereol Suppl.* 1980; 92: 44-7). According to the Japanese and foreign AD clinical practice guidelines, drug therapy is basically the use of topical anti-inflammatory agents, mainly TCS, under continuous use of emollients, and if patients have responded inadequately to these topical therapies, systemic therapy should be considered (*J Am Acad Dermatol.* 2014; 70: 338-351, AD clinical practice guidelines 2018). The treatment paradigm for AD is also similar between Japan and overseas. Furthermore, given that the results of a phase I study in healthy adult subjects (Study B7451001) [see Section 6.2.1.1] and the results of a population pharmacokinetic analysis including the data from Study B7451001 and a phase II study in AD patients (Study B7451006) indicated that there are no clear differences in the pharmacokinetics of abrocitinib between Japanese and non-Japanese populations, etc., the efficacy and safety of abrocitinib in Japanese AD patients can be evaluated by conducing global studies involving Japan and constructing a clinical data package.

"Study population," "efficacy endpoint," "dosing regimen," and "concomitant medications" for phase III studies including global studies in which Japanese patients participated were selected as follows.

● Study population

Based on the above-mentioned treatment paradigm for AD, the following AD patients who were candidates for systemic therapy were eligible for inclusion in phase III studies (Studies B7451012, B7451013, B7451029, and B7451036): AD patients with certain disease activity levels (affected BSA ≥10%, EASI score ≥16, IGA score ≥3, pruritus NRS score ≥4) who had a prior inadequate response to treatment with topical medications, such as TCS or TCI, for at least 4 weeks, or had received systemic therapies for control of their disease. In addition, patients for whom topical treatments were otherwise medically inadvisable (e.g., because of important side effects or safety risks) were also eligible for inclusion in Studies B7451012 and B7451013.

Given that the current AD clinical practice guidelines do not distinguish between adolescents aged ≥12 years and adults for diagnosing of AD, evaluation, and treatment paradigm (*Allergy*. 2006; 61: 969-87, AD clinical practice guidelines 2018), adolescents aged ≥12 years were also included in phase III studies. In phase III monotherapy studies including also adolescent patients aged ≥12 years (Studies B7451012 and B7451013), both adolescents 12 to <18 years of age and adults were required to weigh ≥40 kg[36] because at the time of planning these studies, there was no clinical experience with abrocitinib in subjects aged <18 years, and the effect of body weight on the safety of abrocitinib in this patient group was unclear. In a phase III TCS combination study in adolescent patients 12 to <18 years of age (Study B7451036), body weight of ≥25 kg was listed as an inclusion criterion, based on pharmacokinetic simulations using the data from the preceding clinical studies,[37] etc.

● Efficacy endpoint

Since the goals of treatment of AD are to reduce the signs and symptoms of AD, IGA and EASI, which are commonly used for assessment of skin lesions in the drug development for AD in Japan and overseas, were selected as co-primary endpoints for phase III studies. Week 12 was selected as the timing of the primary endpoint because a phase II study (Study B7451006) showed the efficacy of abrocitinib at Week 12.

As a measure of itch, which is an important subjective symptom of AD, the proportion of subjects achieving a ≥4-point improvement in Peak Pruritus Numerical Rating Scale (PP-NRS4 response rate) was selected as a secondary endpoint.

● Dosing regimen

A global phase II study characterized the dose-response relationship of abrocitinib monotherapy (10 mg, 30 mg, 100 mg, or 200 mg) in adult AD patients who had a prior inadequate response to treatment with topical medications, such as TCS or TCI, or for whom topical treatments were medically unadvisable (e.g., because of important side effects or safety risks) [see Section 7.1.1]. Based on the results of this study, the 200 mg QD dose and the 100 mg QD dose were selected for evaluation in phase III studies. The 200 mg QD dose was expected to achieve a target efficacy threshold [a difference in the IGA (0/1) response rate of 30% between abrocitinib and placebo] with a high probability (80%), and the 100 mg QD dose was expected to provide clinically meaningful efficacy.

● Concomitant medications

Since treatment of AD is basically the continuous use of emollients, the use of emollients was permitted throughout the study period in monotherapy studies B7451012 and B7451013. In TCS combination studies

[36] Since body weight was not considered to have a significant effect on PK in a phase II study (Study B7451006), adolescent subjects (≥12 years of age) of the same body weight range as adult subjects were to be enrolled and given the same dose as adults in phase III studies. As the minimum body weight of subjects who participated in the phase II clinical study was 44.5 kg, subjects participating in the phase III studies were required to weigh ≥40 kg.

[37] Simulations using PK data from phase I and II studies and a phase III study including also adolescent patients (Study B7451012) showed no clear differences in abrocitinib exposure between adult and adolescent patients. As to a parameter considered important for the pharmacological effects of JAK inhibitors relating to efficacy and safety (AUC), a 52% higher AUC in subjects weighing 25 kg compared to subjects weighing 70 kg was predicted, but this difference was not considered clinically meaningful.

B7451029 and B7451036, emollients were to be used at least twice daily, starting at least 7 days before baseline and continued throughout the study, and TCS therapy was to be started at baseline and then stopped upon lesion resolution. Concomitant use of oral antihistamines was permitted throughout the study period in all studies.

PMDA accepted the above explanation and concluded that the efficacy and safety of abrocitinib in adolescent AD patients aged ≥12 years and adult AD patients can be evaluated based on the submitted clinical data package, focusing on the results from phase III studies in which Japanese patients participated (B7451013, B7451029, B7451036).

7.R.2 Efficacy

The applicant's explanation about the efficacy of abrocitinib:

Studies B7451012 and B7451013 evaluated the efficacy and safety of abrocitinib monotherapy in AD patients who had a prior inadequate response to treatment with topical medications, such as TCS or TCI, or for whom topical treatments were otherwise medically inadvisable (e.g., because of important side effects or safety risks), or who had required systemic therapies for control of their disease. In these studies, pairwise comparisons between placebo and 100 mg and between placebo and 200 mg showed statistically significant differences in the co-primary endpoints of the IGA (0/1) response rate and the EASI-75 response rate at Week 12, demonstrating the superiority of abrocitinib 100 mg and 200 mg to placebo (Table 45 and Table 48). Table 61 shows the results of the co-primary endpoints of the IGA (0/1) response rate and the EASI-75 response rate over time. The trend consistently favored both abrocitinib 100 mg and 200 mg compared to placebo throughout the treatment period, and the adolescent subgroup also showed a similar trend to that of the overall population. Other secondary efficacy endpoints (EASI-90 response rate, PP-NRS4 response rate, etc.) also showed a similar trend, which was maintained throughout the treatment period.

Table 61 shows the results from the Japanese subgroup of Study B7451013. Except for a trend towards higher IGA (0/1) response rates at Weeks 4 and 12 in the placebo group than in the abrocitinib group in the Japanese subgroup (likely due to the limited number of Japanese subjects evaluated, especially in the placebo group), the trend largely favored abrocitinib compared to placebo in the Japanese subgroup as in the overall population. The number of Japanese adolescent patients evaluated was very limited, i.e. 2 subjects (0 in the placebo group), in Study B7451013, and evaluation is difficult, but there are no results that clearly deny the efficacy of abrocitinib.[38)]

[38)] Patient [redacted] (abrocitinib 200 mg group) did not achieve IGA (0/1) or EASI 75 response at Week 12, but showed a trend towards decreasing IGA score and EASI score at Week 12. Patient [redacted] (abrocitinib 100 mg group) showed an improvement in EASI until Week 8, but IGA score and EASI score increased from baseline at Week 12. The patient had a cold between Weeks 8 and 12, which possibly affected the clinical course of AD.

Table 61. Results of co-primary endpoints in phase III monotherapy studies (Studies B7451012 and B7451013) (FAS, NRI[a)])

Endpoint	Week	B7451012 (Overall population)			B7451013 (Overall population)			B7451013 (Japanese subgroup)		
		100 mg	200 mg	Placebo	100 mg	200 mg	Placebo	100 mg	200 mg	Placebo
IGA(0/1) response rate	2	3.9 (6/155)	9.7 (15/154)	0 (0/77)	5.1 (8/157)	14.5 (22/152)	0 (0/76)	0 (0/15)	9.1 (2/22)	0 (0/7)
	4	10.5 (16/152)	27.0 (41/152)	5.3 (4/76)	14.2 (22/155)	33.3 (51/153)	1.3 (1/77)	0 (0/14)	13.6 (3/22)	14.3 (1/7)
	8	20.3 (31/153)	35.7 (55/154)	6.7 (5/75)	22.3 (35/157)	37.7 (58/154)	10.3 (8/78)	13.3 (2/15)	18.2 (4/22)	14.3 (1/7)
	12 (※)	23.7 (37/156)	43.8 (67/153)	7.9 (6/76)	28.4 (44/155)	38.1 (59/155)	9.1 (7/77)	13.3 (2/15)	9.1 (2/22)	14.3 (1/7)
	24[b)]	30.3 (50/165)	45.2 (61/135)	—	35.8 (62/173)	52.4 (66/126)	—	42.9 (6/14)	47.1 (8/17)	—
	48[b)]	26.7 (44/165)	38.6 (54/140)	—	27.6 (43/156)	39.3 (48/122)	—	42.9 (6/14)	58.8 (10/17)	—
EASI-75 response rate	2	10.3 (16/155)	24.0 (37/154)	3.9 (3/77)	10.2 (16/157)	24.3 (37/152)	1.3 (1/76)	13.3 (2/15)	13.6 (3/22)	0 (0/7)
	4	27.6 (42/152)	47.4 (72/152)	14.5 (11/76)	26.5 (41/155)	51.0 (78/153)	6.5 (5/77)	21.4 (3/14)	27.3 (6/22)	0 (0/7)
	8	38.3 (59/154)	57.8 (89/154)	13.3 (10/75)	43.3 (68/157)	60.4 (93/154)	12.8 (10/78)	26.7 (4/15)	45.5 (10/22)	0 (0/7)
	12 (※)	39.7 (62/156)	62.7 (96/153)	11.8 (9/76)	44.5 (69/155)	61.0 (94/154)	10.4 (8/77)	26.7 (4/15)	45.5 (10/22)	0 (0/7)
	24[b)]	53.9 (89/165)	72.8 (99/136)	—	62.6 (109/174)	73.6 (92/125)	—	57.1 (8/14)	76.5 (13/17)	—
	48[b)]	44.0 (73/166)	57.9 (81/140)	—	50.3 (79/157)	63.4 (78/123)	—	57.1 (8/14)	82.4 (14/17)	—
Endpoint	Week	B7451012 (Adolescent subgroup)			B7451013 (Adolescent subgroup)			B7451013 (Japanese adolescent subgroup)		
		100 mg	200 mg	Placebo	100 mg	200 mg	Placebo	100 mg	200 mg	Placebo
IGA(0/1) response rate	2	2.9 (1/34)	6.1 (2/33)	0 (0/17)	0 (0/17)	13.3 (2/15)	0 (0/8)	0 (0/1)	0 (0/1)	0 (0/0)
	4	11.8 (4/34)	18.2 (6/33)	6.3 (1/16)	13.3 (2/15)	20.0 (3/15)	0 (0/8)	0 (0/1)	0 (0/1)	0 (0/0)
	8	24.2 (8/33)	27.3 (9/33)	6.7 (1/15)	5.9 (1/17)	33.3 (5/15)	12.5 (1/8)	0 (0/1)	0 (0/1)	0 (0/0)
	12	26.5 (9/34)	27.3 (9/33)	12.5 (2/16)	12.5 (2/16)	40.0 (6/15)	0 (0/7)	0 (0/1)	0 (0/1)	0 (0/0)
	24[b)]	26.5 (9/34)	40.6 (13/32)	—	47.6 (10/21)	57.1 (8/14)	—	0 (0/1)	100.0 (1/1)	—
	48[b)]	14.3 (5/35)	30.3 (10/33)	—	30.0 (6/20)	28.6 (4/14)	—	0 (0/1)	0 (0/1)	—
EASI-75 response rate	2	11.8 (4/34)	24.2 (8/33)	0 (0/17)	5.9 (1/17)	6.7 (1/15)	0 (0/8)	0 (0/1)	0 (0/1)	0 (0/0)
	4	35.3 (12/34)	39.4 (13/33)	6.3 (1/16)	26.7 (4/15)	46.7 (7/15)	0 (0/8)	100.0 (1/1)	0 (0/1)	0 (0/0)
	8	50.0 (17/34)	54.5 (18/33)	6.7 (1/15)	35.3 (6/17)	60.0 (9/15)	12.5 (1/8)	0 (0/1)	0 (0/1)	0 (0/0)
	12	44.1 (15/34)	54.5 (18/33)	12.5 (2/16)	43.8 (7/16)	60.0 (9/15)	0 (0/7)	0 (0/1)	0 (0/1)	0 (0/0)
	24[b)]	58.8 (20/34)	72.7 (24/33)	—	66.7 (14/21)	78.6 (11/14)	—	0 (0/1)	100.0 (1/1)	—
	48[b)]	31.4 (11/35)	51.5 (17/33)	—	42.9 (9/21)	64.3 (9/14)	—	0 (0/1)	100.0 (1/1)	—

% (n), ※Co-primary endpoints for Studies B7451012 and B7451013; —, No data

a) Subjects who did not discontinue from the study, but had missing data at time point were excluded from the FAS.

b) The results from subjects who entered Study B7451015 from a parent study (Data cutoff date of April 22, 2020 for the overall population, Data cutoff date of December 18, 2020 for the Japanese subgroup). Concomitant use of topical medications was permitted in Study B7451015.

Study B7451029 (adult patients) and Study B7451036 (adolescent patients) evaluated the efficacy and safety of abrocitinib in combination with background TCS in AD patients who had a prior inadequate response to treatment with topical medications, such as TCS or TCI, or a need for systemic therapy. In these studies, pairwise comparisons between placebo and 100 mg and between placebo and 200 mg showed statistically significant differences in the co-primary endpoints of the IGA (0/1) response rate and the EASI-75 response rate at Week 12, demonstrating the superiority of abrocitinib 100 mg and 200 mg to placebo (Table 52 and Table 56). Table 62 and Table 63 show the results of main efficacy endpoints over time in these studies. The

trend favored abrocitinib compared to placebo in all endpoints, and its efficacy was largely maintained throughout the treatment period. The efficacy of 200 mg abrocitinib tended to generally be higher than that of 100 mg abrocitinib for all endpoints, throughout the treatment period.

Table 62. Results of main efficacy endpoints in TCS combination study in adult AD patients (Study B7451029) (FAS, NRI[a)])

Endpoint	Week	Overall population				Japanese subgroup			
		100 mg	200 mg	Dupixent	Placebo	100 mg	200 mg	Dupixent	Placebo
IGA(0/1) response rate	2	15.2 (35/230)	18.4 (41/223)	4.7 (11/236)	6.3 (8/128)	15.8 (3/19)	32.0 (8/25)	4.8 (1/21)	9.1 (1/11)
	4	25.2 (59/234)	31.4 (70/223)	18.9 (45/238)	6.2 (8/129)	31.6 (6/19)	28.0 (7/25)	28.6 (6/21)	9.1 (1/11)
	8	35.8 (83/232)	50.7 (114/225)	28.5 (68/239)	10.1 (13/129)	31.6 (6/19)	44.0 (11/25)	38.1 (8/21)	18.2 (2/11)
	12 (※)	36.6 (86/235)	48.4 (106/219)	36.5 (88/241)	14.0 (18/129)	42.1 (8/19)	48.0 (12/25)	47.6 (10/21)	18.2 (2/11)
	16	34.8 (80/230)	47.5 (105/221)	38.8 (90/232)	12.9 (16/124)	47.4 (9/19)	41.7 (10/24)	47.6 (10/21)	9.1 (1/11)
	24[b)]	44.8 (90/201)	51.0 (102/200)	—	—	36.8 (7/19)	43.5 (10/23)	—	—
	36[b)]	43.5 (77/177)	47.1 (89/189)	—	—	52.6 (10/19)	47.8 (11/23)	—	—
	48[b)]	38.8 (26/67)	41.1 (29/70)	—	—	31.6 (6/19)	43.5 (10/23)	—	—
EASI-75 response rate	2	25.4 (58/228)	30.0 (67/223)	14.0 (33/235)	10.9 (14/128)	33.3 (6/18)	48.0 (12/25)	9.5 (2/21)	18.2 (2/11)
	4	44.6 (104/233)	57.4 (128/223)	38.2 (91/238)	15.6 (20/128)	57.9 (11/19)	76.0 (19/25)	38.1 (8/21)	9.1 (1/11)
	8	55.6 (129/232)	67.9 (152/224)	52.7 (126/239)	18.6 (24/129)	63.2 (12/19)	72.0 (18/25)	61.9 (13/21)	18.2 (2/11)
	12(※)	58.7 (138/235)	70.3 (154/219)	58.1 (140/241)	27.1 (35/129)	63.2 (12/19)	68.0 (17/25)	66.7 (14/21)	27.3 (3/11)
	16	60.3 (138/229)	71.0 (157/221)	65.5 (152/232)	30.6 (38/124)	47.4 (9/19)	62.5 (15/24)	57.1 (12/21)	18.2 (2/11)
	24[b)]	75.1 (151/201)	82.6 (166/201)	—	—	73.7 (14/19)	87.0 (20/23)	—	—
	36[b)]	71.8 (127/177)	73.0 (138/189)	—	—	68.4 (13/19)	87.0 (20/23)	—	—
	48[b)]	61.2 (41/67)	66.2 (47/71)	—	—	52.6 (10/19)	82.6 (19/23)	—	—
EASI-90 response rate	2	8.3 (19/228)	11.2 (25/223)	2.6 (6/235)	2.3 (3/128)	11.1 (2/18)	16.0 (4/25)	0 (0/21)	0 (0/11)
	4	20.2 (47/233)	32.3 (72/223)	12.2 (29/238)	6.3 (8/128)	21.1 (4/19)	40.0 (10/25)	0 (0/21)	9.1 (1/11)
	8	30.6 (71/232)	47.3 (106/224)	24.3 (58/239)	7.8 (10/129)	21.1 (4/19)	52.0 (13/25)	28.6 (6/21)	9.1 (1/11)
	12	36.6 (86/235)	46.1 (101/219)	34.9 (84/241)	10.1 (13/129)	42.1 (8/19)	48.0 (12/25)	47.6 (10/21)	9.1 (1/11)
	16	38.0 (87/229)	48.9 (108/221)	38.8 (90/232)	11.3 (14/124)	42.1 (8/19)	45.8 (11/24)	42.9 (9/21)	9.1 (1/11)
	24[b)]	45.3 (91/201)	54.2 (109/201)	—	—	31.6 (6/19)	78.3 (18/23)	—	—
	36[b)]	46.9 (83/177)	53.4 (101/189)	—	—	47.4 (9/19)	69.6 (16/23)	—	—
	48[b)]	40.3 (27/67)	49.3 (35/71)	—	—	36.8 (7/19)	52.2 (12/23)	—	—
EASI-100 response rate	2	1.3 (3/228)	4.5 (10/223)	0.4 (1/235)	0 (0/128)	5.6 (1/18)	4.0 (1/25)	0 (0/21)	0 (0/11)
	4	2.6 (6/233)	7.2 (16/223)	2.5 (6/238)	0 (0/128)	0 (0/19)	4.0 (1/25)	0 (0/21)	0 (0/11)
	8	6.0 (14/232)	11.6 (26/224)	2.1 (5/239)	0 (0/129)	0 (0/19)	8.0 (2/25)	0 (0/21)	0 (0/11)
	12	8.1 (19/235)	12.3 (27/219)	6.6 (16/241)	1.6 (2/129)	0 (0/19)	8.0 (2/25)	4.8 (1/21)	9.1 (1/11)
	16	12.7 (29/229)	13.6 (30/221)	5.2 (12/232)	4.0 (5/124)	5.3 (1/19)	4.2 (1/24)	9.5 (2/21)	9.1 (1/11)
	24[b)]	13.9 (28/201)	14.9 (30/201)	—	—	0 (0/19)	13.0 (3/23)	—	—
	36[b)]	11.3 (20/177)	18.5 (35/189)	—	—	5.3 (1/19)	13.0 (3/23)	—	—
	48[b)]	9.0 (6/67)	15.5 (11/71)	—	—	0 (0/19)	8.7 (2/23)	—	—
PP-NRS4 response rate[c)]	2	30.4 (63/207)	49.0 (102/208)	26.5 (56/211)	11.1 (13/117)	42.1 (8/19)	50.0 (12/24)	38.1 (8/21)	10.0 (1/10)
	4	44.6 (100/224)	59.3 (127/214)	45.3 (105/232)	20.2 (25/124)	52.6 (10/19)	60.0 (15/25)	47.6 (10/21)	36.4 (4/11)
	8	47.5 (105/221)	64.0 (137/214)	50.7 (116/229)	27.0 (33/122)	57.9 (11/19)	64.0 (16/25)	66.7 (14/21)	36.4 (4/11)
	12	47.5 (105/221)	63.1 (137/217)	54.5 (122/224)	28.9 (35/121)	52. 6 (10/19)	60.0 (15/25)	61.9 (13/21)	27.3 (3/11)
	16	47.0 (79/168)	62.8 (108/172)	57.1 (108/189)	28.7 (27/94)	61.1 (11/18)	54.5 (12/22)	70.0 (14/20)	36.4 (4/11)
	24[b)]	61.0 (122/200)	70.8 (143/202)	—	—	57.9 (11/19)	73.9 (17/23)	—	—
	36[b)]	54.5 (97/178)	65.8 (125/190)	—	—	57.9 (11/19)	73.9 (17/23)	—	—
	48[b)]	40.9 (27/66)	59.7 (43/72)	—	—	47.4 (9/19)	69.6 (16/23)	—	—

% (n); ※Co-primary endpoints for Study B7451029; －, No data

a) Subjects who did not discontinue from the study, but had missing data at time point were excluded from the FAS.

b) The results from subjects who entered Study B7451015 from a parent study (Data cutoff date of April 22, 2020 for the overall population, Data cutoff date of December 18, 2020 for the Japanese subgroup). Concomitant use of topical medications was permitted in Study B7451015.

c) Proportion of subjects achieving a ≥4-point improvement from baseline in PP-NRS score

Table 63. Results of main efficacy endpoints in TCS combination study in adolescent AD patients (Study B7451036) (FAS, NRI[a])

Endpoint	Week	Overall adolescent population			Japanese adolescent subgroup		
		100 mg	200 mg	Placebo	100 mg	200 mg	Placebo
IGA(0/1) response rate	2	6.5 (6/92)	12.8 (12/94)	1.1 (1/91)	22.2 (2/9)	22.2 (2/9)	0 (0/8)
	4	19.6 (18/92)	38.3 (36/94)	3.1 (3/96)	33.3 (3/9)	33.3 (3/9)	12.5 (1/8)
	8	30.8 (28/91)	48.9 (45/92)	16.0 (15/94)	22.2 (2/9)	33.3 (3/9)	25.0 (2/8)
	12 (※)	41.6 (37/89)	46.2 (43/93)	24.5 (23/94)	55.6 (5/9)	33.3 (3/9)	62.5 (5/8)
	24[b)]	50.8 (61/120)	52.7 (59/112)	―	77.8 (7/9)	50.0 (5/10)	―
	36[b)]	50.0 (58/116)	59.1 (68/115)	―	44.4 (4/9)	50.0 (5/10)	―
	48[b)]	47.5 (47/99)	54.5 (48/88)	―	66.7 (6/9)	44.4 (4/9)	―
EASI-75 response rate	2	19.6 (18/92)	25.5 (24/94)	4.4 (4/91)	55.6 (5/9)	22.2 (2/9)	12.5 (1/8)
	4	41.3 (38/92)	63.8 (60/94)	14.6 (14/96)	66.7 (6/9)	55.6 (5/9)	12.5 (1/8)
	8	60.4 (55/91)	68.5 (63/92)	33.3 (31/93)	55.6 (5/9)	88.9 (8/9)	50.0 (4/8)
	12 (※)	68.5 (61/89)	72.0 (67/93)	41.5 (39/94)	77.8 (7/9)	100.0 (9/9)	75.0 (6/8)
	24[b)]	75.8 (91/120)	78.6 (88/112)	―	88.9 (8/9)	70.0 (7/10)	―
	36[b)]	69.0 (80/116)	76.7 (89/116)	―	66.7 (6/9)	70.0 (7/10)	―
	48[b)]	68.7 (68/99)	71.6 (63/88)	―	88.9 (8/9)	77.8 (7/9)	―
EASI-90 response rate	2	8.7 (8/92)	10.6 (10/94)	0 (0/91)	44.4 (4/9)	22.2 (2/9)	0 (0/8)
	4	17.4 (16/92)	30.9 (29/94)	2.1 (2/96)	33.3 (3/9)	33.3 (3/9)	0 (0/8)
	8	29.7 (27/91)	40.2 (37/92)	14.0 (13/93)	44.4 (4/9)	44.4 (4/9)	12.5 (1/8)
	12	41.6 (37/89)	49.5 (46/93)	18.1 (17/94)	66.7 (6/9)	44.4 (4/9)	25.0 (2/8)
	24[b)]	52.5 (63/120)	59.8 (67/112)	―	66.7 (6/9)	50.0 (5/10)	―
	36[b)]	53.4 (62/116)	62.1 (72/116)	―	55.6 (5/9)	70.0 (7/10)	―
	48[b)]	45.5 (45/99)	54.5 (48/88)	―	88.9 (8/9)	55.6 (5/9)	―
EASI-100 response rate	2	1.1 (1/92)	0 (0/94)	0 (0/91)	11.1 (1/9)	0 (0/9)	0 (0/8)
	4	2.2 (2/92)	5.3 (5/94)	0 (0/96)	11.1 (1/9)	11.1 (1/9)	0 (0/8)
	8	3.3 (3/91)	9.8 (9/92)	0 (0/93)	0 (0/9)	11.1 (1/9)	0 (0/8)
	12	2.2 (2/89)	8.6 (8/93)	2.1 (2/94)	0 (0/9)	11.1 (1/9)	0 (0/8)
	24[b)]	10.0 (12/120)	17.9 (20/112)	―	11.1 (1/9)	10.0 (1/10)	―
	36[b)]	7.8 (9/116)	19.0 (22/116)	―	0 (0/9)	10.0 (1/10)	―
	48[b)]	12.1 (12/99)	25.0 (22/88)	―	0 (0/9)	0 (0/9)	―
PP-NRS4 response rate[c)]	2	27.2 (25/92)	38.6 (34/88)	12.6 (12/95)	44.4 (4/9)	33.3 (3/9)	12.5 (1/8)
	4	31.5 (28/89)	50.0 (42/84)	20.7 (19/92)	55.6 (5/9)	55.6 (5/9)	25.0 (2/8)
	8	41.4 (36/87)	56.5 (48/85)	31.5 (29/92)	62.5 (5/8)	55.6 (5/9)	50.0 (4/8)
	12	52.6 (40/76)	55.4 (41/74)	29.8 (25/84)	75.0 (6/8)	44.4 (4/9)	50.0 (4/8)
	24[b)]	55.5 (66/119)	56.4 (62/110)	―	66.7 (6/9)	40.0 (4/10)	―
	36[b)]	53.9 (62/115)	61.1 (69/113)	―	77.8 (7/9)	50.0 (5/10)	―
	48[b)]	56.7 (55/97)	55.2 (48/87)	―	77.8 (7/9)	22.2 (2/9)	―

% (n); ※Co-primary endpoints for Study B7451036; ―, No data

a) Subjects who did not discontinue from the study, but had missing data at time point were excluded from the FAS.

b) The results from subjects who entered Study B7451015 from a parent study (Data cutoff date of December 4, 2020 for the overall population, Data cutoff date of December 18, 2020 for the Japanese subgroup). Concomitant use of topical medications was permitted in Study B7451015.

c) Proportion of subjects achieving a ≥4-point improvement from baseline in PP-NRS score

In Study B7451029, the results of the co-primary endpoints in the Japanese subgroup showed a similar trend to that of the overall population (Table 52). Also as to the results of other main efficacy endpoints over time (Table 62), the trend favored abrocitinib compared to placebo, and its efficacy throughout the treatment period was suggested.

In the Japanese subgroup of Study B7451036, the co-primary endpoint of the IGA (0/1) response rate at Week 12 tended to be higher in the placebo group than in the abrocitinib group, whereas a similar trend as in the overall population was seen for the EASI 75 response rate (Table 56). Also as to the results of other main efficacy endpoints over time, the trend largely favored abrocitinib compared to placebo, and its efficacy throughout the treatment period was shown (Table 63). The possible reasons for the higher IGA (0/1) response rate at Week 12 in the placebo group than in the abrocitinib group are as follows: the number of subjects in the Japanese subgroup was limited; the proportion of patients with moderate AD (IGA score 3) at baseline was higher in the Japanese subgroup than in the overall population (Table 64); and the results of a subgroup analysis

showed that patients with moderate AD (IGA score 3) tended to have a higher IGA (0/1) response rate than patients with severe AD (IGA score 4) across all groups including the placebo group.[39)]

Table 64. Subject characteristics in Study B7451036

	Overall population			Japanese subgroup		
	100 mg (N = 95)	200 mg (N = 94)	Placebo (N = 96)	100 mg (N = 9)	200 mg (N = 9)	Placebo (N = 8)
Disease activity at baseline						
Proportion of subjects with IGA score of 3	60.0 (57/95)	64.9 (61/94)	59.4 (57/96)	66.7 (6/9)	88.9 (8/9)	87.5 (7/8)
Proportion of subjects with IGA score of 4	40.0 (38/95)	35.1 (33/94)	40.6 (39/96)	33.3 (3/9)	11.1 (1/9)	12.5 (1/8)

% (n)

Based on the above, the efficacy of abrocitinib in Japanese AD patients including adolescent patients was demonstrated.

PMDA's view:

Phase III monotherapy studies (Studies B7451012 and B7451013) and phase III TCS combination studies (Studies B7451029 and B7451036) demonstrated the superiority of abrocitinib 100 mg and 200 mg to placebo with regard to the co-primary endpoints of the IGA (0/1) response rate and the EASI-75 response rate at Week 12. The results of other efficacy endpoints also favored abrocitinib over placebo, and its efficacy tended to be maintained throughout the treatment period. Thus, the efficacy of abrocitinib in the treatment of AD has been demonstrated. Although Studies B7451013 and B7451036 showed a trend towards differences in the results of some endpoints between the overall population and the Japanese subgroup, the applicant's view (these results were due to the limited number of subjects in the Japanese subgroup, etc.) is understandable to some extent. Given that multiple endpoints such as the EASI-75 response rate at multiple time points tended to favor abrocitinib over placebo also in the Japanese subgroup, the obtained results do not deny the efficacy of abrocitinib in Japanese AD patients. In addition, since the overall population and the Japanese subgroup showed a similar trend in Study B7451029, the efficacy of abrocitinib is expected in Japanese AD patients.

In a phase IIb study (Study B7451006), phase III monotherapy studies (Studies B7451012 and B7451013), and phase III TCS combination studies (Studies B7451029 and B7451036), subjects who did not discontinue from the study, but had missing data at the time point were excluded from the FAS. In the phase IIb study (Study B7451006), all subjects from 1 study site were excluded from the FAS due to major protocol deviations. These exclusion rules were not specified in the protocol or statistical analysis plan, which was not appropriate. However, as there were no major differences in the analysis results, regardless of including these excluded cases as non-responders in the FAS, the efficacy of abrocitinib can be evaluated based on the results presented by the applicant.

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

[39)] Among patients with moderate AD (IGA score 3), the IGA (0/1) response rates at Week 12 in the placebo, 100 mg, and 200 mg groups were 32.7% (18 of 55 subjects), 48.1% (26 of 54 subjects), and 50.8% (31 of 61 subjects), respectively. Among patients with severe AD (IGA score 4), the IGA (0/1) response rates at Week 12 in the placebo, 100 mg, and 200 mg groups were 12.8% (5 of 39 subjects), 31.4% (11 of 35 subjects), and 37.5% (12 of 32 subjects), respectively.

7.R.3 Safety

The applicant's explanation about the safety of abrocitinib in AD patients, based on the pooled data from Japanese and foreign clinical studies presented in Table 65:

Table 65. Definitions of pooled populations used for safety analyses

Term of pooled population	Studies included (Data cutoff date)
Primary Pool (Placebo-controlled studies)	B7451006, B7451012, B7451013, B7451029, B7451036
All Exposure Pool	B7451006, B7451012, B7451013, B7451029, B7451036, B7451014 (open-label phase), B7451015 (data cutoff date of July 24, 2020)
Adolescent Primary Pool (Placebo-controlled studies)	Adolescent subject data from B7451012, B7451013, and B7451036
Adolescent All Exposure Pool	Adolescent subject data from B7451012, B7451013, B7451036, B7451014 (open-label phase), and B7451015 (data cutoff dates of July 24, 2020 and December 4, 2020)

7.R.3.1 Summary of safety

Table 66 shows a summary of safety of abrocitinib in clinical studies in AD patients. In the Primary Pool, the incidence rates of adverse events and adverse drug reactions were higher in the abrocitinib group than in the placebo group, and a trend towards higher incidence rates in the 200 mg group than in the 100 mg group was suggested. In the All Exposure Pool, although there were no clear differences in the occurrence of adverse events, serious adverse events, and adverse events leading to discontinuation between the different doses, a trend towards a higher incidence rate of adverse drug reactions in the 200 mg group than in the 100 mg group was suggested.

There were no clear differences in the safety profile of abrocitinib between the Japanese subgroup and the overall population, except that the incidence rate of adverse events tended to be slightly higher in the Japanese subgroup than in the overall population.

Table 66. Summary of safety of abrocitinib (Safety analysis set)

	AD patients					
	Primary Pool (Placebo-controlled studies)			All Exposure Pool		
	100 mg	200 mg	Placebo	100 mg	200 mg	All abrocitinib[a)]
Overall population						
N	703	684	438	1,023	2,105	3,128
Total drug exposure	170.8	168.5	100.3	849.9	1,238.9	2,088.8
All adverse events	425 (60.5) 248.9	462 (67.5) 274.1	238 (54.3) 237.3	747 (73.0) 87.9	1,547 (73.5) 124.9	2,294 (73.3) 109.8
Serious adverse events	19 (2.7) 11.1	12 (1.8) 7.1	13 (3.0) 13.0	57 (5.6) 6.7	88 (4.2) 7.1	145 (4.6) 6.9
Adverse events leading to discontinuation	34 (4.8) 19.9	34 (5.0) 20.2	33 (7.5) 32.9	93 (9.1) 10.9	177 (8.4) 14.3	270 (8.6) 12.9
Adverse drug reactions	162 (23.0) 94.9	232 (33.9) 137.7	79 (18.0) 78.8	307 (30.0) 36.1	924 (43.9) 74.6	1,231 (39.4) 58.9
Death	1 (0.1) 0.6	0	0	1 (0.1) 0.1	2 (0.1) 0.2	3 (0.1) 0.1
Japanese subgroup						
N	43	56	26	62	73	135
Total drug exposure	11.1	13.8	6.2	55.4	63.5	119.0
All adverse events	28 (65.1) 252.4	38 (67.9) 274.7	10 (38.5) 161.9	54 (87.1) 97.4	62 (84.9) 97.6	116 (85.9) 97.5
Serious adverse events	0	0	0	2 (3.2) 3.6	0	2 (1.5) 1.7
Adverse events leading to discontinuation	0	4 (7.1) 28.9	1 (3.8) 16.2	2 (3.2) 3.6	5 (6.8) 7.9	7 (5.2) 5.9
Adverse drug reactions	7 (16.3) 63.1	16 (28.6) 115.7	1 (3.8) 16.2	13 (21.0) 23.5	26 (35.6) 40.9	39 (28.9) 32.8
Death	0	0	0	0	0	0

Upper row, n (%); Lower row, Incidence rate adjusted for total exposure[b] (Number of subjects with events per 100 patient-years)
a) Patients who received at least 1 dose of abrocitinib, b) The approximate total exposure for adverse events was calculated as the sum of the durations of exposures of the subjects.

Table 67, Table 68, and Table 69 show the occurrence of main adverse events, serious adverse events, and adverse events leading to discontinuation in the All Exposure Pool, respectively. There were 1 death in subjects treated with 100 mg (sudden death) and 3 deaths in subjects treated with 200 mg (COVID-19 infection; gastric adenocarcinoma[40)]; and cardiac failure [1 subject each]), but a causal relationship to study drug was denied by the investigator for all those cases.

Table 67. Adverse events reported by ≥5% of subjects in either group (All Exposure Pool)

	Overall population		Japanese subgroup	
	100 mg (N = 1,023)	200 mg (N = 2,105)	100 mg (N = 62)	200 mg (N = 73)
Nasopharyngitis	161 (15.7)	223 (10.6)	16 (25.8)	16 (21.9)
Atopic dermatitis	150 (14.7)	189 (9.0)	7 (11.3)	8 (11.0)
Upper respiratory tract infection	90 (8.8)	173 (8.2)	0	0
Headache	62 (6.1)	197 (9.4)	2 (3.2)	6 (8.2)
Nausea	61 (6.0)	333 (15.8)	5 (8.1)	13 (17.8)
Acne	41 (4.0)	146 (6.9)	10 (16.1)	18 (24.7)
Herpes simplex	25 (2.4)	64 (3.0)	4 (6.5)	5 (6.8)
Folliculitis	27 (2.6)	59 (2.8)	4 (6.5)	5 (6.8)
Influenza	27 (2.6)	52 (2.5)	3 (4.8)	4 (5.5)
Herpes zoster	16 (1.6)	52 (2.5)	2 (3.2)	4 (5.5)
Gastroenteritis	18 (1.8)	37 (1.8)	1 (1.6)	4 (5.5)

n (%)

[40)] Gastric adenocarcinoma reported 8 months after study discontinuation was not counted to determine incidence rate because it did not meet the definition of adverse event collection.

Table 68. Serious adverse events reported by ≥2 subjects in either group (All Exposure Pool)

Event term	100 mg (N = 1,023)	200 mg (N = 2,105)
Atopic dermatitis	7 (0.7)	7 (0.3)
Eczema herpeticum	4 (0.4)	1 (<0.1)
Asthma	3 (0.3)	5 (0.2)
Pneumonia	2 (0.2)	2 (0.1)
Intervertebral disc protrusion	2 (0.2)	2 (0.1)
Drug-induced liver injury	2 (0.2)	1 (<0.1)
Anaphylactic reaction	2 (0.2)	0
Ankle fracture	2 (0.2)	0
Herpes simplex	1 (0.1)	2 (0.1)
Herpes zoster	0	6 (0.3)
Cellulitis	0	3 (0.1)
Pulmonary embolism	0	3 (0.1)
Microcytic anaemia	0	2 (0.1)
Thrombocytopenia	0	2 (0.1)
Myocardial infarction	0	2 (0.1)
Chest pain	0	2 (0.1)
Myositis	0	2 (0.1)
Ovarian neoplasm	0	2 (0.1)
Suicidal ideation	0	2 (0.1)

n (%)

Table 69. Adverse events leading to discontinuation reported by ≥3 subjects in either group (All Exposure Pool)

Event term	100 mg (N = 1,023)	200 mg (N = 2,105)
Atopic dermatitis	25 (2.4)	36 (1.7)
Eczema	4 (0.4)	2 (0.1)
Eczema herpeticum	4 (0.4)	1 (<0.1)
Nausea	3 (0.3)	14 (0.7)
Pregnancy	3 (0.3)	2 (0.1)
Upper abdominal pain	3 (0.3)	0
Haemoglobin decreased	0	6 (0.3)
Herpes zoster	1 (0.1)	5 (0.2)
Fatigue	1 (0.1)	4 (0.2)
Ophthalmic herpes simplex	1 (0.1)	4 (0.2)
ALT increased	0	4 (0.2)
AST increased	0	4 (0.2)
Thrombocytopenia	0	4 (0.2)
Dizziness	2 (0.2)	3 (0.1)
Herpes simplex	2 (0.2)	3 (0.1)

n (%)

The results of subgroup analyses by patient characteristics and concomitant medications[41)] using the All Exposure Pool showed no clear differences across subgroups, except for age. While the incidence rates of adverse events and adverse drug reactions in elderly subjects aged ≥65 years were similar to those in other age groups (subjects <18 years of age or 18 to <65 years of age), the incidence rates of serious adverse events and adverse events leading to discontinuation tended to be higher in elderly subjects aged ≥65 years than in other age groups (subjects <18 years of age or 18 to <65 years of age) (Table 70).

41) Intrinsic factors (age [12 to <18 years, 18 to <65 years, ≥65 years], sex, race [White, Black, Asian, others], baseline disease severity [IGA score 3, moderate; IGA score 4, severe], EASI [<25, ≥25], BMI [<25 kg/m^2, 25 to <30 kg/m^2, ≥30 kg/m^2], body weight [≤100 kg, >100 kg], presence or absence of comorbidities and comorbidities [asthma, allergic rhinitis, food allergy]) and extrinsic factors (prior topical therapy, prior systemic therapy, prior biologic use, geographical region [the US, Canada, Australia, Western Europe, Eastern Europe/Russia, Asia]) were assessed.

Table 70. Summary of safety of abrocitinib by age group (All Exposure Pool)

	<18 years			≥18 and <65 years			≥65 years		
	100 mg	200 mg	All abrocitinib[a)]	100 mg	200 mg	All abrocitinib[a)]	100 mg	200 mg	All abrocitinib[a)]
N	201	434	635	771	1,577	2,348	51	94	145
Total drug exposure	156.3	269.6	425.9	651.3	916.7	1,568.0	42.3	52.6	94.9
All adverse events	144 (71.6) 92.1	331 (76.3) 122.8	475 (74.8) 111.5	572 (74.2) 87.8	1,150 (72.9) 125.4	1,722 (73.3) 109.8	31 (60.8) 73.2	66 (70.2) 125.5	97 (66.9) 102.2
Serious adverse events	8 (4.0) 5.1	17 (3.9) 6.3	25 (3.9) 5.9	42 (5.4) 6.4	59 (3.7) 6.4	101 (4.3) 6.4	7 (13.7) 16.5	12 (12.8) 22.8	19 (13.1) 20.0
Adverse events leading to discontinuation	13 (6.5) 8.3	24 (5.5) 8.9	37 (5.8) 8.7	71 (9.2) 10.9	134 (8.5) 14.6	205 (8.7) 13.1	9 (17.6) 21.3	19 (20.2) 36.1	28 (19.3) 29.5
Adverse drug reactions	62 (30.8) 39.7	199 (45.9) 73.8	261 (41.1) 61.3	237 (30.7) 36.4	684 (43.4) 74.6	921 (39.2) 58.7	8 (15.7) 18.9	41 (43.6) 78.0	49 (33.8) 51.6
Death	0	0	0	0	1 (0.1) 0.1	1 (<0.1) 0.1	1 (2.0) 2.4	1 (1.1) 1.9	2 (1.4) 2.1

Upper row, n (%); Lower row, Incidence rate adjusted for total exposure [b)] (Number of subjects with events per 100 patient-years)
a) Patients who received at least 1 dose of abrocitinib
b) The approximate total exposure for adverse events was calculated as the sum of the durations of exposures of the subjects.

7.R.3.2 Adverse events potentially related to abrocitinib

Taking account of the occurrence of adverse events in clinical studies, the pharmacological effects of abrocitinib, the reported safety profile of the currently approved JAK inhibitors, etc., PMDA focused its safety review on adverse events potentially related to abrocitinib.

The applicant's explanation:

Table 71 and Table 72 show the occurrence of adverse events potentially related to abrocitinib in the Primary Pool (placebo-controlled studies) and the All Exposure Pool.

The incidence rates of herpes zoster, herpes simplex, acne-related events, dyslipidaemia, anaemia, decreased neutrophil count, decreased lymphocyte count, decreased platelet count, CK increased, and hepatic disorders were higher in the abrocitinib group than in the placebo group and were dose-dependent. Although the incidence rates of malignancies, lymphoma, gastrointestinal perforation, interstitial lung disease, major adverse cardiovascular events (MACE), other cardiovascular events, venous thromboembolic events (VTE), and pancytopenia were low, these events occurred only in the abrocitinib group. These events have been reported with the currently approved JAK inhibitors. Though comparison has limitations due to differences in patient characteristics etc. among the studies, the occurrence of these events with abrocitinib did not show a trend clearly different from that of an approved JAK inhibitor indicated for AD, baricitinib (Review Report on Olumiant tablets 2 mg etc. as of November 25, 2020).

As events characteristic of abrocitinib, the incidence rates of gastrointestinal disorders (nausea, vomiting, upper abdominal pain), dizziness, and headache were higher in the abrocitinib group than in the placebo group and were dose-dependent.

While the incidence rates of herpes zoster, herpes simplex, skin infections, and acne-related events tended to be higher in the Japanese subgroup than in the overall population, there were no clear differences in the

incidence rates of other events between the Japanese subgroup and the overall population.

Based on the above, there were no clear differences between the safety profiles of abrocitinib and the currently approved JAK inhibitors, except for events characteristic of abrocitinib, i.e., gastrointestinal disorders such as nausea and vomiting, headache, and dizziness. Thus, the safety risk of abrocitinib can be managed by providing similar preauction/warning information and taking similar safety measures as those for the currently approved JAK inhibitors, e.g., abrocitinib should be used under the supervision of physicians with adequate knowledge of abrocitinib and knowledge of and experience in drug therapy for AD.

Table 71. Occurrence of adverse events potentially related to abrocitinib (Safety analysis set, Overall population)

	Primary Pool (Placebo-controlled studies)			All Exposure Pool		
	100 mg	200 mg	Placebo	100 mg	200 mg	All abrocitinib[a)]
N (Total drug exposure)	703 (170.8)	684 (168.5)	438 (100.3)	1,023 (849.9)	2,105 (1,238.9)	3,128 (2,088.8)
Adverse events of special interest						
Infections	245 (34.9) 168.8	238 (34.8) 165.0	120 (27.4) 131.6	488 (47.7) 92.1	908 (43.1) 120.1	1,396 (44.6) 108.6
Serious infections	6 (0.9) 3.3	2 (0.3) 1.1	2 (0.5) 1.8	19 (1.9) 2.2	27 (1.3) 2.1	46 (1.5) 2.1
Herpes zoster	4 (0.6) 2.2	8 (1.2) 4.5	0	18 (1.8) 2.1	54 (2.6) 4.3	72 (2.3) 3.4
Herpes simplex[b)]	20 (2.8) 11.2	29 (4.2) 16.5	6 (1.4) 5.5	60 (5.9) 7.1	134 (6.4) 11.1	194 (6.2) 9.5
Skin infections[c)]	37 (5.3) 21.0	35 (5.1) 20.1	16 (3.7) 14.8	96 (9.4) 11.8	199 (9.5) 16.8	295 (9.4) 14.8
Acne-related events	13 (1.8) 7.2	36 (5.3) 20.8	1 (0.2) 0.9	42 (4.1) 4.9	158 (7.5) 13.1	200 (6.4) 9.7
NMSC	0	1 (0.1) 0.6	0	3 (0.3) 0.3	4 (0.2) 0.3	7 (0.2) 0.3
Malignancies (excluding NMSC)	0	0	0	1 (0.1) 0.1	2 (0.1) 0.2	3 (0.1) 0.1
Lymphoma	0	0	0	1 (0.1) 0.1	0 0	1 (<0.1) <0.1
Gastrointestinal disorders	95 (13.5) 58.4	157 (23.0) 107.7	34 (7.8) 32.5	164 (16.0) 21.5	568 (27.0) 59.0	732 (23.4) 42.4
Nausea	44 (6.3) 25.6	103 (15.1) 66.0	8 (1.8) 7.4	61 (6.0) 7.3	333 (15.8) 30.7	394 (12.6) 20.5
Vomiting	13 (1.8) 7.2	24 (3.5) 13.7	2 (0.5) 1.8	25 (2.4) 2.9	79 (3.8) 6.3	104 (3.3) 4.9
Upper abdominal pain	4 (0.6) 2.2	15 (2.2) 8.5	0	11 (1.1) 1.3	59 (2.8) 4.7	70 (2.2) 3.3
Gastrointestinal perforation	1 (0.1) 0.6	0	0	2 (0.2) 0.2	1 (<0.1) 0.1	3 (0.1) 0.1
Headache	40 (5.7) 23.1	54 (7.9) 32.2	19 (4.3) 17.7	62 (6.1) 7.5	197 (9.4) 16.7	259 (8.3) 12.9
Dizziness	11 (1.6) 6.1	23 (3.4) 13.2	4 (0.9) 3.7	18 (1.8) 2.1	64 (3.0) 5.1	82 (2.6) 3.9
Interstitial lung disease	1 (0.1) 0.6	0	0	1 (0.1) 0.1	0 0	1 (<0.1) <0.1
Dyslipidaemia	3 (0.4) 1.7	9 (1.3) 5.1	1 (0.2) 0.9	14 (1.4) 1.6	47 (2.2) 3.7	61 (2.0) 2.9
MACE	1 (0.1) 0.6	0	0	1 (0.1) 0.1	3 (0.1) 0.2	4 (0.1) 0.2
Other cardiovascular events	1 (0.1) 0.6	0	0	2 (0.2) 0.2	0 0	2 (0.1) 0.1
VTE	0	0	0	0 0	6 (0.3) 0.5	6 (0.2) 0.3
Anaemia	2 (0.3) 1.1	9 (1.3) 5.1	0	7 (0.7) 0.8	60 (2.9) 4.8	67 (2.1) 3.1
Decreased neutrophil count	1 (0.1) 0.6	4 (0.6) 2.2	0	1 (0.1) 0.1	15 (0.7) 1.2	16 (0.5) 0.7
Decreased lymphocyte count	1 (0.1) 0.6	4 (0.6) 2.2	0	5 (0.5) 0.6	27 (1.3) 2.1	32 (1.0) 1.5
Decreased platelet count	1 (0.1) 0.6	13 (1.9) 7.4	0	2 (0.2) 0.2	51 (2.4) 4.1	53 (1.7) 2.5
Pancytopenia	1 (0.1) 0.6	0	0	1 (0.1) 0.1	2 (0.1) 0.2	3 (0.1) 0.1
CK increased	15 (2.1) 8.4	20 (2.9) 11.4	4 (0.9) 3.6	45 (4.4) 5.3	93 (4.4) 7.5	138 (4.4) 6.6
Rhabdomyolysis/myopathy	0	0	0	0	1 (<0.1) <0.1	1 (<0.1) <0.1
Hepatic disorders	7 (1.0) 3.9	7 (1.0) 3.9	3 (0.7) 2.7	24 (2.3) 2.8	57 (2.7) 4.5	81 (2.6) 3.8
Renal disorders	1 (0.1) 0.6	0	0	3 (0.3) 0.1	5 (0.2) 0.4	8 (0.3) 0.4
Depression or suicide/self-injury	2 (0.3) 1.1	4 (0.6) 2.2	1 (0.2) 0.9	13 (1.3) 1.5	28 (1.3) 2.2	41 (1.3) 1.9

Upper row, n (%); Lower row, Incidence rate adjusted for total exposure[d)] (Number of subjects with events per 100 patient-years)
In the pooled analysis, opportunistic infection, active tuberculosis, latent tuberculosis, PCP, viral reactivation, hepatitis B, or hepatitis C was not reported.
a) Patients who received at least 1 dose of abrocitinib, b) Including oral herpes, Kaposi's varicelliform eruption, eczema herpeticum, and ophthalmic herpes simplex. c) bacterial skin infection, fungal skin infection, viral skin infection, d) Total follow-up time for adverse events of special interest was calculated up to the day of the first event (up to the end of risk period for subjects who did not have an event).

Table 72. Occurrence of adverse events potentially related to abrocitinib (Safety analysis set, Japanese subgroup)

	Primary Pool (Placebo-controlled studies)			All Exposure Pool		
	100 mg	200 mg	Placebo	100 mg	200 mg	All abrocitinib[a)]
N (Total drug exposure)	43 (11.1)	56 (13.8)	26 (6.2)	62 (55.4)	73 (63.5)	135 (119.0)
Adverse events of special interest						
Infections	19 (44.2) 205.9	16 (28.6) 134.0	6 (23.1) 106.3	41 (66.1) 128.8	35 (47.9) 89.2	76 (56.3) 106.9
Serious infections	0	0	0	2 (3.2) 3.6	0	2 (1.5) 1.7
Herpes zoster	0 0	2 (3.6) 13.9	0	2 (3.2) 3.6	4 (5.5) 6.4	6 (4.4) 5.1
Herpes simplex[b)]	3 (7.0) 26.4	5 (8.9) 36.0	0	8 (12.9) 16.1	6 (8.2) 9.9	14 (10.4) 12.7
Skin infections[c)]	6 (14.0) 55.2	8 (14.3) 59.6	2 (7.7) 31.8	12 (19.4) 24.2	11 (15.1) 19.8	23 (17.0) 21.9
Acne-related events	3 (7.0) 26.7	10 (17.9) 78.4	0 0	10 (16.1) 19.3	18 (24.7) 33.6	28 (20.7) 26.6
NMSC	0	0	0	0	0	0
Malignancies (excluding NMSC)	0	0	0	0	0	0
Lymphoma	0	0	0	0	0	0
Gastrointestinal disorders	8 (18.6) 81.9	13 (23.2) 108.9	0	10 (16.1) 20.4	16 (21.9) 29.4	26 (19.3) 25.2
Nausea	5 (11.6) 48.2	11 (19.6) 91.4	0	5 (8.1) 9.4	13 (17.8) 23.0	18 (13.3) 16.4
Vomiting	1 (2.3) 8.8	0	0	1 (1.6) 1.8	0	1 (0.7) 0.8
Upper abdominal pain	1 (2.3) 8.8	0	0	1 (1.6) 1.8	0	1 (0.7) 0.8
Gastrointestinal perforation	1 (2.3) 8.8	0	0	1 (1.6) 1.8	0	1 (0.7) 0.8
Headache	0	6 (10.7) 45.0	1 (3.8) 15.5	2 (3.2) 3.7	6 (8.2) 9.7	8 (5.9) 6.9
Dizziness	0	0	0	0	0	0
Interstitial lung disease	0	0	0	0	0	0
Dyslipidaemia	0	1 (1.8) 6.9	0	2 (3.2) 3.6	2 (2.7) 3.1	4 (3.0) 3.3
MACE	0	0	0	0	0	0
Other cardiovascular events	0	0	0	0	0	0
VTE	0	0	0	0	0	0
Anaemia	0	1 (1.8) 6.9	0	0	1 (1.4) 1.6	1 (0.7) 0.8
Decreased neutrophil count	0	0	0	0	0	0
Decreased lymphocyte count	0	0	0	0	0	0
Decreased platelet count	0	0	0	0	0	0
Pancytopenia	0	0	0	0	0	0
CK increased	0	1 (1.8) 6.9	0	0	3 (4.1) 4.7	3 (2.2) 2.5
Rhabdomyolysis/myopathy	0	0 0	0	0	0	0
Hepatic disorders	0	1 (1.8) 6.9	0	0	2 (2.7) 3.1	2 (1.5) 1.7
Renal disorders	0	0	0	0	0	0
Depression or suicide/self-injury	0	0	0	0	0	0

Upper row, n (%), Lower row, Incidence rate adjusted for total exposure [d)] (Number of subjects with events per 100 patient-years)
In the pooled analysis, opportunistic infection, active tuberculosis, latent tuberculosis, PCP, viral reactivation, hepatitis B, or hepatitis C was not reported.
a) Patients who received at least 1 dose of abrocitinib, b) Including oral herpes, Kaposi's varicelliform eruption, eczema herpeticum, and ophthalmic herpes simplex. c) bacterial skin infection, fungal skin infection, viral skin infection, d) Total follow-up time for adverse events of special interest was calculated up to the day of the first event (up to the end of risk period for subjects who did not have an event).

PMDA's view:

There were no clear differences between the safety profiles of abrocitinib in clinical studies submitted and the currently approved JAK inhibitors, except for events characteristic of abrocitinib, i.e., gastrointestinal disorders such as nausea and vomiting, headache, and dizziness. Thus, it is necessary to provide similar precaution/warning information and take similar safety measures as those for the currently approved JAK inhibitors, e.g., abrocitinib should be used under the supervision of physicians with adequate knowledge of

abrocitinib and knowledge of and experience in drug therapy for AD.

In the sections below, PMDA focuses its review on events characteristic of abrocitinib (gastrointestinal disorders such as nausea and vomiting, headache, dizziness) and skin infections, which is a concern following administration of JAK inhibitors in AD patients.

A marketing application was filed for abrocitinib as a drug with a new active ingredient. During the regulatory review, FDA issued Drug Safety Communication concerning the risk of MACE and malignancies with tofacitinib, an approved JAK inhibitor, based on a foreign, open-label, randomized, post-marketing safety clinical trial of tofacitinib in RA patients aged ≥50 years who had at least 1 cardiovascular risk factor (Study A3921133).[42)] Given these points, PMDA focused its review on MACE, VTE, and malignancies as well.

(1) Skin infections

The applicant's explanation about the occurrence of skin infections:

Table 73 shows the occurrence of skin infections and herpes zoster in the pooled populations. While there were no clear differences in the occurrence of bacterial skin infection and fungal skin infection among the treatment groups, the incidence rates of herpes simplex virus infection and herpes zoster were higher in the abrocitinib group than in the placebo group and were dose-dependent. The incidences of serious herpes simplex virus infection were 0.5% (5 of 1,023 subjects) in the 100 mg group and 0.1% (3 of 2,105 subjects) in the 200 mg group, and a causal relationship to study drug could not be ruled out for 4 cases in the 100 mg group (eczema herpeticum [4 subjects]) and 2 cases in the 200 mg group (eczema herpeticum [1 subject]; and herpes simplex [1 subject]). Serious herpes zoster occurred in 6 subjects in the 200 mg group (herpes zoster [3 subjects]; and ophthalmic herpes zoster; intercostal herpes zoster on the left back with generalization of the initial episode; and abdominal herpes zoster [1 subject each]), and a causal relationship to study drug could not be ruled out for all those events.

Based on the above clinical study results and taking also account of a decline in skin barrier function and deficits in skin immune activity in AD patients, etc., the package insert etc. will advise that attention should be paid to the possible occurrence of herpes virus infection (herpes zoster, herpes simplex, etc.).

[42)] https://www.fda.gov/media/145590/download: It was reported that a foreign, open-label, randomized, post-marketing safety clinical trial of tofacitinib (Study A3921133 in RA patients aged ≥50 years who had at least 1 cardiovascular risk factor) failed to show non-inferiority of tofacitinib over a TNF inhibitor with regard to the risk of cardiovascular events (MACE) and malignancies (excluding non-melanoma skin cancer) (the risk with tofacitinib is not inferior to the risk with a TNF inhibitor).

Table 73. Occurrence of skin infections and herpes zoster (Safety analysis set)

	Primary Pool (Placebo-controlled studies)			All Exposure Pool		
	100 mg	200 mg	Placebo	100 mg	200 mg	All abrocitinib[a)]
N	703	684	438	1,023	2,105	3,128
Total drug exposure (patient-years)	170.8	168.5	100.3	849.9	1,238.9	2,088.8
Skin infections[b)]	37 (5.3) 21.0	35 (5.1) 20.1	16 (3.7) 14.8	96 (9.4) 11.8	199 (9.5) 16.8	295 (9.4) 14.8
Bacterial skin infection (contagious impetigo, cellulitis, etc.)	17 (2.4) 9.5	9 (1.3) 5.1	11 (2.5) 10.1	37 (3.6) 4.3	69 (3.3) 5.5	106 (3.4) 5.0
Fungal skin infection (tinea, etc.)	5 (0.7) 2.8	0	2 (0.5) 1.8	18 (1.8) 2.1	23 (1.1) 1.8	41 (1.3) 1.9
Viral skin infection (herpes simplex virus infection[c)])	18 (2.6) 10.1	26 (3.8) 14.8	3 (0.7) 2.7	49 (4.8) 5.8	124 (5.9) 10.2	173 (5.5) 8.4
Herpes zoster	4 (0.6) 2.2	8 (1.2) 4.5	0	18 (1.8) 2.1	54 (2.6) 4.3	72 (2.3) 3.4

Upper row, n (%); Lower row, Incidence rate adjusted for total exposure[d)] (Number of subjects with events per 100 patient-years)
a) Patients who received at least 1 dose of abrocitinib, b) bacterial skin infection, fungal skin infection, viral skin infection, c) Including Kaposi's varicelliform eruption, d) Total follow-up time for adverse events of special interest was calculated up to the day of the first event (up to the end of risk period for subjects who did not have an event).

PMDA's view:

A decline in skin barrier function and deficits in skin immune activity increase the likelihood of bacterial, fungal, and viral infections in AD patients (AD clinical practice guidelines 2018). Also in clinical studies of abrocitinib, viral skin infection occurred in a dose-dependent manner, and some cases of serious skin infections for which a causal relationship to abrocitinib could not be ruled out were also reported, etc. Thus, the package insert etc. should advise that attention should be paid to the possible occurrence of skin infections as well as herpes virus infection following administration of abrocitinib having immunosuppressive effects in AD patients.

(2) Gastrointestinal disorders (nausea, vomiting, upper abdominal pain), headache, and dizziness

The applicant's explanation about the occurrence of gastrointestinal disorders, headache, and dizziness:

Table 71 and Table 72 show the occurrence of gastrointestinal disorders such as nausea, vomiting, and upper abdominal pain, headache, and dizziness in the pooled populations. Table 74 shows an overview of each event in the All Exposure Pool. The incidence rates of all events were higher in the abrocitinib group than in the placebo group and were dose-dependent. Many of these events observed in abrocitinib-treated subjects were non-serious, and no serious events were reported, except for gastrointestinal disorders (7 subjects) and dizziness (1 subject). The incidence rates of events leading to treatment discontinuation were low for all events, and most patients were able to continue treatment with abrocitinib after appropriate treatment intervention as needed.

Table 75 shows the occurrence of events by time from onset of therapy and the time to event resolution. Many of the events occurred within 1 week after the initiation of treatment with abrocitinib, and the times to resolution of nausea, upper abdominal pain, dizziness, headache, and vomiting were approximately 2 weeks, approximately 11 days, approximately 11.5 days, approximately 4 days, and approximately 1 day. Taking also into account that non-clinical studies showed no clinical signs suggestive of CNS effects (change in activity, convulsion, etc.) or associated histopathological changes, these events were unlikely to be caused by the direct effects of abrocitinib on the CNS.

Table 74. Occurrence of gastrointestinal disorders, headache, and dizziness (All Exposure Pool)

Event term		100 mg (N = 1,023)	200 mg (N = 2,105)	All abrocitinib[a] (N = 3,128)
Gastrointestinal disorders	Adverse events	164 (16.0)	568 (27.0)	732 (23.4)
	Events requiring treatment intervention[b]	62 (37.8)	166 (29.2)	228 (31.1)
	Serious adverse events	4 (0.4)	3 (0.1)	7 (0.2)
	Adverse events leading to discontinuation	11 (1.1)	20 (1.0)	31 (1.0)
	Adverse drug reactions	77 (7.5)	416 (19.8)	493 (15.8)
Nausea	Adverse events	61 (6.0)	333 (15.8)	394 (12.6)
	Events requiring treatment intervention[b]	9 (14.8)	52 (15.6)	61 (15.5)
	Serious adverse events	0	0	0
	Adverse events leading to discontinuation	3 (0.3)	14 (0.7)	17 (0.5)
	Adverse drug reactions	43 (4.2)	302 (14.3)	345 (11.0)
Vomiting	Adverse events	25 (2.4)	79 (3.8)	104 (3.3)
	Events requiring treatment intervention[b]	4 (16.0)	13 (16.5)	17 (16.3)
	Serious adverse events	0	0	0
	Adverse events leading to discontinuation	0	2 (0.1)	2 (0.1)
	Adverse drug reactions	7 (0.7)	48 (2.3)	55 (1.8)
Upper abdominal pain	Adverse events	11 (1.1)	59 (2.8)	70 (2.2)
	Events requiring treatment intervention[b]	4 (36.4)	11 (18.6)	15 (21.4)
	Serious adverse events	0	0	0
	Adverse events leading to discontinuation	3 (0.3)	0	3 (0.1)
	Adverse drug reactions	5 (0.5)	38 (1.8)	43 (1.4)
Headache	Adverse events	62 (6.1)	197 (9.4)	259 (8.3)
	Events requiring treatment intervention[b]	32 (51.6)	102 (51.8)	134 (51.7)
	Serious adverse events	0	0	0
	Adverse events leading to discontinuation	1 (0.1)	11 (0.5)	12 (0.4)
	Adverse drug reactions	23 (2.2)	115 (5.5)	138 (4.4)
Dizziness	Adverse events	18 (1.8)	64 (3.0)	82 (2.6)
	Events requiring treatment intervention[b]	0	4 (6.3)	4 (4.9)
	Serious adverse events	1 (0.1)	0	1 (<0.1)
	Adverse events leading to discontinuation	2 (0.2)	3 (0.1)	5 (0.2)
	Adverse drug reactions	12 (1.2)	50 (2.4)	62 (2.0)

n (%)
a) Patients who received at least 1 dose of abrocitinib
b) Calculated using the number of subjects with a specific adverse event as the denominator.

Table 75. Occurrence by time from onset of therapy and time to event resolution (All Exposure Pool)

Event term	No. of subjects with event	Weeks 0-1	Weeks 1-2	Weeks 2-3	Weeks 3-4	Weeks 4-5	Weeks 5-8	Weeks 8-12	Week 12 onwards	Time to event resolution [Days]
Nausea	394	250 (63.5)	41 (10.4)	15 (3.8)	9 (2.3)	12 (3.0)	23 (5.8)	44 (11.2)		15.0 [12.0, 22.0]
Vomiting	104	20 (19.2)	8 (7.7)	12 (11.5)	15 (14.4)	3 (2.9)	10 (9.6)	13 (12.5)	23 (22.1)	1.0 [NE, NE]
Upper abdominal pain	70	37 (52.9)	3 (4.3)	2 (2.9)	1 (1.4)	1 (1.4)	6 (8.6)	20 (28.6)		11.0 [6.0, 16.0]
Headache	259	114 (44.0)	34 (13.1)	14 (5.4)	16 (6.2)	12 (4.6)	25 (9.7)	44 (17.0)		4.0 [3.0, 6.0]
Dizziness	82	40 (48.8)	9 (11.0)	4 (4.9)	3 (3.7)	4 (4.9)	11 (13.4)	11 (13.4)		11.5 [8.0, 21.0]

n (%), Median time to event resolution [95% CI]; NE, Not estimable

PMDA's view:

The incidence rates of gastrointestinal disorders such as nausea and vomiting, headache, and dizziness were higher in the abrocitinib group than in the placebo group and were dose-dependent, and some events required treatment intervention. Meanwhile, many of the observed events were non-serious, and most patients were able to continue treatment. The package insert etc. should advise that attention should be paid to the possible occurrence of gastrointestinal disorders such as nausea, headache, and dizziness during treatment with abrocitinib.

(3) VTE

The applicant's explanation about the occurrence of VTE including deep vein thrombosis (DVT) and pulmonary embolism (PE).

Table 71 and Table 72 show the occurrence of VTE in the pooled populations. VTE occurred in only 6 subjects in the 200 mg group in the All Exposure Pool (PE; and DVT [3 subjects each]), and a causal relationship to study drug could not be ruled out for 2 cases (PE; and DVT [1 subject each]). No VTE was reported in the Japanese subgroup.

Table 76 shows the occurrence of VTE-related events in clinical studies of abrocitinib or baricitinib and external cohort studies. The incidence rates of VTE in abrocitinib-treated patients in the All Exposure Pool were similar to those with baricitinib. When compared to external cohort studies, the incidence rates of DVT in abrocitinib-treated patients in the All Exposure Pool were similar to those in AD patients in external cohort studies, whereas the incidence rates of PE tended to be higher than those in AD patients in external cohort studies.

Based on the above, as with the currently approved JAK inhibitors, the package insert will advise about the risk of VTE.

Table 76. Occurrence of VTE-related events in clinical studies of abrocitinib or baricitinib and external cohort studies

	All Exposure Pool		Baricitinib pooled data[a)]		KPNC cohort study (≥12 years)[b)]	Cohort study using THIN database (adults)[c)]	Cohort study in Denmark (≥12 years)[d)]
	200 mg	All abrocitinib	Baricitinib-treated patients	Baricitinib-treated patients			
Population	AD patients		AD patients	RA patients	AD patients		
N	2,105	3,128	2,157	3,770	8,197	—	—
Total drug exposure (patient-years)	1,238.9	2,088.8	2,364.4	10,127	—	—	—
VTE	6 (0.29) 0.47	6 (0.19) 0.28	3 (0.1) 0.1	49 (1.3) 0.5	70 (0.85) 0.20 [0.15, 0.25]	—	—
DVT	3 (0.14) 0.23	3 (0.10) 0.14	—	—	57 (0.7) 0.16 [0.12, 0.21]	— 0.11 [moderate]/0.16 [severe]	— 0.06 [0.05, 0.08]
PE	3 (0.14) 0.23	3 (0.10) 0.14	—	—	25 (0.30) 0.07 [0.05, 0.10]	— 0.06 [moderate]/0.09 [severe]	— 0.06 [0.05, 0.08]

Upper row, n (%); Lower row, Incidence rate adjusted for total exposure (Number of patients with events per 100 patient-years)

a) Review Report on Olumiant tablets 2 mg and 4 mg as of November 25, 2020, b) A cohort study in members of Kaiser Permanente Northern California (KPNC) diagnosed with moderate to severe AD between 2000 and 2018 (≥12 years of age), using the KPNC database (a closed, pre-paid, integrated health care delivery system with a membership of 3.2 million people in northern California) (Study B7451044), c) A retrospective cohort study including approximately 1.1 million AD patients and 4.7 million non-AD patients, using the Health Improvement Network (THIN) database (the UK) (Study B7451045), d) A population-based cohort study designed to evaluate the incidence rates of venous thromboembolic events in AD patients, using the data from the Danish registries (January 2000 to December 2018): 17341 patients with AD (≥12 years of age) were identified and matched for age and sex with controls in the general population in a 1:10 ratio.

PMDA's view:

Cases of VTE were reported in the 200 mg group only in clinical studies, and a causal relationship to study drug could not be ruled out for some events. Since the incidence rates of PE with abrocitinib tended to be higher than those in external cohort studies, as with the currently approved JAK inhibitors, the package insert etc. should advise about the risk of VTE. It is also necessary to collect post-marketing information on the occurrence of VTE in clinical practice, including published literature, and provide the obtained information to healthcare professionals in clinical practice as appropriate.

(4) MACE

The applicant's explanation about the occurrence of MACE:

Table 71 and Table 72 show the occurrence of MACE in the pooled populations. There were no clear differences in incidence rate among the treatment groups, and a causal relationship to study drug was denied for all of 4 cases of MACE in subjects treated with abrocitinib in the All Exposure Pool (myocardial infarction [2 subjects]; and sudden death; and cardiac failure [1 subject each]). MACE was not reported in the Japanese subgroup. Though comparisons across different studies have limitations, the incidence rate of MACE with abrocitinib in the All Exposure Pool (0.2/100 patient-years) did not tend to exceed the incidence rates of MACE based on the baricitinib pooled data (0.1/100 patient-years in AD patients [pooled data from 6 Japanese and foreign studies], 0.5/100 patient-years in RA patients [pooled data from 10 Japanese and foreign studies] [see Review Report on Olumiant tablets 2 mg and 4 mg as of November 25, 2020]) or the incidence rate of MACE in patients with moderate to severe AD aged ≥12 years in a cohort study using the KPNC database (0.26/100 patient-years [95% CI, 0.21, 0.32]).

Elevations of lipid parameters such as total, LDL, and HDL cholesterol have been reported with the currently approved JAK inhibitors, and dyslipidaemia occurred in a dose-dependent manner also in clinical studies of abrocitinib (Table 71 and Table 72). Although the relationship between elevated lipid parameters associated with abrocitinib and an increase in cardiovascular events is unclear, hyperlipidemia is generally considered a risk factor for MACE. Thus, as with the currently approved JAK inhibitors, the package insert will include a precaution regarding the risk of hyperlipidemia and advise that lipid tests should be performed regularly to monitor for elevated lipid parameters.

PMDA's view:

Although a small number of cases of MACE were reported in clinical studies of abrocitinib, a causal relationship to study drug was denied for all those cases, and the incidence rate of MACE with abrocitinib did not tend to far exceed those with an approved JAK inhibitor or in an external cohort. However, dyslipidaemia occurred in a dose-dependent manner following administration of abrocitinib, and the possibility that abnormal lipid values associated with abrocitinib increase the risk of MACE cannot be ruled out. Thus, as with the currently approved JAK inhibitors, the package insert etc. should advise about the risk of dyslipidaemia and regular monitoring of lipid parameters during treatment with abrocitinib, etc. It is also necessary to collect post-marketing information on the occurrence of MACE in clinical practice, including published literature, and provide the obtained information to healthcare professionals in clinical practice as appropriate.

(5) Malignancies

The applicant's explanation about the occurrence of malignancies:

Table 71 and Table 72 show the occurrence of malignancies (excluding NMSC) and NMSC in the pooled populations. There were no clear differences in incidence rate among the treatment groups, and no cases were reported in the Japanese subgroup. Three cases of malignancies (excluding NMSC) (prostate cancer [2 subjects]; and gastric adenocarcinoma [1 subject]) and 7 cases of NMSC (basal cell carcinoma [2 subjects]; lip

squamous cell carcinoma; squamous cell carcinoma of skin; squamous cell carcinoma; cutaneous T-cell lymphoma stage I; and actinic keratosis [1 subject each]) were reported among abrocitinib-treated patients in the All Exposure Pool, but a causal relationship to study drug was denied for all those cases, except for 1 case of prostate cancer. None of the 7 abrocitinib-treated patients with NMSC had prior UV therapy.

Though comparisons across different studies have limitations, the incidence rates of malignancies (excluding NMSC) and NMSC in abrocitinib-treated patients in the All Exposure Pool (0.1/100 patient-years and 0.3/100 patient-years, respectively) were comparable to those based on the baricitinib pooled data (0.1/100 patient-years and 0.3/100 patient-years in AD patients, respectively [pooled data from 6 Japanese and foreign AD studies]) (see Review Report on Olumiant tablets 2 mg and 4 mg as of November 25, 2020). When compared to external cohort studies, the incidence rates of malignancies (excluding NMSC and cervix carcinoma in situ) and NMSC in adult patients with moderate to severe AD in the KPNC cohort study were 0.51/100 patient-years [95% CI, 0.44, 0.6] and 0.48/100 patient-years [95% CI, 0.41, 0.56], respectively, and the incidence rates of NMSC in a cohort study using the THIN database were 0.25/100 patient-years [95% CI, 0.25, 0.26] in patients with moderate AD and 0.88/100 patient-years [95%CI, 0.86, 0.90] in patients with severe AD. Comparisons of these results suggested no trend towards higher risk of malignancies in abrocitinib-treated patients.

Although the direct effects of abrocitinib are unclear, as the immunomodulatory effect of abrocitinib is considered to reduce the immune surveillance against malignancies, malignancies will be included as an important potential risk, and a relevant precautionary statement will be included in the package insert etc., as with the currently approved JAK inhibitors.

PMDA's view:
Since the number of cases, the duration of treatment, etc., were limited in clinical studies conducted to date, it is difficult to reach a conclusion on the risk of malignancies. Given the pharmacological effects etc. of abrocitinib, the possibility that chronic immunosuppression caused by abrocitinib increases the carcinogenic risk cannot be ruled out, and the incidence rates of malignancies with abrocitinib were also comparable to those with an approved JAK inhibitor. Thus, as with the currently approved JAK inhibitors, the WARNINGS section etc. of the package insert should advise about the risk of malignancies. It is also necessary to collect post-marketing information on the occurrence of malignancies in clinical practice, including published literature, and provide the obtained information to healthcare professionals in clinical practice as appropriate.

7.R.3.3 Safety in adolescents

The applicant's explanation about the safety of abrocitinib in adolescent AD patients, based on the Adolescent Primary Pool (placebo-controlled studies) and the Adolescent All Exposure Pool defined in Table 65:
Table 77 and Table 78 show a summary of safety of abrocitinib and the occurrence of adverse events potentially related to abrocitinib in adolescent AD patients. There were no clear differences in the safety profile of abrocitinib between the overall population (Table 71 and Table 72) and the adolescent population. Though

comparison between the overall adolescent population and the Japanese adolescent subgroup has limitations due to the small number of subjects in the Japanese adolescent subgroup, there were no clear differences in safety profile, except for a trend towards higher incidence rates of acne-related events, gastrointestinal disorders, and nausea in the Japanese adolescent subgroup.

Table 77. Summary of safety of abrocitinib and occurrence of adverse events potentially related to abrocitinib (Safety analysis set, Adolescent population)

	Adolescent Primary Pool (Placebo-controlled studies)			Adolescent All Exposure Pool[e)]		
	100 mg	200 mg	Placebo	100 mg	200 mg	All abrocitinib[a)]
N	146	142	120	201	434	635
Total drug exposure	33.8	32.6	27.3	156.3	269.6	425.9
Overview of adverse events						
All adverse events	88 (60.3) 260.5	96 (67.6) 294.6	63 (52.5) 230.7	144 (71.6) 92.1	331 (76.3) 122.8	475 (74.8) 111.5
Serious adverse events	1 (0.7) 3.0	4 (2.8) 12.3	2 (1.7) 7.3	8 (4.0) 5.1	17 (3.9) 6.3	25 (3.9) 5.9
Adverse events leading to discontinuation	2 (1.4) 5.9	3 (2.1) 9.2	4 (3.3) 14.6	13 (6.5) 8.3	24 (5.5) 8.9	37 (5.8) 8.7
Adverse drug reactions	30 (20.5) 88.8	50 (35.2) 153.5	21 (17.5) 76.9	62 (30.8) 39.7	199 (45.9) 73.8	261 (41.1) 61.3
Death	0	0	0	0	0	0
Adverse events of special interest						
Infections	56 (38.4) 209.2	55 (38.7) 214.9	37 (30.8) 157.2	103 (51.2) 110.2	198 (45.6) 128.2	301 (47.4) 121.4
Serious infections	0	1 (0.7) 3.0	0	3 (1.5) 1.9	4 (0.9) 1.4	7 (1.1) 1.6
Herpes zoster	1 (0.7) 2.9	1 (0.7) 3.0	0	3 (1.5) 1.9	5 (1.2) 1.8	8 (1.3) 1.8
Herpes simplex[b)]	1 (0.7) 2.9	7 (4.9) 21.1	0	4 (2.0) 2.5	25 (5.8) 9.6	29 (4.6) 6.9
Skin infections[c)]	4 (2.7) 11.6	5 (3.5) 15.0	0	11 (5.5) 7.1	31 (7.1) 12.3	42 (6.6) 10.3
Acne-related events	3 (2.1) 8.7	7 (4.9) 21.4	1 (0.8) 3.5	16 (8.0) 10.5	35 (8.1) 13.2	51 (8.0) 12.2
Gastrointestinal disorders	25 (17.1) 81.5	36 (25.4) 134.9	9 (7.5) 33.2	36 (17.9) 25.7	130 (30.0) 64.1	166 (26.1) 48.4
Nausea	11 (7.5) 33.9	26 (18.3) 91.5	2 (1.7) 7.1	16 (8.0) 10.6	79 (18.2) 34.3	95 (15.0) 24.9
Vomiting	5 (3.4) 14.6	9 (6.3) 27.9	0	7 (3.5) 4.5	32 (7.4) 12.3	39 (6.1) 9.4
Dyslipidaemia	2 (1.4) 5.8	3 (2.1) 9.0	0	4 (2.0) 2.5	9 (2.1) 3.3	13 (2.0) 3.0
VTE	0	0	0	0	1 (0.2) 0.4	1 (0.2) 0.2
Anaemia	1 (0.7) 2.9	4 (2.8) 11.9	0	2 (1.0) 1.3	11 (2.5) 4.1	13 (2.0) 3.0
Decreased neutrophil count	0	1 (0.7) 3.0	0	0	2 (0.5) 0.7	2 (0.3) 0.5
Decreased lymphocyte count	0	0	0	1 (0.5) 0.6	0	1 (0.2) 0.2
Decreased platelet count	0	2 (1.4) 5.9	0	0	6 (1.4) 2.2	6 (0.9) 1.4
CK increased	4 (2.7) 11.7	5 (3.5) 15.0	0	8 (4.0) 5.2	17 (3.9) 6.4	25 (3.9) 6.0
Hepatic disorders	1 (0.7) 2.9	1 (0.7) 3.0	0	1 (0.5) 0.6	6 (1.4) 2.2	7 (1.1) 1.6
Renal disorders	1 (0.7) 2.9	0	0	1 (0.5) 0.6	0	1 (0.2) 0.2
Depression or suicide/self-injury	0	1 (0.7) 3.0	0	3 (1.5) 1.9	12 (2.8) 4.4	15 (2.4) 3.5

Upper row, n (%); Lower row, Incidence rate adjusted for total exposure[d)] (Number of subjects with events per 100 patient-years)
In the pooled analysis, opportunistic infection, active tuberculosis, latent tuberculosis, PCP, viral reactivation, hepatitis B, hepatitis C, malignancies, NMSC, malignancies (excluding NMSC), lymphoma, gastrointestinal perforation, interstitial lung disease, MACE, other cardiovascular events, pancytopenia, or rhabdomyolysis/myopathy was not reported.
a) Patients who received at least 1 dose of abrocitinib, b) Including oral herpes, Kaposi's varicelliform eruption, eczema herpeticum, and ophthalmic herpes simplex. c) bacterial skin infection, fungal skin infection, viral skin infection, d) Total follow-up time for adverse events of special interest was calculated up to the day of the first event (up to the end of risk period for subjects who did not have an event). The approximate total exposure for adverse events was calculated as the sum of the durations of exposures of the subjects. e) Data cutoff date of July 24, 2020

Table 78. Summary of safety of abrocitinib and occurrence of adverse events potentially related to abrocitinib (Safety analysis set, Japanese adolescent subgroup)

	Adolescent Primary Pool (Placebo-controlled studies)			Adolescent All Exposure Pool[e)]		
	100 mg	200 mg	Placebo	100 mg	200 mg	All abrocitinib[a)]
N	10	10	8	12	13	25
Total drug exposure	2.3	2.3	1.9	13.8	12.6	26.4
Overview of adverse events						
All adverse events	8 (80.0) 342.6	7 (70.0) 301.1	4 (50.0) 215.8	12 (100.0) 86.9	12 (92.3) 95.6	24 (96.0) 91.0
Serious adverse events	0	0	0	0	0	0
Adverse events leading to discontinuation	0	0	1 (12.5) 54.0	0	0	0
Adverse drug reactions	3 (30.0) 128.5	4 (40.0) 172.1	1 (12.5) 54.0	5 (41.7) 36.2	7 (53.8) 55.7	12 (48.0) 45.5
Death	0	0	0	0	0	0
Adverse events of special interest						
Infections	6 (60.0) 365.3	1 (10.0) 44.0	3 (37.5) 196.4	11 (91.7) 264.7	8 (61.5) 121.9	19 (76.0) 177.3
Serious infections	0	0	0	0	0	0
Herpes zoster	0	0	0	0	0	0
Herpes simplex[b)]	0	0	0	0	0	0
Skin infections[c)]	0	0	0	0	0	0
Acne-related events	2 (20.0) 90.9	2 (20.0) 94.4	0	5 (41.7) 47.3	6 (46.2) 83.5	11 (44.0) 62.0
Gastrointestinal disorders	5 (50.0) 383.7	4 (40.0) 272.1	0	5 (41.7) 65.7	5 (38.5) 61.2	10 (40.0) 63.4
Nausea	3 (30.0) 174.2	4 (40.0) 272.1	0	3 (25.0) 26.8	5 (38.5) 61.2	8 (32.0) 41.3
Vomiting	1 (10.0) 43.5	0	0	1 (8.3) 8.0	0	1 (4.0) 4.0
Dyslipidaemia	0	0	0	0	0	0
VTE	0	0	0	0	0	0
Anaemia	0	0	0	0	0	0
Decreased neutrophil count	0	0	0	0	0	0
Decreased lymphocyte count	0	0	0	0	0	0
Decreased platelet count	0	0	0	0	0	0
CK increased	0	0	0	0	0	0
Hepatic disorders	0	0	0	0	0	0
Renal disorders	0	0	0	0	0	0
Depression or suicide/self-injury	0	0	0	0	0	0

Upper row, n (%); Lower row, Incidence rate adjusted for total exposure[d)] (Number of subjects with events per 100 patient-years)
In the Adolescent All Exposure Pool (Data cutoff date of July 24, 2020, Overall adolescent population), opportunistic infection, active tuberculosis, latent tuberculosis, PCP, viral reactivation, hepatitis B, hepatitis C, malignancies, NMSC, malignancies (excluding NMSC), lymphoma, gastrointestinal perforation, interstitial lung disease, MACE, other cardiovascular events, pancytopenia, or rhabdomyolysis/myopathy was not reported.
a) Patients who received at least 1 dose of abrocitinib, b) Including oral herpes, Kaposi's varicelliform eruption, eczema herpeticum, and ophthalmic herpes simplex. c) bacterial skin infection, fungal skin infection, viral skin infection, d) Total follow-up time for adverse events of special interest was calculated up to the day of the first event (up to the end of risk period for subjects who did not have an event). The approximate total exposure for adverse events was calculated as the sum of the durations of exposures of the subjects. e) Data cutoff date of December 4, 2020

Given the following points, the effect of abrocitinib on the height standard deviation score (SDS) was examined in adolescent subjects who entered a long-term extension study (Study B7451015). The SDS standardized to the US population by age and gender was calculated at each time point where height measurement was available.

● Abnormal skeletal development in Jak-1 knockout mice and Stat mutant mice that have mutations in the JAK-STAT signaling pathway has been reported (*JAK-STAT*. 2013; 2: e23930).

● Based on abrocitinib non-clinical data, histopathological examination revealed bone dystrophy in rapidly growing rats in short-term toxicity studies of ≤1 month duration [see Section 5.2].

Table 79 shows height SDS over time in adolescent subjects <15 or 15 to <18 years of age at enrollment or baseline (first abrocitinib dosing), suggesting no meaningful change in the subjects' growth curves in both

subgroups. Figure 5 and Figure 6 show the heights of individual subjects (including past data) in the overall adolescent population or the Japanese adolescent subgroup in comparison with the standard growth curves by gender. Subjects in both the population and the subgroup largely seemed to gain height according to the standard growth curves.

Table 79. Height SDS over time in adolescent subjects (Study B7451015)

	Age at enrollment in Study B7451015					
	<15 years			≥15 and <18 years		
	100 mg	200 mg	All abrocitinib	100 mg	200 mg	All abrocitinib
6 months	0.0 ± 0.4 (47) (-0.7, 1.5)	-0.0 ± 0.5 (67) (-3.0, 1.3)	-0.0 ± 0.5 (114) (-3.0, 1.5)	0.0 ± 0.4 (80) (-3.2, 1.1)	0.0 ± 0.2 (101) (-0.6, 0.9)	0.0 ± 0.3 (181) (-3.2, 1.1)
12 months	-0.1 ± 0.4 (16) (-0.9, 0.5)	0.0 ± 0.5 (30) (-0.9, 1.1)	-0.0 ± 0.5 (46) (-0.9, 1.1)	0.1 ± 0.3 (22) (-0.5, 1.2)	-0.1 ± 0.3 (47) (-0.6, 0.8)	0.0 ± 0.3 (69) (-0.6, 1.2)
18 months	-0.2 ± 0.4 (2) (-0.5, 0.1)	-0.0 ± 0.6 (5) (-0.8, 0.7)	-0.1 ± 0.5 (7) (-0.8, 0.7)	0.4 ± 0.4 (6) (-0.1, 1.2)	-0.1 ± 0.3 (9) (-0.5, 0.4)	0.1 ± 0.4 (15) (-0.5, 1.2)
	Age at baseline					
	<15 years			≥15 and <18 years		
	100 mg	200 mg	All abrocitinib	100 mg	200 mg	All abrocitinib
6 months	-0.0 ± 0.4 (55) (-0.7, 1.5)	-0.0 ± 0.5 (80) (-3.0, 1.3)	-0.0 ± 0.4 (135) (-3.0, 1.5)	0.0 ± 0.4 (80) (-3.2, 1.1)	0.0 ± 0.2 (99) (-0.6, 0.9)	0.0 ± 0.3 (179) (-3.2, 1.1)
12 months	-0.1 ± 0.4 (17) (-0.9, 0.5)	-0.0 ± 0.5 (34) (-0.9, 1.1)	-0.0 ± 0.4 (51) (-0.9, 1.1)	0.1 ± 0.3 (21) (-0.5, 1.2)	-0.0 ± 0.3 (46) (-0.6, 0.8)	0.0 ± 0.3 (67) (-0.6, 1.2)
18 months	-0.2 ± 0.4 (2) (-0.5, 0.1)	-0.1 ± 0.5 (7) (-0.8, 0.7)	-0.1 ± 0.5 (9) (-0.8, 0.7)	0.4 ± 0.4 (6) (-0.1, 1.2)	-0.1 ± 0.3 (8) (-0.4, 0.4)	0.2 ± 0.4 (14) (-0.4, 1.2)

Upper row, Mean ± SD (N); Lower row, Range (Min., Max.)

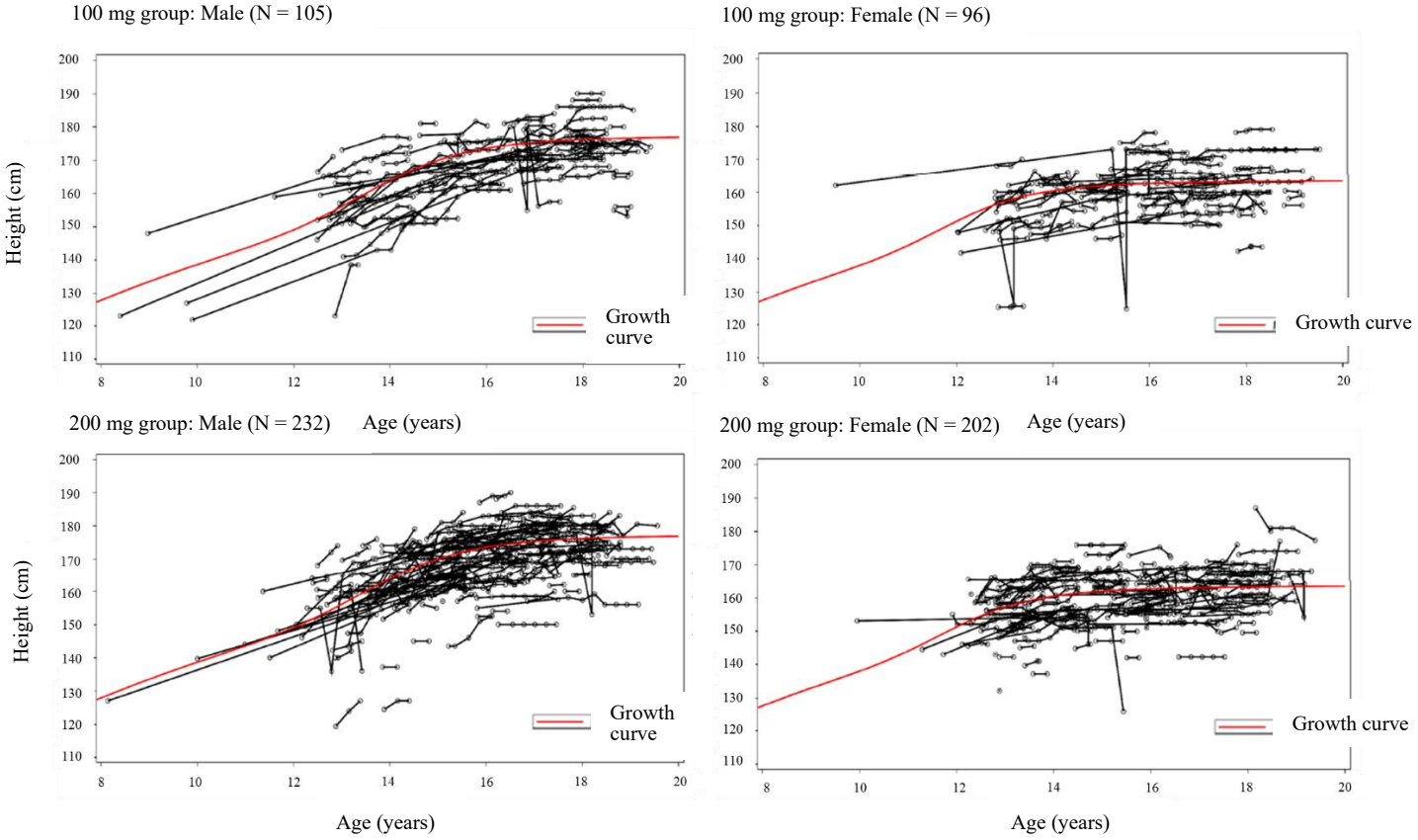


Figure 5. Heights of adolescents in comparison with the standard growth curve (US Centers for Disease Control and Prevention) (Study B7451015)

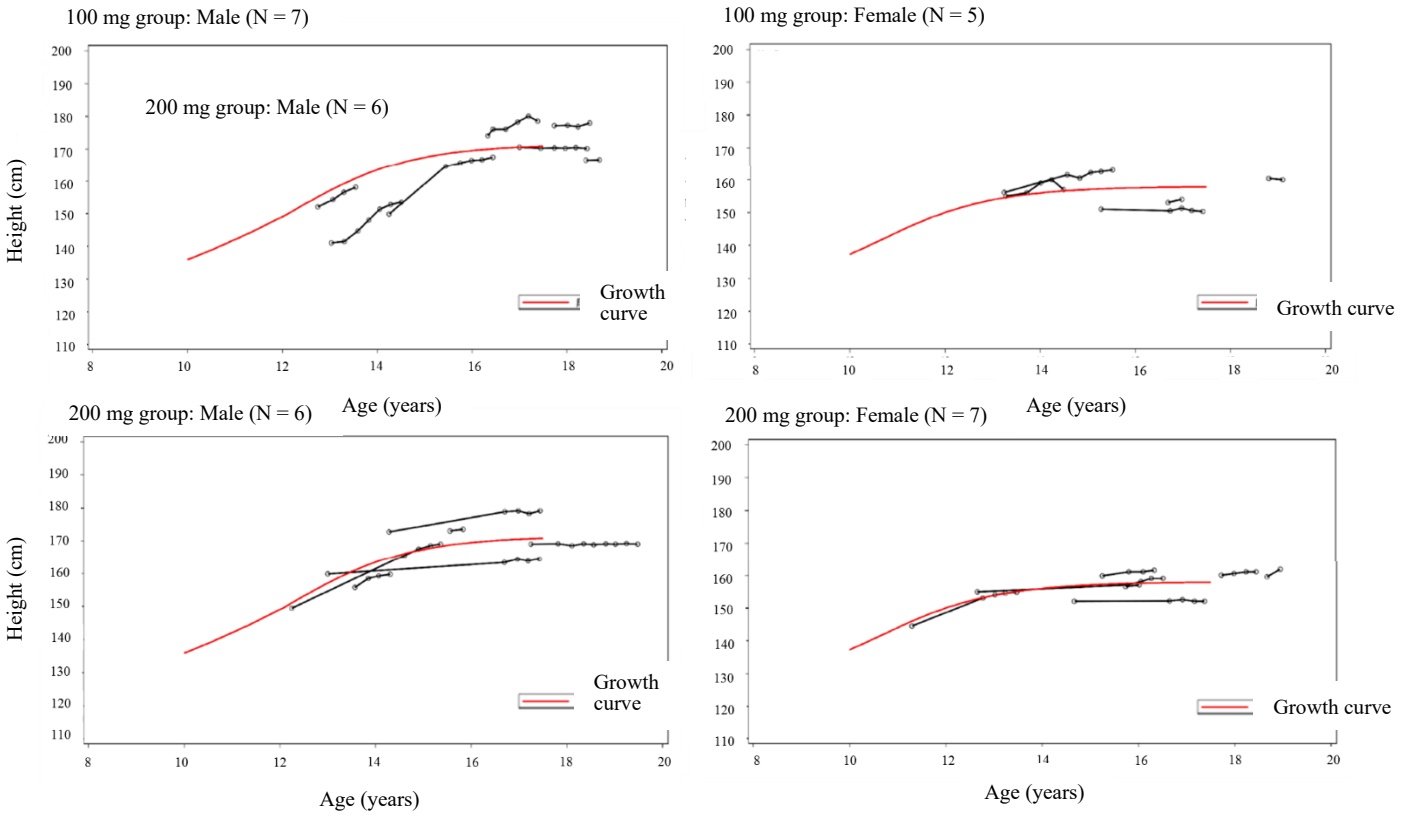


Figure 6. Heights of adolescents in comparison with the standard growth curve (The Japanese Society for Pediatric Endocrinology) (Study B7451015, Japanese subgroup)

Among adolescent subjects, 1 case of fracture was reported in the abrocitinib 100 mg group (0.5%, 0.63/100 patient-years) and 3 cases of fracture were reported in the abrocitinib 200 mg group (0.7%, 1.08/100 patient-years) in the All Exposure Pool, which were lower than the incidence rate of fracture [2.72/100 patient-years] in the Danish database containing ample information on adolescent patients (≥12 years of age) (3,909 AD patients aged 12 to <18 years). Individual events were caused by sports etc. and resolved without study drug discontinuation. A relationship to study drug was denied for all those events. There were no growth-related adverse events.

Increased CK occurred in a dose-dependent manner in abrocitinib-treated subjects, and 2 cases of serious myositis for which a causal relationship to abrocitinib could not be ruled out were reported among adolescent subjects. One subject (200 mg group, 1[redacted] years of age) had arthritis, osteomyelitis, and muscle abscess due to bacterial infection and myositis associated with sepsis, and the other subject (200 mg group, 1[redacted] years of age) experienced increased CK and myalgia, but had no signs of muscle injury or myositis on MRI. The events in these 2 subjects do not suggest the effect of abrocitinib on muscle growth during secondary sexual characteristics, and histopathological examination revealed no muscle-related changes associated with abrocitinib in rat (up to 6 months) and monkey (up to 9 months) repeated-dose toxicity studies. Thus, the use of abrocitinib in adolescent patients is unlikely to affect the occurrence of myositis and muscle growth.

Given the obtained non-clinical (Section 5.2) and clinical data, abrocitinib is unlikely to affect marked bone

development during secondary sexual characteristics in humans. Thus, there is no need to take additional safety measures against the potential growth effect, when administering abrocitinib in adolescent AD patients.

PMDA's view:
The currently available clinical study results have suggested no safety concerns unique to adolescent patients. Although an investigation of the effect of abrocitinib on bone development of adolescent patients in clinical studies was limited, taking also into account that no bone toxicity was observed following repeated administration of abrocitinib in cynomolgus monkeys that have bone physiology and bone development similar to humans as described in Section 5.R.4, abrocitinib is unlikely to affect marked bone development during secondary sexual characteristics in humans. However, as safety evaluation in Japanese adolescent patients in clinical studies was very limited, it is important to collect post-marketing information on the safety of abrocitinib in adolescent patients (including its effects on bone development), including published literature, and provide the obtained information to healthcare professionals in clinical practice as appropriate.

The above conclusion by PMDA presented in Section 7.R.3 will be discussed at the Expert Discussion.

7.R.4 Clinical positioning

The applicant's explanation about the expected clinical positioning of abrocitinib:
Treatment of AD basically consists of (1) drug therapy, (2) skin care such as the use of emollients for physiological abnormalities in the skin, and (3) investigations/elimination of exacerbating factors. Following definite diagnosis and severity assessment, these measures are adequately combined, based on the condition of eczema, patient characteristics, etc. As to drug therapy, it is important to appropriately use topical anti-inflammatory agents, such as TCS and TCI, at a necessary dose for a necessary duration of time, according to the severity of eczema. If patients have responded inadequately to these topical therapies, oral cyclosporine as a systemic agent, and oral corticosteroids etc. to induce the remission of acute exacerbation or severe/the most severe conditions will be considered (AD clinical practice guidelines 2018). In recent years, dupilumab and baricitinib have become new systemic therapy options for patients with an inadequate response to topical therapies. As with the currently approved systemic agents, abrocitinib is also positioned as a treatment option for AD patients with an inadequate response to appropriate treatment with topical anti-inflammatory agents, based on the efficacy and safety results obtained from phase III monotherapy studies (Studies B7451012 and B7451013) and phase III TCS combination studies (Studies B7451029 and B7451036).

The package insert will advise that continuous use of emollients, which play an important role in the restoration of the skin barrier, is needed during treatment with abrocitinib. While abrocitinib may be used with or without topical anti-inflammatory agents, it is important that physicians combine appropriate therapies, taking account of the condition of eczema, patient characteristics, etc.

PMDA's view:
Given the efficacy and safety profiles of abrocitinib obtained to date and the treatment paradigm for AD,

abrocitinib is expected to be positioned similarly as systemic agents such as the currently approved JAK inhibitors indicated for AD.

With regard to concomitant medications, clinical studies demonstrated the efficacy of abrocitinib with or without topical anti-inflammatory agents and identified no serious safety concerns. Meanwhile, concomitant use of emollients and topical anti-inflammatory agents is the standard of care for AD in Japan, and the efficacy of abrocitinib in combination with TCS tended to be consistently higher than the efficacy of abrocitinib monotherapy, though comparisons across different studies have limitations. Given these points, as a rule, abrocitinib should be used concomitantly with topical anti-inflammatory agents under continuous use of emollients. Since abrocitinib has immunosuppressive effects, it is necessary to provide a similar precaution as those for the currently approved JAK inhibitors, e.g., concomitant use of abrocitinib with biologics for AD, other oral JAK inhibitors, or immunosuppressants such as cyclosporine (excluding topical formulations) should be avoided.

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

7.R.5 Indication

PMDA's view:

Based on the submitted data and the considerations in Sections 7.R.2, 7.R.3, and 7.R.4, the appropriate indication for abrocitinib should be "atopic dermatitis in patients who have had an inadequate response to conventional treatments," as with the currently approved JAK inhibitors indicated for AD.

As with the currently approved JAK inhibitors and biologics indicated for AD, the following precautionary statements should be included in the package insert.

● Abrocitinib should be used in patients with widespread eczema associated with severe inflammation who have had an inadequate response to appropriate treatment with topical anti-inflammatory agents such as TCS and TCI that were given for a certain period of time.

● As a rule, abrocitinib should be used concomitantly with topical anti-inflammatory agents according to the condition of AD lesions.

● Emollients should be continued also during treatment with abrocitinib.

Furthermore, information on the inclusion criteria etc. for clinical studies should be provided as a reference for selecting eligible patients, and it is important to advise that abrocitinib should be used by physicians who are familiar with the diagnosis and treatment of AD so as to ensure appropriate selection of eligible patients and the proper use of abrocitinib.

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

7.R.6 Dosage and administration

The applicant's explanation about the proposed dosage and administration for abrocitinib:

Taking account of the following points, the proposed dosage and administration statement is "the usual dosage for adults and adolescents aged 12 years and older is 100 or 200 mg of abrocitinib administered orally once daily." After assessment of the signs and symptoms of AD, the 100 mg or 200 mg dose may be chosen (including dose increase/reduction), based on the treatment goal and risk of adverse drug reactions for individual patients. Although body weight of ≥25 kg was listed as an inclusion criterion in a clinical study in adolescent patients, given the body weights of 12-year-old adolescents in Japan (the median is 44 kg and the 3rd percentile is 30 kg in boys; the median is 43 kg and the 3rd percentile is 31 kg in girls),[43)] a body weight limit was considered unnecessary in the proposed dosage and administration statement.

● Phase III monotherapy studies (Studies B7451012 and B7451013) and phase III TCS combination studies (Studies B7451029 and B7451036) demonstrated the superiority of both 100 mg and 200 mg abrocitinib to placebo (Table 45, Table 48, Table 52, Table 56). The results of other efficacy endpoints also favored abrocitinib over placebo throughout the treatment period (Table 61 to Table 63). Furthermore, the efficacy of 200 mg tended to be higher than that of 100 mg for multiple efficacy endpoints (Table 61 to Table 63).

● Figure 7 shows the median time to flare (a loss of at least 50% of the EASI response from randomization and an IGA score of 2 or higher) in Study B7451014 (a randomized withdrawal study following response to induction treatment with abrocitinib 200 mg QD without TCS) (could not be estimated for the 200 mg or 100 mg group; 28.0 days in the placebo group). The proportion of subjects who did not experience flares by Week 40 of randomized treatment was 81.1% for subjects continuing abrocitinib 200 mg, 57.4% for a step-down to 100 mg, and 19.1% for placebo.

Figure 8 shows the rate of recapture of the EASI-75 response in subjects who experienced flares and received rescue treatment with abrocitinib 200 mg QD plus topical therapy. The EASI-75 response rate increased in subjects with loss of response in the 100 mg QD group.

[43)] 2020 School Health Statistical Survey: Physical growth values and growth curves based on school health statistical survey

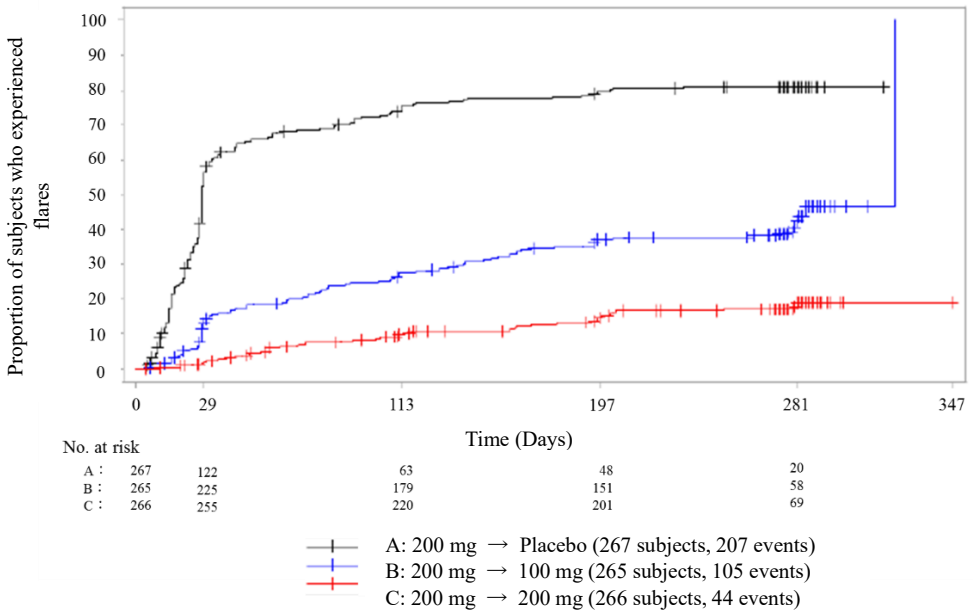


Figure 7. Kaplan-Meier curves for time to flare

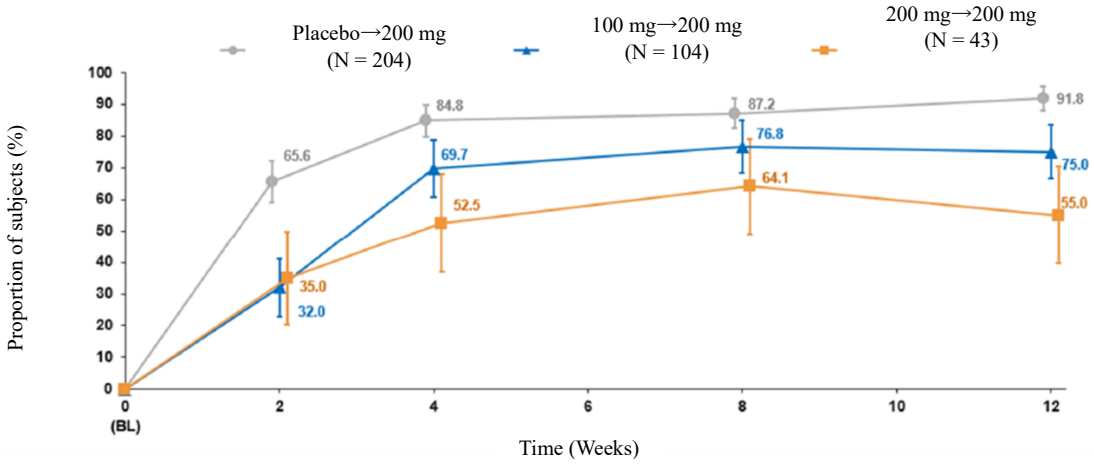


Figure 8. Rate of recapture of EASI-75 response

● Regarding safety, the incidence rates of some events such as herpes zoster, decreased platelet count, and decreased lymphocyte count tended to be higher with 200 mg compared with 100 mg, and this risk tended to increase especially in subjects aged ≥65 years. Although there were differences in the safety risk of abrocitinib between the doses, both the 100 mg and 200 mg doses had acceptable tolerability [see Section 7.R.3].

PMDA's view based on the above explanation by the applicant, the submitted data, and the considerations in Sections 7.R.2 and 7.R.3:

From the efficacy standpoint, the efficacy of 200 mg tended to be slightly higher than that of 100 mg for multiple efficacy endpoints, and the applicant's explanation that abrocitinib 200 mg is more useful for some patients is understood. However, there should be a certain number of subjects who are expected to respond adequately to the 100 mg dose. Regarding safety, there was a trend towards dose-dependent increases in adverse

events of herpes zoster, herpes simplex, dyslipidaemia, anaemia, decreased lymphocyte count, decreased neutrophil count, decreased platelet count, etc.

Based on the above, the labeled dosage of abrocitinib should be 100 mg once daily, with the option of 200 mg once daily, according to the patient's symptoms or condition.

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

7.R.6.2 Dosing regimen of abrocitinib for patients with renal impairment

The applicant's explanation about the dosing regimen of abrocitinib for patients with renal impairment, based on the results of a clinical pharmacology study in subjects with renal impairment [see Section 6.2.2.2] and the safety data from clinical studies in AD patients:

Based on the results of a clinical pharmacology study in subjects with renal impairment [see Section 6.2.2.2], an approximately 2.1-fold increase in AUC is predicted in subjects with moderate renal impairment (eGFR, 30-60 mL/min) and an approximately 2.9-fold increase in AUC is predicted in subjects with severe renal impairment (eGFR, 30 mL/min). Thus, the usual dose of abrocitinib should be reduced by half to 50 mg or 100 mg once daily in patients with moderate or severe renal impairment (including end-stage renal disease).

Subjects with mild or moderate renal impairment were also enrolled in clinical studies in AD patients. Table 80 shows the occurrence of adverse events by renal impairment in the All Exposure Pool. Though the number of subjects with moderate renal impairment (eGFR, 30-60 mL/min) was limited, the incidence rates of serious adverse events and adverse events leading to discontinuation were higher in subjects with moderate renal impairment than in subjects with mild renal impairment (eGFR, 60-90 mL/min) and subjects with normal renal function (eGFR ≥90 mL/min/1.73 m^2). The incidence rate of adverse events was similar between subjects with mild renal impairment (eGFR, 60-90 mL/min) and subjects with normal renal function (eGFR ≥90 mL/min).

Based on the above analyses and the consideration in Section 6.R.3, no dose adjustment is required in patients with mild renal impairment, whereas the usual dose of abrocitinib should be reduced by half to 50 mg or 100 mg once daily in patients with moderate or severe renal impairment (including end-stage renal disease).

Table 80. Summary of safety by severity of renal impairment (All Exposure Pool)

	Normal renal function (eGFR ≥90 mL/min)			Mild renal impairment (eGFR 60-90 mL/min)			Moderate renal impairment (eGFR 30-60 mL/min)		
	100 mg	200 mg	All abrocitinib[a)]	100 mg	200 mg	All abrocitinib[a)]	100 mg	200 mg	All abrocitinib[a)]
N	706	1,491	2,197	303	574	877	14	34	48
Total drug exposure (patient-years)	588.2	896.9	1,485.0	249.5	315.4	564.9	12.2	23.5	35.7
All adverse events	520 (73.7) 88.4	1,102 (73.9) 122.9	1,622 (73.8) 109.2	217 (71.6) 87.0	417 (72.6) 132.2	634 (72.3) 112.2	10 (71.4) 81.9	22 (64.7) 93.8	32 (66.7) 89.7
Serious adverse events	38 (5.4) 6.5	67 (4.5) 7.5	105 (4.8) 7.1	17 (5.6) 6.8	15 (2.6) 4.8	32 (3.6) 5.7	2 (14.3) 16.4	6 (17.6) 25.6	8 (16.7) 22.4
Adverse events leading to discontinuation	63 (8.9) 10.7	125 (8.4) 13.9	188 (8.9) 12.7	27 (8.9) 10.8	45 (7.8) 14.3	72 (8.2) 12.7	3 (21.4) 24.6	7 (20.6) 29.8	10 (20.8) 28.0
Adverse drug reactions	211 (29.9) 35.9	643 (43.1) 71.7	854 (38.9) 57.5	93 (30.7) 37.3	259 (45.1) 82.1	352 (40.1) 62.3	3 (21.4) 24.6	17 (50.0) 72.5	20 (41.7) 56.1
Death	0	1 (0.1) 0.1	1 (<0.1) 0.1	1 (0.3) 0.4	1 (0.2) 0.3	2 (0.2) 0.4	0	0	0

Upper row, n (%); Lower row, Incidence rate adjusted for total exposure[b)] (Number of subjects with events per 100 patient-years)
Six subjects with missing eGFR in the 200 mg group were not counted.
a) Patients who received at least 1 dose of abrocitinib, b) The approximate total exposure for adverse events was calculated as the sum of the durations of exposures of the subjects.

PMDA's view:

No dose adjustment is required in patients with mild renal impairment. For patients with moderate renal impairment, abrocitinib 50 mg should be administered once daily, and a dose of 100 mg once daily may be given according to the patient's condition. Given the following points, 50 mg once daily may be chosen for patients with severe renal impairment (including end-stage renal disease) because the exposures at 50 mg are not expected to far exceed the exposures at the doses investigated in phase III studies. However, since there is no clinical experience with abrocitinib in AD patients with severe renal impairment, whether to use abrocitinib in these patients should be decided carefully. The patient's condition should be closely monitored for the possible occurrence of adverse drug reactions during treatment with abrocitinib, and dose increase should be avoided.

● The results of a clinical pharmacology study in subjects with renal impairment [see Section 6.R.3] suggested that the active moiety AUC may increase by approximately 3-fold compared to that in subjects with normal renal function.

● There was a trend towards a dose-dependent increase in the risk of some adverse events in clinical studies in AD patients (Table 71).

● The results of a subgroup analysis showed a trend towards a higher incidence rate of serious adverse events in patients with moderate renal impairment in which increased exposure is expected (Table 80).

Furthermore, as there is limited clinical experience with abrocitinib in patients with moderate or severe renal impairment in clinical studies in AD patients, it is necessary to collect information on the safety and efficacy of abrocitinib in patients with renal impairment via post-marketing surveillance etc., and provide the obtained information to healthcare professionals in clinical practice as appropriate.

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

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

PMDA's view:

As evaluated in Section 7.R.3, compared with the safety profiles of other JAK inhibitors approved for AD, no serious safety concerns unique to abrocitinib have been suggested at present. Thus, the safety risk of abrocitinib can be managed by taking similar safety measures as those for the currently approved JAK inhibitors, e.g., abrocitinib is used under the supervision of physicians with adequate knowledge of abrocitinib and knowledge of and experience in the treatment of AD; and serious infections etc. are managed in cooperation with other departments/medical institutions, as needed.

Meanwhile, since the number of Japanese AD patients on long-term treatment with abrocitinib was limited, the safety of abrocitinib in clinical practice, including its long-term safety (VTE, malignancies, serious infections, MACE, etc.), should be assessed via post-marketing surveillance etc. In addition, given that the number of Japanese adolescent patients evaluated in clinical studies was even limited, the surveillance should be planned to collect a certain amount of information on the safety and efficacy of abrocitinib in the adolescent population. It is necessary to appropriately provide the collected information to healthcare professionals in clinical practice as appropriate.

The above conclusion by PMDA and the need for further safety measures will be discussed at the Expert Discussion.

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

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

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

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

The new drug application data (CTD 5.3.5.1.3, CTD 5.3.5.1.4, CTD 5.3.5.1.5, CTD 5.3.5.2.1, pooled safety analysis [phase II and III studies, Japanese population, 48 weeks (data cut-off date of December 18, 2020)]) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that since the clinical studies as a whole were performed in compliance with GCP, there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following finding at the sponsor, although which did not affect the overall assessment of the studies significantly. The sponsor was notified of this matter and asked for a corrective action.

[Finding requiring corrective action]

Sponsor

● Delay in annual reporting on safety information to the heads of study sites

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

On the basis of the data submitted, PMDA has concluded that abrocitinib has efficacy in the treatment of AD in patients with an inadequate response to conventional treatments, and that abrocitinib has acceptable safety in view of its benefits. Abrocitinib is clinically meaningful because it offers a new treatment option for AD patients with an inadequate response to conventional treatments. Regarding safety, as serious adverse drug reactions such as infections, herpes zoster, malignancies, and VTE may occur, similar safety measures as those for other JAK inhibitors indicated for AD should be taken. The safety etc. of abrocitinib in Japanese AD patients should be further investigated in clinical practice via post-marketing surveillance etc.

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

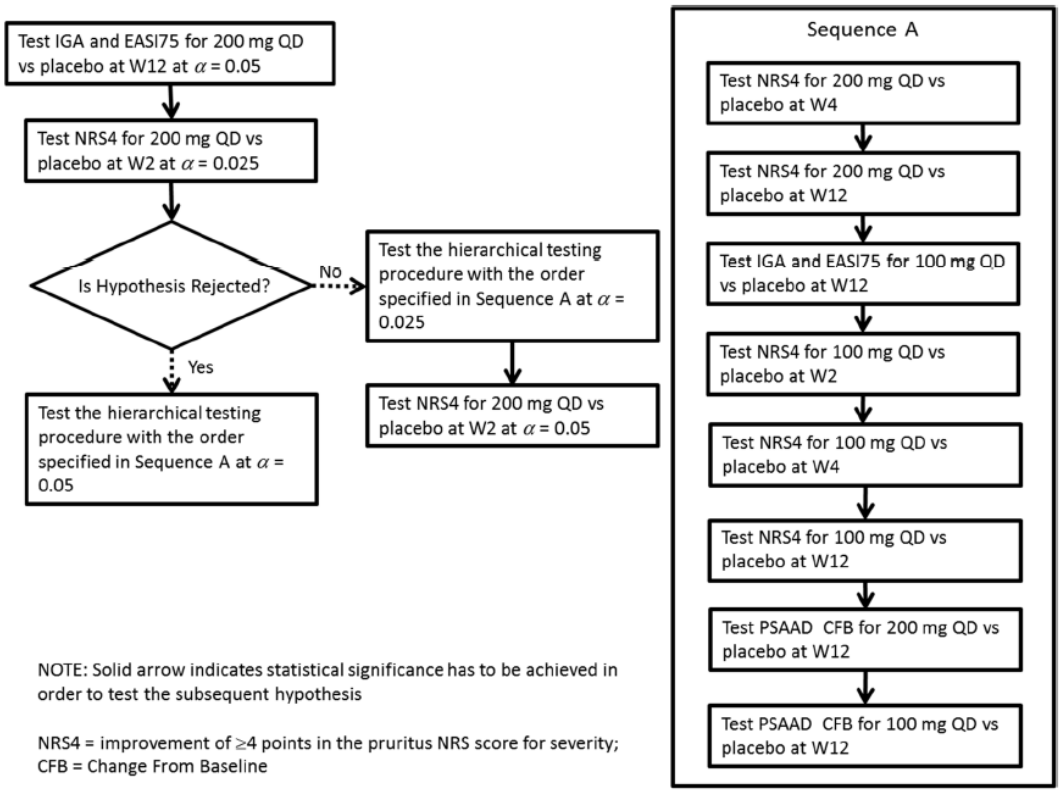
10. Others

Efficacy assessment tools and the definitions of endpoints in clinical studies of abrocitinib are shown below.

Endpoint	Definition
EASI score	In each of 4 body regions (head and neck, trunk, upper limbs, lower limbs), the sum of the clinical signs severity scores for 4 signs of eczema (erythema, induration/papulation, excoriation, lichenification) (Absent = 0, Mild = 1, Moderate = 2, Severe = 3) is multiplied by the area score (0% = 0, 1%-9% = 1, 10%-29% = 2, 30%-49% = 3, 50%-69% = 4, 70%-89% = 5, 90%-100% = 6) and by the body region weighting to provide a body region value (head and neck = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4), which is then summed across all 4 body regions resulting in an EASI score. The EASI score ranges from 0 to 72.
IGA score	The investigator's global assessment (IGA) of atopic dermatitis is scored on a 5-point scale using the descriptors below that best describe the overall appearance of the lesions. 0 = Clear (No inflammatory signs of AD. Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.) 1 = Almost clear (Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.) 2 = Mild (Slight but definite erythema [pink], slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.) 3 = Moderate (Clearly perceptible erythema [dull red], clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.) 4 = Severe (Marked erythema [deep or bright red], marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.)
Pruritus NRS score	A subject-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no itch" and 10 representing "worst itch imaginable." A score obtained by selecting the number that best describes the worst level of itching in the past 24 hours.
EASI-75 response rate EASI-90 response rate EASI-100 response rate	Proportion of subjects with ≥75%, ≥90%, or 100% reduction from baseline in EASI score
IGA (0/1) response rate	Proportion of subjects with IGA score of clear (0) or almost clear (1) and a reduction from baseline of ≥2 points

For the analyses of the primary and secondary endpoints for clinical studies, graphical approach was used to adjust for multiplicity. The details of graphical approach are shown in the figure below.

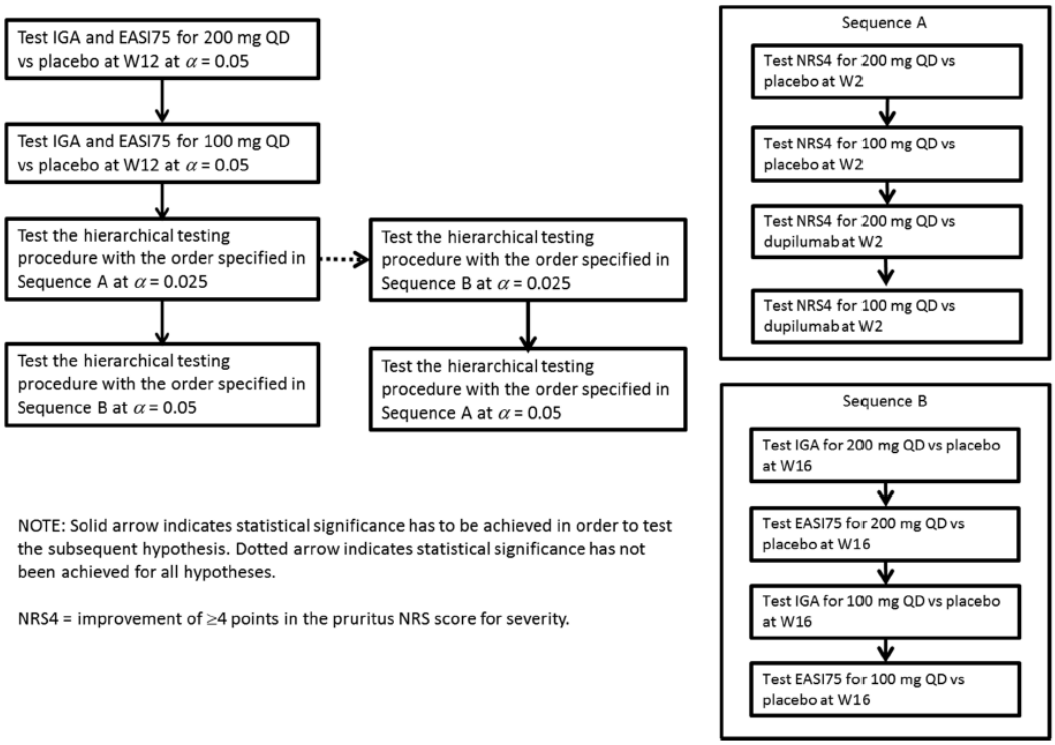
[Study B7451012, Study B7451013, Study B7451036]



NOTE: Solid arrow indicates statistical significance has to be achieved in order to test the subsequent hypothesis

NRS4 = improvement of ≥4 points in the pruritus NRS score for severity;
CFB = Change From Baseline

[Study B7451029]



NOTE: Solid arrow indicates statistical significance has to be achieved in order to test the subsequent hypothesis. Dotted arrow indicates statistical significance has not been achieved for all hypotheses.

NRS4 = improvement of ≥4 points in the pruritus NRS score for severity.

Review Report (2)

August 26, 2021

Product Submitted for Approval

Brand Name	Cibinqo Tablets 50 mg, Cibinqo Tablets 100 mg, Cibinqo Tablets 200 mg
Non-proprietary Name	Abrocitinib
Applicant	Pfizer Japan Inc.
Date of Application	December 9, 2020

List of Abbreviations

See Appendix.

1. Content of the Review

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

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

At the Expert Discussion, the expert advisors supported PMDA's conclusions concerning the efficacy, clinical positioning, indication, and dosage and administration of abrocitinib presented in the Review Report (1).

1.2 Safety, post-marketing investigations, and safety measures

At the Exert Discussion, the expert advisors supported PMDA's conclusions concerning the safety of abrocitinib, post-marketing investigations, and safety measures presented in the Review Report (1) and commented that information regarding the long-term safety, etc. of abrocitinib in patients with AD, which is a chronic disease, should be collected via post-marketing surveillance, etc.

In view of the discussions presented in Section “7.R.7 Post-marketing investigations and safety measures” in the Review Report (1) and the comments from the expert advisers at the Expert Discussion, etc., PMDA has concluded that the risk management plan (draft) for abrocitinib should include the safety and efficacy specifications presented in Table 81, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 82, and instructed the applicant to conduct post-marketing surveillance etc. that cover these issues.

Table 81. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
・ Venous thromboembolic events ・ Serious infections (including tuberculosis, pneumonia, pneumocystis pneumonie, sepsis, and opportunistic infection) ・ Herpes zoster ・ Gastrointestinal perforation ・ Hepatitis B virus reactivation ・ Interstitial pneumonia ・ Decreased neutrophil count, decreased lymphocyte count, decreased hemoglobin, decreased platelet count ・ Hepatic dysfunction	・ Malignancies ・ Rhabdomyolysis, myopathy ・ Cardiovascular events	None
Efficacy specification		
None		

Table 82. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
・ Early post-marketing phase vigilance ・ Long-term specified use-results survey ・ Post-marketing clinical study[a)]	None	・ Dissemination of data gathered during early post-marketing phase vigilance ・ Preparation and distribution of information materials for healthcare professionals (Proper use guide) ・ Preparation and distribution of information materials for patients Thorough provision of proper use information before delivery of the product

a) Study B7451015 in AD patients (ongoing) will be continued as a post-marketing clinical study after the approval of abrocitinib.

The applicant's explanation:

As shown in Table 83, a specified use-results survey will be conducted in adolescent AD patients aged ≥12 years and adult AD patients, with an observation period of ≥2 years (patients treated for >2 years will be followed up to 3 years until the end of the survey period) and a target sample size of 1,200 patients to assess the long-term safety and efficacy of abrocitinib in clinical practice.

Table 83. Outline of specified use-results survey (draft)

Objective	To assess the long-term safety and efficacy of abrocitinib in clinical practice
Survey method	Central registry system
Population	AD patients
Observation period	2 years (Patients treated for >2 years will be followed up to 3 years until the end of the survey period)
Planned sample size	1,200 patients (for the safety analysis)
Main survey items	・ Safety specification: Important identified risks and important potential risks presented in Table 81 ・ Patient characteristics (age, body weight, severity of AD, disease duration, medical history/comorbidities, degree of renal impairment, etc.) ・ Use of abrocitinib ・ Previous treatments for AD ・ Concomitant medications/therapies ・ Clinical laboratory test ・ Adverse events ・ Efficacy assessment

PMDA accepted these measures and considers that it is necessary to provide the collected information to healthcare professionals etc. appropriately and promptly.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration as shown below, with the following condition. As the product is a drug with a new active ingredient, 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

Atopic dermatitis in patients who have had an inadequate response to conventional treatments ~~(including improvement in itch)~~

(The strike-through denotes deletion from the proposed text.)

Dosage and Administration

The usual dosage for adults and adolescents aged 12 years and older is 100 ~~or 200~~ mg of abrocitinib administered orally once daily. A dose of 200 mg once daily may be given according to the patient's condition.

(The strike-through denotes deletion from the proposed text and
the underline denotes addition.)

Approval Condition

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

Appendix

List of Abbreviations

Abrocitinib	abrocitinib
AD	Atopic dermatitis
AD clinical practice guidelines 2018	Clinical Practice Guidelines for the Management of Atopic Dermatitis 2018, edited by Japanese Dermatological Association/Japanese Society of Allergology
A/G	Albumin/globulin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration versus time curve
AUC_{0-t}	AUC from time zero to time t
AUC_{inf}	AUC from time zero to infinity
AUC_{last}	AUC from zero to the time of last measurement
BCRP	Breast cancer resistance protein
BMI	Body mass index
BSEP	Bile salt export pump
CD	Cluster of differentiation
CHO	Chinese hamster ovary
CI	Confidence interval
CK	Creatine kinase
CL	Clearance
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
DMSO	Dimethyl sulfoxide
DVT	Deep vein thrombosis
EASI	Eczema Area and Severity Index
eGFR	Estimated glomerular filtration rate
EPO	Erythropoietin
F	Bioavailability
FAS	Full analysis set
filgotinib	Filgotinib maleate [Brand name: Jyseleca Tablets 100 mg and 200 mg]
FISH	Fluorescent in situ hybridization
GALT	Gut-associated lymphoid tissue
GC	Gas chromatography
GM-CSF	Granulocyte-macrophage colony-stimulating factor
hERG	Human ether-à-go-go-related gene
HDL	High density lipoprotein
HPC	hydroxypropyl cellulose
HPLC	High performance liquid chromatography
HPMCAS-HF	Hydroxypropyl methylcellulose acetate succinate-high fine
HPMCAS-MG	Hydroxypropyl methylcellulose acetate succinate-medium granular
IC_{50}	50% inhibitory concentration
IFN	Interferon
Ig	Immunoglobulin
IGA	Investigator`s Global Assessment
IL	Interleukin
IP-10	Interferon inducible protein 10
IR	Infrared absorption spectrum
JAK	Janus kinase

Km	Michaelis Menton constant
KLH	Keyhole limpet hemocyanin
KPNC	Kaiser Permanente Northern California
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDL	Low-density lipoprotein
LOEL	Lowest observed effect level
MAO	Monoamine oxidase
MACE	Major adverse cardiovascular event
MATE	Multidrug and toxin extrusion
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MRI	Magnetic resonance imaging
m/z	Mass to charge ratio
NIR	Near infrared spectrometry
NK	Natural killer
NMSC	Non-melanoma skin cancer
NMR	Nuclear magnetic resonance spectrum
NRI	Non-responder imputation
NRS	Numerical rating scale
NZW	New Zealand White
OAT	Organic anion transporter
OATP	Organic anion transporter polypeptide
OCT	Organic cation transporter
PBMC	Peripheral blood mononuclear cells
PCP	Pneumocystis pneumonie
PE	Pulmonary embolism
peficitinib	Peficitinib hydrobromide [Brand name: Smyraf Tablets 50 mg and 100 mg]
P-gp	P-glycoprotein
PLS	Partial least squares regression
PMDA	Pharmaceuticals and Medical Devices Agency
PTP	Press through packaging
RA	Rheumatoid arthritis
RH	Relative humidity
SBECD	Sulfobutylether-β-cyclodextrin
SD	Sprague Dawley
SDD	Spray dried dispersion
SDS	Standard deviation score
SS	Softsensor
STAT	Signal transducer and activator of transcription
SULT	Sulfotransferase
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroids
TDAR	T cell dependent antibody response
The product	Cibinqo Tablets 50 mg, Cibinqo Tablets 100 mg, Cibinqo Tablets 200 mg
THIN	The Health Improvement Network
t_{max}	Time to first occurrence of C_{max}
TNF	Tumor necrosis factor
tofacitinib	Tofacitinib citrate [Brand name: Xeljanz Tablets 5 mg]
TPO	Thrombopoietin
TSLP	Thymic stromal lymphopoietin
TYK2	Tyrosine-kinase 2
$t_{1/2}$	Terminal plasma half-life
UGT	Uridine diphosphate glucronosyl transferase

upadacitinib	Upadacitinib hydrate [Brand name: Rinvoq Tablets 7.5 mg etc.]
UV	Ultraviolet
VEGFR	Vascular endothelial growth factor receptor
VTE	Venous thromboembolic event
V_{ss}	Volume of distribution at steady state
V_z/F	Apparent volume of distribution