Report on the Deliberation Results

June 1, 2023
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Litfulo Capsules 50 mg
Non-proprietary Name	Ritlecitinib Tosilate (JAN*)
Applicant	Pfizer Japan Inc.
Date of Application	August 25, 2022

Results of Deliberation

In its meeting held on May 29, 2023, 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)*

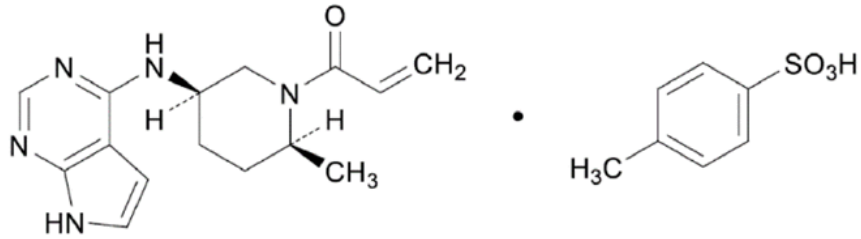
Review Report

May 17, 2023
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	Litfulo Capsules 50 mg
Non-proprietary Name	Ritlecitinib Tosilate
Applicant	Pfizer Japan Inc.
Date of Application	August 25, 2022
Dosage Form/Strength	Capsules: Each capsule contains 80.128 mg of Ritlecitinib Tosilate (equivalent to 50 mg of ritlecitinib).
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{15}H_{19}N_5O \cdot C_7H_8O_3S$
Molecular weight: 457.55
Chemical name: 1-{(2*S*,5*R*)-2-Methyl-5-[(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]piperidin-1-yl}prop-2-en-1-one mono(4-methylbenzenesulfonate)

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 intractable alopecia areata with extensive hair loss, 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 of the product, as practiced with existing oral Janus kinase inhibitors. The safety etc. of the product should be further investigated in clinical practice via post-marketing surveillance etc.

Indication

Alopecia areata (limited to intractable cases involving extensive hair loss)

Dosage and Administration

The usual dosage for adults and adolescents aged 12 years and older is 50 mg of ritlecitinib administered orally once daily.

Approval Condition

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

Attachment

Review Report (1)

April 20, 2023

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	Litfulo Capsules 50 mg
Non-proprietary Name	Ritlecitinib Tosilate
Applicant	Pfizer Japan Inc.
Date of Application	August 25, 2022
Dosage Form/Strength	Capsules: Each capsule contains 80.128 mg of Ritlecitinib Tosilate (equivalent to 50 mg of ritlecitinib).

Proposed Indication

Alopecia areata in patients who are eligible for systemic therapy (including alopecia totalis and alopecia universalis)

Proposed Dosage and Administration

The usual dosage for adults and adolescents aged 12 years and older is 50 mg of ritlecitinib 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

"Litfulo Capsules 50 mg" contains the active substance Ritlecitinib Tosilate (ritlecitinib). Ritlecitinib is a small molecule discovered by Pfizer (the US). It irreversibly inhibits a member of the Janus kinase (JAK) family, JAK3, and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family by covalently binding to a cysteine residue in the adenosine triphosphate (ATP) binding site of these enzymes.

Alopecia areata (AA) is considered an autoimmune disease that targets hair follicles. This is an acquired disease characterized by nonscarring hair loss, usually presented as circular patches of hair loss. Hair loss may involve all hair-bearing areas, e.g., eyebrow and eyelash, as well as the scalp. AA is clinically classified according to the number and extent of patches of scalp hair loss: alopecia areata simplex (a single patch of hair loss), alopecia areata multiplex (multiple patches of hair loss), alopecia totalis (total hair loss on the scalp), and alopecia ophiasis (band-like hair loss limited to the periphery of the scalp). Alopecia universalis consists of complete hair loss on all parts of the body (the Japanese clinical practice guidelines). According to a foreign epidemiological study, the onset of AA can occur at any age, and AA patients experience their first onset of AA by age 20 years in 40.2% of patients and by age 40 years in 82.6% to 88.0% of patients (*Clin Cosmet Investig Dermatol*. 2015; 8: 397-403). The AA prevalence in Japan was reported to be 2.45% according to a nationwide, multi-center study conducted by the Japanese Dermatological Association at 170 medical institutions in 2007 to 2008 to clarify the prevalence of skin disorders among dermatology patients (*J Dermatol*. 2011; 38: 310-20) and 0.16% to 0.27% according to a study using the JMDC database in 2012 to 2019.

AA is treated taking account of AA subtype, severity, age, etc. The Japanese clinical practice guidelines recommend intralesional corticosteroid injection, topical corticosteroids, and contact immunotherapy as symptomatic treatment. In June 2022, a JAK inhibitor, baricitinib was approved for the indication of alopecia areata (limited to intractable cases involving extensive hair loss) and added as a treatment option for adult patients with AA.

CD8+ T cells, natural killer (NK) cells, and mast cells are likely involved in the pathogenesis of AA (*Nat Med.* 2014; 20: 989-90, *J Invest Dermatol*. 2008; 128: 1196-206, *Plos One*. 2014; 9: e94260), and their differentiation and function are known to be regulated by JAK3 and the TEC family kinases (*J Immunol*. 2006; 176: 1571-81, *J Biol Chem*. 2012; 287: 23769-78, *J Exp Med*. 1997; 185: 197-206, etc.). As an inhibitor of JAK3 and the TEC family kinases, ritlecitinib was developed with an expectation of its therapeutic effects for AA.

The clinical development of ritlecitinib began in December 2014. Recently, 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. 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 pink solid. Its appearance, solubility, dissociation constant, partition coefficient, hygroscopicity, thermal analysis (differential scanning calorimetry, thermogravimetric analysis), optical rotation, and crystalline polymorphism (X-ray powder diffraction) have been determined.

Its chemical structure has been elucidated by ultraviolet-visible spectroscopy, infrared absorption spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR) (^{1}H- NMR, ^{13}C- NMR, ^{15}N-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], [redacted], and [redacted] as starting materials.

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 quality control strategy (Drug substance)

CQA	Method of control
Content	Specification
Appearance	Specification
Identity	Specification
Related substances	Manufacturing process, Specification
API polymer	Manufacturing process, Specification
Residual solvents	Manufacturing process, Specification
Water content	Specification
Residue on ignition	Specification
[redacted]	Manufacturing process, Specification

[redacted] and [redacted] have been defined as critical steps. [redacted] and 1-{(2*S*,5*R*)-2-Methyl-5-[(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]piperidin-1-yl}prop-2-en-1-one mono(4-methylbenzenesulfonate) (the drug substance before purification) 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, [redacted] chromatography, tosic acid (high performance liquid chromatography [HPLC])], purity [related substances (HPLC), active pharmaceutical ingredient (API) polymer (HPLC), residual solvents (gas chromatography)], water content, 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. Primary stability studies (Drug substance)

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 pilot-scale batches	25°C	60%RH	double low-density polyethylene bags + high-density polyethylene drum	[redacted] months
Accelerated	3 pilot-scale batches	40°C	75%RH		6 months

Based on the above, a re-test period of 36 months was proposed for the drug substance when stored in double low-density polyethylene bags within a high-density polyethylene drum at room temperature, in accordance with the ICH Q1E guideline. The long-term testing will be continued up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an immediate-release hard capsule containing 80.128 mg ritlecitinib tosilate (equivalent to 50 mg ritlecitinib) and the following excipients: microcrystalline cellulose, lactose monohydrate, crospovidone, and glycerol esters of fatty acids.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of [redacted], packaging, and packaging/labeling/testing/storage. [redacted] has been defined as a critical step.

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

- Identification of CQAs
- Identification of CPPs through quality risk assessment

Table 3. Overview of quality control strategy (Drug product)

CQA	Method of control
Strength	Manufacturing process, Specification
Appearance (visual)	Manufacturing process, Specification
Identity	Manufacturing process, Specification
Degradation products	Manufacturing process, Specification
Uniformity of dosage units	Manufacturing process, Specification
Dissolution	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 (by weight variation), dissolution (ultraviolet-visible spectrophotometry), water activity, and assay (HPLC). Water activity was included in the specifications in the course of regulatory review.

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. Primary stability studies (Drug product)

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches	25°C	60%RH	Aluminum/aluminum blister pack	24 months
	3 commercial-scale batches	[redacted]°C	[redacted]%RH		[redacted] months
Accelerated	3 commercial-scale batches	40°C	75%RH		6 months

Based on the above, a shelf-life of 36 months was proposed for the drug product when packaged in an aluminum/aluminum blister pack (a 3-layer laminate of polyamide, aluminum foil, and polyvinyl chloride/a heat-seal coated aluminum lidding foil) and stored at room temperature, in accordance with the ICH Q1E guideline. 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, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled. A nitrosamine compound that may theoretically be formed, i.e., Impurity A, has not been detected as an impurity or a degradation product in the drug substance or the drug product.

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 the inhibition and occupancy of various kinases, effects on signal transducer and activator of transcription (STAT) phosphorylation, and effects on various signaling pathways other than STAT phosphorylation, studies in various animal models, etc. The applicant submitted the results from secondary pharmacodynamic studies investigating effects on various enzymes and receptors, etc. and the results from safety pharmacology studies assessing effects on the central nervous, cardiovascular, and respiratory systems.

In the pharmacology studies, Ritlecitinib Tosilate, free ritlecitinib, and ritlecitinib malonate were used as ritlecitinib. In this section, all of these test articles are referred to as ritlecitinib, and doses are expressed in terms of ritlecitinib. Pharmacologic parameters are expressed as the mean.

3.1 Primary pharmacodynamics

3.1.1 Inhibition of various kinases (CTD 4.2.1.1.1 to 4.2.1.1.4)

In assays using recombinant human JAK and TEC family kinases, the IC_{50} values of ritlecitinib and its primary metabolite, M2 (a cysteine conjugate) [see Section 4.3.2] for kinase activity of the JAK family (JAK1, JAK2, JAK3, tyrosine kinase 2 [TYK2]) and the TEC family (bone marrow tyrosine kinase gene in chromosome X [BMX], Bruton's tyrosine kinase [BTK], interleukin-2-inducible T-cell kinase [ITK], TEC, tyrosine protein kinase encoded by the TXK gene [TXK]) were determined. The results are shown in Table 5.

Table 5. Inhibitory activities of ritlecitinib and M2 for JAK and TEC family kinases (IC_{50}: nmol/L)

JAK family			TEC family		
Kinase	Ritlecitinib	M2	Kinase	Ritlecitinib	M2
JAK1	>9,710	>9,890	BMX	606	>10,000
JAK2	>10,000	>10,000	BTK	608	>10,000
JAK3	33.1	>10,000	ITK	8,510	>10,000
TYK2	>10,000	>10,000	TEC	592	>10,000
In the presence of 1 mmol/L ATP			TXK	194	>10,000

The inhibitory potency of ritlecitinib by covalent inactivation was determined for JAK3 and other kinases (BTK, B lymphoid tyrosine kinase [BLK], BMX, ITK, TEC, TXK, Ste20-like kinase [SLK], tyrosine protein kinase encoded by the *FGR* gene [FGR], FMS-like tyrosine kinase 3 [FLT3]) by a time-resolved fluorescence resonance energy transfer (TR-FRET) assay. Ritlecitinib was suggested to covalently bind to JAK3, and the TEC kinase family members (BTK, BMX, ITK, TEC, TXK) and BLK, which each have a cysteine at the equivalent position of C909 in JAK3 (at position H10 near the ATP binding pocket), and irreversibly inhibit these kinases. On the other hand, kinases possessing a cysteine residue at a different position within the ATP binding pocket (SLK, FGR, FLT3) were not irreversibly inhibited by ritlecitinib.

3.1.2 Occupancy of various kinases (CTD 4.2.1.1.15)

The occupancy of JAK3 and the TEC kinase family members by ritlecitinib in human peripheral blood mononuclear cells (PBMC) was measured. The 50% occupancy concentrations of ritlecitinib for JAK3 and the TEC kinase family members (BTK, BMX, ITK, RLK, TEC) were 73 nmol/L and 58 to 176 nmol/L, respectively.

3.1.3 Effects on STAT phosphorylation (CTD 4.2.1.1.6 to 4.2.1.1.8, 4.2.1.1.14, 4.2.1.1.16)

Tables 6 and 7 show the IC_{50} values of ritlecitinib for STAT phosphorylation following various stimulations in human cells and whole blood and in whole blood of rats and dogs, respectively.

Table 6. Potency of ritlecitinib to inhibit STAT phosphorylation (Human cells and whole blood)

JAK involved	Stimulation[a)]	STAT phosphorylation	Used cells etc.	IC_{50} (nmol/L)
JAK1/TYK2	IFNα	STAT3	PBMC	12,100
			Whole blood	>60,000
	IL-10		PBMC	>60,000
			Whole blood	>60,000
	IL-22		Primary keratinocytes	>20,000
			Primary intestinal epithelial cells	>20,000
JAK1/JAK2/TYK2	IL-27		PBMC	17,800
			Whole blood	>60,000
	IL-6	STAT1/3	Whole blood (Cell type to be detected: T cells)	>20,000
		STAT3	Megakaryocyte precursor cells	>20,000
	IL-13	STAT6	Whole blood (Cell type to be detected: B cells)	>20,000
			Whole blood (Cell type to be detected: monocytes)	>20,000
			HT-29 [Colon adenocarcinoma cells]	>20,000
	IL-31	STAT3	THP-1 [Monocyte cells]	4,400
JAK1/JAK2	IFNγ	STAT1	Whole blood	>20,000
JAK1/JAK3	IL-15	STAT5	PBMC	51.7
			Whole blood	198
	IL-21	STAT3		362
	IL-4	STAT6	Whole blood (Cell type to be detected: B cells)	1,000
			Whole blood (Cell type to be detected: T cells)	226
			Whole blood (Cell type to be detected: monocytes)	>20,000
			HT-29 [Colonic adenocarcinoma cells]	>20,000
JAK2/TYK2	IL-23	STAT3	Whole blood	>20,000
	IL-12	STAT4		>20,000
JAK2/JAK2	EPO	STAT5	CD34+ cells	>20,000
			Whole blood＋CD34+ cells	>20,000
	TPO		Megakaryocyte precursor cells	>20,000

a) IFNα = 6,000 U/mL (5,000 U/mL for PBMC), IL-10 = 30 ng/mL (15 ng/mL for PBMC), IL-22 = 100 ng/mL, IL-27 = 1,200 ng/mL (200 ng/mL for PBMC), IL-6 = 100 ng/mL, IL-13 = 1 ng/mL, IL-31 = 1 μg/mL, IFNγ = 500 ng/mL, IL-15 = 30 ng/mL (41 ng/mL for PBMC), IL-21 = 50 ng/mL, IL-4 = 0.3 ng/mL, IL-23 = 100 ng/mL, IL-12 = 5 ng/mL, EPO = 2 U/mL, TPO = 100 ng/mL

Table 7. Potency of ritlecitinib to inhibit STAT phosphorylation (Whole blood of rats and dogs)

JAK involved	Stimulation (50 ng/mL)	STAT phosphorylation	Species	IC_{50} (nmol/L)
JAK1/JAK3	IL-15	STAT5	Rat	137
			Dog	170
	IL-21	STAT3	Rat	302
			Dog	212

3.1.4 Effects on various signaling pathways other than STAT phosphorylation (CTD 4.2.1.1.9 to 4.2.1.1.13)

Table 8 shows the IC_{50} values of ritlecitinib for various signaling pathways other than STAT phosphorylation following various stimulations in human cells.

Table 8. Potency of ritlecitinib to inhibit various signaling pathways other than STAT phosphorylation in human cells

JAK/TEC involved (Cytokine involved)	Stimulation	Reaction investigated	Used cells etc.	IC_{50} (nmol/L)
JAK1/TYK2 (IL-10)	LPS[a)]	Inhibition of IL-1β production	Monocyte-derived macrophages	>15,000
		Inhibition of IL-6 production		
		Inhibition of TNFα production		
JAK1/JAK2/TYK2 (IL-27)	TNFα[b)] or IL-1β[b)]	IL-8 mRNA suppression	IL-27-primed macrophages	>20,000
		SOCS1 mRNA induction		
		Induction of PD-L1 expression		
JAK1/JAK2/JAK3/ TYK2/ITK	IL-2, IL-12, anti-IL-4/ anti-CD3/anti-CD28 antibodies[c)]	IFNγ production (Differentiation into Th1 cells)	CD4+ T cells	34-49
JAK1/JAK3/TYK2	IL-2, IL-4, IL-10, anti-IFNγ antibody[d)]	IL-5 production (Differentiation into Th2 cells)		17.1
		IL-13 production (Differentiation into Th2 cells)		24.1
JAK1/JAK2/TYK2	IL-6, IL-23, IL-1β, TGFβ1, anti-CD28 antibody[e)]	IL-17A production (Differentiation into Th17 cells)		211-278
JAK1/JAK3	IL-21, CD40 ligand[f)]	IgG production	CD19+ B cells	86
BTK	Anti-IgD antibody[g)]	CD69 upregulation	Whole blood leukocytes (Cell type to be detected: CD19+ B cells)	344
ITK	Anti-CD3/anti-CD28/anti-CD2 antibodies		CD4+ T cells	380
	K562 [Leukemia cells]	Surface expression of CD107a	PBMC (Cell type to be detected: NK cells)	509
		IFNγ production		188
	Anti-CD3/anti-CD28 antibodies	Surface expression of CD107a	PBMC (Cell type to be detected: CD8+ T cells)	210
		IFNγ production		188

a) 20 ng/mL
b) 10 ng/mL
c) IL-2 = 10 ng/mL, IL-12 = 5 ng/mL, anti-IL-4 antibody = 5 ng/mL, anti-CD3 antibody = 10 µg/mL, anti-CD28 antibody = 0.1 µg/mL
d) IL-2 or IL-4 = 5 ng/mL, IL-10 = 500 ng/mL, anti-IFNγ = 1,000 ng/mL
e) IL-6 or IL-23 = 25 ng/mL, IL-1β = 12.5 ng/mL, TGFβ1 = 5 ng/mL, anti-CD28 antibody = 1 µg/mL
f) IL-21 = 100 ng/mL, CD40 ligand = 1 µg/mL
g) 20 µg/ml

3.1.5 Effects in animal models

3.1.5.1 Effects in a model of adjuvant-induced arthritis in rats (CTD 4.2.1.1.18)

Inflammation was induced by intradermal injection of complete Freund's adjuvant (the base of the tail) in female rats. After arthritis of the hindpaw was confirmed by plethysmography, vehicle or ritlecitinib 0.1 to 80 mg/kg was administered orally once daily for 7 days. Ritlecitinib at ≥3 mg/kg reduced hindpaw swelling.

3.1.5.2 Effects in inflammatory bowel disease mouse models (CTD 4.2.1.1.19)

Enteritis was induced by dextran sulfate sodium (DSS) (3% DSS solution, instead of drinking water, was given on Days 0-7) or 2, 4, 6-trinitrobenzene sulfonic acid (TNBS) (TNBS 2 mg was administered rectally on Day 0) in female mice. At the same time, vehicle or ritlecitinib 10 mg/kg was administered orally twice daily for 6 or 11 days. Compared to vehicle, ritlecitinib tended to reduce disease activity[1)] and body weight loss in both DSS- and TNBS-induced enteritis mice.

3.1.5.3 Effects in a model of multiple sclerosis in mice (CTD 4.2.1.1.21)

Experimental autoimmune encephalomyelitis (EAE) was induced[2)] in female mice. At the same time, vehicle or ritlecitinib 20 or 60 mg/kg was administered orally twice daily for 29 days. Compared to vehicle, ritlecitinib

[1)] DSS-induced enteritis: Fecal occult blood occurrence, stool consistency, and body weight loss were scored on a 4-point scale (from 1 to 4).
TNBS-induced enteritis: Colonic inflammation, stool volume, and body weight loss were scored on a 4-point scale (from 1 to 4).
[2)] EAE was induced by subcutaneous injection of a myelin oligodendrocyte glycoprotein peptide followed by intraperitoneal injection of pertussis toxin.

at 20 and 60 mg/kg delayed EAE onset by 2.5 and 13.5 days, respectively, and decreased disease severity (the average maximum EAE score,[3)] the average end EAE score) in a dose-dependent manner. In a separate study, vehicle or ritlecitinib 30 or 100 mg/kg was administered twice daily for 14 days, beginning from the day of EAE onset (EAE score ≥0.5). Ritlecitinib dose-dependently decreased disease severity.

3.2 Secondary pharmacodynamics

3.2.1 Effects on various enzymes, receptors, etc. (CTD 4.2.1.1.2, 4.2.1.2.1 to 4.2.1.2.3)

Ritlecitinib was screened for its activity against 12 enzymes, 35 receptors, 5 transporters, and 10 ion channels. Ritlecitinib (10 μmol/L) showed ≥50% binding or activity inhibition for abelson tyrosine protein kinase (Abl kinase), epidermal growth factor receptor (EGFR) kinase, and vascular endothelial growth factor receptor 2 (VEGFR2) kinase, with the IC_{50} values of 2.8, 2.2, and 1.3 μmol/L, respectively. A kinase panel assay to assess Abl kinase inhibition and VEGFR2 cell assay were performed as follow-up assays, and the IC_{50} values in these assays were both >30 μmol/L. In the presence of 1 mmol/L ATP, the inhibitory activity of ritlecitinib was determined for 10 kinases that have a cysteine at the equivalent position of that in the JAK3 ATP binding pocket. Except for the 5 TEC family kinases listed in Table 5, the IC_{50} values for BLK and human epidermal growth factor receptor 4 (HER4) were 19.9 and 25.2 μmol/L, respectively, and the IC_{50} values for EGFR, HER2, and mitogen-activated protein kinase kinase 7 (MAP2K7) were all >50 μmol/L.

3.3 Safety pharmacology

Table 9 shows the results of safety pharmacology studies.

Table 9. Overview of safety pharmacology studies

Organ systems evaluated	Test system	Endpoints/Method of assessment, etc.	Doses (Route of administration)	Findings	CTD
CNS	Wister Han rat (6 males/group)	FOB, body temperature, locomotor activity (Conscious)	75, 175, 400 mg/kg (Oral gavage)	No effects	4.2.1.3.3
Respiratory system		Respiratory rate, tidal volume, minute volume (Conscious)		400: Approximately 30% increase in respiratory rate at 240 minutes post-dose	
Cardiovascular system	hERG-transfected HEK293 cells	hERG current	30, 100, 300 μmol/L	100: 16.5% inhibition 300: 31.0% inhibition	4.2.1.3.2
	Beagle dog (3 males)	ECG, blood pressure, heart rate, clinical signs (Conscious)	3, 15, 45 mg/kg (Oral gavage)	45: Increased heart rate (15 bpm) and decreased QT interval (11 msec) at 0.5-3.5 hours post-dose	4.2.1.3.6

3.R Outline of the review conducted by PMDA

The applicant's explanation about the mechanism of action of ritlecitinib in AA:

Unlike other kinases belonging to the JAK family (JAK1, JAK2, TYK2), which are universally expressed, JAK3 is predominantly expressed in immune cells and plays an important role in the

[3)] Typical clinical observations for each score are as follows.
0: No obvious changes in motor function.
0.5: Tip of tail is limp.
1: Limp tail.
2: Limp tail and weakness of hind legs with wobbly walk.
3: Limp tail and complete paralysis of hind legs or limp tail with paralysis of one front and one hind leg.
4: Complete hind leg and partial front leg paralysis.
5: Complete hind leg and front leg paralysis and no movement in the cage.

differentiation/proliferation, etc. of lymphocytes via γ-common cytokines (interleukin-2 [IL-2], IL-4, IL-7, IL-9, IL-15, IL-21) signaling. The TEC family kinases such as BTK and ITK are also expressed in immune cells and play an important role in T-cell or B-cell signaling and the activation of NK cells (*J Immunol*. 2006; 176: 1571-81, *J Biol Chem*. 2012; 287: 23769-78).

Although the complex pathophysiology of AA is still not completely understood, CD8+ T cells, NK cells, and mast cells are likely involved in the pathogenesis of AA (*Nat Med*. 2014; 20: 989-90, *J Invest Dermatol*. 2008; 128: 1196-206, *Plos One*. 2014; 9: e94260). IL-2 or IL-15 blockade prevented disease development in a mouse model of AA (*Nat Med*. 2014; 20: 1043-9), and there was a correlation between serum levels of IL-15 and AA severity in AA patients (*Int J Trichology*. 2019; 11: 26-30, *Egypt J Dermatology Venerology*. 2022; 42: 34-9).

Ritlecitinib was shown to inhibit the activities of JAK3 and the TEC family of kinases and signaling mediated by these kinases in various kinase and cell assays [see Sections 3.1.1, 3.1.3, and 3.1.4]. Additionally, ritlecitinib inhibits the TEC family of kinases including ITK, resulting in reduced cytolytic activity of NK cells and CD8+ T cells (*ACS Chem Biol*. 2019; 14: 1235-42). Furthermore, studies in multiple inflammatory animal models showed that ritlecitinib tended to reduce inflammation [see Section 3.1.5]. Ritlecitinib prevented the onset of AA and reversed AA in a mouse model of AA (*JCI Insight*. 2021; 6: e142205). The above findings indicate that ritlecitinib is expected to potentially prevent the onset of AA and reverse AA via inhibition of JAK3 and the TEC family kinases.

PMDA's conclusion:
The submitted data have demonstrated the pharmacological effects of ritlecitinib, and the therapeutic effect of ritlecitinib on AA is expected. However, as decreased lymphocyte counts are anticipated based on the mechanism of action of ritlecitinib, and toxicity studies showed effects on red blood cell parameters and lymphocyte counts [see Section 5.2], attention should be paid to the effects of ritlecitinib on the hematopoietic and immune systems [for safety, see Section 7.R.3]. The effects on heart rate and QT interval observed in a safety pharmacology study, including the findings in a toxicity study, will be discussed in Section 5.R.1.4.

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 ritlecitinib, in the form of the results from oral or intravenous studies in mice, rats, and dogs. Ritlecitinib concentrations (Lower limit of quantitation [LLOQ], 1.0 or 2.5 ng/mL in plasma, 1.0 ng/mL in milk, 15.0 ng/mL in brain tissue) and concentrations of its primary metabolite (M2) (LLOQ, 1.0 ng/mL in plasma) were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Radioactivity concentrations in samples were determined by quantitative whole-body autoradiography. In these studies, ritlecitinib tosilate, free ritlecitinib, and ritlecitinib malonate were used as ritlecitinib. In this section, all of these test articles are referred to as ritlecitinib, and doses are expressed in terms of ritlecitinib. 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 to 4.2.2.2.3)

Table 10 shows the pharmacokinetic parameters of ritlecitinib following a single oral or intravenous dose of ritlecitinib in mice, rats, and dogs.

Table 10. Pharmacokinetic parameters of ritlecitinib following a single dose

Species	Route of administration[a)]	Dose (mg/kg)	Number. of animals	C_{max} (μg/mL)	AUC_{inf} (μg·h/mL)	t_{max} (h)	CL (mL/min/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)	F (%)
Mouse	IV	3	3M	―	1.12 ± 0.13	―	45.2 ± 5.8	0.84 ± 0.33	1.25 ± 0.52	―
	Oral	30	3M	10.2 ± 2.3	6.91 ± 2.42	0.25 [0.25, 0.25]	―	―	1.25 ± 0.29	61.3 ± 21.6
Rat	IV	0.71	2M	―	0.157, 0.191	―	62.0, 75.4	1.41, 1.41	0.30, 0.36	―
	Oral	3	2M	0.122, 0.224	0.359, 0.533	0.50, 0.50	―	―	0.89, 0.97	48.8, 72.5
Dog	IV	1	2M	―	1.20, 1.29	―	12.9, 13.9	1.00, 1.14	1.02, 1.18	―
	Oral	3	2M	2.39, 2.45	3.84, 4.36	0.25, 0.25	―	―	0.94, 0.99	102, 116

Mean ± SD (Individual values are listed for n = 2); Median [Range] for t_{max} (Individual values are listed for n = 2); ―, Not applicable or not calculated
a) IV administration under non-fasting conditions. Oral administration under fasting conditions except for rats (fed at 4 hours post-dose).

4.1.2 Repeated-dose studies (CTD 4.2.2.2.4, 4.2.3.2.2, 4.2.3.2.7)

Table 11 shows the pharmacokinetic parameters of ritlecitinib following repeated oral doses of ritlecitinib in rats and dogs. No clear sex differences in ritlecitinib exposure or no accumulation were noted in rats or dogs. In dogs, the C_{max} and $AUC_{0\text{-}24h}$ increased approximately dose-proportionally over the dose range tested. In rats, the C_{max} increased approximately dose-proportionally between 75 and 175 mg/kg but less than dose-proportionally between 175 and 400 mg/kg, and the $AUC_{0\text{-}24h}$ increased slightly more than dose-proportionally. In a study in which ritlecitinib 200 mg/kg/day was administered orally for 1 week in rats, no clear sex differences in M2 (ritlecitinib primary metabolite) [see Section 4.3.2] exposure were observed.

Table 11. Pharmacokinetic parameters of ritlecitinib and M2 following repeated oral doses

Species	Duration of dosing	Analyte	Number 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	1 week	Ritlecitinib	5M5F	Day 7	200	28.6 ± 7.3[a)]	26.2 ± 8.3	126 ± 38[a)]	118 ± 31	0.63 [0.25, 1.0][a)]	0.25 [0.25, 0.25]
		M2				16.9 ± 6.7[a)]	16.0 ± 7.1	70.7 ± 14.5[a)]	78.5 ± 22.8	1.5 [1.0, 2.0][a)]	1.0 [1.0, 2.0]
	8 weeks	Ritlecitinib	3M3F	Day 1	75	8.78 ± 0.88	8.91 ± 0.65	24.8 ± 5.2	20.8 ± 3.0	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]
					175	20.0 ± 2.0	25.0 ± 7.5	67.1 ± 3.2	64.3 ± 7.6	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]
					400	29.0 ± 2.4	29.1 ± 2.5	235 ± 43	164 ± 13	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]
				Day 53/32[b)]	75	12.2 ± 2.4	10.9 ± 2.5	27.1 ± 4.3	24.2 ± 3.3	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]
					175	24.3 ± 1.7	24.2 ± 3.3	90.8 ± 8.3	67.8 ± 8.5	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]
					400	34.8 ± 10.4	37.3, 49.3[c)]	215 ± 45	194, 196[c)]	1.0 [1.0, 1.0]	1.0, 1.0[c)]
Dog	9 months	Ritlecitinib	4M4F or 7M7F[d)]	Day 1	10	3.64 ± 0.46	3.57 ± 0.41	8.79 ± 1.18	8.87 ± 1.15	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]
					20	7.13 ± 0.85	7.04 ± 1.53	19.1 ± 2.8	18.0 ± 2.3	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]
					20 (10 BID)	3.22 ± 0.15	3.19 ± 0.65	20.8 ± 1.4	19.8 ± 3.8	7.0 [1.0, 7.0]	1.0 [1.0, 1.0]
					40	13.5 ± 1.5	12.7 ± 2.3	38.4 ± 3.0	41.2 ± 7.0	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]
				Day 273	10	1.94 ± 0.42	2.72 ± 0.96	9.38 ± 0.46	9.98 ± 0.68	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]
					20	4.40 ± 1.69	4.02 ± 1.01	18.8 ± 2.2	16.7 ± 1.7	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]
					20 (10 BID)	3.32 ± 0.35	2.92 ± 0.72	20.7 ± 1.1	20.6 ± 1.2	7.0 [1.0, 7.0]	7.0 [1.0, 7.0]
					40	9.82 ± 3.73	11.4 ± 4.7[e)]	40.7 ± 6.5	45.4 ± 3.3[e)]	1.0 [1.0, 3.0]	1.0 [1.0, 1.0][e)]

Mean ± SD (Individual values are listed for n = 2); Median [Range] for t_{max} (Individual values are listed for n = 2); BID, twice daily
a) n = 4, b) Day 32 in the 400 mg/kg/day group and Day 53 in other groups, c) n = 2,
d) 4 males and 4 females in the 10 or 20 (10 BID) mg/kg/day group, 7 males and 7 females in the 20 or 40 mg/kg/day group, e) n = 6

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.3.1)

Following a single oral dose of ^{14}C-ritlecitinib 10 mg/kg in male Long-Evans rats, the tissue distribution of radioactivity[4)] was examined by quantitative whole-body autoradiography. After administration, ^{14}C-ritlecitinib was distributed into systemic tissues rapidly with the highest radioactivity levels occurring at 0.25 to 0.5 hours post-dose in most tissues. Except for the brain, spinal cord, bone (femur), white fat, thymus, testes, and nasal turbinates, the tissue to plasma AUC ratios of all evaluated tissues were higher than 1. By 672 hours post-dose, radioactivity fell below the LLOQ (26.7 ng eq/g) in tissues other than the adrenal gland, aorta, blood (cardiac), heart, liver, lung, kidney, spleen, eye, uveal tract, and lens (<8% of the C_{max}).

The applicant's explanation:
Although ritlecitinib showed an affinity for melanin-containing tissues such as the lens and uveal tract, as no abnormal findings in the eyes or skin were observed following administration of ritlecitinib in an *in vivo* phototoxicity study in rats [see Section 5.6.1], there is little safety concern about ritlecitinib accumulation in melanin-containing tissues.

4.2.2 Brain distribution (CTD 4.2.2.4.2, 4.2.3.7.3.1)

Dogs were dosed orally once daily with ritlecitinib 40 mg/kg/day for 3 days. At approximately 1 hour after the last dose, ritlecitinib concentrations in the brain tissues (the superior olivary nucleus, cochlear nucleus, and hippocampus) and plasma were 1,080 to 1,350 ng/g and 11,300 ng/mL, respectively. The metabolite

[4)] The adrenal gland, adrenal cortex, adrenal medulla, aorta, blood (cardiac), bone (femur), bone marrow (femur), brain (whole), brown fat, esophagus wall, ex-orbital lacrimal gland, eye, harderian gland, heart, intra-orbital lachrymal gland, kidney, kidney cortex, kidney medulla, large intestine contents, large intestine wall, lens, liver, lung, lymph node (cervical), muscle (femoral), nasal turbinates, non-pigmented skin, oral mucosa, pancreas, pigmented skin, pituitary gland, prostate gland, salivary gland, small intestine contents, small intestine wall, spinal cord, spleen, stomach contents, stomach wall (glandular), stomach wall (non-glandular), testis, thymus, thyroid gland, trachea, urinary bladder wall, uveal tract, and white fat (inguinal) were evaluated.

profiles in the brain tissues were similar, and ritlecitinib and its primary metabolite, M2, were detected as in the plasma.

4.2.3 Plasma protein binding and distribution in blood cells (CTD 4.2.2.3.2 to 4.2.2.3.7)

Table 12 shows the plasma protein binding (an equilibrium dialysis method; the concentration tested was 2 μmol/L) and blood to plasma concentration ratios (the concentration tested was 1 μmol/L) of ritlecitinib and M2 in mice, rats, rabbits, dogs, monkeys, and humans. Ritlecitinib was bound primarily to human serum albumin and did not bind to platelets, α1-acid glycoprotein, high-density lipoprotein, fibrinogen, or γ-globulin.

Table 12. Plasma protein binding and blood to plasma concentration ratios of ritlecitinib and M2

Plasma protein binding						
Analyte	Mouse	Rat	Rabbit	Dog	Monkey	Human
Ritlecitinib	77.6%	32.6%	71.2%	18.1%	14.0%	13.6%
M2	Not binding	Not binding	Not binding	Not binding	－	5.3%
Blood to plasma concentration ratio						
Analyte	Mouse	Rat	Rabbit	Dog	Monkey	Human
Ritlecitinib	－	0.99	－	1.57	－	1.62
M2	0.55	0.55	0.83	0.52	－	0.68

－, Not tested; "Not binding" is stated for plasma protein binding when the fraction unbound was ≥1.

4.2.4 Placental transfer (CTD 4.2.3.5.2.2, 4.2.3.5.2.4, 4.2.3.5.3.1)

Although the placental transfer of ritlecitinib and its metabolites has not been studied, embryo-fetal development studies in rats and rabbits showed visceral/skeletal malformations, skeletal variations, etc., as toxicity findings, and a rat study for effects on pre- and postnatal development, including maternal function, showed decreases in postnatal survival and pup body weight gain [see Section 5.5], suggesting that ritlecitinib or its metabolites may cross the placenta.

4.3 Metabolism

4.3.1 *In vitro* studies (CTD 4.2.2.4.1, 4.2.2.4.5, 4.2.2.4.6)

When ritlecitinib (10 μmol/L) was incubated with rat, dog, or human liver microsomes or hepatocytes, the primary metabolic pathways of ritlecitinib were suggested to be P450-mediated oxidation and glutathione-related conjugation. Metabolites formed via hydroxylation, *N*-acetylcysteine conjugation, cysteine-glycine conjugation, cysteine conjugation, glutathione conjugation, etc., were detected.

A study using human liver microsomes and selective inhibitors of CYP isoforms[5)] suggested that ritlecitinib is metabolized by CYP3A4/5, CYP2C8, CYP1A2, and CYP2C9 (The fraction metabolized [f_m] was 29%, 9.1%, 6.8%, and 1.6%, respectively).

A study using human recombinant glutathione-S-transferase (GST) suggested that multiple isoforms present in the cytosolic fraction (GSTA1, GSTA3, GSTM1, GSTM3, GSTM5, GSTP1, GSTS1, GSTT2, GSTZ1) and the microsomal fraction (MGST1, MGST2, MGST3) are involved in the glutathione conjugation of ritlecitinib.

[5)] As selective inhibitors of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5, furafylline, montelukast, sulfaphenazole, benzylnirvanol, quinidine, and ketoconazole/troleandomycin were used, respectively.

4.3.2 *In vivo* studies (CTD 4.2.2.4.1, 4.2.2.4.3)

Mice were dosed orally once daily with ritlecitinib 200 mg/kg for 3 days. Up to 24 hours after dosing, ritlecitinib, M2, M4 (an oxidative metabolite), M5 (a metabolite formed via oxidation and internal hydrolysis), *m/z* 350-2, and *m/z* 366-1 were mainly detected in the plasma, and ritlecitinib, M3 (an N-acetylcysteine conjugate), M4, M5, and *m/z* 350-2 were mainly detected in the urine.

Bile-duct cannulated and intact rats were dosed orally once daily with ritlecitinib 200 mg/kg for 3 days. In both bile-duct cannulated and intact rats, the main drug-related components up to 24 hours after dosing were ritlecitinib, M2, and M3 in the plasma, ritlecitinib, M1 (an N-acetylcysteine sulfoxide conjugate), M2, M3, M4, and *m/z* 350-2 in the urine, and ritlecitinib, M1, M2, M3, M4, *m/z* 350-2, and *m/z* 593 in the bile.

Following a single intravenous dose of ritlecitinib 3 mg/kg in bile-duct cannulated rats, the main drug-related components up to 24 hours after dosing were ritlecitinib and M4 in the plasma and ritlecitinib and M3 in the urine and bile.

Dogs were dosed orally once daily with ritlecitinib 75 mg/kg for 15 days. Up to 2 hours after dosing, ritlecitinib, M2, M4, *m/z* 302-1, *m/z* 304, *m/z* 464, and *m/z* 593 were mainly detected in the plasma, urine, and bile. In addition, m/z 350-1/2 was present in the urine, and M3, *m/z* 320-1, *m/z* 350-1/2, and *m/z* 366 were present in the bile.

The results of a mass balance study that determined the plasma, urinary, and fecal metabolite profiles following a single oral dose of ritlecitinib 200 mg in humans are described in Section 6.1.1.

Based on the above metabolism studies, the proposed metabolic pathways of ritlecitinib in humans are shown in Figure 1.

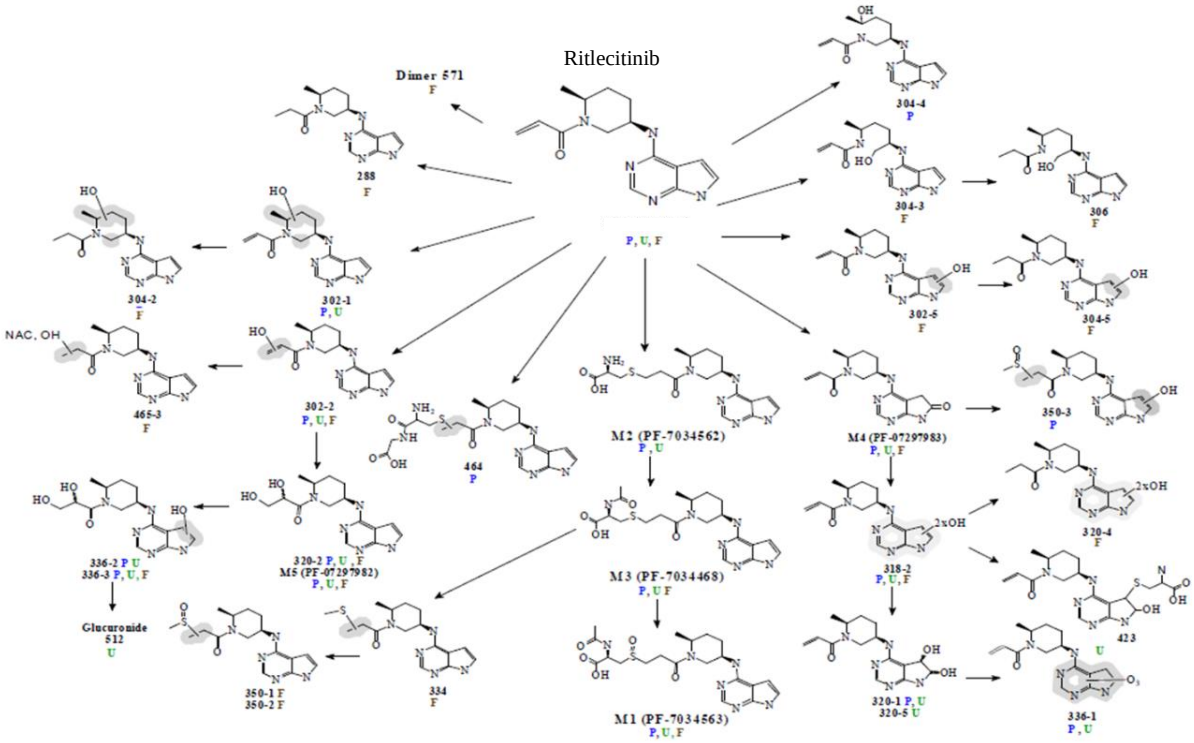


Figure 1. Proposed metabolic pathways of ritlecitinib in humans (P, blood; U, urine; F, feces)

4.4 Excretion

4.4.1 Urinary and biliary excretion (CTD 4.2.2.2.2 and 4.2.2.2.3)

Following a single intravenous dose of ritlecitinib 1 mg/kg in intact rats, 0.90% of the dose was excreted unchanged in the urine, up to 24 hours post-dose. Following a single intravenous dose of ritlecitinib 1.5 mg/kg in bile-duct cannulated rats, 0.11% of the dose was excreted unchanged in the bile, up to 24 hours post-dose.

Following a single intravenous dose of ritlecitinib 1 mg/kg in dogs, 3.0% of the dose was excreted unchanged in the urine, up to 24 hours post-dose.

4.4.2 Excretion into milk (CTD 4.2.2.5.1)

Table 13 shows plasma and milk concentrations of ritlecitinib following a single oral dose of ritlecitinib 30 mg/kg in lactating female rats. Ritlecitinib was excreted in milk.

Table 13. Plasma and milk concentrations of ritlecitinib following a single oral dose of ritlecitinib in lactating rats (ng/mL)

Matrix	N	Time after single dose administration			
		1 hour	3 hours	8 hours	24 hours
Plasma	4	2,720 ± 582	1,480 ± 1,880	42.1 ± 27.6	BLQ
Milk	4	9,680 ± 1,170	1,660 ± 1,510	132 ± 65	BLQ

Mean ± SD; BLQ, below limit of quantitation (1 ng/mL)

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition and enzyme induction (CTD 4.2.2.6.1 to 4.2.2.6.7 and 4.2.2.6.9 to 4.2.2.6.12)

Using human liver microsomes, ritlecitinib and M2 were evaluated for their potential as inhibitors of CYP

isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5).[6)] Ritlecitinib was a reversible inhibitor of CYP3A4/5 (substrate: testosterone) (IC_{50} = 90 μmol/L), but not a reversible inhibitor of CYP3A4/5 (substrate: midazolam and nifedipine) or other CYP isoforms (IC_{50} >100 μmol/L). In the presence of NADPH, ritlecitinib was a time-dependent inhibitor of CYP1A2 and CYP3A4/5.[7)] M2 was not a reversible inhibitor or a time-dependent inhibitor of any of the isoforms (IC_{50} >96.5 μmol/L [CYP2C9, CYP2C19, CYP2D6] or >100 μmol/L [other isoforms]).

Using human liver microsomes, ritlecitinib and M2 were evaluated for their potential as inhibitors of uridine 5' diphospho glucuronosyltransferase (UGT) isoforms (UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7).[8)] Ritlecitinib inhibited UGT1A1 and UGT1A4 (IC_{50} = 54 and 81 μmol/L, respectively) in the absence of bovine serum albumin (BSA) and UGT1A4 (IC_{50} = 97 μmol/L) in the presence of BSA, but did not inhibit other isoforms (IC_{50} >100 μmol/L). M2 did not inhibit any of the isoforms (IC_{50} >96.5 μmol/L).

Using human liver cytosol, the potential of ritlecitinib to inhibit sulfotransferase (SULT) isoforms (SULT1E1, SULT1A1, SULT2A1) was evaluated.[9)] Ritlecitinib did not inhibit any of the isoforms (IC_{50} >100 μmol/L).

A study using human recombinant GST and 1-chloro-2,4-dinitrobenzene (CDNB) showed no clear effects of ritlecitinib on glutathione conjugation of CDNB.

Using human primary hepatocytes, the potential of ritlecitinib (the concentrations tested were 0.3-100 μmol/L) and M2 (the concentrations tested were 0.3-250 μmol/L) to induce CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4) was evaluated. While M2 did not induce any of the CYP isoforms, ritlecitinib induced increases in the mRNA expression of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4, suggesting that ritlecitinib has the potential to induce these enzymes.

The applicant's explanation:
Based on the above results, ritlecitinib exposure at steady state following once daily oral administration of ritlecitinib 50 mg in AA patients,[10)] etc., ritlecitinib at the clinical dose has the potential to inhibit CYP1A2 and CYP3A or induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4.

4.5.2 Transporter substrate potential (CTD 4.2.2.6.17 to 4.2.2.6.19)

Studies using Madin-Darby canine kidney (MDCK) cells expressing human P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP)[11)] suggested that ritlecitinib may be a substrate for P-gp and BCRP.

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

[7)] Ritlecitinib was evaluated as a time-dependent inhibitor of CYP1A2 and CYP3A. The K_I (concentration at half-maximal rate of inactivation) for phenacetin (CYP1A2 substrate) metabolic activity was 327 μmol/L, and the k_{inact} (maximal inactivation rate) was 0.0917 min^{-1}. The K_I or k_{inact} for midazolam (CYP3A substrate) metabolic activity could not be determined because inhibition was not saturated over the concentration range tested (3-200 μmol/L), but the k_{inact}/K_I was estimated at 0.871 mL/min/μmol.

[8)] 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, *S*-oxazepam for UGT2B15 (M2 only)

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

[10)] Based on the estimated steady-state unbound C_{max} of ritlecitinib (1.1 μmol/L) following once daily oral administration of ritlecitinib 50 mg

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

Studies using human embryonic kidney (HEK) 293 cells expressing human organic anion transporting polypeptide 1B1 (OATP1B1) or OATP1B3 were conducted. While the uptake ratio[12] of a positive control, rosuvastatin, was 11.0 for OATP1B1 and 5.3 for OATP1B3, the uptake ratio of ritlecitinib was almost 1 for both transporters at the concentrations tested, suggesting that ritlecitinib is unlikely to be a substrate for OATP1B1 or OATP1B3.

4.5.3 Transporter inhibition potential (CTD 4.2.2.6.13 to 4.2.2.6.16)

Using MDCKII cells or HEK293 cells expressing human P-gp and HEK293 cells expressing human BCRP, bile salt export pump (BSEP), OATP1B1, OATP1B3, organic cation transporter 1 (OCT1), organic anion transporter 1 (OAT1), OAT3, OCT2, multidrug and toxin extrusion 1 (MATE1), or MATE2K, ritlecitinib and M2 were evaluated for their potential as inhibitors of these drug transporters.[13] The results are shown in Table 14.

The applicant's explanation:

Based on the above results, ritlecitinib exposure at steady state following once daily oral administration of ritlecitinib 50 mg in AA patients,[14] etc., ritlecitinib at the clinical dose has the potential to inhibit BCRP, OAT3, MATE1, MATE2K, and OCT1, and M2 has the potential to inhibit BCRP, OATP1B1, OATP1B3, and OCT1.

Table 14. Inhibition of drug transporters by ritlecitinib and M2

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	Ritlecitinib	50-300	>300 (21%)	OCT2	Ritlecitinib	0.07-300	55.2 (89%)
	M2	0.018-300	44.1 (90%)		M2	0.018-300	>300 (45%)
BCRP	Ritlecitinib	0.061-1000	27.0 (97%)	OAT1	Ritlecitinib	0.061-1000	156 (85%)
	M2	0.018-300	5.6 (96%)		M2	0.018-300	>300 (40%)
OATP1B1	Ritlecitinib	0.018-1000	312 (74%)	OAT3	Ritlecitinib	0.018-300	41.3 (84%)
	M2	0.018-300	2.0 (100%)		M2	0.018-300	>300 (43%)
OATP1B3	Ritlecitinib	0.018-1000	934 (55%)	MATE1	Ritlecitinib	0.07-300	51.4 (77%)
	M2	0.018-300	8.4 (100%)		M2	0.018-300	>300 (7%)
OCT1	Ritlecitinib	0.018-1000	3.7 (100%)	MATE2K	Ritlecitinib	0.07-300	48.3 (74%)
	M2	0.018-300	0.86 (99%)		M2	0.018-300	>300 (8%)
BSEP	Ritlecitinib	0.82-200	>200 (19%)				

4.R Outline of the review conducted by PMDA

PMDA concluded that the submitted study results and the following considerations gave a grasp of the in vivo behavior of ritlecitinib to a certain extent. Based on the results of *in vitro* drug interaction studies, the potential of ritlecitinib to induce drug interactions via metabolic enzymes or drug transporters (excluding MATE1 and MATE2K) in clinical use needs to be assessed, taking also account of the clinical study results [see Section 6.2.3].

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[12] The ratio of the uptake in the transporter-expressing cells to the uptake in the parental cells. Uptake ratios of >2 were considered a substrate.

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

[14] Based on the following estimates at steady state after once daily oral administration of ritlecitinib 50 mg: unbound C_{max} of ritlecitinib = 1.1 μmol/L, unbound C_{max} of M2 = 0.31 μmol/L, gut ritlecitinib concentration = 0.70 mmol/L, unbound liver inlet ritlecitinib concentration = 8 μmol/L

4.R.1 Drug interactions

The applicant's explanation about the potential of ritlecitinib to induce drug interactions via MATE1 and MATE2K inhibition:

Although no clinical study was conducted to evaluate the drug-drug interaction potential of ritlecitinib via MATE1 and MATE2K inhibition, there were no clear differences in the incidence of adverse events between subjects with or without concomitant metformin, a substrate for MATE1 and MATE2K, in the All 50 mg group in the All Exposure Pool (the pooled data from 4 clinical studies in AA patients [see Section 7.R.3.1]) (87.0% [20 of 23 subjects] in the subgroup with concomitant metformin, 80.4% [969 of 1,205 subjects] in the subgroup without concomitant metformin). Although the incidence of serious adverse events was numerically higher in the subgroup with concomitant metformin (17.4% [4 of 23 subjects]) than in the subgroup without concomitant metformin (4.0% [48 of 1,205 subjects]), the events observed in the subgroup with concomitant metformin were syncope, thermal burn, acute myocardial infarction, and COVID-19, which were not adverse events characteristic of metformin (hypoglycaemia, lactic acidosis, etc.), and a causal relationship to study drug was denied for all those events. In addition, given that there were no changes in endogenous biomarkers (N^1-methylnicotinamide, creatinine) following administration of ritlecitinib, ritlecitinib is unlikely to induce drug interactions via MATE1 and MATE2K inhibition.

PMDA's view:

Based on the clinical study results etc. obtained to date, there has been no serious safety concern about concomitant use of ritlecitinib with a substrate for MATE1 and MATE2K, metformin. However, as information on drug-drug interactions via MATE1 and MATE2K inhibition is important for the proper use of ritlecitinib, the applicant should ensure the provision of currently available information via the package insert, etc., further information collection, and appropriate communication of newly available information to healthcare professionals.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the results from the following toxicity studies of ritlecitinib: single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, and reproductive and developmental toxicity studies and other toxicity studies (a phototoxicity study, immunotoxicity evaluation, studies on impurities, mechanistic studies on neurotoxicity). Unless otherwise specified, 0.5% methylcellulose solution was used as vehicle in rat, mouse, rabbit, and dog studies.

5.1 Single-dose toxicity

The acute toxicity of ritlecitinib was assessed in single oral dose toxicity studies in rats and dogs, and no acute symptoms or mortality occurred in rats or dogs (Table 15). Following the first dose of ritlecitinib in a 2-week repeated oral dose toxicity study in mice, mortalities occurred at 1,000 mg/kg, and squinting eyes, hypoactivity, recumbency, and cold to touch (entire body) were noted as acute symptoms in the dead animals (Table 16). Based on the above, the approximate lethal doses were determined to be 1,000 mg/kg in mice, >1,000 mg/kg

in rats, and >300 mg/kg in dogs.

Table 15. 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 (Wistar)	Oral gavage	0, 250, 500, 1,000	None	>1,000	4.2.3.1.1
Male and female dogs (Beagle)	Oral gavage	20, 90, 300	≥20: emesis (male) 300: partially closed eyes (male and female), emesis (female)	>300	4.2.3.1.3

5.2 Repeated-dose toxicity

Repeated oral dose toxicity studies were conducted in mice and rats (Table 16). The no-observed-adverse-effect level (NOAEL) in a 6-month repeated oral dose toxicity study in rats was determined to be 200 mg/kg/day for both males and females. The unbound $AUC_{0\text{-}24h}$ of ritlecitinib at the NOAEL on Day 176 was 53,700 ng·h/mL (the combined sex mean), which was approximately 50-fold the human exposure[15] ($AUC_{0\text{-}24h}$ = 1,070 ng·hr/mL).

The noteworthy systemic toxicities or abnormal findings of ritlecitinib were mortalities associated with poor clinical condition, decreased body weight, decreases in white blood cell count/lymphocyte count/monocyte count/eosinophil count/basophil count, decreases in thymus and spleen weights, decreased lymphoid cellularity in the thymus/spleen/lymph nodes, decreased eosinophil count in the lung, multiple inflammation in the gastrointestinal tract, decreases in red blood cell parameters, increased reticulocyte count, decreased bone marrow cellularity, and increased mean platelet volume. Multiple inflammation in the gastrointestinal tract and increased neutrophil count were considered secondary to stress associated with poor clinical condition.

Other abnormal findings were decreases in blood potassium, cholesterol, aspartate aminotransferase (AST), glucose, and triglycerides, decreased adrenal weights, increased urine volume, vacuolation of the adrenal cortex, hyaline droplet accumulation in tubular epithelial cells of the kidney, and increased urine protein. However, these findings were considered of little toxicological significance because no associated laboratory abnormalities or histopathological abnormal findings were observed, these findings were of low human relevance, etc.

[15] Plasma unbound ritlecitinib exposure at steady state at the recommended clinical dose (50 mg/day) of oral ritlecitinib in AA patients (predicted exposure from the PPK analysis [see Section 6.3] corrected for plasma protein binding [see Section 4.2.3]).

Table 16. Overview of repeated-dose toxicity studies in mice and rats

Test system	Route of administration	Duration of dosing	Doses (mg/kg)	Noteworthy findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female mice (C57BL/6N)	Oral gavage	2 weeks (QD)	0, 30, 100, 300, 1,000	[Mortality] 1000: 12 of 12 males,[a)] 12 of 12 females[a)] squinting eyes, hypoactivity, recumbency, cold to touch (entire body), dark red spleen 300: 1 of 12 males,[b) c)] 1 of 12 females[b) c)] No findings 100: 1 of 12 females[c) d)] decreased body weight, hunched posture, ataxia, hypoactivity, limited use of left hind leg [Surviving animals] 100: squinting eyes, ataxia, hypoactivity, hunched posture, limited use of left hind leg (female)	—	4.2.3.4.2.1
Male and female rats (Wistar)	Oral gavage	8 weeks (QD)	0, 75, 175, 400	[Unscheduled death or euthanasia[e)]] 400: 3 of 10 females[f)] decreased activity, rough haircoat, staining (forepaws), hunched posture, decreased skin turgor, decreases in body weight/food consumption, multiple inflammation in the stomach/duodenum/jejunum/ileum/cecum, decreased lymphoid cellularity in the thymus/spleen/mesenteric lymph node/inguinal lymph node, decreased bone marrow cellularity, centrilobular hepatocellular hypertrophy in the liver, skeletal muscle degeneration, myocardial inflammation, decreased lipids in adipose tissue around the mesenteric lymph node [Unscheduled necropsy[g)]] 400: decreases in body weight/body weight gain/food consumption, increases in red cell distribution width/reticulocyte count, increases in neutrophil count/monocyte count, decreased eosinophil count, decreased lymphoid cellularity in the thymus/spleen/mesenteric lymph node/inguinal lymph node, decreased bone marrow cellularity, multiple inflammation in the stomach/duodenum/jejunum/ileum/cecum, decreased infiltrates of eosinophils in the lung (male and female), skin lesion, red staining (forepaws), decreases in red blood cell count/hemoglobin/hematocrit, increased mean platelet volume, decreased lymphocyte count, vacuolation of the adrenal cortex, vacuolation of periportal hepatocytes in the liver (male), hair loss (forelimb/hindlimb/abdomen/forepaw), small thymuses, decreased lipids in adipose tissue around the mesenteric lymph node, centrilobular hepatocellular hypertrophy in the liver (female) [Surviving animals] 75 and 175: decreases in white blood cell count/lymphocyte count/monocyte count/eosinophil count/basophil count, increased urine volume, decreased thymus/spleen weights, decreased lymphoid cellularity in the thymus/spleen/mesenteric lymph node, decreased infiltrates of eosinophils in the lung (male and female), decreases in body weight gain[h)]/food consumption,[h)] increased mean platelet volume, decreased blood cholesterol, decreased adrenal weights, decreased bone marrow cellularity, vacuolation of the adrenal cortex (male), small thymuses (female) 175: increases in red cell distribution width/reticulocyte count (male and female), small thymuses (male), decreased adrenal weights (female)	175	4.2.3.2.2
Male and female rats (Wistar)	Oral gavage	6 months (QD) + 3-month recovery period	0, 50, 100, 200	[Systemic toxicity evaluation] <u>Hematology/clinical chemistry evaluation (Day 90/91)</u> ≥50: decreases in lymphocyte count/basophil count, increased neutrophil count, decreased blood AST, decreased blood potassium (male and female), decreased white blood cell count, increased urine protein (male), decreased blood glucose (female) ≥100: increases in reticulocyte count/mean platelet volume, decreased eosinophil count (male), decreased blood triglycerides (female) 200: decreased red blood cell count, increases in mean corpuscular volume/red cell distribution width, poikilocytosi (male and female), decreased monocyte count, decreased blood triglycerides (male), increases in reticulocyte count/mean platelet volume, decreases in white blood cell count/eosinophil count (female) <u>Evaluation during dosing period and after the last dose</u> ≥50: decreases in white blood cell count/lymphocyte count/monocyte count/eosinophil count/basophil count, increased neutrophil count, decreases in blood AST/potassium, decreased thymus weights, decreased lymphoid	200	4.2.3.2.3

				cellularity in the thymus/spleen (male and female), small thymuses, decreased spleen weights, hyaline droplet accumulation in tubular epithelial cells of the kidney (male) ≥100: decreased blood triglycerides (male and female), decreases in red blood cell count/hemoglobin/hematocrit, small thymuses, decreased spleen weights, hyaline droplet accumulation in tubular epithelial cells of the kidney (female) 200: decreases in body weight[h]/body weight gain,[h] increases in mean corpuscular volume/red cell distribution width, decreased blood glucose, decreased lymphoid cellularity in the mesenteric lymph node, decreased bone marrow cellularity (male and female), decreases in red blood cell count/hemoglobin/hematocrit, increased mean platelet volume, increased urine protein (male), decreased lymphoid cellularity in the inguinal lymph node (female)		
				These findings were reversible.		

a) Euthanized on Day 1. b) Found dead on Day 7 (female) and Day 8 (male).
c) Clinical pathological and histopathological examinations etc. were not performed.
d) Euthanized on Day 8. e) Excluding abnormal findings associated with poor clinical condition.
f) Euthanized on Day 10, Day 14, and Day 28, respectively.
g) All surviving animals were also necropsied on Day 32 due to poor clinical condition. Excluding abnormal findings secondary to poor clinical condition.
h) These changes were transient and considered of little toxicological significance.

Repeated oral dose toxicity studies were conducted in dogs (Table 17). The NOAEL in a 9-month repeated oral dose toxicity study in dogs (CTD 4.2.3.2.6) was determined to be 5 mg/kg/day for both males and females, and the unbound $AUC_{0\text{-}24h}$ of ritlecitinib at the NOAEL on Day 273 was 4,020 ng·h/mL (the combined sex mean), which was approximately 3.8-fold the human exposure[15] ($AUC_{0\text{-}24h}$ = 1,070 ng·h/mL). The NOAEL in another 9-month repeated oral dose toxicity study in dogs, which was conducted focusing on neurotoxicity (CTD 4.2.3.2.7), was determined to be 10 mg/kg/day for both males and females. The unbound $AUC_{0\text{-}24h}$ of ritlecitinib at the NOAEL on Day 273 was 7,940 ng·h/mL (the combined sex mean), which was approximately 7.4-fold the human exposure[15] ($AUC_{0\text{-}24h}$ = 1,070 ng·h/mL).

The noteworthy systemic toxicities or abnormal findings of ritlecitinib were hearing loss; BAEP (brainstem auditory evoked potential) abnormalities; axonal dystrophies in the lateral superior olivary nucleus and lateral lemniscus/ventral nucleus in the brainstem, rostral cerebellar vermis, various organs in the body, and peripheral nerves in tissues; decreases in circulating T cells/B cells/NK cells/basophils/eosinophils; decreased lymphoid cellularity in the thymus/spleen/lymph nodes/gut-associated lymphoid tissue (GALT); decreased cellularity of all lineages in the bone marrow; infection-related epidermal hyperplasia with viral inclusions in the skin; parasite present in the hair follicle and chronic active inflammation around the hair follicle; chronic mixed cell inflammation in the lung; decreases in red blood cell parameters; increased heart rate and associated decreases in PR/QT intervals; and decreases in blood albumin and albumin/globulin (A/G) ratio and increased blood globulin, which were considered secondary to inflammatory changes in the skin. Axonal dystrophy in the rostral cerebellar vermis observed in the ritlecitinib groups was considered a worsening of spontaneous lesions that occur in beagle dogs. The lesions in the 10 mg/kg group were considered of little toxicological significance because these changes were localized and not observed in other axons, and no associated abnormal findings were observed.

Other abnormal findings were decreases in blood inorganic phosphorus/calcium/total cholesterol/creatinine and increases in platelet count/fibrinogen, which were considered of little toxicological significance because

of low severity, no associated laboratory abnormalities or histopathological abnormal findings, etc.

Table 17. Overview of repeated-dose toxicity studies in dogs

Test system	Route of administration	Duration of dosing	Doses (mg/kg)	Noteworthy findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female dogs (Beagle)	Oral gavage	8 weeks (QD)	0, 5, 15, 45	[Systemic toxicity evaluation] ≥5: emesis, vacuolation of the zona glomerulosa of the adrenal cortex (male and female) ≥15: decreased lymphoid cellularity in the thymus (male and female), decreased lymphoid cellularity in the mesenteric lymph node (female) 45: increased heart rate,[a)] decreases in PR[a)]/QT[a)] intervals (male and female), decreased lymphoid cellularity in the mesenteric lymph node, mucoid/red discolored feces (male), decreased lymphoid cellularity in the bone marrow/ decreased cellularity of all lineages in the bone marrow (female) [Immunotoxicity evaluation (Day 57)] ≥5: decreases in circulating total lymphocytes/total T cells/helper T cells/cytotoxic T cells/NK cells (male and female) 45: decreased circulating B cells (male and female)	45	4.2.3.2.5
Male and female dogs (Beagle)	Oral gavage	9 months (QD) + 3-month recovery period	0, 5, 20, 40	[Systemic toxicity evaluation] <u>Hematology/clinical chemistry evaluation (Day 87)</u> ≥5: decreases in lymphocyte count/red blood cell count/reticulocyte count[b)] (male and female), decreased eosinophil count, decreases in blood inorganic phosphorus/total cholesterol (male), decreased basophil count (female) ≥20: increased monocyte count, decreases in red blood cell count/hemoglobin/hematocrit (male and female), decreased basophil count (male), increases in white blood cell count/platelet count (female) 40: increased fibrinogen, decreased blood albumin/decreased A/G ratio (male and female), increases in white blood cell count/platelet count (male), decreased blood total cholesterol (female) <u>Evaluation during dosing period and on Day 274 (at the end of dosing)</u> ≥5: decreases in lymphocyte count/reticulocyte count, decreased lymphoid cellularity in the mesenteric lymph node/popliteal lymph node (male and female), decreased eosinophil count, decreases in blood inorganic phosphorus/total cholesterol, decreased lymphoid cellularity in the thymus/spleen/GALT (male), decreased basophil count (female) ≥20: decreases in body weight/body weight gain, decreases in red blood cell count/hemoglobin/hematocrit, axonal dystrophy in the olivary nucleus of the brainstem (male and female), decreased basophil count, decreased cellularity of all lineages in the bone marrow (male), increases in neutrophil count/platelet count, decreased blood inorganic phosphorus, decreased lymphoid cellularity in the thymus/spleen/GALT (female) 40: increased incidence of soft feces, focal scabs/papules/nodules in the skin, increases in white blood cell count/monocyte count/fibrinogen, decreased blood albumin/decreased A/G ratio, increased blood globulin, decreased blood creatinine, decreased spleen weights, scabs/nodules in the skin, discolored foci in the lung, chronic active inflammation around the hair follicle in the skin, chronic mixed cell inflammation in the lung (male and female), red skin, increases in neutrophil count/platelet count, parasite present in the hair follicle in the skin (male), decreased total cholesterol (female) <u>Transmission electron microscopy of superior olivary nucleus/cochlear nucleus specimens (Day 274)</u> 40: axosomatic bouton enlargement in the superior olivary nucleus, widely spaced mitochondria in the enlargement, poorly demarcated non-membrane bound oval to spherical structures which were moderately electron dense, either single or merged and with a homogenous internal appearance [Immunotoxicity evaluation (Day 87 and Day 274)] ≥5: decreases in circulating total T cells/helper T cells/cytotoxic T cells/B cells[c)]/NK cells (male and female) Recovery period 40: increased incidence of soft feces, thin fur, red skin/scabs/nodules/flaking skin/oily skin, interdigital cysts, axonal dystrophy in the olivary nucleus of the brainstem (male and female), hearing loss,[d)] waveform defects in BAEP testing[d)] (male) Other abnormal findings were reversible.	5	4.2.3.2.6

Male and female dogs (Beagle)	Oral gavage	9 months (QD or BID) + 6-month recovery period	QD: 0, 10, 20, 40 BID: 10	[Systemic toxicity evaluation] <u>Hematology/clinical chemistry evaluation (Day 80)</u> ≥10: decreases in lymphocyte count/reticulocyte count, decreased blood cholesterol (male and female), decreases in basophil count/eosinophil count (female) ≥20: decreases in blood A/G ratio/creatinine (male and female), decreased eosinophil count (male), decreases in red blood cell count/hemoglobin/hematocrit, increased fibrinogen (female) 40: increases in white blood cell count/monocyte count (male and female), increased neutrophil count, decreases in red blood cell count/hemoglobin/hematocrit, decreases in blood inorganic phosphorus/calcium (male) 10 BID: decreases in lymphocyte count/red blood cell count/reticulocyte count, decreases in blood A/G ratio/creatinine/cholesterol (male and female), decreases in basophil count/eosinophil count, increased monocyte count, decreases in hemoglobin/hematocrit, increased fibrinogen (female) <u>Evaluation during dosing period and on Day 274 (at the end of dosing)</u> ≥10: decreases in body weight/body weight gain, decreases in reticulocyte count/lymphocyte count, increased blood globulin, decreases in blood A/G ratio/cholesterol, decreased lymphoid cellularity in the spleen/GALT/thymus/ popliteal lymph node/mesenteric lymph node (male and female), chronic mixed cell inflammation in the lung (male), decreased food consumption, increased neutrophil count, decreases in basophil count/eosinophil count, increased fibrinogen, decreased blood albumin (female) ≥20: red skin/papules, thin fur (male and female), decreased food consumption, decreased eosinophil count, increases in white blood cell count/monocyte count, decreases in blood albumin/inorganic phosphorus/calcium (male), thin appearance, decreases in red blood cell count/hemoglobin/hematocrit, increased red cell distribution width, decreased blood creatinine, chronic mixed cell inflammation in the lung (female) 40: pale foci in the lung, decreased cellularity of all lineages in the bone marrow (male and female), decreased basophil count, decreases in red blood cell count/hemoglobin/hematocrit, skin nodules/epidermal hyperplasia with viral inclusions/hair follicle inflammation (male), increases in white blood cell count/monocyte count, decreases in blood inorganic phosphorus/calcium (female) 10 BID: decreases in body weight/body weight gain/food consumption, decreases in lymphocyte count/basophil count/eosinophil count, increases in white blood cell count/monocyte count, decreases in red blood cell count/hemoglobin/hematocrit/reticulocyte count, decreases in blood albumin/A/G ratio/cholesterol, increased blood globulin, decreased lymphoid cellularity in the spleen/GALT/thymus/popliteal lymph node/mesenteric lymph node, chronic mixed cell inflammation in the lung, epidermal hyperplasia with viral inclusions in the skin (male and female), decreases in blood inorganic phosphorus/calcium, skin nodules, decreased cellularity of all lineages in the bone marrow, hair follicle inflammation in the skin (male), thin appearance, increased neutrophil count, increased red cell distribution width, increased fibrinogen, decreased blood creatinine, skin masses/cysts/neutrophilic inflammation (female) [Immunotoxicity evaluation (Day 14, Day 80, Day 274] ≥10: decreases in circulating total T cells/helper T cells/cytotoxic T cells/NK cells (male and female) 10 BID: decreases in circulating total T cells/helper T cells/cytotoxic T cells/NK cells (male and female) [Neurotoxicity evaluation (Month 7 and Month 9)] <u>BAEP testing</u> 40: mild auditory threshold deficits (unilateral, 58 dB), mild hearing deficit that precluded processing an auditory signal less than 46 dB (unilateral), significant asymmetry in threshold across ears, loss of clarity and amplitude for Waves IV and V (male and female) <u>Organs/tissues in which axonal dystrophies occurred (Day 274)</u> ≥10: rostral cerebellar vermis (male and female) ≥20: lateral superior olivary nucleus in the brainstem, lateral lemniscus/ ventral nucleus, sciatic nerve, vagus nerve branches in the stomach, Auerbach's plexus in the stomach/duodenum/jejunum (male and female), white/gray matter in the spinal cord (increased severity), Auerbach's plexus in the ileum/urinary bladder (male), Auerbach's plexus in the colon (female) 40: Auerbach's plexus in the cecum, vagus nerve branches in the kidney (male and female), Meissner's plexus in the cecum, Auerbach's plexus in the colon, vagus nerve branches in the heart/spleen/mesenteric lymph node (male),	10	4.2.3.2.7

				vagus nerve branches in the duodenum/aorta, Auerbach's plexus in the urinary bladder, white/gray matter in the spinal cord (increased severity) (female) 10 BID: lateral lemniscus/ventral nucleus, rostral cerebellar vermis, Auerbach's plexus in the stomach/jejunum (male and female), lateral superior olivary nucleus in the brainstem, white/gray matter in the spinal cord (increased severity), Auerbach's plexus in the ileum/cecum, Meissner's plexus in the ileum/cecum (male), sciatic nerve, vagus nerve branches in the stomach/colon /mesenteric lymph node, Auerbach's plexus in the duodenum/vagina, Meissner's plexus in the jejunum/colon (female) 20: vagus nerve branches in the pancreas (male), Meissner's plexus in the duodenum/ileum/cecum, autonomic nerves of the adrenal gland, vagus nerve branches in the mesenteric lymph node (female)		
				These findings were reversible.		

a) Combined sexes. b) Excluding females in the 40 mg/kg group. c) Not performed on Day 87. d) Testing was conducted during the recovery period only. QD, once daily; BID, twice daily

5.3 Genotoxicity

An *in vitro* bacterial reverse mutation assay (Ames assay), an *in vitro* micronucleus assay in TK6 human lymphoblastoid cells, and an *in vivo* peripheral blood micronucleus assay in rats were performed (Table 18). Although ritlecitinib induced micronuclei in the *in vitro* micronucleus assay, as ritlecitinib did not induce micronuclei at the highest dose tested in the rat micronucleus assay, ritlecitinib was thought to have little genotoxic potential.

Table 18. 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*: WP2 *uvrA* pKM101	S9−/+	0,[a] 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,[a] 48.3, 66.3, 125 µg/mL	Positive	4.2.3.3.1.2
			S9− (4 hours)	0,[a] 205, 242, 285 µg/mL	Negative	
			S9+ (4 hours)			
In vivo	Rat micronucleus assay	Male and female rats (Wistar) peripheral blood		0, 75, 175, 400 mg/kg/day (oral gavage, 3 consecutive days)	Negative	4.2.3.3.2.1

a) DMSO

5.4 Carcinogenicity

A 6-month oral carcinogenicity study was conducted in Tg rasH2 hemizygous (Tg rasH2) mice (Table 19). Ritlecitinib did not increase the incidence of neoplastic lesions. As non-neoplastic lesions related to the immunosuppressive effects of ritlecitinib, a decreased incidence of mixed cell infiltrate in the liver and decreased lymphoid cellularity in the lymph node were noted.

Based on the above, the no-observed-effect level (NOEL) for carcinogenicity was determined to be 300 mg/kg/day. The unbound $AUC_{0\text{-}24h}$ of ritlecitinib at the NOEL for carcinogenicity on Day 28 was 12,100 ng·h/mL (the combined sex mean), which was approximately 11-fold the human exposure [15] ($AUC_{0\text{-}24h}$ = 1,070 ng·h/mL).

Table 19. 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	Ritlecitinib				
					0	30	100	300		
				N	25M25F	25M25F	25M25F	25M25F		
Male and female mice (Tg rasH2)	Oral gavage	26 weeks	Neoplastic lesions						300	4.2.3.4.2.3
			Thymus/Thymoma	M	0	0	0	0		
				F	0	1	0	0		
			Malignant lymphoma	M	0	0	0	0		
				F	0	1	0	0		
			Liver/Hepatocellular adenoma	M	0	0	0	1		
				F	0	0	0	0		
			Mammary gland/Carcinoma	M	0	0	0	0		
				F	0	0	1	0		
			Other findings							
			Survival rate (%)	M	96	96	96	92		
				F	100	84	92	81		
			≥30: decreased incidence of mixed cell infiltrate in the liver (male and female), decreased lymphoid cellularity in the inguinal lymph node (female) ≥100: decreased lymphoid cellularity in the inguinal lymph node (male) 300: decreases in body weight gain/food consumption (female)							

A 104-week oral carcinogenicity study was conducted in rats (Table 20). Although ritlecitinib increased the incidences of thymoma and thyroid follicular cell adenoma, ritlecitinib was thought to have little carcinogenic potential in humans based on the following points. The incidence of thymoma in females at 30 mg/kg (24.1%) exceeded the historical control range of the laboratory (0%-11.9%), but was not statistically significant. Thus, this finding was considered of little toxicological significance.

- While the mechanism underlying the increased incidence of thymoma in rats may be the immunosuppressive effects of ritlecitinib, thymoma risk was not elevated among immunosuppressed people with AIDS (*J Thorac Oncol.* 2010; 5: S260-5).
- Since there was no increased incidence of thyroid follicular cell adenoma in carcinogenicity studies of other JAK inhibitors, this finding appears to be an off-target effect. Thyroid tumors are common in rats, which is attributable to higher sensitivity of the thyroid to thyroid stimulating hormone (which is involved in thyroid follicular cell growth) in rats than in other species. Thus, this finding is considered of low human relevance (*Am J Ther.* 2006; 13: 141-4).

As other proliferative lesions, increased multinucleated hepatocytes in the liver were noted in the ritlecitinib groups. However, as this finding was considered an exacerbation of background lesions (Background lesions in laboratory animals: a color atlas 1st ed: *Saunders Elsevier*. 2012; 17-36, Toxicologic Pathology: nonclinical safety assessment 2nd ed: 2018; 451-513), and the incidence of hepatocellular carcinoma was not increased, ritlecitinib was considered to have little carcinogenic potential.

Based on the above, the NOEL for carcinogenicity was determined to be 30 mg/kg/day. The unbound $AUC_{0\text{-}24h}$ of ritlecitinib at the NOEL for carcinogenicity at Week 26 was 6,770 ng·h/mL (the combined sex mean), which was approximately 6.3-fold the human exposure[15] ($AUC_{0\text{-}24h}$ = 1,070 ng·h/mL).

Table 20. 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	Ritlecitinib				
					0	10	30	100		
				N	60M60F	60M60F	60M60F	60M60F		
Male and female rats (Wistar)	Oral gavage	104 weeks	Neoplastic lesions						30	4.2.3.4.1.1
			Thymus/Thymoma	M	2	5	3	7		
				F	8	7	14$	16*		
			Thymus/Malignant thymoma	M	0	0	0	1		
				F	0	0	1	2		
			Thymus/Thymoma + Malignant thymoma	M	2	5	3	8		
				F	8	7	15$	18*		
			Thyroid/Follicular cell adenoma	M	7	12	13	19*		
				F	2	4	4	6		
			Thyroid/Follicular cell carcinoma	M	2	1	1	4		
				F	0	1	2	0		
			Thyroid/Follicular cell adenoma/carcinoma	M	7	13	14	21*		
				F	2	5	6	6		
			Liver/Carcinoma	M	0	0	0	1		
				F	1	0	0	0		
			Mammary gland/Fibroadenoma	M	1	1	0	0		
				F	9	10	3	3		
			Mammary gland/Adenoma	M	0	0	0	0		
				F	1	1	0	1		
			Mammary gland/Carcinoma	M	0	0	0	0		
				F	3	4	0	1		
			Proliferative lesions							
			Thymus/Hyperplasia	M	0	0	0	0		
				F	4	4	3	7*		
			Thyroid/Follicular cell hyperplasia	M	7	11	8	9		
				F	2	4	5	3		
			Liver/Increased multinucleated hepatocytes	M	0	0	0	0		
				F	0	0	3	7		
			Other findings							
			Survival rate (%)	M	60	53	57	52		
				F	65	75	67	67		
			≥30 mg/kg/day: increased multinucleated hepatocytes in the liver (female) 100 mg/kg/day: decreases in body weight/food consumption, decreased incidence/severity of mononuclear cell infiltrate in the liver, increased incidence/severity of kidney tubule pigment, decreased lymphocyte cellularity in the mesenteric lymph node/spleen/thymus (male and female)							

*: Considered a significant effect of ritlecitinib. $: Exceeding the historical control range of the laboratory.

5.5 Reproductive and developmental toxicity

A study of fertility and early embryonic development to implantation was conducted in rats (Table 21). When males dosed with ritlecitinib were mated with non-dosed females, increased pre-implantation loss and fewer implantation sites and viable embryos were observed. When dosed females were mated with non-dosed males, increased mean number of corpora lutea and longer estrous cycles were noted. These findings were considered of little toxicological significance, for being non-dose-related, remaining within physiological changes, or giving no impact on the reproductive performance. Based on the above, the NOAEL for male fertility was determined to be 60 mg/kg/day, and the NOAEL for female fertility and early embryonic development was determined to be 200 mg/kg/day. The unbound $AUC_{0\text{-}24h}$ values of ritlecitinib[16)] at the NOAELs on Day 62 were 14,700 ng·h/mL (male fertility) and 58,600 ng·h/mL (female fertility and early embryonic development), which were approximately 14-fold and 55-fold the human exposure [15)] ($AUC_{0\text{-}24h}$ = 1,070 ng·h/mL), respectively.

[16)] Since plasma ritlecitinib concentrations were determined in males only, ritlecitinib exposure in males was compared with the human exposure.

Embryo-fetal development studies were conducted in rats and rabbits (Table 21). The noteworthy toxicity findings in the fetuses were skeletal malformations and variations in rats and visceral/skeletal malformations and skeletal variations in rabbits. Based on the above, the NOAELs for embryo-fetal development in rats and rabbits were determined to be 75 mg/kg/day and 25 mg/kg/day, respectively. The unbound $AUC_{0\text{-}24h}$ values of ritlecitinib at the NOAELs were 17,000 ng·h/mL (rats on gestation day 17) and 13,200 ng·h/mL (rabbits on gestation day 19), which were approximately 16-fold (rats) and 12-fold (rabbits) the human exposure[15] ($AUC_{0\text{-}24h}$ = 1,070 ng·h/mL).

A study for effects on pre- and postnatal development, including maternal function, was conducted in rats (Table 21). There were no effects on maternal reproductive performance. As effects on the F_1 offspring, decreased postnatal survival, decreased body weight gain, delayed sexual maturation, and decreased numbers of corpora lutea, implantation sites, and viable embryos were observed. These effects were considered potentially related to ritlecitinib exposure because ritlecitinib crosses the placenta and due to a certain amount of ritlecitinib present in the milk of lactating rats [see Section 4.4.2]. Based on the above, the NOAEL for the F_1 offspring was determined to be 75 mg/kg/day. The maternal unbound $AUC_{0\text{-}24h}$ of ritlecitinib at the NOAEL for the F_1 offspring on gestation day 17 was 15,400 ng·h/mL, which was approximately 14-fold the human exposure[15] ($AUC_{0\text{-}24h}$ = 1,070 ng·h/mL).

Table 21. Overview of reproductive and developmental toxicity studies

Type of study	Test system	Route of administration	Duration of dosing	Doses (mg/kg)	Noteworthy findings	NOAEL (mg/kg/day)	Attached document CTD
Fertility and early embryonic development to implantation	Male and female rats (Wistar)	Oral gavage	Males: from 28 days prior to mating (84 days prior to second mating) until the day before necropsy (QD)	0, 20, 60, 200	<u>Parental animals (male)</u> 200: decreased body weight gain <u>Reproductive performance (male)</u> None <u>Early embryonic development</u> 200: increased pre-implantation loss, fewer implantation sites/viable embryos	Parental animals General toxicity: 60 Fertility: 60	4.2.3.5.1.1
			Females: from 14 days prior to mating through gestation day 7 (QD)	0, 20, 60, 200	<u>Parental animals (female)</u> ≥60: increased mean number of corpora lutea 200: longer estrous cycles <u>Reproductive performance (female)</u> None <u>Early embryonic development</u> None	Parental animals General toxicity: 200 Fertility: 200 Early embryonic development: 200	
Embryo-fetal development	Female rat (Wistar)	Oral gavage	From gestation day 6 through gestation day 17 (QD) Caesarean section: Gestation day 21	0, 75, 175, 325	<u>Dams</u> 325: decreases in body weight/body weight gain/food consumption <u>Embryo-fetal development</u> ≥175: decreased fetal weights, branched ribs,* increased incidences of unossified forepaw phalanges/ unossified hindlimb metatarsals/unossified sternebrae**/nodulated ribs**/wavy ribs** 325: fused ribs,* fused thoracic centra/fused lumbar centra,* fused thoracic arches,* supernumerary vertebra,* increased incidences of unossified forepaw phalanges **/misshapen ribs**/short ribs/incompletely ossified sternebrae**/misshapen cervical arches**/bipartite ossification in lumbar vertebrae**/misshapen arches in thoracic vertebrae**/bipartite ossification in thoracic vertebrae**/unilateral thoracic centra ossification** 175: thoracic hemivertebra*	Dams: 175 Embryo-fetal development: 75	4.2.3.5.2.2
	Female rabbit (NZW)	Oral gavage	From gestation day 7 through gestation day 19 (QD) Caesarean section: Gestation day 29	0, 5, 25, 75	<u>Dams</u> 75: decreased uterine weights[a)] <u>Embryo-fetal development</u> 75: increased post-implantation loss, decreased fetal weights, malpositioned kidneys,* supernumerary sternebra,* absence of the 13th thoracic vertebral arch,* fusion of the 13th thoracic vertebra and the 1st lumbar vertebra,* fusion of the 9th thoracic vertebra and the 10th thoracic vertebra,* increased incidences of unossified forepaw phalanges/unossified forepaw metacarpals/unossified pubis/unossified sternebrae,** increased incidences of posterior fontanelle enlargement**/unilateral ossification in thoracic vertebrae **/isolated ossification site of the calvaria**/aplasia of the thoracic arch**/misshapen thoracic centra**	Dams: 75 Embryo-fetal development: 25	4.2.3.5.2.4
Pre- and postnatal development, including maternal function	Female rat (Wistar)	Oral gavage	From gestation day 6 through lactation day 20 (QD)	0, 25, 75, 175	<u>Dams</u> 175: decreased food consumption (Lactation days 4-7) <u>F_1 offspring</u> 175: decreases in postnatal survival/body weight gain, delayed balanopreputial separation/vaginal patency, decreased numbers of corpora lutea/implantation sites/viable embryos	Dams: 175 Postnatal development: 75	4.2.3.5.3.1

*Malformations, **Variations, a) The finding was considered secondary to decreased fetal weights.

5.6 Other toxicity studies

5.6.1 Phototoxicity

Ritlecitinib absorbs UVB and visible light (the wavelengths of maximum absorbance are 211 nm and 277 nm) and is distributed into the uveal tract of pigmented rats [see Section 4.2.1], a phototoxicity study was conducted in pigmented rats (Table 22). There were no ritlecitinib-related abnormal findings in the eyes or skin, and ritlecitinib was considered negative for phototoxicity.

Table 22. Overview of phototoxicity study

Type of study	Test system	Test method	Noteworthy findings	Attached document CTD
Phototoxicity	Female pigmented rat (Long-Evans)	Rats received ritlecitinib 0, 50, 100, or 200 mg/kg by oral gavage once daily for 3 days and were exposed to UV-A (9.8-10.8 J/cm^2) and UV-B (138-152 mJ/cm^2) for 40-44 minutes at approximately 60 minutes after the last dose.	None	4.2.3.7.7.1

5.6.2 Immunotoxicity

5.6.2.1 Peripheral blood immunophenotyping

In 8-week (CTD 4.2.3.2.5) and 9-month (CTD 4.2.3.2.6 and 4.2.3.2.7) repeated dose toxicity studies in dogs, immunophenotyping was performed. Ritlecitinib decreased circulating total T cells, helper T cells, cytotoxic T cells, B cells, and NK cells (Table 17), which was considered reversible after a recovery period.

5.6.2.2 Risk for hypersensitivity reactions

Ritlecitinib is a small-molecule covalent inhibitor. Because drugs that covalently modify proteins may induce hypersensitivity reactions, the mouse allergy model (MAM) and the modified MAM were used to determine whether ritlecitinib administration can lead to hypersensitivity reactions due to covalent binding to off-target proteins (Table 23). Ritlecitinib was considered to have a low potential to induce hypersensitivity reactions.

Table 23. Overview of study on the risk for hypersensitivity reactions

Test system	Test method	Test result	Attached document CTD
Study on the risk for hypersensitivity reactions	[MAM] Female C57BL/6 mice were injected subcutaneously with ritlecitinib 0, 1, 10, or 100 mg/kg QD for 3 days. The brachial lymph nodes were collected on Day 6, and lymph node cellularity was measured by flow cytometry to assess the potential of ritlecitinib to induce hypersensitivity reactions. [Modified MAM] Female C57BL/6 mice received ritlecitinib 0, 1, 10, or 100 mg/kg by oral gavage QD on Days 1-5 and were injected subcutaneously with ofloxacin (a positive control) on Days 1-3 to assess the effect of ritlecitinib on ofloxacin-induced hypersensitivity reactions.	[MAM] No effects [Modified MAM] Ritlecitinib at ≥10 mg/kg suppressed ofloxacin-induced hypersensitivity reactions.	4.2.3.7.2.1

5.6.3 Mechanistic studies on axonal dystrophy

A series of studies to probe the mechanism underlying axonal dystrophy in dogs following repeated dosing of ritlecitinib were conducted (Table 24), but the pathogenesis of axonal dystrophy was not identified.

Table 24. Overview of mechanistic studies on axonal dystrophy

Test system	Test method	Test result	Attached document CTD
Comparison of ritlecitinib concentrations in plasma and brain tissues in dogs	Female beagle dogs received ritlecitinib 0 or 40 mg/kg by oral gavage QD for 3 days, and ritlecitinib concentrations in plasma, right and left superior olivary nuclei, cochlear nucleus, and hippocampus were determined.	Approximately 10% of the ritlecitinib plasma levels were detected in the brain tissues. There were no clear differences in ritlecitinib concentration among the right and left superior olivary nuclei, cochlear nucleus, and hippocampus.	Reference data 4.2.3.7.3.1
Gene expression profiling of dog brainstem regions	The superior olivary nucleus, cochlear nucleus, and hippocampus of male beagle dogs were collected to determine the relative mRNA expression of oxidative stress genes, JAK/TEC family kinases, and other kinases by qPCR and RNA-seq.	No clear differences in the expression of oxidative stress genes, JAK/TEC family kinases, and other kinases were noted between the superior olivary nucleus and cochlear nucleus or hippocampus. As to JAK family mRNA expression, JAK1 mRNA was highest, and JAK3 mRNA was lowest.	Reference data 4.2.3.7.3.2
Identification of off-target binding sites in dog brain tissues	Hippocampus and rostral cerebellar vermis from beagle dogs were lysed and homogenized. The homogenates were pretreated with ritlecitinib and then incubated with an alkyne containing ritlecitinib analog followed by coupling of mass tags to the alkyne group for analysis by mass spectrometry.	As off-target binding proteins of ritlecitinib, DOCK10 in the hippocampus and rostral cerebellar vermis, and MAP2K7 in the rostral cerebellar vermis were identified.	Reference data 4.2.3.7.3.3
Comparison of binding affinities of ritlecitinib for rat, dog, and human MAP2K7	Lysate from HEK293F cells overexpressing rat, dog, or human MAP2K were incubated with ritlecitinib (0.12-30 μmol/L) to determine its binding affinities.	The difference in the binding affinity of ritlecitinib for MAP2K7 between human and dog was 2-fold (dog > human)	Reference data 4.2.3.7.3.4
Cerebellar expression of DOCK10 in mice, rats, dogs, and humans	Using external and in-house RNA-seq databases, cerebellar expression of DOCK10 in mice, rats, dogs, and humans was compared.	DOCK10 expression was significantly higher in mice, rats, and dogs compared to humans.	Reference data 4.2.3.7.3.5

5.6.4 Toxicologic evaluation of metabolites

In a mass balance study in humans, M2 was identified as a metabolite accounting for >10% of the systemic exposure of drug-related material following administration of ritlecitinib 200 mg QD [see Section 6.1.1]. Using the data from a 1-week repeated oral dose study in rats in which blood M2 concentrations were determined [see Section 4.1.2], blood M2 exposure was calculated assuming linear dose-proportional increase in exposure. Since blood M2 exposures in a 6-month repeated dose toxicity study in rats (CTD 4.2.3.2.3), a carcinogenicity study in rats (CTD 4.2.3.4.1.1), and an embryo-fetal development study in rats (CTD 4.2.3.5.2.2) were estimated to be higher than blood M2 exposure in humans (The rat to human ratio for the $AUC_{0\text{-}24h}$ >1), the toxicity related to M2 exposure was fully characterized in these studies.

5.6.5 Toxicologic evaluation of impurities

The impurities present in the drug substance were evaluated for mutagenicity in the Ames assay. Impurity B was mutagenic in the assay (Table 25) and was classified as Class 2 according to Impurities Classification with Respect to Mutagenic and Carcinogenic Potential. Impurity B is removed to a level below the acceptable daily limit as indicated by the ICH-M7 (R1) guideline,[17)] in the drug substance.

As an impurity in the drug product, a nitrosamine compound that may theoretically be formed based on the WHO NAP test[18)] and acetic acid standard conditions, i.e., Impurity A, was identified, which was mutagenic in the Ames assay (Table 26). Since this impurity was not detected by analysis of the drug substance and the

17) "Partial revision of the Guideline on Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk" (PSEHB/PED Notification No. 0627-1 dated June 27, 2018)

18) Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, vol. 24, Some Pharmaceutical Drugs, General Considerations on N-Nitrosatable Drugs, IARC, Lyon, France, 1980, pp. 297-314.

drug product for impurities and degradation products [see Section 2.R], there should be little safety concern.

Table 25. Overview of genotoxicity study on Impurity B

Type of study		Test system	Metabolic activation (Treatment time)	Concentrations	Test result	Attached document CTD
In vitro	Ames assay	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2 *uvrA* pKM101	S9−/+	0,[a] 313, 625, 1,250, 2,500, 5,000 μg/plate	Positive TA1535 (S9−/+)	4.2.3.7.6.5
		Salmonella typhimurium: TA1535	S9+	0,[a] 2,000, 3,000, 4,000, 5,000 μg/plate	Positive	

a) DMSO

Table 26. Overview of genotoxicity study on Impurity A

Type of study		Test system	Metabolic activation (Treatment time)	Concentrations	Test result	Attached document CTD
In vitro	Ames assay	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2 *uvrA* pKM101	Rat S9−/+	0,[a] 15, 50, 150, 500, 1,500, 5,000 μg/plate	Positive TA1535 (S9−/+)	4.2.3.7.6.14
		Salmonella typhimurium: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2 *uvrA* pKM101	Hamster S9+	0,[a] 313, 625, 1,250, 2,500, 5,000 μg/plate	Positive TA100, TA1535 (S9+)	
		Salmonella typhimurium: TA100, TA1535	Rat S9−/+	0,[a] 1,250, 2,500, 5,000 μg/plate	Positive TA1535 (S9−/+)	

a) DMSO

Impurity C, Impurity D, Impurity E, Impurity F, Impurity G, Impurity H, Impurity I, Impurity J, Impurity K, Impurity L, and Impurity M may arise during the drug substance manufacturing process, and a 13-week repeated oral dose toxicity study with the drug substance spiked with these impurities was conducted in rats (Table 27). No enhanced or new toxicities were detected with these impurities.

Table 27. Overview of repeated oral dose toxicity study with the drug substance spiked with impurities

Test system	Route of administration	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 spiked with impurities[a]: 200 Drug substance without impurities: 200 Vehicle: 0	[Drug substance spiked with impurities] decreased body weight gain, increases in MCV/hemoglobin/red cell distribution width, decreases in white blood cell count/lymphocyte count/eosinophil count, poikilocytosis, decreases in thymus/spleen weights, decreased cellularity of lymphoid follicles in the thymus/spleen/bone marrow, decreased cellularity of all lineages in the bone marrow, decreased lymphoid cellularity in the mesenteric and inguinal lymph nodes, hyaline droplet accumulation in the renal tubule, decreased mononuclear cell infiltrates in the liver/kidney (male and female), decreased monocyte count, decreased blood chloride, decreased mononuclear cell infiltrates in the epididymis/prostate gland (male), decreases in blood total protein/albumin/calcium, increased blood ALT, small thymuses (female) [Drug substance without impurities] decreased body weight gain, increases in hemoglobin/red cell distribution width, decreases in white blood cell count/lymphocyte count/eosinophil count, poikilocytosis, decreases in thymus/spleen weights, decreased lymphoid cellularity in the thymus/spleen, decreased cellularity of all lineages in the bone marrow, decreased lymphoid cellularity in the mesenteric and inguinal lymph nodes, hyaline droplet accumulation in the renal tubule, mononuclear cell infiltrates in the liver/kidney (male and female), increased MCV, decreased monocyte count, decreased blood chloride, mononuclear cell infiltrates in the epididymis/prostate gland (male), decreases in blood total protein/albumin/calcium, increased blood ALT (female)	Drug substance spiked with impurities: 200 Drug substance without impurities: 200	4.2.3.7.6.15

a) The spiked lot contained 4.37% total impurities, including the following: 0.37% Impurity C, 0.23% Impurity D, 0.28% Impurity E, 0.30% Impurity F, 0.27% Impurity G, 0.34% Impurity H, 0.56% Impurity I, 0.52% Impurity J, ≤0.05% Impurity K, 1.0% Impurity L, 0.24% Impurity M, and 0.31% others.

5.R Outline of the review conducted by PMDA

5.R.1 Systemic toxicity

5.R.1.1 Effects on nervous system

PMDA's view:

With respect to axonal dystrophies in the central and peripheral nervous systems observed in 9-month repeated oral dose toxicity studies in dogs, there are acceptable safety margins between ritlecitinib (unbound) exposure at which these findings were not observed and the human exposure. However, since functional effects on hearing, tested using BAEP, were suggested, its pathogenesis has not been identified, and human relevance is unknown, ritlecitinib may be associated with potential risk of functional impairment of and tissue damage to the axons of human neurons. Taking also account of the following points, the effects of ritlecitinib on the nervous system in humans, including its effects on physical as well as hearing functions, need to be discussed, based on the clinical study results [see Section 7.R.3.9]. Moreover, these toxicity findings should be mentioned in the package insert to communicate to healthcare professionals in clinical practice.

- Not all animals with axonal dystrophy in the CNS had BAEP abnormalities, and non-clinical evaluation of functional effects on the CNS using BAEP testing seems limited.
- While axonal dystrophy was observed in the central and peripheral nervous systems throughout the body, testing for hearing function only was conducted, and detailed investigation of the physical function of the whole body was not conducted in these toxicity studies.

5.R.1.2 Effects on immune system

PMDA's view:

Decreased lymphocytes were noted in repeated oral dose toxicity studies in rats and dogs, and the findings in the skin and lung suggestive of an increased susceptibility to infection resulting from immunosuppression, etc., were also observed in repeated oral dose toxicity studies in dogs. Thus, ritlecitinib has immunosuppressive effects and thus increases susceptibility to infection. Although there are acceptable safety margins between ritlecitinib (unbound) exposure at which these findings were not observed and the human exposure, the risk of infectious disease following administration of ritlecitinib in humans and the safety of ritlecitinib in humans with infectious disease need to be discussed, taking account of the clinical study results [see Section 7.R.3.2].

5.R.1.3 Effects on red blood cell parameters

PMDA's view:

There were effects of ritlecitinib on red blood cell parameters at the lowest doses in 9-month repeated oral dose toxicity studies in dogs, and the no-observed-effect-level (NOEL) was not determined [see Section 5.2]. Ritlecitinib has JAK3 inhibitory activity [see Section 3.1]. Decreases in red blood cell parameters were noted also in non-rodent repeated dose toxicity studies of the currently approved JAK3 inhibitors, i.e., tofacitinib and peficitinib, and adverse events of decreases in red blood cell count and hemoglobin, etc., were reported in clinical studies of tofacitinib (Review Report on Xeljanz Tablets 5 mg etc. as of February 28, 2013 and Review Report on Smyraf Tablets 50 mg etc. as of February 14, 2019). Thus, since as with other JAK3 inhibitors, repeated dosing of ritlecitinib may affect red blood cell parameters, the safety of ritlecitinib in humans needs to be discussed, taking account of the clinical study results [see Section 7.R.3.6].

5.R.1.4 Effects on cardiovascular system

The applicant's explanation:

Decreases in PR and QT intervals associated with increased heart rate observed in a cardiovascular safety pharmacology study in dogs [see Section 3.3] and a repeated oral dose toxicity study in dogs are considered of little toxicological significance because no histopathological changes in the cardiovascular system were noted.

PMDA's view:

Increased heart rate in cynomolgus monkeys was observed with a currently approved JAK3 inhibitor, tofacitinib, and there was a trend towards decreased QTc in humans with another currently approved JAK3 inhibitor, peficitinib (Review Report on Xeljanz Tablets 5 mg etc. as of February 28, 2013 and Review Report on Smyraf Tablets 50 mg etc. as of February 14, 2019). Whether there is a direct relationship between decreases in PR and QT intervals associated with increased heart rate observed in the non-clinical studies and JAK3 inhibition, and its toxicological significance are unknown at present, but abnormal cardiac function is not necessarily associated with tissue injury, and ritlecitinib may have a potential effect on the heartbeat function. Although there is an acceptable safety margin between the unbound C_{max} (4,720 ng/mL) of ritlecitinib

at the NOEL for these findings on Day 54 and the C_{max}[19] (318 ng/mL) at the clinical dose, the safety of ritlecitinib in humans needs to be discussed, taking account of the clinical study results [see Section 7.R.3.5].

5.R.2 Carcinogenicity

PMDA's view:

Given the following points, immunosuppression caused by chronic administration of ritlecitinib promotes spontaneous tumor development in rats, and the possibility that ritlecitinib increases the risk of malignancies in humans cannot be ruled out. Thus, the risk of malignancies associated with ritlecitinib should be managed carefully, taking account of risk-benefit discussion based on the clinical study results [see Section 7.R.3.4].

- An increased incidence of thymoma in females at 30 mg/kg in a carcinogenicity study in rats far exceeded the historical control range of the laboratory. Thus, its relationship to ritlecitinib cannot be ruled out, and there is no adequate safety margin because the ratio of ritlecitinib (unbound) exposure at the NOEL for thymoma of 10 mg/kg/day to the human exposure is approximately 1.9.
- As to an increased incidence of thyroid follicular cell adenoma in the ritlecitinib group in a carcinogenicity study in rats, no findings suggestive of an effect of ritlecitinib on thyroid hormone metabolism were observed, and its pathogenesis, including a direct relationship to JAK3 inhibition, is unknown. However, immunosuppression caused by ritlecitinib may have promoted the development of thyroid follicular cell adenoma, which is known to be a common spontaneous lesion in Wistar Han rats (*J Toxicol Pathol*. 2020; 33: 189-96, *J Toxicol Pathol*. 2016; 201-6).
- Immunosuppression such as decreased NK cells observed with ritlecitinib is generally thought to increase the risk of malignancies, and patients who receive immunosuppressive drugs are susceptible to developing a lymphoproliferative disorder (*Int J Toxicol*. 2010; 29: 435-66).
- An increased incidence of thymoma, which is a common spontaneous lesion in Wistar Han rats, was noted in a carcinogenicity study of an immunosuppressive drug, pimecrolimus (FDA Pharmacology review, NDA 21-302), and immunosuppressive effects can promote spontaneous tumor development.
- Tofacitinib and peficitinib having JAK3 inhibitory activity as a pharmacological effect also promoted spontaneous tumor development resulting from immunosuppression in rat carcinogenicity studies (Review Report on Xeljanz Tablets 5 mg as of February 28, 2013 and Review Report on Smyraf Tablets 100 mg etc. as of February 14, 2019), and cases of malignancies were also reported in clinical studies (Review Report on Xeljanz Tablets 5 mg as of February 28, 2013).

5.R.3 Reproductive and developmental toxicity

5.R.3.1 Effects on fertility and early embryonic development

PMDA's view:

Though pre-implantation embryonic development was affected in male rats dosed with ritlecitinib in a study of fertility and early embryonic development to implantation, as this effect was not observed with the currently approved JAK3 inhibitors (Review Report on Xeljanz Tablets 5 mg as of February 28, 2013 and Review Report

[19] Plasma unbound ritlecitinib concentration at steady state at the recommended clinical dose (50 mg/day) of oral ritlecitinib in AA patients (predicted concentration from the PPK analysis [see Section 6.3] corrected for plasma protein binding [see Section 4.2.3]).

on Smyraf Tablets 100 mg etc. as of February 14, 2019), this is a toxic change unique to ritlecitinib. Although there is an acceptable safety margin between ritlecitinib (unbound) exposure at the NOAEL for embryonic development and the human exposure, given that an effect on early embryonic development in males dosed with a non-genotoxic substance is a rare event, and that human relevance based on the pathogenesis etc. is unknown at present, the package insert should provide specific information on this toxicity finding.

5.R.3.2 Effects on fetal development

PMDA's conclusion:

Visceral or skeletal malformations were observed in embryo-fetal development studies in rats and rabbits, and there are acceptable safety margins between unbound ritlecitinib blood exposure at the NOAEL for fetal development and the human exposure. However, as with tofacitinib and peficitinib having JAK3 inhibitory activity as a pharmacological effect (Review Report on Xeljanz Tablets 5 mg as of February 28, 2013 and Review Report on Smyraf Tablets 100 mg etc. as of February 14, 2019), ritlecitinib is considered to have a potential teratogenic risk. Thus, the package insert should state that ritlecitinib is contraindicated in pregnant women or women who may be pregnant and provide specific information on toxicity findings etc. observed in non-clinical studies.

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: absolute bioavailability, relative bioavailability, bioequivalence, and food effect studies, etc.

In the clinical development of ritlecitinib, 4 types of formulations (oral solution,[20] oral solution and IV solution for Study B7981011,[21] the tablets [containing 10 or 50 mg of ritlecitinib], the proposed commercial capsules [containing 30, 50, or 100 mg of ritlecitinib]) were mainly used.[22] The tablets were used in a global phase II/III study (Study B7981015, see Section 7.2.1), and Study B7981029 [see Section 6.1.3] demonstrated the bioequivalence between the tablet formulation (50 mg) and the proposed commercial capsule formulation (100 mg). The proposed commercial 100 mg capsule formulation and the 50 mg capsule formulation to be marketed in Japan share the same qualitative and quantitative composition of a powder blend and exhibited similar dissolution profiles in an *in vitro* dissolution testing.

Concentrations of ritlecitinib and M2 in human plasma or urine were determined by LC-MS/MS (LLOQ, 0.5-3 ng/mL for ritlecitinib and 0.5 ng/mL for M2 in plasma, 1 ng/mL for ritlecitinib in urine). Unless otherwise

[20] Oral solution extemporaneously prepared with ritlecitinib malonate (0.03-8.5 mg/mL of ritlecitinib)

[21] Oral solution: extemporaneously prepared oral solution containing ^{14}C-ritlecitinib or ritlecitinib (2.0 mg/mL of ritlecitinib)
IV solution: ^{14}C-ritlecitinib dissolved in saline (6.0 μg/mL of ritlecitinib)

[22] Oral solution was used in phase I studies (Studies B7981001 and B7981003). Oral solution and IV solution for Study B7981011 were used in a phase I study (Study B7981011). The tablets were used in phase I studies (Studies B7981003, B7981008, B7981016, B7981017, B7981018, B7981020, B7981022, B7981023, B7981024, B7981025, B7981026, B7981029, B7981035, B7981036, and B7981054), phase II studies (Studies B7931005, B7981019, and B7981037), a phase II/III study (Study B7981015), and a phase III study (Study B7981032). The proposed commercial capsules were used in phase I studies (Studies B7981022, B7981029, B7981030, and B7981069).

specified, doses of the formulations are expressed in terms of ritlecitinib, and pharmacokinetic parameters and the data are expressed as the mean ± SD.

6.1.1 Absolute bioavailability study (CTD 5.3.3.1.3, Study B7981011 [April 2019 to July 2019])

The study consisted of Part A and Part B. In Part A, non-Japanese healthy volunteers (N = 6) received a single oral dose of ^{14}C-ritlecitinib 200 mg (oral solution) under fasting conditions. In Part B, a single dose of unlabeled ritlecitinib 200 mg (oral solution) was administered under fasting conditions approximately 0.5 hours before IV ^{14}C-ritlecitinib 60 μg (IV solution). The absolute bioavailability and mass balance of ritlecitinib were assessed.

In Part A, the total recovery of the orally administered radioactive dose over a period of 240 hours post-dose was 85.6 ± 9.2%, with 66.1 ± 13.4% in the urine and 19.5 ± 4.0% in the feces. The total recovery of the IV administered radioactive dose over a period of 144 hours post-dose was 83.0 ± 4.7%, with 70.5 ± 4.3% in the urine and 12.5 ± 3.7% in the feces in Part B, and 4.2% of the ritlecitinib dose was excreted unchanged in the urine.

Based on the urinary recoveries of the orally administered or IV administered radioactive dose and the dose-normalized AUC_{inf},[23)] the fraction absorbed after oral administration was estimated at 89.2%, and the absolute bioavailability of ritlecitinib [90% confidence interval (CI)] was estimated at 64.3% [58.1%, 71.1%]. The volume of distribution at steady state after IV administration was 73.8 L, suggesting the extravascular distribution of ritlecitinib.

After oral administration, the major circulating drug-related components (≥10% of circulating radioactivity) (up to 48 hours post-dose) were ritlecitinib (30.4%) and M2 (16.5%). In the pooled urine (up to 24 hours post-dose), the major drug-related components (≥10% of the administered dose) were M4 (16.3%) and M3 (10.3%). In the pooled feces (24-96 hours post-dose), various metabolites were detected, but no single metabolite was greater than 1% of the administered dose.

6.1.2 Relative bioavailability study (CTD 5.3.1.1.1, Study B7981003 [February 2016 to May 2016])

A randomized, open-label, 6-treatment, 3-period, crossover study was conducted in non-Japanese healthy volunteers (N = 14) to determine the bioavailability of the tablet formulation relative to the oral solution after a single oral dose of ritlecitinib 50 mg under fasting conditions and characterize the effect of food on the bioavailability of the tablet formulation. The results are shown in Table 28. Under the fasting conditions, ritlecitinib exposure (C_{max} and AUC) with the oral solution was similar to that with the tablet formulation. As to the effect of food on ritlecitinib exposure with the tablet formulation, although administration of ritlecitinib with food tended to decrease the rate of absorption and reduce the C_{max}, there were no clear differences in the AUC between fasted and fed administration.

[23)] The dose-normalized AUC_{inf} values of ritlecitinib (mean ± SD) after oral administration of unlabeled ritlecitinib 200 mg and after IV administration of ^{14}C-ritlecitinib 60 μg were 15.2 ± 4.1 and 23.3 ± 4.8 ng·h/mL/mg, respectively.

Table 28. Pharmacokinetic parameters of ritlecitinib following a single oral dose of ritlecitinib 50 mg

Formulation (Dosing condition)	N	C_{max} (μg/mL)	AUC_{last} (μg·h/mL)	AUC_{inf} (μg·h/mL)	t_{max} (h)	Adjusted geometric mean ratio [90% CI]		
						C_{max}	AUC_{last}	AUC_{inf}
Oral solution/50 mg (Fasted)	14	0.311 ± 0.125	0.472 ± 0.251	0.474 ± 0.251	0.50 [0.25, 1.00]			
Tablet/50 mg (Fasted)	12	0.271 ± 0.089	0.420 ± 0.202	0.422 ± 0.202	0.50 [0.25, 2.12]	Ratio of tablet (fasted) to oral solution (fasted)		
						0.90 [0.72, 1.13]	0.94 [0.88, 1.00]	0.94 [0.88, 1.00]
Tablet/50 mg (After a high-fat meal)	11	0.180 ± 0.098	0.426 ± 0.204	0.430 ± 0.204	1.02 [0.25, 4.00]	Ratio of tablet (fed) to tablet (fasted)		
						0.61 [0.49, 0.78]	1.01 [0.95, 1.09]	1.02 [0.95, 1.09]

Mean ± SD, Median [Range] for t_{max}

6.1.3 Bioequivalence study (CTD 5.3.1.2.2, Study B7981029 [September 2020 to July 2021])

A randomized, open-label, 4-treatment, 2- or 3-period, crossover study was conducted in non-Japanese healthy volunteers (N = 160) to assess the bioequivalence of the proposed commercial capsule formulation to the tablet formulation after a single oral dose of ritlecitinib 100 mg under fasting conditions and estimate the effect of food[24] on the bioavailability of the proposed commercial capsule formulation. The results are shown in Table 29. The 90% confidence intervals for the adjusted geometric mean ratios of the C_{max}, AUC_{last}, and AUC_{inf} for the proposed commercial capsule formulation vs. the tablet formulation met the predefined bioequivalence criteria (0.80-1.25). As to the effect of food on ritlecitinib exposure with the proposed commercial capsule formulation, although administration of ritlecitinib with food tended to decrease the rate of absorption and reduce the C_{max}, there were no clear differences in the AUC between fasted and fed administration.

Table 29. Pharmacokinetic parameters of ritlecitinib following a single oral dose of ritlecitinib 100 mg

Formulation (Dosing condition)	N	C_{max} (μg/mL)	AUC_{last} (μg·h/mL)	AUC_{inf} (μg·h/mL)	t_{max} (h)	Adjusted geometric mean ratio [90% CI]		
						C_{max}	AUC_{last}	AUC_{inf}
Tablet/50 mg × 2 (Fasted)	122	0.660 ± 0.247	1.318 ± 0.535 [a)]	1.324 ± 0.533 [b)]	0.50 [0.50, 1.58]			
Proposed commercial capsule/100 mg (Fasted)	119	0.668 ± 0.264	1.364 ± 0.540	1.372 ± 0.538	1.00 [0.50, 2.00]	Ratio of proposed commercial capsule (fasted) to tablet (fasted)		
						1.01 [0.95, 1.06]	1.03 [1.00, 1.05]	1.03 [1.00, 1.05]
Proposed commercial capsule/100 mg (After a high-fat meal)	12	0.337 ± 0.079	1.189 ± 0.388	1.196 ± 0.387	3.00 [0.50, 4.00]	Ratio of proposed commercial capsule (fed) to proposed commercial capsule (fasted)[c)]		
						0.68 [0.54, 0.85]	1.11 [0.98, 1.26]	1.11 [0.98, 1.25]

Mean ± SD, Median [Range] for t_{max}

a) N = 121, b) N = 120

c) Compared in subjects who ingested a high-fat meal. The adjusted geometric means of the pharmacokinetic parameters in this subject population are as follows.

Fasted: C_{max} = 0.483 μg/mL, AUC_{last} = 1.02 μg·h/mL, AUC_{inf} = 1.03 μg·h/mL

After a high-fat meal: C_{max} = 0.328 μg/mL, AUC_{last} = 1.13 μg·h/mL, AUC_{inf} = 1.14 μg·h/mL

6.2 Clinical pharmacology

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

[24] The effect of food was assessed using a high-fat meal (approximately 800-1,000 kcal and approximately 50% fat).

6.2.1 Studies in health subjects

6.2.1.1 Phase I studies (CTD 5.3.3.1.1, Study B7981001 [December 2014 to April 2016], CTD 5.3.3.1.2, Study B7981008 [August 2017 to November 2017])

Non-Japanese healthy volunteers (N = 115) received single oral doses of ritlecitinib 5 to 800 mg (oral solution) or placebo or multiple oral doses of ritlecitinib 50 to 400 mg (oral solution) or placebo QD or BID for 14 days, and the pharmacokinetics of ritlecitinib were evaluated. The pharmacokinetic parameters of ritlecitinib are shown in Table 30. After a single oral dose, the C_{max} increased approximately dose-proportionally over the dose range tested, and the AUC_{inf} increased approximately dose-proportionally up to 200 mg. The multiple oral dosing data indicated that a steady state was reached by Day 4 of QD dosing or by Day 6 of BID dosing. The C_{max} increased approximately dose-proportionally over the dose range tested, and the AUC_{tau} increased more than dose-proportionally.[25)]

The pharmacokinetic parameters of ritlecitinib following once daily oral administration of ritlecitinib (the tablet) 200 mg or placebo for 10 days in Japanese healthy volunteers (N = 6) are shown in Table 30. Given that there were no clear differences in ritlecitinib exposure between the different dosage forms (the oral solution and the tablet) [see Section 6.1.2], there were no marked differences in ritlecitinib exposure (C_{max} and AUC) between Japanese and non-Japanese subjects.

Table 30. Pharmacokinetic parameters of ritlecitinib after a single oral dose or multiple oral doses

Subjects (Study)	Regimen	Dose (mg)	N	C_{max} (μg/mL)	AUC [a)] (μg·h/mL)	$t_{1/2}$ (h)	t_{max} (h)	CL/F (L/h)	V_z/F (L)
Non-Japanese (B7981001)	Single dose	5	6	0.028 ± 0.009	0.045 ± 0.012	1.20 ± 0.11	0.50 [0.50, 0.50]	116.8 ± 28.3	203.0 ± 47.5
		20	6	0.134 ± 0.068	0.225 ± 0.089	1.20 ± 0.17	0.50 [0.50, 1.00]	100.0 ± 35.7	167.5 ± 43.0
		50	6	0.272 ± 0.100	0.415 ± 0.173	1.13 ± 0.17	0.50 [0.50, 1.00]	141.9 ± 69.3	222.3 ± 87.1
		100	6	0.663 ± 0.156	1.11 ± 0.25	1.48 ± 0.18	0.50 [0.50, 0.62]	94.2 ± 21.7	197.8 ± 35.7
		200	6	1.10 ± 0.43	2.63 ± 0.95	1.75 ± 0.43	0.75 [0.50, 2.00]	87.0 ± 36.5	206.5 ± 56.2
		400	12	2.77 ± 0.71	8.18 ± 2.38	2.18 ± 0.34	1.00 [0.50, 2.00]	53.9 ± 19.7	166.8 ± 57.8
		800	6	5.02 ± 0.57	17.0 ± 2.9	2.48 ± 0.46	1.50 [1.00, 2.02]	48.4 ± 9.2	169.8 ± 25.9
	QD	50	6	0.332 ± 0.103	0.570 ± 0.202	1.30 ± 0.24	0.50 [0.50, 1.00]	98.2 ± 38.5	175.7 ± 49.4
		200	5	1.47 ± 0.42	4.15 ± 0.92	1.84 ± 0.41	1.00 [0.50, 1.00]	50.1 ± 10.9	131.7 ± 31.9
		400	15	3.23 ± 0.77	10.2 ± 2.0	2.16 ± 0.10 [c)]	1.00 [0.50, 2.00]	40.6 ± 8.0	128.1 ± 24.4 [c)]
	BID	100	4	0.690 ± 0.209	2.00 ± 0.29	2.11 ± 0.34	0.75 [0.50, 2.00]	50.9 ± 7.5	155.5 ± 43.1
		200	5	1.96 ± 0.54	5.33 ± 1.36	2.27 ± 0.21	1.00 [0.50, 1.00]	39.3 ± 8.7	127.0 ± 22.8
Japanese (B7981008)	Single dose[b)]	200	4	1.88 ± 0.55	3.86 ± 0.92	1.69 ± 0.17	0.53 [0.50, 1.00]	54.3 ± 14.0	131.0 ± 30.8
	QD	200	4	1.89 ± 0.64	5.08 ± 1.10	1.78 ± 0.15	0.50 [0.50, 0.50]	41.0 ± 9.72	104.6 ± 22.2

Mean ± SD, Median [Range] for t_{max}
a) AUC_{inf} after a single dose, AUC_{tau} after multiple doses, b) Day 1 data, c) N = 14

6.2.2 Intrinsic factor pharmacokinetic studies

6.2.2.1 Study in subjects with hepatic impairment (CTD 5.3.3.3.1, Study B7981016 [July 2019 to March 2020])

The pharmacokinetics of ritlecitinib were evaluated in 10 non-Japanese subjects with moderate hepatic impairment (Child-Pugh class B) and 8 non-Japanese healthy volunteers with normal hepatic function[26)]

[25)] The cause for a lower AUC value in the 50 mg QD group could not be identified. The applicant discussed that this may be attributable to the limited number of subjects and differences in demographic factors such as body weight.

[26)] The study consisted of Part 1 (to evaluate the effect of moderate hepatic impairment on pharmacokinetics) and Part 2 (to evaluate the effect of mild hepatic impairment on pharmacokinetics). Since the pre-defined decision criterion to proceed to Part 2 ($AUC_{0\text{-}24h}$ geometric mean ratio for the moderate hepatic impairment group compared to normal group was ≥2.0 in Part 1) was not met in Part 1, Part 2 was not conducted.

following once daily oral administration of ritlecitinib (the tablet) 30 mg. Table 31 shows the pharmacokinetic parameters of ritlecitinib.

The applicant's explanation:
Since there were no clear differences in ritlecitinib exposure between subjects with moderate hepatic impairment and subjects with normal hepatic function, no dose adjustment of ritlecitinib is required in patients with mild or moderate hepatic impairment.

Ritlecitinib has not been studied in subjects with severe hepatic impairment (Child-Pugh class C).

The applicant's explanation:
Given that ritlecitinib has immunosuppressive effects and is associated with the risk of infections, and that patients with severe hepatic impairment are at risk of infections due to liver disease, ritlecitinib will be contraindicated in these patients.

Table 31. Effect of hepatic function on pharmacokinetic parameters of ritlecitinib

Degree of hepatic impairment	N	C_{max} (μg/mL)	AUC_{0-24h} (μg·h/mL)	CL/F (L/h)	Adjusted geometric mean ratio [90% CI] (Hepatic impairment/Normal hepatic function)	
					C_{max}	AUC_{0-24h}
Normal	8	0.192 ± 0.048	0.388 ± 0.064	79.1 ± 12.3	—	—
Moderate	8	0.216 ± 0.118	0.496 ± 0.239	71.1 ± 27.7	1.04 [0.74, 1.45]	1.19 [0.88, 1.60]

Mean ± SD

6.2.2.2 Study in subjects with renal impairment (CTD 5.3.3.3.2, Study B7981020 [August 2019 to March 2020], CTD 5.3.3.5.10)

The pharmacokinetics of ritlecitinib were evaluated in 8 non-Japanese subjects with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min)[27)] following once daily oral administration of ritlecitinib (the tablet) 50 mg. Table 32 shows the pharmacokinetic parameters of ritlecitinib. Based on the data from matched subjects with normal renal function obtained from Study B7981016 [see Section 6.2.2.1], "the adjusted geometric mean ratios of the C_{max} and AUC_{0-24h} for subjects with severe renal impairment vs. subjects with normal renal function [90% CI]" were 1.44 [1.14, 1.83] and 1.55 [1.23, 1.96], respectively. Based on ritlecitinib exposures simulated based on the body weights of subjects enrolled in Study B7981020 using the PPK model,[28)] "the adjusted geometric mean ratios of the C_{max} and AUC_{0-24h} for subjects with severe renal impairment vs. subjects with normal renal function [90% CI]" were 1.43 [1.14, 1.80] and 1.71 [1.35, 2.17], respectively.

[27)] The study consisted of Part 1 (to evaluate the effect of severe renal impairment on pharmacokinetics) and Part 2 (to evaluate the effect of moderate or mild renal impairment on pharmacokinetics). Only if the pre-defined decision criterion to proceed to Part 2 (AUC_{0-24h} geometric mean ratio for the severe renal impairment group compared to normal renal function was ≥2.0 in Part 1) was met in Part 1, Part 2 was to be conducted. Part 1 was planned to enroll subjects with normal renal function after completing enrollment of subjects with severe renal impairment. However, subject enrollment was suspended due to the COVID-19 pandemic, and then the study was terminated because the situation was unlikely to return to normal, and ritlecitinib is an immunosuppressant.

[28)] PPK analysis using the plasma ritlecitinib concentration data obtained from Studies B7981001 and B7981003 in healthy volunteers and Study B7981006 in patients with RA (116 subjects [1,520 sampling points]) (NONMEM ver. 7.3). The final model was a 2-compartment model with first-order absorption, including RA patient and a >100 mg/day dose as covariates on CL/F, food as a covariate on ka, and body weight as a covariate on CL/F and Vc/F.

The applicant's explanation:

Although ritlecitinib exposures in subjects with severe renal impairment were higher than those in subjects with normal renal function, there were no marked differences, and no dose adjustment of ritlecitinib is required in patients with renal impairment.

Table 32. Effect of renal function on pharmacokinetic parameters of ritlecitinib

Degree of renal impairment	N	C_{max} (μg/mL)	$AUC_{0\text{-}24h}$ (μg・h/mL)	CL/F (L/h)	Adjusted geometric mean ratio [90% CI] (Renal impairment/Normal renal function)	
					C_{max}	$AUC_{0\text{-}24h}$
Severe	8	0.453 ± 0.085	1.034 ± 0.346	53.0 ± 16.7	1.44 [1.14, 1.83][a)] 1.43 [1.14, 1.80][b)]	1.55 [1.23, 1.96][a)] 1.71 [1.35, 2.17][b)]

Mean ± SD

a) Ritlecitinib exposures for healthy subjects (subjects with normal renal function [eGFR ≥90 mL/min]) enrolled in Study B7981016 at the 30 mg dose (multiple dosing) were adjusted to 50 mg (multiple dosing) assuming linearity.

b) Ritlecitinib exposures were simulated using the PPK model.

6.2.3 Pharmacokinetic interaction studies[29)]

Based on the results of *in vitro* drug interaction studies and the PK profile of ritlecitinib, e.g., its metabolism and excretion, 9 studies were conducted in healthy volunteers to evaluate the drug-drug interaction potential of ritlecitinib (the tablet formulation or the proposed commercial capsule formulation). The results are shown in Tables 33 and 34.

The applicant's explanation based on the obtained results:

- Ritlecitinib is a CYP1A2 or CYP3A inhibitor. Concomitant use of ritlecitinib at the clinical dose (50 mg) QD may increase the blood concentrations of CYP1A2 or CYP3A substrates. Thus, the package insert will include a precautionary statement about coadministration with these drugs.
- Though concomitant use of rifampicin decreased ritlecitinib exposure, ritlecitinib even at 30 mg, which is about the half of the clinical dose (50 mg), showed higher efficacy over placebo in a clinical study in AA patients (Study B7981015, see Section 7.2.1). Thus, no particular precautionary statement is necessary.

Table 33. Effect of coadministered drugs on pharmacokinetic parameters of ritlecitinib

Dosing regimen (Oral administration)		N	Adjusted geometric mean ratio [90% CI] (Coadministration/Alone)	
Coadministered drug	Ritlecitinib		C_{max}	AUC_{inf}
Itraconazole 200 mg QD	30 mg single dose	12	1.03 [0.83, 1.27]	1.15 [1.05, 1.27]
Rifampicin 600 mg QD	50 mg single dose	12[a)]	0.75 [0.63, 0.89]	0.56 [0.52, 0.60]

Itraconazole is a CYP3A/P-gp inhibitor. Rifampicin is a CYP inducer.

a) N = 10 for coadministration

[29)] CTD 5.3.2.2.1, Study B7981017 [December 2018 to February 2019]; CTD 5.3.2.2.2, Study B7981018 [September 2018 to November 2018]; CTD 5.3.2.2.3, Study B7981023 [February 2019 to June 2019]; CTD 5.3.2.2.4, Study B7981024 [September 2019 to January 2020]; CTD 5.3.2.2.5, Study B7981025 [June 2020 to August 2020]; CTD 5.3.2.2.6, Study B7981026 [June 2020 to September 2020]; CTD 5.3.2.2.7, Study B7981035 [August 2019 to October 2019]; CTD 5.3.2.2.8, Study B7981054 [December 2020 to March 2021]; CTD 5.3.2.2.9, Study B7981069 [November 2021 to January 2022]

Table 34. Effect of ritlecitinib on pharmacokinetic parameters of coadministered drugs

Dosing regimen (Oral administration)		N	Adjusted geometric mean ratio [90% CI] (Coadministration/Alone)	
Ritlecitinib	Coadministered drug (Single dose)		C_{max}	AUC [a)]
200 mg QD	Midazolam 2 mg	12[b)]	1.81 [1.48, 2.21]	2.69 [2.16, 3.36]
200 mg QD	Efavirenz 50 mg	12[b)]	0.88 [0.77, 1.01]	1.00 [0.95, 1.04]
200 mg QD	Caffeine 100 mg	12	1.10 [1.04, 1.16]	2.65 [2.34, 3.00]
200 mg QD	Tolbutamide 500 mg	12[c)]	1.03 [0.97, 1.10]	0.99 [0.92, 1.07]
200 mg QD	Ethinylestradiol 30 μg	12[d)]	0.88 [0.78, 1.00]	0.82 [0.76, 0.89]
	Levonorgestrel 150 μg	12	1.03 [0.97, 1.09]	1.13 [1.04, 1.22]
50 mg QD	Ethinylestradiol 30 μg	28[e)]	0.92 [0.84, 1.01]	0.98 [0.91, 1.06]
	Levonorgestrel 150 μg	28[f)]	0.80 [0.73, 0.88]	0.88 [0.83, 0.93]
200 mg QD	Rosuvastatin 10 mg	12[g)]	0.73 [0.63, 0.83]	0.87 [0.75, 1.01]
400 mg single dose	Sumatriptan 25 mg (coadministration)	10[h)]	0.87 [0.73, 1.03]	1.30 [1.17, 1.44]
400 mg single dose	Sumatriptan 25 mg (staggered administration[i)])	10[h)]	1.50 [1.26, 1.78]	1.50 [1.35, 1.66]

Midazolam is a CYP3A substrate. Efavirenz is a CYP2B6 substrate. Caffeine is a CYP1A2 substrate. Tolbutamide is a CYP2C9 substrate. Rosuvastatin is a substrate for OATP1B1, OATP1B3, BCRP, and OAT3. Sumatriptan is an OCT1 substrate.
a) $AUC_{0\text{-}72h}$ for efavirenz, AUC_{last} for levonorgestrel, AUC_{inf} for others, b) N = 11 for administration alone
c) Administration alone (N = 11 for AUC_{inf}), Coadministration (N = 10 for C_{max}, N = 9 for AUC_{inf})
d) Administration alone (N = 10 for AUC_{inf}), Coadministration (N = 9 for AUC_{inf})
e) Administration alone (N = 24 for AUC_{inf}), Coadministration (N = 25 for C_{max}, N = 20 for AUC_{inf})
f) Coadministration (N = 25 for C_{max} and AUC_{last}), g) Administration alone and Coadministration (N = 11 for AUC_{inf})
h) Administration alone (N = 7 for AUC_{inf}), Coadministration and staggered administration (N = 9 for AUC_{inf})
i) Sumatriptan was administered 8 hours after the ritlecitinib dose.

6.2.4 Assessment of QT interval prolongation risk by concentration-response modeling (CTD 5.3.3.5.9)

Using the single ascending dose period data from a phase I study in healthy volunteers (Study B7981001), a concentration-response analysis was performed using a linear mixed effect model. The model-predicted mean placebo-adjusted change from baseline in the QT interval [90% CI] at the C_{max} of ritlecitinib (the geometric mean = 4.99 μg/mL) after a single oral dose of 800 mg (the highest dose in Study B7981001) was 0.71 [−2.71, 4.13] ms, and the upper bound of the 90% confidence interval was below 10 ms. This C_{max} is approximately 3-fold the steady-state C_{max} (the geometric mean = 1.60 μg/mL)[30)] at 200 mg QD of oral ritlecitinib in AA patients, and taking also into account that no intrinsic or extrinsic factors have a marked effect on ritlecitinib exposure, the applicant explained that the results of this analysis indicated that following oral administration of the clinical dose (50 mg QD) of ritlecitinib in AA patients, the risk of QT interval prolongation is low.

6.3 PPK analyses (CTD 5.3.3.5.2, 5.3.3.5.3)

Using the plasma ritlecitinib concentration data obtained from 9 clinical studies in healthy volunteers, subjects with hepatic impairment, or patients with AA, ulcerative colitis (UC), rheumatoid arthritis (RA), or vitiligo[31)] (668 subjects [5,187 sampling points]) and the previously developed PPK analysis model[32)] as informative prior, a PPK analysis (NONMEM ver. 7.4.3) was performed.

The pharmacokinetics of ritlecitinib were described by a 2-compartment model with first-order absorption with inter-individual variance (IIV) on apparent clearance (CL/F) and apparent central volume of distribution (Vc/F), a proportional random unexplained variability (RUV) model, and non-stationary clearance (CL) and

[30)] Calculated from Study B7931005.
[31)] Studies B7981001, B7981003, B7981008, and B7981022 in healthy volunteers, Study B7981016 in subjects with hepatic impairment, Study B7931005 in AA patients, Study B7981005 in UC patients, Study B7981006 in RA patients, and Study B7981019 in vitiligo patients
[32)] Studies B7981001 and B7981003 in healthy volunteers, Study B7931005 in AA patients, and Study B7981006 in RA patients were included.

bioavailability (F) directly driven by peripheral concentrations. The base model incorporated the effect of body weight[33] on CL/F, apparent inter-compartmental clearance (Q/F), Vc/F, and apparent peripheral volume of distribution (Vp/F), the effect of AA, UC, RA, and vitiligo patients on CL/F, the effect of inflammatory disease patients on IIV in CL/F and Vc/F, the effect of inflammatory disease patients on RUV, the effect of high-fat meal on first-order absorption rate constant (k_a), and the effect of 800 mg single-dose on k_a. Based on the results of covariate exploration,[34] the proposed commercial capsule formulation for k_a, and UC patient and moderate hepatic impairment for F were selected as new covariates in the final model.

In order to evaluate covariate effects not previously assessed in the aforementioned PPK analysis, using the plasma ritlecitinib concentration data obtained from 4 clinical studies in healthy volunteers or AA patients[35] (601 subjects [2,944 sampling points]) and the aforementioned PPK analysis model as informative prior, a PPK analysis (NONMEM ver. 7.5.0) was performed.

The pharmacokinetics of ritlecitinib were described by a 2-compartment model with first-order absorption with IIV on CL/F and Vc/F, RUV, and non-stationary CL and F directly driven by peripheral concentrations. The base model incorporated the effect of body weight[33] on CL/F, Q/F, Vc/F, and Vp/F, the effect of AA on CL/F, the effect of inflammatory disease patients on IIV in CL/F and Vc/F, and the effect of inflammatory disease patients on RUV. Based on the results of covariate exploration,[36] severe renal impairment for F was selected as a new covariate in the final model.

The final models of both PPK analyses were used to evaluate the impact of covariates, and the results are shown in Table 35. No marked differences in ritlecitinib exposure were observed based on any covariate.

The PPK analysis using the data from 4 clinical studies in healthy volunteers or AA patients indicated that the steady-state C_{max} increased approximately dose-proportionally from 10 to 800 mg QD, and the steady-state AUC_{tau} increased approximately dose-proportionally from 30 to 200 mg QD. Table 36 shows the pharmacokinetic parameters of ritlecitinib following administration of ritlecitinib 30, 50, or 200 mg QD in AA patients.

[33] Allometric scaling on CL/F and Q/F, and Vc/F and Vp/F, referenced to a 70 kg individual with exponents of 0.75 and 1, respectively.

[34] The potential covariates evaluated were patient type (AA/RA/UC/vitiligo/moderate hepatic impairment patients), age, sex, race (Asian/White/Black/Others/unknown), hematocrit, creatinine clearance, and hepatic function (AST, ALT, bilirubin, albumin) for CL/F, formulation (oral solution/tablet/proposed commercial capsule) for ka, and patient type (AA/RA/UC/vitiligo/moderate hepatic impairment patients) and formulation (oral solution/tablet/proposed commercial capsule) for F.

[35] Study B7981036 in healthy volunteers, Study B7981020 in subjects with renal impairment, and Studies B7981015 and B7981032 in AA patients

[36] The potential covariates evaluated were age (continuous or categorical variable: adolescent/adult), AA subtype (non-AT/AU, AT/AU), baseline SALT score, renal function (continuous variable: creatinine clearance or eGFR based on MDRD; categorical variable: severe/normal), geographical location (North America/Europe/Asia/Rest of world), and race (Asian/Black/White/Others/unknown) for CL/F, geographical location (North America/Europe/Asia/Rest of world) for ka, and renal function (categorical variable: severe/normal) and geographical location (North America/Europe/Asia/Rest of world) for F.

Table 35. Impact of covariates in the final model

Covariate		$C_{max, ss}$	$AUC_{tau, ss}$
AA patient[a)]		1.08	1.45
Severe renal impairment [a)]		1.41	1.47
Moderate hepatic impairment [b)]		1.30	1.35
High-fat meal[b)]		0.764	1.02
Capsule formulation[b)]		0.857	1.01
Body weight[a)]	38 kg [c)]	1.87	1.74
	47 kg [d)]	1.52	1.45
	101 kg [e)]	0.679	0.703

Ratio compared to the reference scenario (healthy volunteer, 70 kg, fasted, tablet) following ritlecitinib 50 mg QD
a) The impact of covariates was evaluated based on the PPK analysis using the data from 4 clinical studies in healthy volunteers or AA patients.
b) The impact of covariates was evaluated based on the PPK analysis using the data from 9 clinical studies in healthy volunteers or AA, UC, RA, or vitiligo patients.
c) The 5th percentile of Japanese adolescents (12-17 years) based on School Health Statistical Survey (2021)
d) The 5th percentile of the PPK analysis population in footnote a)
e) The 95th percentile of the PPK analysis population in footnote a)

Table 36. Final model-predicted pharmacokinetic parameters of ritlecitinib following multiple oral doses of ritlecitinib in AA patients

Dose (QD)	AUC_{tau} (μg·h/mL)	C_{avg} (ng/mL)	C_{max} (μg/mL)
30 mg	0.648 (75.9)	27.0 (75.9)	0.208 (38.4)
50 mg	1.25 (73.0)	52.0 (73.0)	0.370 (38.5)
200 mg	6.17 (62.6)	257 (62.6)	1.66 (36.2)

Geometric mean (Geometric CV%)

6.4 Exposure-response analyses (CTD 5.3.3.5.5, 5.3.3.5.8)

Using Severity of Alopecia Tool (SALT) scores obtained from Study B7931005 [see Section 7.1.1], Study B7981015 [see Section 7.2.1], and Study B7981032 [see Section 7.3.1] in AA patients and the averaged plasma concentration at steady-state (C_{avg}) based on the PPK analysis [see Section 6.3], an exposure-response analysis for efficacy was performed, which suggested the following points.

- The concentration at half maximum effect (EC_{50}) was 53.6 ng/mL, and given the steady-state C_{avg} in AA patients following multiple oral doses of ritlecitinib 50 mg or 30 mg QD (52.0 or 27.0 ng/mL, respectively, see Section 6.3), the efficacy of ritlecitinib 50 mg QD may be higher than that of ritlecitinib 30 mg QD.
- Based on the results of a longitudinal concentration-response analysis of the SALT score, the SALT ≤20 response rate over time was predicted, and the effect of a loading dose (ritlecitinib 200 mg QD for 4 weeks) was evaluated. While the 200 mg loading dose achieved the clinical onset of efficacy,[37)] 7 weeks faster for 30 mg QD (the clinical onset times were 6 weeks with the loading dose regimen vs. 13 weeks with the non-loading dose regimen) or 3 weeks faster for 50 mg QD (the clinical onset times were 6 weeks with the loading dose regimen vs. 9 weeks with the non-loading dose regimen), the SALT ≤20 response rate at Week 48 was similar between the loading and non-loading dose regimens.

Using the data on infections[38)] and rash obtained from 9 clinical studies in healthy volunteers or AA or vitiligo patients[39)] and time-weighted C_{avg}[40)] based on the PPK analysis [see Section 6.3], an exposure-response analysis for safety was performed. Table 37 shows the predicted incidences of infection and rash per 100 patient-years for multiple oral doses of ritlecitinib 30, 50, 100, or 200 mg QD. The incidence rate tended to increase with

[37)] The clinical onset of efficacy was defined as a significant difference from placebo based on the 95% CI for the placebo-adjusted response rate for SALT ≤20.
[38)] Moderate or severe infections or infections leading to treatment discontinuation
[39)] Studies B7981001, B7981003, B7981008, B7981022, and B7981036 in healthy volunteers, Studies B7931005, B7981015 and B7981032 in AA patients, and Study B7981019 in vitiligo patients
[40)] The cumulative AUC (predicted from the PPK analysis) divided by the time of the adverse event with respect to time of first dose

increasing exposure. In order to evaluate the effect of a loading dose (ritlecitinib 200 mg QD for 4 weeks), the cumulative incidences of infection and rash per 100 patient-years were simulated for placebo or ritlecitinib 50 mg QD with or without a loading dose. The results are shown in Figure 2, indicating that the risk of infection and rash is increased during the early phase of treatment with a loading dose.

Table 37. Predicted incidences of infection and rash per 100 patient-years for multiple oral doses of ritlecitinib based on exposure-response analysis

Dose (QD)	C_{avg} (ng/mL)	Infection	Rash
30 mg	27.0	11.0 [9.61, 12.7]	18.3 [16.5, 20.4]
50 mg	52.0	13.5 [11.9, 15.4]	24.1 [21.9, 26.6]
100 mg	119	19.8 [17.0, 23.0]	40.0 [36.3, 44.1]
200 mg	257	33.2 [25.9, 42.6]	80.1 [70.3, 91.2]

Geometric mean C_{ave}, Mean incidence per 100 patient-years [95% CI]

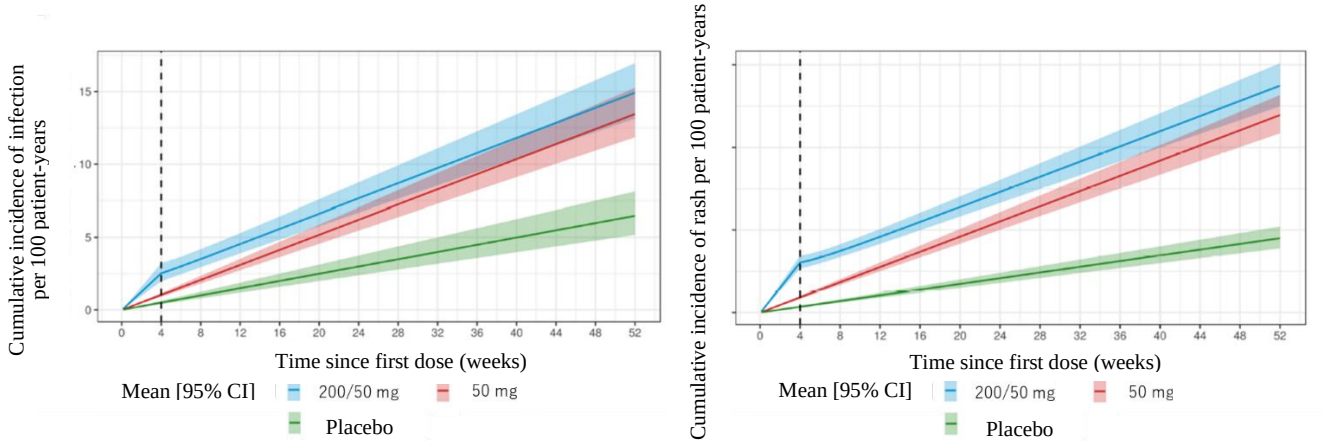


Figure 2. Predicted cumulative incidences of infection (left figure) and rash (right figure) per 100 patient-years over time for ritlecitinib 50 mg QD

6.R Outline of the review conducted by PMDA

PMDA's conclusion:

Based on the submitted data, there were no clinically meaningful differences in the pharmacokinetics of ritlecitinib between Japanese and non-Japanese subjects. Ritlecitinib should be contraindicated in patients with severe hepatic impairment, and no dose adjustment should be required in patients with hepatic impairment (excluding severe hepatic impairment) and patients with renal impairment. The applicant's explanation about precautionary statements about drug interactions and assessment of QT interval prolongation risk is acceptable. A conclusion on the appropriateness of the dosing regimen, including the need for a loading dose, will be made, taking account of the clinical study results [see Section 7.R.6].

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

The applicant submitted the efficacy and safety evaluation data, in the form of the results from 3 studies presented in Table 38. In the subsequent sections, the formulations of ritlecitinib are referred to as ritlecitinib, regardless of dosage form.

Table 38. Main efficacy and safety evaluation data

Phase	Study ID	Geographical location	Study population	Number. of subjects randomized	Dosing regimen[a)] (Once daily oral administration)	Main endpoints [Primary endpoint]
II	B7931005	Foreign	AA patients with extensive scalp hair loss (SALT score ≥50) (18-75 years of age)	(1) 48 (2) 24 (3) 47 (4) 23	(1) Ritlecitinib 200/50 mg [b)] (2) Placebo [matched to ritlecitinib] (3) Brepocitinib 60/30 mg [c)] (4) Placebo [matched to brepocitinib]	Efficacy and safety [Change from baseline in SALT score at Week 24]
II/III	B7981015	Global	AA patients with extensive scalp hair loss (SALT score ≥50) (≥12 years of age)	(1) 63 (2) 132 (3) 130 (4) 130 (5) 132 (6) 66 (7) 65	(1) Ritlecitinib 10 mg (2) Ritlecitinib 30 mg (3) Ritlecitinib 200/30 mg [d)] (4) Ritlecitinib 50 mg (5) Ritlecitinib 200/50 mg [b)] (6) Placebo→Ritlecitinib 50 mg [e)] (7) Placebo → Ritlecitinib 200/50 mg [f)]	Efficacy and safety [SALT ≤20 response rate at Week 24]
III	B7981032	Global	(1) Subjects who completed Study B7931005 or B7981015 (≥34 weeks) (2) AA patients with extensive scalp hair loss (SALT score ≥25[g)]) (≥12 years of age)	(1) 603 (2) 449	(1) Ritlecitinib 50 mg (2) Ritlecitinib 200/50 mg [b)]	Safety and efficacy

a) Dosing regimens during the double-blind period for Study B7931005. b) 200 mg for the first 4 weeks then 50 mg. c) 60 mg for the first 4 weeks then 30 mg. d) 200 mg for the first 4 weeks then 30 mg. e) Placebo for 24 weeks followed by 50 mg. f) Placebo for 24 weeks followed by 200 mg for 4 weeks then 50 mg. g) SALT score ≥50 for subjects aged ≥12 and <18 years enrolled after the Protocol Amendment 4 [amended as of [redacted], 20[redacted]]

7.1 Phase II study

7.1.1 Foreign study in AA patients with extensive scalp hair loss (CTD 5.3.5.1.1, Study B7931005 [December 2016 to May 2019])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in the US, Canada, and Australia to evaluate the efficacy and safety of ritlecitinib and brepocitinib in AA patients with extensive scalp hair loss (Table 39, target sample size, 132 subjects [44 in the ritlecitinib 200/50 mg group, 44 in the brepocitinib 60/30 mg group, 44 in the placebo group [placebo matched to ritlecitinib or brepocitinib, 22 subjects each][41)]).

The study consisted of a double-blind period (24 weeks), an extension period (single-blind,[42)] up to 48 weeks), and a crossover period (open-label, 24 weeks), and Figure 3 shows the study design and the dosing regimens of study drug during these treatment periods.

41) The sample size was based on the primary endpoint of the change from baseline in SALT score at Week 24. Using a between-group comparison at Week 24 for brepocitinib versus placebo and ritlecitinib 200/50 mg versus placebo, 30 subjects in each group would provide approximately 89.9% power for the primary endpoint, assuming a difference of 20 between each active treatment and placebo and a standard deviation of 32.43 in each group, at a one-sided significance level of 2.5%. Assuming approximately a 30% dropout rate, the target sample size was 132 (44 in each group).

42) Sponsor open, investigator open, and subject blind

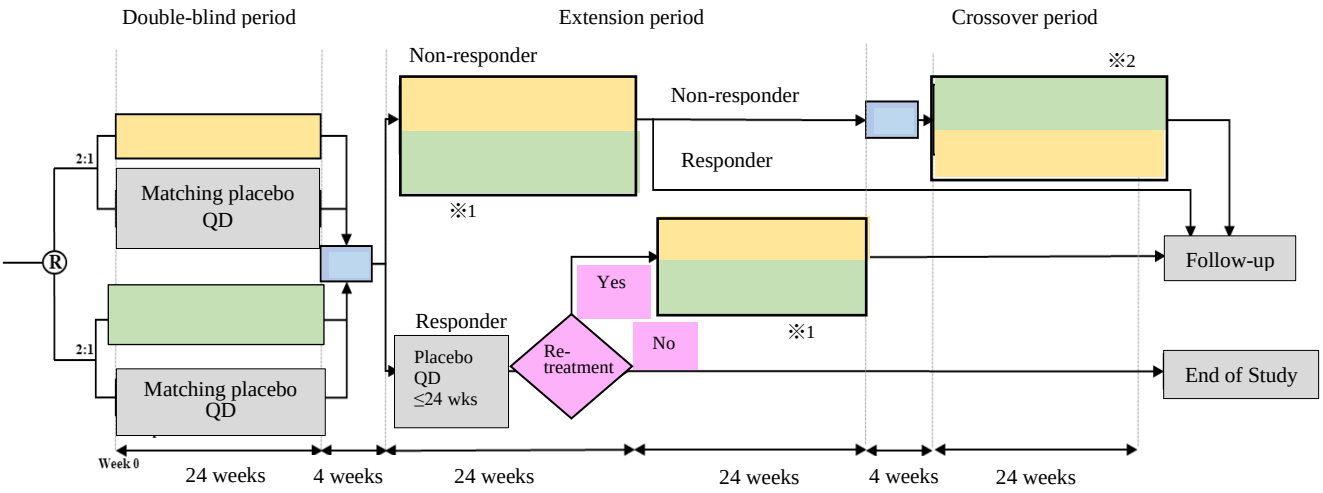


Figure 3. Design of Study B7931005

Responders: Subjects achieving a ≥30% improvement in SALT score from baseline
R: Randomization
Subjects who started with placebo in the extension period were re-treated with active treatment if [% improvement from baseline in SALT score at the end of double-blind period] − [% improvement from baseline in SALT score at visit] >30%.

Ritlecitinib 200/50 mg QD (Induction 4 weeks/Maintenance 20 weeks)
Brepocitinib 60/30 mg QD (Induction 4 weeks/Maintenance 20 weeks)
Drug holiday
※1: The same active treatment received or assigned during the double-blind period
※2: Crossed over to the other active treatment

Table 39. Key inclusion and exclusion criteria

Key inclusion criteria
1. Patients who met all of the following AA criteria
   · SALT score ≥50 at both the screening and baseline visits without evidence of hair regrowth within the previous 6 months
   · Current episode of fixed hair loss ≤7 years
2. 18-75 years of age

Key exclusion criteria
1. Other types of alopecia (including, but not limited to traction and scarring alopecia)
2. Active forms of other inflammatory skin diseases or evidence of skin conditions (e.g., psoriasis, seborrhoeic dermatitis, systemic lupus erythematosus) that in the opinion of the investigator would interfere with evaluation of AA or response to treatment
3. Received any of the following treatment regimens specified in the timeframes outlined below:
   · Any cell-depleting agents including but not limited to rituximab (within 6 months of baseline, or 5 half lives, or until lymphocyte count returned to normal, whichever was longer)
   · JAK inhibitors (within 12 weeks of baseline)
   · Biologics (within 12 weeks of baseline or 5 half lives, whichever was longer)
   · Systemic treatments that could affect AA (within 8 weeks of baseline or 5 half lives, whichever was longer)
   · Oral immunosuppressants [e.g., cyclosporine A, MTX, MMF] (within 8 weeks of baseline or 5 half lives, whichever was longer)
   · Oral steroids, intralesional steroid injection (within 8 weeks of baseline or 5 half lives, whichever was longer)
   · Ultraviolet phototherapy (within 4 weeks of baseline)
   · Topical treatments on areas under assessment [e.g., TCS] (within 2 weeks of baseline)

The full analysis set (FAS) included 142 randomized subjects (48 in the ritlecitinib 200/50 mg group, 47 in the brepocitinib 60/30 mg group, 47 in the placebo group[43)]), and the FAS was used as the efficacy analysis population. All subjects received at least 1 dose of study drug and were included in the safety analysis set.

[43)] 24 subjects for placebo matched to ritlecitinib, 23 subjects for placebo matched to brepocitinib

During the double-blind period, the discontinuation rates[44)] were 6.3% (3 of 48 subjects) in the ritlecitinib 200/50 mg group, 25.5% (12 of 47 subjects) in the brepocitinib 60/30 mg group, and 27.7% (13 of 47 subjects) in the placebo group, and the main reasons for discontinuations were consent withdrawal (none in the ritlecitinib 200/50 mg group, 6.4% [3 of 47 subjects] in the brepocitinib 60/30 mg group, 17.0% [8 of 47 subjects] in the placebo group) and adverse events (4.2% [2 of 48 subjects] in the ritlecitinib 200/50 mg group, 8.5% [4 of 47 subjects] in the brepocitinib 60/30 mg group, 4.3% [2 of 47 subjects] in the placebo group).

Table 40 shows the primary efficacy endpoint during the double-blind period of the change from baseline in SALT score [for the definition, see Section 10] at Week 24, and pairwise comparisons between placebo and ritlecitinib 200/50 mg and between placebo and brepocitinib 60/30 mg showed statistically significant differences.

Table 40. Change from baseline in SALT score at Week 24 (FAS, Observed case [OC], Double-blind period)

	Ritlecitinib 200/50 mg (N = 48)	Brepocitinib 60/30 mg (N = 47)	Placebo (N = 47)
Baseline	89.4 ± 15.8 (48)	86.4 ± 18.1 (47)	88.4 ± 18.1 (47)
Week 24	54.4 ± 40.3 (44)	34.0 ± 36.7 (40)	87.4 ± 20.1 (35)
Change from baseline [95% CI]	32.5 [24.0, 41.1]	50.6 [41.7, 59.5]	1.4 [-7.9, 10.3]
Difference from placebo [95% CI][a), b)]	31.1 [18.8, 43.5]	49.2 [36.6, 61.7]	

Mean ± SD (N) for score at each time point, Least-squares mean for change from baseline
Change from baseline was defined as the baseline score minus the score at a specific visit.
a) A MMRM model with treatment, visit, baseline SALT score, treatment-by-visit interaction, and treatment-by-baseline SALT score interaction as covariates. The MMRM model assumed an unstructured variance-covariance matrix to estimate the correlation between repeated measures.
b) The Hochberg procedure was used to adjust for multiplicity in hypothesis testing. If the lower bounds of the two-sided 95% CIs for between-group comparisons (each active treatment vs. placebo) were both above 0, the superiority of both active treatments to placebo was to be demonstrated. If the lower bound of the two-sided 95% CI for one between-group comparison was not above 0, and the lower bound of the two-sided 97.5% CI for the other between-group comparison was above 0, the superiority of this active treatment only to placebo was to be demonstrated.

During the double-blind period, the incidences of adverse events were 66.7% (32 of 48 subjects) in the ritlecitinib 200/50 mg group, 76.6% (36 of 47 subjects) in the brepocitinib 60/30 mg group, and 74.5% (35 of 47 subjects) in the placebo group, and the main events are shown in Table 41.

No deaths were reported.

Serious adverse events occurred in 4.3% (2 of 47) of subjects in the brepocitinib 60/30 mg group [rhabdomyolysis (2 subjects)]), but a causal relationship to study drug was denied for both cases.

The incidences of adverse events leading to study or treatment discontinuation were 4.2% (2 of 48 subjects) in the ritlecitinib 200/50 mg group, 8.5% (4 of 47 subjects) in the brepocitinib 60/30 mg group, and 6.4% (3 of 47 subjects) in the placebo group.

The incidences of adverse drug reactions were 27.1% (13 of 48 subjects) in the ritlecitinib 200/50 mg group, 42.6% (20 of 47 subjects) in the brepocitinib 60/30 mg group, and 29.8% (14 of 47 subjects) in the placebo group.

[44)] The number of subjects who discontinued treatment and the reasons are listed for Study B7931005.

Table 41. Adverse events occurring in ≥5% of subjects in any group (Double-blind period, Safety analysis set)

Event term	Ritlecitinib 200/50 mg (N = 48)	Brepocitinib 60/30 mg (N = 47)	Placebo (N = 47)
Nasopharyngitis	6 (12.5)	4 (8.5)	6 (12.8)
Headache	6 (12.5)	4 (8.5)	5 (10.6)
Acne	5 (10.4)	5 (10.6)	2 (4.3)
Upper respiratory tract infection	4 (8.3)	11 (23.4)	5 (10.6)
Diarrhoea	4 (8.3)	1 (2.1)	3 (6.4)
Nausea	3 (6.3)	3 (6.4)	5 (10.6)
Folliculitis	3 (6.3)	1 (2.1)	1 (2.1)
Atopic dermatitis	3 (6.3)	1 (2.1)	0
Viral upper respiratory tract infection	2 (4.2)	3 (6.4)	0
Sinusitis	0	3 (6.4)	2 (4.3)
Neutrophil count decreased	0	3 (6.4)	1 (2.1)
Oropharyngeal pain	0	3 (6.4)	0
Abdominal pain	0	3 (6.4)	0
Abdominal discomfort	0	1 (2.1)	4 (8.5)
Fatigue	0	0	3 (6.4)

n (%) MedDRA ver.22.0 (MedDRA/J ver.23.1)

7.2 Phase II/III study

7.2.1 Global study in AA patients with extensive scalp hair loss (CTD 5.3.5.1.2, Study B7981015 [December 2018 to June 2021])

A placebo-controlled, randomized, double-blind, parallel-group, dose-ranging study was conducted in 18 countries or regions including Japan, the US, Canada, and China to confirm the efficacy of ritlecitinib and investigate its safety in AA patients with extensive scalp hair loss (Table 42, target sample size, 660 subjects [60 in the 10 mg group, 120 in the 30 mg group, 120 in the 200/30 mg group, 120 in the 50 mg group, 120 in the 200/50 mg group, 60 in the placebo→50 mg group, 60 in the placebo→200/50 mg group][45]).

The study consisted of a placebo-controlled period (double-blind, 24 weeks) and an extension period (double-blind, 24 weeks), and Figure 4 shows the study design and the dosing regimens of study drug during these treatment periods.

[45] A sample size of 120 subjects for the 200/50 mg group would provide more than 90% power to demonstrate that the 200 mg/50 mg group is superior to placebo by a difference of 24% in the proportion of subjects achieving the primary endpoint (SALT score ≤20 at Week 24), assuming a placebo response rate of no more than 5%, at a two-sided significance level of 5%. A sample size of 120 subjects per group also for the 30 mg, 200/30 mg, and 50 mg groups was chosen. This sample size would provide >90% power also at a more stringent significance level (two-sided, 0.125%), in view of a single, pivotal, clinical trial. The 10 mg group was included only to support the characterization of the exposure response, and a sample size of 60 subjects was chosen. Based on the above, the total target sample size for the study was 660 subjects.

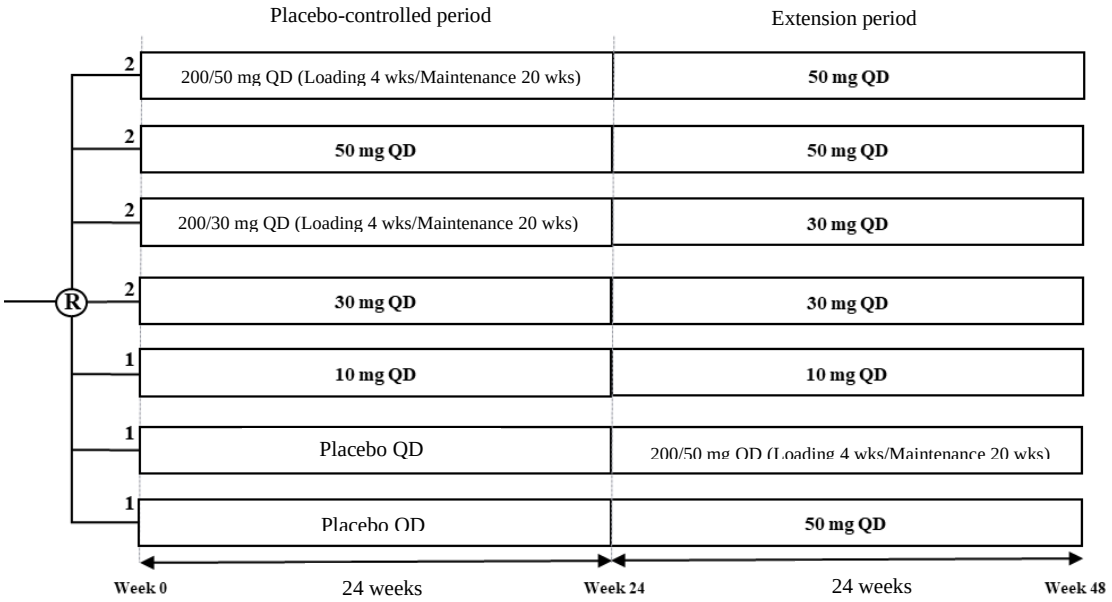


Figure 4. Design of Study B7981015
(The numbers to the left of the treatment groups are the randomization ratios.
The doses of ritlecitinib are listed. R: Randomization)

Table 42. Key inclusion and exclusion criteria

Key inclusion criteria 1. Patients who met all of the following AA criteria · SALT score ≥50 at both the screening and baseline visits without evidence of terminal hair regrowth within the previous 6 months · Current episode of hair loss ≤10 years 2. ≥12 years of age Key exclusion criteria 1. Other types of alopecia (including, but not limited to androgenetic, traction, and scarring alopecia, telogen effluvium) 2. Other scalp disease that may impact AA assessment (e.g., scalp psoriasis, dermatitis) 3. Active systemic diseases that may cause hair loss (e.g., systemic lupus erythematosus, thyroiditis, systemic sclerosis, lichen planus) 4. Hearing loss with progression over the previous 5 years, or sudden hearing loss, or middle or inner ear disease such as otitis media, cholesteatoma, Meniere's disease, and labyrinthitis, or other auditory condition that was considered acute, fluctuating or progressive 5. Previous use of any JAK inhibitor or any non-B-cell selective lymphocyte-depleting agent (e.g., alemtuzumab) 6. Received any of the following treatment regimens specified in the timeframes outlined below: · Any B-cell-depleting agents including but not limited to rituximab (within 6 months of baseline, or 5 half lives, or until lymphocyte count returned to normal, whichever was longer) · Immunomodulatory biologic agents (within 12 weeks of baseline or 5 half lives, whichever was longer) · Systemic treatments that could affect AA (within 8 weeks of baseline or 5 half lives, whichever was longer) · Immunosuppressants [e.g., cyclosporine A, MTX, MMF] (within 8 weeks of baseline or 5 half lives, whichever was longer) · Oral steroids, intralesional steroid injection, 5α-reductase inhibitors [e.g., finasteride] (within 8 weeks of baseline or 5 half lives, whichever was longer) · Ultraviolet phototherapy, contact immunotherapy (within 4 weeks of baseline) · Topical treatments on areas under assessment [e.g., TCS] (within 2 weeks of baseline)

The FAS included 718 randomized subjects (63 in the 10 mg group, 132 in the 30 mg group, 130 in the 200/30 mg group, 130 in the 50 mg group, 132 in the 200/50 mg group, 131 in the placebo group), and the FAS was used as the efficacy analysis population. Among the FAS, 715 subjects who received at least 1 dose of study drug (62 in the 10 mg group, 132 in the 30 mg group, 129 in the 200/30 mg group, 130 in the 50 mg group, 131 in the 200/50 mg group, 131 in the placebo group) were included in the safety analysis set.

The discontinuation rates during the placebo-controlled period were 7.9% (5 of 63 subjects) in the 10 mg group, 11.4% (15 of 132 subjects) in the 30 mg group, 4.6% (6 of 130 subjects) in the 200/30 mg group, 6.9% (9 of

130 subjects) in the 50 mg group, 7.6% (10 of 132 subjects) in the 200/50 mg group, and 5.3% (7 of 131 subjects) in the placebo group, and the main reasons for discontinuations were consent withdrawal (1.6% [1 of 63 subjects] in the 10 mg group, 3.0% [4 of 132 subjects] in the 30 mg group, 3.1% [4 of 130 subjects] in the 200/30 mg group, 3.1% [4 of 130 subjects] in the 50 mg group, 3.0% [4 of 132 subjects] in the 200/50 mg group, 2.3% [3 of 131 subjects] in the placebo group) and adverse events (3.2% [2 of 63 subjects] in the 10 mg group, 3.0% [4 of 132 subjects] in the 30 mg group, none in the 200/30 mg group, 1.5% [2 of 130 subjects] in the 50 mg group, 2.3% [3 of 132 subjects] in the 200/50 mg group, 0.8% [1 of 131 subjects] in the placebo group).

Among the FAS or the safety analysis set, there were 47 subjects in the Japanese subgroup (5 in the 10 mg group, 8 in the 30 mg group, 8 in the 200/30 mg group, 9 in the 50 mg group, 8 in the 200/50 mg group, 9 in the placebo group).

In the Japanese subgroup, the discontinuation rates during the placebo-controlled period were 20.0% (1 of 5 subjects) in the 10 mg group and 12.5% (1 of 8 subjects) in the 200/50 mg group, and the reasons for discontinuations were both adverse events.

The primary efficacy endpoint of the proportion of subjects achieving a SALT score of ≤20 (the SALT ≤20 response rate) at Week 24 is shown in Table 43. Excluding the 10 mg group, which was included only to support the characterization of the exposure response, pairwise comparisons between ritlecitinib and placebo showed statistically significant differences, demonstrating the superiority of ritlecitinib (excluding the 10 mg group) to placebo. The results in the Japanese subgroup are shown in Table 43.

Table 43. Results of primary efficacy endpoint (FAS, Non-responder imputation [NRI][a])

Endpoint	10 mg (N = 63)	30 mg (N = 132)	200/30 mg (N = 130)	50 mg (N = 130)	200/50 mg (N = 132)	Placebo (N = 131)
Overall population						
SALT ≤20 response rate at Week 24	1.7 (1/59)	14.3 (17/119)	22.3 (27/121)	23.4 (29/124)	30.7 (38/124)	1.5 (2/130)
Difference from placebo [99.875% CI][b] *P*-value[c]	0.2 [−8.6, 16.4] —	12.8 [2.4, 26.2] 0.000154	20.8 [9.1, 35.2] <0.000001	21.9 [10.1, 36.2] <0.000001	29.1 [16.3, 43.8] <0.000001	
Japanese subgroup						
SALT ≤20 response rate at Week 24	0 (0/5)	12.5 (1/8)	50.0 (4/8)	11.1 (1/9)	25.0 (2/8)	0 (0/9)
Difference from placebo [99.875% CI][b]	—	12.5 [−47.4, 67.6]	50.0 [−21.9, 88.1]	11.1 [−48.0, 64.2]	25.0 [−39.3, 75.6]	

% (n); —, Not applicable or not calculated
a) Subjects with missing data due to COVID-19 related reasons were excluded from the analysis, and subjects with missing data due to other reasons were imputed as nonresponders.
b) Miettinen and Nurminen method
c) A two-sided significance level of 0.125%; Farrington and Manning method; Graphical approach was used to adjust for multiplicity in hypothesis testing [for the details, see Section 10].

During the placebo-controlled period, the incidences of adverse events were 69.4% (43 of 62 subjects) in the 10 mg group, 72.7% (96 of 132 subjects) in the 30 mg group, 70.5% (91 of 129 subjects) in the 200/30 mg group, 75.4% (98 of 130 subjects) in the 50 mg group, 73.3% (96 of 131 subjects) in the 200/50 mg group, and 71.0% (93 of 131 subjects) in the placebo group, and the main events are shown in Table 44.

No deaths were reported.

Serious adverse events occurred in 3.2% (2 of 62) of subjects in the 10 mg group [suicidal behaviour; and eczema (1 subject each)]), 0.8% (1 of 132) of subjects in the 30 mg group [diverticulitis], 3.1% (4 of 131) of subjects in the 200/50 mg group [invasive lobular breast carcinoma; sepsis and empyema; appendicitis; and spontaneous abortion (1 subject each)], and 2.3% (3 of 131) of subjects in the placebo group [conversion disorder; spontaneous abortion; and heavy menstrual bleeding (1 subject each)]), and a causal relationship to study drug could not be ruled out for eczema in the 10 mg group and sepsis and empyema in the 200/50 mg group.

Adverse events leading to study or treatment discontinuation occurred in 3.2% (2 of 62) of subjects in the 10 mg group, 3.0% (4 of 132) of subjects in the 30 mg group, 1.5% (2 of 130) of subjects in the 50 mg group, 3.1% (4 of 131) of subjects in the 200/50 mg group, and 1.5% (2 of 131) of subjects in the placebo group.

The incidences of adverse drug reactions were 30.6% (19 of 62 subjects) in the 10 mg group, 34.1% (45 of 132 subjects) in the 30 mg group, 35.7% (46 of 129 subjects) in the 200/30 mg group, 36.2% (47 of 130 subjects) in the 50 mg group, 38.2% (50 of 131 subjects) in the 200/50 mg group, and 37.4% (49 of 131 subjects) in the placebo group.

Table 44. Adverse events occurring in ≥5% of subjects in any group (Placebo-controlled period, Safety analysis set)

Event term	10 mg (N = 62)	30 mg (N = 132)	200/30 mg (N = 129)	50 mg (N = 130)	200/50 mg (N = 131)	Placebo (N = 131)
Upper respiratory tract infection	2 (3.2)	11 (8.3)	10 (7.8)	8 (6.2)	16 (12.2)	10 (7.6)
Nasopharyngitis	6 (9.7)	16 (12.1)	18 (14.0)	13 (10.0)	15 (11.5)	8 (6.1)
Headache	11 (17.7)	20 (15.2)	10 (7.8)	12 (9.2)	11 (8.4)	11 (8.4)
Urticaria	1 (1.6)	4 (3.0)	6 (4.7)	6 (4.6)	9 (6.9)	3 (2.3)
Folliculitis	2 (3.2)	3 (2.3)	8 (6.2)	4 (3.1)	9 (6.9)	3 (2.3)
Diarrhoea	0	6 (4.5)	4 (3.1)	12 (9.2)	8 (6.1)	5 (3.8)
Nausea	3 (4.8)	10 (7.6)	2 (1.6)	3 (2.3)	8 (6.1)	7 (5.3)
Dizziness	1 (1.6)	3 (2.3)	7 (5.4)	3 (2.3)	7 (5.3)	1 (0.8)
Urinary tract infection	0	5 (3.8)	2 (1.6)	0	7 (5.3)	2 (1.5)
Acne	3 (4.8)	7 (5.3)	7 (5.4)	8 (6.2)	6 (4.6)	6 (4.6)
Myalgia	5 (8.1)	5 (3.8)	1 (0.8)	1 (0.8)	4 (3.1)	1 (0.8)

n (%) MedDRA ver.24.0 (MedDRA/J ver.24.0)

In the Japanese subgroup, the incidences of adverse events during the placebo-controlled period were 60.0% (3 of 5 subjects) in the 10 mg group, 87.5% (7 of 8 subjects) in the 30 mg group, 100% (8 of 8 subjects) in the 200/30 mg group, 55.6% (5 of 9 subjects) in the 50 mg group, 62.5% (5 of 8 subjects) in the 200/50 mg group, and 66.7% (6 of 9 subjects) in the placebo group, and the main events are shown in Table 45.

There were no deaths or serious adverse events.

Adverse events leading to study or treatment discontinuation occurred in 20.0% (1 of 5) of subjects in the 10 mg group and 12.5% (1 of 8) of subjects in the 200/50 mg group.

The incidences of adverse drug reactions were 20.0% (1 of 5 subjects) in the 10 mg group, 25.0% (2 of 8 subjects) in the 30 mg group, 50.0% (4 of 8 subjects) in the 200/30 mg group, 55.6% (5 of 9 subjects) in the 50 mg group, 37.5% (3 of 8 subjects) in the 200/50 mg group, and 22.2% (2 of 9 subjects) in the placebo group.

Table 45. Adverse events occurring in ≥2 subjects in any group (Placebo-controlled period, Safety analysis set, Japanese subgroup)

Event term	10 mg (N = 5)	30 mg (N = 8)	200/30 mg (N = 8)	50 mg (N = 9)	200/50 mg (N = 8)	Placebo (N = 9)
Nasopharyngitis	2 (40.0)	1 (12.5)	4 (50.0)	1 (11.1)	2 (25.0)	1 (11.1)
Urticaria	0	2 (25.0)	2 (25.0)	0	1 (12.5)	1 (11.1)
Lymphocyte count decreased	0	0	2 (25.0)	0	1 (12.5)	1 (11.1)
Stomatitis	0	0	0	2 (22.2)	0	0
Pharyngitis	0	0	2 (25.0)	0	0	1 (11.1)

n (%) MedDRA ver.24.0 (MedDRA/J ver.24.0)

During the entire study period, the incidences of adverse events were 75.8% (47 of 62 subjects) in the 10 mg group, 80.3% (106 of 132 subjects) in the 30 mg group, 81.4% (105 of 129 subjects) in the 200/30 mg group, 84.6% (110 of 130 subjects) in the 50 mg group, 82.4% (108 of 131 subjects) in the 200/50 mg group, 86.4% (57 of 66 subjects) in the placebo→50 mg group, and 83.1% (54 of 65 subjects) in the placebo→200/50 mg group, and the main events are shown in Table 46.

No deaths were reported.

Serious adverse events occurred in 3.2% (2 of 62) of subjects in the 10 mg group (suicidal behaviour; and eczema [1 subject each]), 0.8% (1 of 132) of subjects in the 30 mg group (diverticulitis), 1.6% (2 of 129) of subjects in the 200/30 mg group (chemical poisoning and suicidal behaviour; and appendicitis [1 subject each]), 1.5% (2 of 130) of subjects in the 50 mg group (pulmonary embolism; and breast cancer [1 subject each]), 3.1% (4 of 131) of subjects in the 200/50 mg group (invasive lobular breast carcinoma; sepsis and empyema; appendicitis; and spontaneous abortion [1 subject each]), and 4.5% (3 of 66) of subjects in the placebo→50 mg group (conversion disorder; spontaneous abortion; and heavy menstrual bleeding [1 subject each]), and a causal relationship to study drug could not be ruled out for eczema in the 10 mg group, breast cancer in the 50 mg group, and sepsis and empyema in the 200/50 mg group.

Adverse events leading to study or treatment discontinuation occurred in 3.2% (2 of 62) of subjects in the 10 mg group, 4.5% (6 of 132) of subjects in the 30 mg group, 1.6% (2 of 129) of subjects in the 200/30 mg group, 3.1% (4 of 130) of subjects in the 50 mg group, 3.1% (4 of 131) of subjects in the 200/50 mg group, and 6.1% (4 of 66) of subjects in the placebo→50 mg group.

The incidences of adverse drug reactions were 38.7% (24 of 62 subjects) in the 10 mg group, 39.4% (52 of 132 subjects) in the 30 mg group, 42.6% (55 of 129 subjects) in the 200/30 mg group, 46.2% (60 of 130 subjects) in the 50 mg group, 42.7% (56 of 131 subjects) in the 200/50 mg group, 54.5% (36 of 66 subjects) in the placebo→50 mg group, and 49.2% (32 of 65 subjects) in the placebo→200/50 mg group.

Table 46. Adverse events occurring in ≥5% of subjects in any group (Entire study period, Safety analysis set)

Event term	10 mg (N = 62)	30 mg (N = 132)	200/30 mg (N = 129)	50 mg (N = 130)	200/50 mg (N = 131)	Placebo→ 50 mg (N = 66)	Placebo→ 200/50 mg (N = 65)
Nasopharyngitis	7 (11.3)	21 (15.9)	21 (16.3)	18 (13.8)	19 (14.5)	4 (6.1)	7 (10.8)
Upper respiratory tract infection	2 (3.2)	16 (12.1)	12 (9.3)	11 (8.5)	18 (13.7)	6 (9.1)	7 (10.8)
Headache	12 (19.4)	24 (18.2)	14 (10.9)	16 (12.3)	17 (13.0)	8 (12.1)	8 (12.3)
Folliculitis	4 (6.5)	5 (3.8)	11 (8.5)	8 (6.2)	11 (8.4)	4 (6.1)	4 (6.2)
Nausea	3 (4.8)	12 (9.1)	3 (2.3)	3 (2.3)	11 (8.4)	1 (1.5)	8 (12.3)
Urinary tract infection	0	5 (3.8)	3 (2.3)	1 (0.8)	11 (8.4)	2 (3.0)	4 (6.2)
Diarrhoea	0	8 (6.1)	4 (3.1)	12 (9.2)	9 (6.9)	1 (1.5)	4 (6.2)
Urticaria	1 (1.6)	5 (3.8)	9 (7.0)	7 (5.4)	9 (6.9)	4 (6.1)	4 (6.2)
Dizziness	1 (1.6)	8 (6.1)	8 (6.2)	4 (3.1)	9 (6.9)	2 (3.0)	0
Influenza	3 (4.8)	3 (2.3)	1 (0.8)	3 (2.3)	8 (6.1)	0	1 (1.5)
Acne	3 (4.8)	12 (9.1)	10 (7.8)	12 (9.2)	6 (4.6)	8 (12.1)	5 (7.7)
Myalgia	6 (9.7)	5 (3.8)	3 (2.3)	3 (2.3)	6 (4.6)	1 (1.5)	0
Cough	0	3 (2.3)	0	3 (2.3)	6 (4.6)	2 (3.0)	4 (6.2)
Vomiting	1 (1.6)	5 (3.8)	7 (5.4)	2 (1.5)	6 (4.6)	3 (4.5)	2 (3.1)
Rash	0	1 (0.8)	3 (2.3)	7 (5.4)	5 (3.8)	1 (1.5)	1 (1.5)
Fatigue	4 (6.5)	6 (4.5)	6 (4.7)	6 (4.6)	4 (3.1)	2 (3.0)	3 (4.6)
Oropharyngeal pain	0	1 (0.8)	6 (4.7)	6 (4.6)	4 (3.1)	5 (7.6)	2 (3.1)
Arthralgia	2 (3.2)	4 (3.0)	5 (3.9)	2 (1.5)	4 (3.1)	6 (9.1)	2 (3.1)
Pruritus	1 (1.6)	3 (2.3)	7 (5.4)	1 (0.8)	4 (3.1)	1 (1.5)	1 (1.5)
Insomnia	1 (1.6)	1 (0.8)	0	2 (1.5)	3 (2.3)	4 (6.1)	1 (1.5)
Upper abdominal pain	0	3 (2.3)	5 (3.9)	5 (3.8)	1 (0.8)	0	4 (6.2)
Nasal congestion	4 (6.5)	3 (2.3)	1 (0.8)	2 (1.5)	1 (0.8)	1 (1.5)	1 (1.5)
Constipation	1 (1.6)	7 (5.3)	0	1 (0.8)	1 (0.8)	0	1 (1.5)

n (%); Including events occurring while on placebo. MedDRA ver.24.0 (MedDRA/J ver.24.0)

In the Japanese subgroup, the incidences of adverse events during the entire study period were 60.0% (3 of 5 subjects) in the 10 mg group, 87.5% (7 of 8 subjects) in the 30 mg group, 100% (8 of 8 subjects) in the 200/30 mg group, 77.8% (7 of 9 subjects) in the 50 mg group, 87.5% (7 of 8 subjects) in the 200/50 mg group, 66.7% (4 of 6 subjects) in the placebo→50 mg group, and 100% (3 of 3 subjects) in the placebo→200/50 mg group, and the main events are shown in Table 47.

There were no deaths or serious adverse events.

Adverse events leading to study or treatment discontinuation occurred in 20.0% (1 of 5) of subjects in the 10 mg group and 12.5% (1 of 8) of subjects in the 200/50 mg group.

The incidences of adverse drug reactions were 20.0% (1 of 5 subjects) in the 10 mg group, 37.5% (3 of 8 subjects) in the 30 mg group, 50.0% (4 of 8 subjects) in the 200/30 mg group, 77.8% (7 of 9 subjects) in the 50 mg group, 50.0% (4 of 8 subjects) in the 200/50 mg group, 50.0% (3 of 6 subjects) in the placebo→50 mg group, and 33.3% (1 of 3 subjects) in the placebo→200/50 mg group.

Table 47. Adverse events occurring in ≥2 subjects in any group (Entire study period, Safety analysis set, Japanese subgroup)

Event term	10 mg (N = 5)	30 mg (N = 8)	200/30 mg (N = 8)	50 mg (N = 9)	200/50 mg (N = 8)	Placebo→ 50 mg (N = 6)	Placebo→ 200/50 mg (N = 3)
Nasopharyngitis	2 (40.0)	1 (12.5)	4 (50.0)	1 (11.1)	3 (37.5)	0	2 (66.7)
Urticaria	0	3 (37.5)	2 (25.0)	0	1 (12.5)	2 (33.3)	0
Lymphocyte count decreased	0	0	2 (25.0)	0	1 (12.5)	1 (16.7)	0
Folliculitis	1 (20.0)	2 (25.0)	1 (12.5)	2 (22.2)	0	0	0
Acne	0	1 (12.5)	0	2 (22.2)	0	1 (16.7)	0
Stomatitis	0	0	0	2 (22.2)	0	0	0
Pharyngitis	0	0	2 (25.0)	0	0	1 (16.7)	0

n (%); Including events occurring while on placebo. MedDRA ver.24.0 (MedDRA/J ver.24.0)

7.3 Phase III study

7.3.1 Long-term study (CTD 5.3.5.2.1, Study B7981032 [ongoing since July 2019 (February 2022 data cutoff)])

An open-label, uncontrolled study was conducted in 17 countries or regions including Japan, the US, Canada, and Australia to evaluate the long-term safety and efficacy of ritlecitinib in patients with AA including subjects who had completed the prior studies (Study B7931005 or B7981015 [≥34 weeks]) (Table 48, target sample size, 960 subjects[46)]).

Table 48. Key inclusion and exclusion criteria (De novo subjects)

Key inclusion criteria
1. Patients who met all of the following AA criteria
   · SALT score ≥25 due to AA (SALT score ≥50 for subjects aged ≥12 and <18 years enrolled after the Protocol Amendment 4 [amended as of [redacted], 20[redacted]]) at both the screening and baseline visits which, in the opinion of the investigator, was appropriate for systemic therapy, without evidence of terminal hair regrowth within the previous 6 months
   · Current episode of hair loss ≤10 years
2. ≥12 years of age

Key exclusion criteria
1. Other types of alopecia (including, but not limited to traction and scarring alopecia, telogen effluvium) (Androgenetic alopecia coexistent with AA was allowed provided that the inclusion criteria were met.)
2. Other scalp disease that may impact AA assessment (e.g., scalp psoriasis, dermatitis)
3. Active systemic diseases that may cause hair loss (e.g., systemic lupus erythematosus, thyroiditis, systemic sclerosis, lichen planus)
4. Hearing loss with progression over the previous 5 years, or sudden hearing loss, or middle or inner ear disease such as otitis media, cholesteatoma, Meniere's disease, and labyrinthitis, or other auditory condition that was considered acute, fluctuating or progressive
5. Previous use of any non-B-cell selective lymphocyte-depleting agent (e.g., alemtuzumab)
6. Received any of the following treatment regimens specified in the timeframes outlined below:
   · Any B-cell-depleting agents including but not limited to rituximab (within 6 months of baseline, or 5 half lives, or until lymphocyte count returned to normal, whichever was longer)
   · JAK inhibitors, immunomodulatory biologic agents (within 12 weeks of baseline or 5 half lives, whichever was longer)
   · Systemic treatments that could affect AA (within 8 weeks of baseline or 5 half lives, whichever was longer)
   · Immunosuppressants [e.g., cyclosporine A, MTX, MMF] (within 8 weeks of baseline or 5 half lives, whichever was longer)
   · Oral steroids, intralesional steroid injection, oral minoxidil (within 8 weeks of baseline or 5 half lives, whichever was longer)
   · Ultraviolet phototherapy, contact immunotherapy (within 4 weeks of baseline)
   · Topical treatments on areas under assessment [e.g., TCS] (within 2 weeks of baseline)

Roll-over subjects (subjects rolling over from the prior studies) were to orally receive ritlecitinib 50 mg QD, and de novo subjects were to orally receive ritlecitinib 200 mg for the first 4 weeks followed by 50 mg QD. Subjects aged ≥12 and <18 years were allowed to continue to receive study drug if they met the study continuation criteria.[47)]

[46)] The number of de novo subjects was approximately 450, which was to be adjusted according to the number of subjects rolling over from the prior studies.

[47)] The study continuation criteria for adolescents were added in the Protocol Amendment 4 [amened as of [redacted], 20[redacted]] to limit exposure to study drug in adolescent subjects if limited treatment effects were observed. ≥50% improvement in SALT score from baseline of Study B7981015 by Month 3 for roll-over subjects (Criteria at Month 3), SALT score ≤20 by Month 6 for roll-over subjects (Criteria at Month 6), SALT score ≤20 by Month 6 for de novo subjects (Criteria at Month 6)

The FAS included 1,052 subjects enrolled in the study (603 roll-over subjects, 449 de novo subjects), of whom 1,050 subjects who received at least 1 dose of study drug (603 roll-over subjects, 447 de novo subjects) were included in the safety analysis set. The FAS was used as the efficacy analysis population.

The discontinuation rates were 24.9% (150 of 603 subjects) in the roll-over cohort and 21.6% (97 of 449 subjects) in the de novo cohort, and the main reasons for discontinuations were lack of efficacy (7.5% [45 of 603 subjects] in the roll-over cohort, 3.3% [15 of 449 subjects] in the de novo cohort), consent withdrawal (5.3% [32 of 603 subjects] in the roll-over cohort, 5.3% [24 of 449 subjects] in the de novo cohort), and no longer meets eligibility criteria (including failure to meet the study continuation criteria for adolescents) (4.6% [28 of 603 subjects] in the roll-over cohort, 4.0% [18 of 449 subjects] in the de novo cohort).

Among the FAS or the safety analysis set, there were 76 subjects in the Japanese subgroup (45 roll-over subjects, 31 de novo subjects).

In the Japanese subgroup, the discontinuation rates were 4.4% (2 of 45 subjects [consent withdrawal; and no longer meets eligibility criteria (including failure to meet the study continuation criteria for adolescents), 1 subject each]) in the roll-over cohort and 6.5% (2 of 31 subjects [consent withdrawal; and no longer meets eligibility criteria (including failure to meet the study continuation criteria for adolescents), 1 subject each]) in the de novo cohort.

The incidences of adverse events were 74.3% (448 of 603 subjects) in the roll-over cohort and 78.3% (350 of 447 subjects) in the de novo cohort, and the main events are shown in Table 49.

Death occurred in 0.2% (1 of 603) of roll-over subjects (acute respiratory failure and cardio-respiratory arrest) and 0.2% (1 of 447) of de novo subjects (breast cancer), and a causal relationship to study drug was denied for both cases.

The incidences of serious adverse events were 4.1% (25 of 603 subjects) in the roll-over cohort (appendicitis [3 subjects]; spontaneous abortion [2 subjects]; and cholelithiasis; staphylococcal sepsis; bipolar disorder and suicidal ideation; malignant melanoma; urinary calculus; breast cancer; acute respiratory failure and cardio-respiratory arrest; ileus; aortic aneurysm; pyelonephritis and flank pain; joint dislocation and ligament rupture; anaphylactic reaction; tendon rupture; subdural haematoma; Bell's palsy; basal cell carcinoma; cervical polyp; acute respiratory failure and COVID-19 pneumonia; COVID-19; and thermal burn [1 subject each]) and 4.0% (18 of 447 subjects) in the de novo cohort [acute myocardial infarction; hypersensitivity; retinal artery occlusion; major depression; bipolar I disorder; COVID-19; vulval abscess; acute respiratory failure, COVID-19 pneumonia, delirium, and septic shock; gastrointestinal haemorrhage; intervertebral disc protrusion; varicose vein; testis cancer; foot deformity; cervical dysplasia; cyst rupture; papillary thyroid cancer; meniscus injury; and breast cancer [1 subject each]), and a causal relationship to study drug could not be ruled out for

spontaneous abortion (2 subjects); and malignant melanoma; breast cancer; and pyelonephritis (1 subject each) in the roll-over cohort and hypersensitivity; and testis cancer (1 subject each) in the de novo cohort.

The incidences of adverse events leading to study or treatment discontinuation were 4.3% (26 of 603 subjects) in the roll-over cohort and 4.9% (22 of 447 subjects) in the de novo cohort.

The incidences of adverse drug reactions were 23.4% (141 of 603 subjects) in the roll-over cohort and 35.8% (160 of 447 subjects) in the de novo cohort.

Table 49. Adverse events occurring in ≥5% of roll-over or de novo subjects (Safety analysis set)

Event term	Roll-over subjects (N = 603)	De novo subjects (N = 447)
Headache	53 (8.8)	73 (16.3)
SARS-CoV-2 test positive	70 (11.6)	60 (13.4)
Acne	28 (4.6)	52 (11.6)
Nasopharyngitis	20 (3.3)	38 (8.5)
Urticaria	12 (2.0)	36 (8.1)
Pyrexia	30 (5.0)	35 (7.8)
Fatigue	19 (3.2)	30 (6.7)
Cough	34 (5.6)	26 (5.8)
Upper respiratory tract infection	34 (5.6)	26 (5.8)

n (%) MedDRA ver.24.1 (MedDRA/J ver.24.1)

In the Japanese subgroup, the incidences of adverse events were 77.8% (35 of 45 subjects) in the roll-over cohort and 87.1% (27 of 31 subjects) in the de novo cohort, and the main events are shown in Table 50.

There were no deaths or adverse events leading to study or treatment discontinuation.

The incidences of serious adverse events were 4.4% (2 of 45 subjects [subdural haematoma; and Bell's palsy (1 subject each)]) in the roll-over cohort and 3.2% (1 of 31 subjects [cervical dysplasia]) in the de novo cohort, but a causal relationship to study drug was denied for all those events.

The incidences of adverse drug reactions were 28.9% (13 of 45 subjects) in the roll-over cohort and 58.1% (18 of 31 subjects) in the de novo cohort.

Table 50. Adverse events occurring in ≥5% of roll-over or de novo subjects (Safety analysis set, Japanese subgroup)

Event term	Roll-over subjects (N = 45)	De novo subjects (N = 31)	Event term	Roll-over subjects (N = 45)	De novo subjects (N = 31)
Urticaria	3 (6.7)	6 (19.4)	Constipation	2 (4.4)	2 (6.5)
Nasopharyngitis	5 (11.1)	5 (16.1)	Contusion	2 (4.4)	2 (6.5)
Pyrexia	4 (8.9)	5 (16.1)	Fall	2 (4.4)	2 (6.5)
Acne	4 (8.9)	5 (16.1)	Iron deficiency anaemia	1 (2.2)	2 (6.5)
Lymphocyte count decreased	0	5 (16.1)	Eczema	1 (2.2)	2 (6.5)
Contact dermatitis	2 (4.4)	4 (12.9)	Anaemia	0	2 (6.5)
Headache	3 (6.7)	3 (9.7)	Neurosensory deafness	0	2 (6.5)
Atopic dermatitis	2 (4.4)	3 (9.7)	Tonsillitis	0	2 (6.5)
Gastroenteritis	1 (2.2)	3 (9.7)	ALT increased	0	2 (6.5)
Folliculitis	3 (6.7)	2 (6.5)	AST increased	0	2 (6.5)

n (%) MedDRA ver.24.1 (MedDRA/J ver.24.1)

7.R Outline of the review conducted by PMDA

7.R.1 Development plan

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

According to the AA guidelines in Japan and the US/Europe, etc., there are no major differences in the definition of or diagnostic criteria for AA between Japan and overseas. Though different drugs are approved for AA in different countries, there are no major differences in the treatment options recommended by the guidelines etc. (Japanese clinical practice guidelines, *Br J Dermatol*. 2012; 166: 916-26, *J Am Acad Dermatol*. 2020; 83: 123-30, etc.). Phase I studies in Japanese or non-Japanese healthy volunteers (Studies B7981008 and B7981001) showed no clear ethnic differences in the pharmacokinetics of ritlecitinib between Japanese and non-Japanese subjects [see Section 6.R]. Based on the above, the efficacy and safety of ritlecitinib in Japanese patients with AA can be evaluated by conducting a global study involving Japan and constructing a clinical data package.

The study population, the primary endpoint, and the dosing regimens for a global phase II/III study involving Japan (Study B7981015, see Section 7.2.1) were chosen as follows.

● Study population

AA is divided into the acute phase (approximately 6 months) during which the hair loss rapidly spreads after becoming aware of its symptoms, and the fixed phase during which alopecia persists beyond the acute phase. AA is treated, taking account of disease type, severity,[48)] age, disease activity, etc. Since patients who present acutely with a few circular patches of scalp hair loss often recover within 1 year, these patients may be followed without treatment. On the other hand, contact immunotherapy, ultraviolet phototherapy, etc., should be considered for severe AA in the fixed phase (the Japanese clinical practice guidelines). Given such treatment paradigm for AA, Study B7981015 enrolled the intended patient population for ritlecitinib, i.e., AA patients with extensive hair loss who were eligible for systemic therapy without evidence of terminal hair regrowth within the previous 6 months. Taking also into account that the rate of spontaneous remission is low (approximately 8%) in patients with extensive disease (>50% scalp involvement) (*J Am Acad Dermatol*. 2018; 78: 15-24), eligible patients were required to have a SALT score of ≥50. AA can affect people of any ethnicity, sex, or age (*N Engl J Med*. 2012; 366: 1515-25, *J Investig Dermatol Symp Proc*. 2013; 16: S13-5), and non-clinical study data etc., which are required to conduct studies in adolescents aged ≥12 years, were available. Thus, adolescent patients aged ≥12 years were also enrolled in the study. Based on a report on a series of AA patients treated with tofacitinib (*J Am Acad Dermatol*. 2017; 76: 22-28), a duration of current episode of hair loss >10 years was thought to increase the likelihood of being refractory to ritlecitinib, and therefore such patients were excluded from the clinical study.

[48)] According to the Japanese clinical practice guidelines, patients with AA involving ≥25% scalp hair loss are considered severe cases. Foreign guidelines and consensus statements (*G Ital Dermatol Venereol*. 2019; 154: 609-23, *J Am Acad Dermatol*. 2020; 83: 123-30, etc.) define AA involving ≥50% scalp hair loss as "extensive" or "severe" AA.

● Primary endpoint

The SALT score, a standard measure for quantitative assessment of AA severity based on scalp terminal hair loss [for the details, see Section 10] was used as the primary endpoint. Though there were no Japanese or foreign guidelines for clinical evaluation of AA or no definition of clinically meaningful improvement in SALT score at the time of planning the study, the proportion of patients achieving a SALT score of ≤10, i.e., ≥90% scalp hair coverage, as an indicator of expected high patient satisfaction, was chosen as the primary endpoint. After the initiation of the study, the results of qualitative interviews conducted with expert dermatologists and with patients with AA who had experienced ≥50% scalp hair loss were reported, and nearly all clinicians and patients in this study agreed that successful treatment would be hair regrowth resulting in ≤20% scalp hair loss (*Br J Dermatol*. 2020; 183: 702-9). Based on this finding etc., the primary endpoint was changed from SALT score ≤10 to SALT score ≤20.

Based on the results from Study B7931005 (a phase II study, see Section 7.1.1),[49)] Week 24 was chosen as the timing of the primary endpoint, in terms of a duration sufficient to evaluate the efficacy of ritlecitinib and an acceptable duration of placebo treatment. Given the situation of the COVID-19 pandemic occurring while the study was ongoing, the methods for handling missing data in the primary analysis of the primary endpoint were added to exclude subjects with missing data due to COVID-19 related reasons from the primary analysis. Taking also account of a single pivotal clinical trial, the alpha level was changed (a two-sided significance level of 5% → a two-sided significance level of 0.125%).

● Dosing regimen

Based on the following points, the study was planned to evaluate 5 dosing regimens including 3 regimens of oral ritlecitinib 10, 30, or 50 mg QD and 2 regimens of oral ritlecitinib 200 mg QD (a loading dose) for the first 4 weeks followed by 30 or 50 mg QD, for both adult patients and adolescent patients aged ≥12 years, and determine the optimal dosing regimen, including the need for a loading dose.

- In Study B7931005, subjects orally received ritlecitinib 200 mg QD for the first 4 weeks, then 50 mg QD for 20 weeks. Ritlecitinib showed greater efficacy over placebo, and there were no clear safety concerns.
- A dose/exposure-response analysis using a ritlecitinib-related biomarker, interferon gamma-induced protein 10 (IP-10), indicated that the dose of 10 mg is likely to be a minimally efficacious dose.
- The primary clearance mechanisms for ritlecitinib are glutathione conjugation and CYP-mediated oxidation with the major contributing isoform being CYP3A4. As to the major metabolizing enzymes of ritlecitinib, the expression level of glutathione S-transferase and CYP3A4 activity level are similar between adolescents aged ≥12 years and adults (*J Pharmacol Exp Ther*. 2002; 300: 361-6, *Drug Metab Dispos*. 2000; 28: 379-82, *Clin Pharmacokinet*. 2014; 53: 625-36).
- Using the data obtained from phase I studies in healthy volunteers (Studies B7981001 and B7981003) and a phase II study in patients with rheumatoid arthritis (Study B7981006), a PPK analysis was performed.

[49)] The SALT ≤10 response rates at Week 24 (FAS, NRI, double-blind period) were 25.0% (12 of 48 subjects) in the ritlecitinib 200/50 mg group and 0% (0 of 47 subjects) in the placebo group.

Simulations conducted with the developed model[50] showed no clinically relevant differences in systemic exposures between adolescents aged ≥12 years and adults.

PMDA accepted the above explanation and concluded that the efficacy and safety of ritlecitinib in AA patients with extensive scalp hair loss can be evaluated based on the submitted clinical data package [for changes to the primary endpoint and the handling of missing data in the primary analysis of Study B7981015, see Section 7.R.2].

7.R.2 Efficacy

[Changes etc. to the study plan while Study B7981015 was ongoing]

As described in Section 7.R.1, the primary endpoint, the handling of missing data in the primary analysis, and the alpha level for Study B7981015 were changed while the study was ongoing. Instead of the method specified in the statistical analysis plan (the Miettinen and Nurminen method [MN method]), the Farrington and Manning method (FM method) was used to calculate *P*-values in the primary analysis of the primary endpoint.

The applicant's explanation about the above points:

Table 51 shows the results before and after the primary endpoint and the handling of missing data in the primary analysis were changed. Under both conditions at the start of the study (the primary endpoint of the SALT ≤10 response rate; subjects with missing data due to COVID-19 related reasons were not excluded; a two-sided significance level of 5%) and at the final analysis (the primary endpoint of the SALT ≤20 response rate; subjects with missing data due to COVID-19 related reasons were excluded[51]; a two-sided significance level of 0.125%), a pairwise comparison between the proposed dosing regimen of ritlecitinib 50 mg and placebo showed a statistically significant difference, and other ritlecitinib regimens were also statistically significantly different from placebo. Among the conditions at the final analysis, subjects with missing data due to COVID-19 related reasons were also imputed as non-responders for a sensitivity analysis, which produced similar results to the primary analysis. Based on the above, these changes had no substantial impact on efficacy assessment, and the efficacy of ritlecitinib was consistently demonstrated.

Before study unblinding, it was decided to use the FM method to calculate *P*-values.[52] The change in the calculation method had little impact on p-values, resulting in no differences in the interpretation of the results.

[50] When AA patients with a body weight of 40 kg (taking account of body weights of Japanese adolescents aged 12 years [2017 School Health Statistical Survey, 44.0 ± 9.6 kg (mean ± SD) in boys, 43.6 ± 8.0 kg in girls]) or a body weight of 75 kg orally received a loading dose of ritlecitinib 200 mg followed by 50 mg QD, the predicted steady-state C_{avg} values are as shown below.
A loading dose of 200 mg QD: 281.3 ± 135.9 ng/mL for body weight of 40 kg, 168.7 ± 69.0 ng/mL for body weight of 75 kg
A 50 mg QD dose: 46.8 ± 22.6 ng/mL for body weight of 40 kg, 28.1 ± 11.5 ng/mL for body weight of 75 kg

[51] Subjects who (1) discontinued from the study prior to the Week 24 visit, (2) did not complete the Week 24 visit, or (3) were missing the SALT assessment at Week 24, due to COVID-19 related reasons, were to be excluded.

[52] This could be verified by the timing of creation of analysis programs etc.

Table 51. Results of primary endpoint before and after changes to the study plan were made (Study B7981015, FAS)

Primary endpoint	10 mg (N = 63)	30 mg (N = 132)	200/30 mg (N = 130)	50 mg (N = 130)	200/50 mg (N = 132)	Placebo (N = 131)
At start of study[a) c)]						
SALT ≤10 response rate at Week 24	1.6 (1/63)	9.9 (13/132)	12.3 (16/130)	13.1 (17/130)	20.5 (27/132)	1.5 (2/131)
Difference from placebo [95% CI] *P*-value (MN method) *P*-value (FM method)	0.1 [−4.1, 7.1] — —	8.3 [3.1, 14.8] 0.003683 0.003618	10.8 [5.2, 17.7] 0.000603 0.000589	11.6 [5.8, 18.6] 0.000338 0.000329	18.9 [12.2, 26.8] 0.000001 <0.000001	
At final analysis[b) d)]						
SALT ≤20 response rate at Week 24	1.7 (1/59)	14.3 (17/119)	22.3 (27/121)	23.4 (29/124)	30.7 (38/124)	1.5 (2/130)
Difference from placebo [95% CI] *P*-value (MN method) *P*-value (FM method)	0.2 [−4.1, 7.6] — —	12.8 [6.7, 20.4] 0.000159 0.000154	20.8 [13.7, 29.2] <0.000001 <0.000001	21.9 [14,7, 30.2] <0.000001 <0.000001	29.1 [21.2, 37.9] <0.000001 <0.000001	
Analysis in which subjects with missing data due to COVID-19 related reasons were also imputed as non-responders,[d)] among the conditions at the final analysis						
SALT ≤20 response rate at Week 24	1.6 (1/63)	12.9 (17/132)	20.8 (27/130)	22.3 (29/130)	28.8 (38/132)	1.5 (2/131)
Difference from placebo [95% CI] *P*-value (MN method) *P*-value (FM method)	0.1 [−4.1, 7.1] — —	11.4 [5.7, 18.3] 0.000387 0.000377	19.2 [12.5, 27.2] <0.000001 <0.000001	20.8 [13.8, 28.9] <0.000001 <0.000001	27.3 [19.7, 35.7] <0.000001 <0.000001	

% (n); —, Not applicable; The MN method was used to calculate 95% CIs.
a) Subjects with missing data were imputed as non-responders. b) Subjects with missing data due to COVID-19 related reasons were excluded from the analysis, and subjects with missing data due to other reasons were imputed as non-responders. c) A two-sided significance level of 5%, d) A two-sided significance level of 0.125%

PMDA's view:

Given that changes to the primary efficacy endpoint, the handling of missing data in the primary analysis, and the alpha level have substantial impact on the efficacy results, the changes to these items after the initiation of the study should have been avoided because such changes may decrease the reliability of the study results. However, these changes were made in a blinded manner; new findings on clinical evaluation of AA became available during the study; the changed primary endpoint should also be clinically meaningful [see Section 7.R.1]; it was difficult to foresee the COVID-19 pandemic; and both analyses before and after the changes were made demonstrated the efficacy of ritlecitinib. Given these points, the efficacy of ritlecitinib can be analyzed in accordance with the final analysis procedures. Thus, the following efficacy evaluation is based on the results from the final analysis procedures.

The method to calculate *P*-values should have been pre-specified in the protocol and the statistical analysis plan so as to define the final calculation method, although, given the obtained data, there are no differences in the interpretation of the results between the two methods.

[Efficacy of ritlecitinib]

The applicant's explanation about the efficacy of ritlecitinib:

In Study B7981015 in AA patients with extensive scalp hair loss, pairwise comparisons between ritlecitinib and placebo showed statistically significant differences in the primary endpoint of the SALT ≤20 response rate at Week 24, except for the 10 mg group, which was included only to support the characterization of the exposure response. The study demonstrated the superiority of ritlecitinib (excluding the 10 mg group) to placebo (Table 43).

Table 52 shows the results of clinician-reported efficacy endpoints of scalp terminal hair, eyebrow, and eyelash

regrowth in Study B7981015. There was a trend towards a greater improvement in the ritlecitinib groups included in efficacy testing than in the placebo group for almost all endpoints at almost all time points. Table 53 shows the results in the Japanese subgroup. There was a trend towards a greater improvement in the ritlecitinib groups included in efficacy testing than in the placebo group in the Japanese subgroup as in the overall population.

Table 52. Results of clinician-reported efficacy endpoints of scalp terminal hair, eyebrow, and eyelash regrowth (Study B7981015, FAS)

Endpoint		Week	30 mg (N = 132)	200/30 mg (N = 130)	50 mg (N = 130)	200/50 mg (N = 132)	Placebo (N = 131)
SALT ≤20 response[a)]		12	3.3 (4/122)	8.9 (11/124)	6.3 (8/126)	11.9 (15/126)	1.6 (2/124)
		24	14.3 (17/119)	22.3 (27/121)	23.4 (29/124)	30.6 (38/124)	1.5 (2/130)
		34	28.7 (35/122)	27.6 (34/123)	33.9 (42/124)	38.4 (48/125)	
		48	31.1 (38/122)	34.4 (42/122)	43.2 (54/125)	39.5 (51/129)	
SALT ≤10 response[a)]		12	0.8 (1/122)	5.6 (7/124)	5.6 (7/126)	6.3 (8/126)	0.8 (1/124)
		24	10.9 (13/119)	13.2 (16/121)	13.7 (17/124)	21.8 (27/124)	1.5 (2/130)
		34	22.1 (27/122)	18.7 (23/123)	23.4 (29/124)	30.4 (38/125)	
		48	25.4 (31/122)	27.9 (34/122)	31.2 (39/125)	33.3 (43/129)	
Change from baseline/Response rate	SALT score	BL	90.0 ± 15.1 (132)	90.5 ± 14.3 (130)	90.3 ± 14.7 (130)	90.3 ± 15.1 (132)	93.0 ± 11.5 (131)
	Change (OC)	12	−10.7 ± 19.2 (115)	−20.3 ± 26.0 (120)	−12.6 ± 23.4 (121)	−23.7 ± 27.6 (121)	−2.4 ± 12.1 (122)
		24	−23.7 ± 29.1 (114)	−29.7 ± 31.6 (119)	−33.7 ± 32.2 (119)	−38.7 ± 34.5 (118)	−5.3 ± 16.6 (125)
		34	−33.5 ± 35.0 (115)	−35.5 ± 35.5 (118)	−43.6 ± 34.4 (117)	−48.2 ± 36.2 (113)	
		48	−40.1 ± 35.9 (107)	−40.5 ± 37.3 (112)	−48.9 ± 36.6 (116)	−49.4 ± 36.1 (114)	
	≥50% improvement[a)]	12	8.2 (10/122)	20.2 (25/124)	11.1 (14/126)	24.6 (31/126)	1.6 (2/124)
		24	29.4 (35/119)	36.4 (44/121)	39.5 (49/124)	42.7 (53/124)	6.9 (9/130)
		34	40.2 (49/122)	38.2 (47/123)	48.4 (60/124)	52.0 (65/125)	
		48	43.4 (53/122)	45.1 (55/122)	55.2 (69/125)	53.5 (69/129)	
	≥75% improvement[a)]	12	2.5 (3/122)	8.1 (10/124)	6.3 (8/126)	11.9 (15/126)	1.6 (2/124)
		24	13.4 (16/119)	20.7 (25/121)	22.6 (28/124)	31.5 (39/124)	2.3 (3/130)
		34	28.7 (35/122)	32.5 (40/123)	38.7 (48/124)	38.4 (48/125)	
		48	31.1 (38/122)	36.1 (44/122)	46.4 (58/125)	39.5 (51/129)	
	≥90% improvement[a)]	12	0.8 (1/122)	4.0 (5/124)	4.8 (6/126)	5.6 (7/126)	0.8 (1/124)
		24	9.2 (11/119)	10.7 (13/121)	12.1 (15/124)	18.5 (23/124)	1.5 (2/130)
		34	19.7 (24/122)	17.1 (21/123)	21.8 (27/124)	28.8 (36/125)	
		48	22.1 (27/122)	23.8 (29/122)	29.6 (37/125)	31.0 (40/129)	
	100% improvement[a)]	12	0 (0/122)	0.8 (1/124)	1.6 (2/126)	0 (0/126)	0 (0/124)
		24	2.5 (3/119)	1.7 (2/121)	4.8 (6/124)	7.3 (9/124)	0.8 (1/130)
		34	4.9 (6/122)	3.3 (4/123)	6.5 (8/124)	12.8 (16/125)	
		48	7.4 (9/122)	4.9 (6/122)	10.4 (13/125)	14.0 (18/129)	
EBA response (at least a 2-grade improvement from baseline or a score of 3 in EBA scale)[a), b)]		12	7.6 (8/105)	17.5 (18/103)	9.6 (10/104)	22.9 (24/105)	2.0 (2/101)
		24	16.7 (17/102)	25.5 (26/102)	29.0 (29/100)	34.0 (35/103)	4.7 (5/107)
		34	31.4 (33/105)	30.8 (32/104)	34.7 (35/101)	41.3 (43/104)	
		48	33.3 (35/105)	32.7 (33/101)	43.6 (44/101)	43.0 (46/107)	
ELA response (at least a 2-grade improvement from baseline or a score of 3 in ELA scale)[a), b)]		12	7.4 (7/95)	11.0 (10/91)	11.7 (11/94)	16.5 (16/97)	0 (0/91)
		24	26.1 (24/92)	21.3 (19/89)	28.9 (26/90)	30.2 (29/96)	5.2 (5/97)
		34	26.3 (25/95)	26.4 (24/91)	38.9 (35/90)	34.0 (33/97)	
		48	30.5 (29/95)	29.5 (26/88)	40.0 (36/90)	38.4 (38/99)	

% (n) for response rate; Mean ± SD (N) for SALT score at baseline and change from baseline

a) Subjects with missing data due to COVID-19 related reasons were excluded from the analysis, and subjects with missing data due to other reasons were imputed as non-responders.

b) Subjects with eyebrow or eyelash involvement at baseline (EBA/ELA score ≤2) were evaluated.

Table 53. Results of clinician-reported efficacy endpoints of scalp terminal hair, eyebrow, and eyelash regrowth (Study B7981015, FAS, Japanese subgroup)

Endpoint		Week	30 mg (N = 8)	200/30 mg (N = 8)	50 mg (N = 9)	200/50 mg (N = 8)	Placebo (N = 9)
SALT ≤20 response[a)]		12	0 (0/8)	25.0 (2/8)	11.1 (1/9)	12.5 (1/8)	0 (0/9)
		24	12.5 (1/8)	50.0 (4/8)	11.1 (1/9)	25.0 (2/8)	0 (0/9)
		34	37.5 (3/8)	62.5 (5/8)	44.4 (4/9)	50.0 (4/8)	
		48	50.0 (4/8)	62.5 (5/8)	66.7 (6/9)	25.0 (2/8)	
SALT ≤10 response[a)]		12	0 (0/8)	12.5 (1/8)	11.1 (1/9)	0 (0/8)	0 (0/9)
		24	12.5 (1/8)	25.0 (2/8)	11.1 (1/9)	25.0 (2/8)	0 (0/9)
		34	37.5 (3/8)	50.0 (4/8)	33.3 (3/9)	25.0 (2/8)	
		48	50.0 (4/8)	50.0 (4/8)	55.6 (5/9)	25.0 (2/8)	
Change from baseline/Response rate	SALT score	BL	100 ± 0 (8)	94.7 ± 14.9 (8)	92.7 ± 14.8 (9)	89.3 ± 19.8 (8)	98.1 ± 5.6 (9)
	Change (OC)	12	−15.8 ± 28.6 (8)	−27.3 ± 32.0 (8)	−4.6 ± 21.5 (9)	−20.6 ± 20.4 (7)	−2.2 ± 6.2 (9)
		24	−30.6 ± 34.9 (8)	−48.0 ± 40.1 (8)	−34.6 ± 28.1 (9)	−44.2 ± 40.0 (7)	−2.4 ± 7.0 (9)
		34	−49.8 ± 43.9 (8)	−59.7 ± 40.1 (8)	−54.2 ± 35.2 (9)	−50.4 ± 43.2 (7)	
		48	−57.6 ± 44.0 (8)	−63.2 ± 39.5 (8)	−61.6 ± 38.4 (9)	−33.7 ± 34.0 (7)	
	≥50% improvemnt[a)]	12	12.5 (1/8)	25.0 (2/8)	11.1 (1/9)	12.5 (1/8)	0 (0/9)
		24	25.0 (2/8)	62.5 (5/8)	44.4 (4/9)	50.0 (4/8)	0 (0/9)
		34	50.0 (4/8)	62.5 (5/8)	66.7 (6/9)	50.0 (4/8)	
		48	50.0 (4/8)	75.0 (6/8)	66.7 (6/9)	25.0 (2/8)	
	≥75% improvement[a)]	12	12.5 (1/8)	25.0 (2/8)	11.1 (1/9)	0 (0/8)	0 (0/9)
		24	12.5 (1/8)	50.0 (4/8)	11.1 (1/9)	37.5 (3/8)	0 (0/9)
		34	37.5 (3/8)	62.5 (5/8)	55.6 (5/9)	50.0 (4/8)	
		48	50.0 (4/8)	62.5 (5/8)	66.7 (6/9)	25.0 (2/8)	
	≥90% improvement[a)]	12	0 (0/8)	0 (0/8)	11.1 (1/9)	0 (0/8)	0 (0/9)
		24	12.5 (1/8)	25.0 (2/8)	11.1 (1/9)	25.0 (2/8)	0 (0/9)
		34	37.5 (3/8)	50.0 (4/8)	33.3 (3/9)	25.0 (2/8)	
		48	50.0 (4/8)	50.0 (4/8)	55.6 (5/9)	25.0 (2/8)	
	100% improvement[a)]	12	0 (0/8)	0 (0/8)	0 (0/9)	0 (0/8)	0 (0/9)
		24	0 (0/8)	0 (0/8)	0 (0/9)	0 (0/8)	0 (0/9)
		34	0 (0/8)	0 (0/8)	11.1 (1/9)	0 (0/8)	
		48	0 (0/8)	0 (0/8)	11.1 (1/9)	12.5 (1/8)	
EBA response (at least a 2-grade improvement from baseline or a score of 3 in EBA scale)[a), b)]		12	12.5 (1/8)	33.3 (2/6)	12.5 (1/8)	14.3 (1/7)	0 (0/9)
		24	25.0 (2/8)	50.0 (3/6)	62.5 (5/8)	28.6 (2/7)	0 (0/9)
		34	37.5 (3/8)	83.3 (5/6)	75.0 (6/8)	28.6 (2/7)	
		48	37.5 (3/8)	83.3 (5/6)	100 (8/8)	28.6 (2/7)	
ELA response (at least a 2-grade improvement from baseline or a score of 3 in ELA scale)[a), b)]		12	14.3 (1/7)	0 (0/6)	0 (0/8)	0 (0/7)	0 (0/9)
		24	28.6 (2/7)	50.0 (3/6)	50.0 (4/8)	42.9 (3/7)	0 (0/9)
		34	42.9 (3/7)	83.3 (5/6)	50.0 (4/8)	42.9 (3/7)	
		48	42.9 (3/7)	100 (6/6)	62.5 (5/8)	28.6 (2/7)	

% (n) for response rate; Mean ± SD (N) for SALT score at baseline and change from baseline

a) Subjects with missing data due to COVID-19 related reasons were excluded from the analysis, and subjects with missing data due to other reasons were imputed as non-responders.

b) Subjects with eyebrow or eyelash involvement at baseline (EBA/ELA score ≤2) were evaluated.

Table 54 shows the results of the key efficacy endpoints of patient-reported outcomes in Study B7981015. There was a trend towards a greater improvement in the ritlecitinib groups included in efficacy testing than in the placebo group for all endpoints at all time points, except for Alopecia Areata Patient Priority Outcome (AAPPO) emotional symptoms and activity limitations scores. There were no clear differences in AAPPO emotional symptoms and activity limitations scores between the placebo group and the ritlecitinib groups included in efficacy testing, which may have been attributable to low mean AAPPO emotional symptoms and activity limitations scores at baseline due to the inclusion/exclusion criteria (Subjects with clinically significant depression or psychiatric disorder were excluded, etc.). Table 55 shows the results in the Japanese subgroup, which showed a similar trend to those in the overall population.

Table 54. Results of key efficacy endpoints of patient-reported outcomes (Study B7981015, FAS)

Endpoint		Week	30 mg (N = 132)	200/30 mg (N = 130)	50 mg (N = 130)	200/50 mg (N = 132)	Placebo (N = 131)
PGI-C response[a)]		12	26.8 (33/123)	41.9 (52/124)	28.0 (35/125)	40.9 (52/127)	10.6 (13/123)
		24	42.1 (51/121)	47.1 (57/121)	49.6 (62/125)	53.2 (67/126)	9.2 (12/130)
		34	47.5 (58/122)	52.9 (64/121)	52.8 (65/123)	55.2 (69/125)	
		48	49.2 (60/122)	52.0 (64/123)	56.0 (70/125)	58.1 (75/129)	
P-Sat response[a)]	Overall	12	51.2 (63/123)	68.5 (85/124)	53.6 (67/125)	70.9 (90/127)	22.0 (27/123)
		24	59.2 (71/120)	61.2 (74/121)	64.0 (80/125)	64.3 (81/126)	21.5 (28/130)
		34	62.3 (76/122)	62.0 (75/121)	69.9 (86/123)	64.8 (81/125)	
		48	62.3 (76/122)	61.8 (76/123)	68.0 (85/125)	64.3 (83/129)	
	Amount of hair	12	51.2 (63/123)	68.5 (85/124)	55.2 (69/125)	69.3 (88/127)	22.8 (28/123)
		24	59.2 (71/120)	62.0 (75/121)	64.8 (81/125)	64.3 (81/126)	21.5 (28/130)
		34	62.3 (76/122)	64.5 (78/121)	69.9 (86/123)	63.2 (79/125)	
		48	61.5 (75/122)	63.4 (78/123)	68.0 (85/125)	64.3 (83/129)	
	Quality of hair	12	49.6 (61/123)	63.7 (79/124)	48.8 (61/125)	66.1 (84/127)	19.5 (24/123)
		24	56.7 (68/120)	60.3 (73/121)	61.6 (77/125)	62.7 (79/126)	22.3 (29/130)
		34	60.7 (74/122)	59.5 (72/121)	67.5 (83/123)	61.6 (77/125)	
		48	59.8 (73/122)	60.2 (74/123)	68.8 (86/125)	62.0 (80/129)	
Improvement on AAPPO hair loss items[a), b)]	Scalp	12	13.3 (16/120)	19.5 (24/123)	12.7 (15/118)	20.7 (25/121)	5.8 (7/121)
		24	24.6 (29/118)	30.0 (36/120)	26.3 (31/118)	35.8 (43/120)	8.6 (11/128)
		34	30.3 (36/119)	34.5 (41/119)	29.3 (34/116)	42.0 (50/119)	
		48	32.8 (39/119)	33.6 (41/122)	42.4 (50/118)	42.3 (52/123)	
	Eyebrows	12	16.0 (15/94)	27.8 (27/97)	18.1 (17/94)	27.8 (27/97)	9.0 (8/89)
		24	29.3 (27/92)	33.0 (31/94)	30.4 (28/92)	32.3 (31/96)	11.5 (11/96)
		34	31.9 (30/94)	38.7 (36/93)	38.9 (35/90)	42.7 (41/96)	
		48	39.4 (37/94)	34.0 (32/94)	44.0 (40/91)	44.9 (44/98)	
	Eyelashes	12	19.0 (16/84)	26.7 (23/86)	16.5 (13/79)	29.4 (25/85)	11.7 (9/77)
		24	28.0 (23/82)	42.2 (35/83)	31.2 (24/77)	31.4 (27/86)	8.3 (7/84)
		34	34.5 (29/84)	36.6 (30/82)	37.3 (28/75)	40.0 (34/85)	
		48	34.5 (29/84)	37.3 (31/83)	38.2 (29/76)	41.9 (36/86)	
	Body	12	14.3 (13/91)	19.1 (18/94)	14.9 (14/94)	17.0 (16/94)	9.3 (8/86)
		24	22.2 (20/90)	28.0 (26/93)	20.4 (19/93)	25.8 (24/93)	14.0 (13/93)
		34	26.1 (24/92)	33.7 (31/92)	31.5 (29/92)	33.3 (31/93)	
		48	30.4 (28/92)	34.4 (32/93)	36.6 (34/93)	34.7 (33/95)	
AAPPO emotional symptoms score		BL	1.68 ± 1.21 (132)	1.78 ± 1.01 (130)	1.81 ± 1.10 (129)	1.70 ± 1.05 (131)	1.98 ± 1.13 (131)
	Change from baseline (OC)	12	−0.45 ± 0.85 (116)	−0.56 ± 0.75 (120)	−0.49 ± 0.80 (119)	−0.51 ± 0.84 (122)	−0.44 ± 0.85 (121)
		24	−0.54 ± 0.95 (116)	−0.64 ± 0.93 (118)	−0.69 ± 0.90 (119)	−0.56 ± 1.00 (120)	−0.52 ± 0.84 (125)
		34	−0.71 ± 1.06 (113)	−0.72 ± 1.00 (116)	−0.72 ± 0.93 (114)	−0.78 ± 0.95 (112)	
		48	−0.72 ± 1.15 (107)	−0.84 ± 1.07 (112)	−0.85 ± 1.04 (115)	−0.96 ± 0.99 (114)	
AAPPO activity limitations score		BL	0.69 ± 0.94 (132)	0.66 ± 0.86 (130)	0.64 ± 0.85 (129)	0.68 ± 0.85 (131)	0.80 ± 0.96 (131)
	Change from baseline (OC)	12	−0.26 ± 0.79 (116)	−0.20 ± 0.70 (120)	−0.17 ± 0.71 (119)	−0.27 ± 0.79 (122)	−0.27 ± 0.74 (121)
		24	−0.26 ± 0.73 (115)	−0.29 ± 0.70 (118)	−0.25 ± 0.70 (119)	−0.27 ± 0.79 (120)	−0.35 ± 0.71 (125)
		34	−0.37 ± 0.78 (115)	−0.31 ± 0.78 (116)	−0.26 ± 0.73 (114)	−0.37 ± 0.71 (112)	
		48	−0.36 ± 0.85 (107)	−0.39 ± 0.84 (112)	−0.29 ± 0.76 (115)	−0.43 ± 0.79 (114)	

% (n) for response rate; Mean ± SD (N) for AAPPO emotional symptoms/activity limitations scores

a) Subjects with missing data due to COVID-19 related reasons were excluded from the analysis, and subjects with missing data due to other reasons were imputed as non-responders.

b) Subjects with moderate to complete hair loss in each body area at baseline were evaluated.

Table 55. Results of key efficacy endpoints of patient-reported outcomes (Study B7981015, FAS, Japanese subgroup)

Endpoint		Week	30 mg (N = 8)	200/30 mg (N = 8)	50 mg (N = 9)	200/50 mg (N = 8)	Placebo (N = 9)
PGI-C response[a)]		12	12.5 (1/8)	12.5 (1/8)	11.1 (1/9)	12.5 (1/8)	0 (0/9)
		24	25.0 (2/8)	62.5 (5/8)	44.4 (4/9)	62.5 (5/8)	0 (0/9)
		34	25.0 (2/8)	75.0 (6/8)	66.7 (6/9)	50.0 (4/8)	
		48	62.5 (5/8)	75.0 (6/8)	66.7 (6/9)	50.0 (4/8)	
P-Sat response[a)]	Overall	12	25.0 (2/8)	50.0 (4/8)	33.3 (3/9)	75.0 (6/8)	0 (0/9)
		24	37.5 (3/8)	62.5 (5/8)	88.9 (8/9)	62.5 (5/8)	0 (0/9)
		34	25.0 (2/8)	62.5 (5/8)	77.8 (7/9)	62.5 (5/8)	
		48	50.0 (4/8)	62.5 (5/8)	77.8 (7/9)	62.5 (5/8)	
	Amount of hair	12	37.5 (3/8)	75.0 (6/8)	55.6 (5/9)	62.5 (5/8)	11.1 (1/9)
		24	37.5 (3/8)	62.5 (5/8)	88.9 (8/9)	62.5 (5/8)	0 (0/9)
		34	25.0 (2/8)	62.5 (5/8)	77.8 (7/9)	62.5 (5/8)	
		48	37.5 (3/8)	75.0 (6/8)	77.8 (7/9)	62.5 (5/8)	
	Quality of hair	12	37.5 (3/8)	37.5 (3/8)	22.2 (2/9)	75.0 (6/8)	0 (0/9)
		24	37.5 (3/8)	62.5 (5/8)	88.9 (8/9)	50.0 (4/8)	0 (0/9)
		34	25.0 (2/8)	62.5 (5/8)	77.8 (7/9)	50.0 (4/8)	
		48	25.0 (2/8)	62.5 (5/8)	77.8 (7/9)	50.0 (4/8)	
Improvement on AAPPO hair loss items[a), b)]	Scalp	12	0 (0/8)	12.5 (1/8)	0 (0/9)	0 (0/7)	0 (0/9)
		24	12.5 (1/8)	25.0 (2/8)	22.2 (2/9)	28.6 (2/7)	0 (0/9)
		34	12.5 (1/8)	50.0 (4/8)	22.2 (2/9)	42.9 (3/7)	
		48	25.0 (2/8)	50.0 (4/8)	44.4 (4/9)	42.9 (3/7)	
	Eyebrows	12	25.0 (2/8)	16.7 (1/6)	25.0 (2/8)	14.3 (1/7)	0 (0/9)
		24	37.5 (3/8)	50.0 (3/6)	50.0 (4/8)	28.6 (2/7)	0 (0/9)
		34	50.0 (4/8)	83.3 (5/6)	50.0 (4/8)	42.9 (3/7)	
		48	50.0 (4/8)	83.3 (5/6)	75.0 (6/8)	28.6 (2/7)	
	Eyelashes	12	42.9 (3/7)	33.3 (2/6)	0 (0/8)	0 (0/7)	0 (0/8)
		24	28.6 (2/7)	83.3 (5/6)	50.0 (4/8)	28.6 (2/7)	0 (0/8)
		34	42.9 (3/7)	66.7 (4/6)	50.0 (4/8)	42.9 (3/7)	
		48	42.9 (3/7)	66.7 (4/6)	62.5 (5/8)	28.6 (2/7)	
	Body	12	0 (0/6)	25.0 (2/8)	12.5 (1/8)	0 (0/8)	0 (0/9)
		24	0 (0/6)	37.5 (3/8)	12.5 (1/8)	25.0 (2/8)	0 (0/9)
		34	16.7 (1/6)	50.0 (4/8)	25.0 (2/8)	12.5 (1/8)	
		48	16.7 (1/6)	62.5 (5/8)	25.0 (2/8)	50.0 (4/8)	
AAPPO emotional symptoms score		BL	1.38 ± 1.46 (8)	1.88 ± 0.64 (8)	1.47 ± 1.21 (9)	1.91 ± 0.90 (8)	1.33 ± 0.63 (9)
	Change from baseline (OC)	12	−0.31 ± 0.61 (8)	−0.97 ± 0.54 (8)	−0.39 ± 0.95 (9)	−0.68 ± 1.08 (7)	−0.14 ± 0.87 (9)
		24	−0.31 ± 0.48 (8)	−1.31 ± 0.56 (8)	−0.58 ± 1.10 (9)	−1.07 ± 1.05 (7)	−0.22 ± 0.84 (9)
		34	−0.56 ± 0.87 (8)	−1.53 ± 0.75 (8)	−0.78 ± 1.24 (9)	−1.21 ± 0.81 (7)	
		48	−0.53 ± 0.57 (8)	−1.47 ± 0.43 (8)	−0.97 ± 1.26 (9)	−1.07 ± 0.79 (7)	
AAPPO activity limitations score		BL	0.63 ± 1.01 (8)	0.46 ± 0.43 (8)	0.15 ± 0.34 (9)	0.63 ± 0.38 (8)	0.15 ± 0.24 (9)
	Change from baseline (OC)	12	−0.38 ± 0.60 (8)	−0.08 ± 0.75 (8)	0.22 ± 0.58 (9)	0.00 ± 0.98 (7)	0.00 ± 0.33 (9)
		24	−0.46 ± 0.73 (8)	−0.29 ± 0.52 (8)	0.15 ± 0.47 (9)	−0.19 ± 0.69 (7)	0.00 ± 0.37 (9)
		34	−0.58 ± 0.92 (8)	−0.33 ± 0.50 (8)	−0.04 ± 0.20 (9)	−0.24 ± 0.60 (7)	
		48	−0.38 ± 0.55 (8)	−0.29 ± 0.52 (8)	0.07 ± 0.28 (9)	−0.29 ± 0.56 (7)	

% (n) for response rate; Mean ± SD (N) for AAPPO emotional symptoms/activity limitations scores

a) Subjects with missing data due to COVID-19 related reasons were excluded from the analysis, and subjects with missing data due to other reasons were imputed as non-responders.

b) Subjects with moderate to complete hair loss in each body area at baseline were evaluated.

Table 56 shows the results of the primary endpoint (SALT ≤20 response rate at Week 24) by patient characteristics in Study B7981015. The response rate tended to be generally higher in the ritlecitinib groups included in efficacy testing than in the placebo group across all subgroups.

Table 56. Results of primary endpoint by patient characteristics (Study B7981015, FAS, NRI)

Patient characteristics		30 mg (N = 132)	200/30 mg (N = 130)	50 mg (N = 130)	200/50 mg (N = 132)	Placebo (N = 131)
Age	12-17 years	16.7 (3/18)	17.6 (3/17)	25.0 (4/16)	27.8 (5/18)	0 (0/19)
	≥18 years	13.9 (14/101)	23.1 (24/104)	23.1 (25/108)	31.1 (33/106)	1.8 (2/111)
Body weight	<67.9 kg	10.3 (6/58)	27.3 (15/55)	27.0 (17/63)	41.7 (25/60)	2.8 (2/72)
	≥67.9 kg	18.0 (11/61)	18.2 (12/66)	19.7 (12/61)	20.3 (13/64)	0 (0/58)
Sex	Male	12.2 (6/49)	14.3 (6/42)	7.3 (4/55)	21.3 (10/47)	0 (0/45)
	Female	15.7 (11/70)	26.6 (21/79)	36.2 (25/69)	36.4 (28/77)	2.4 (2/85)
Geographical location	North America	18.2 (8/44)	18.0 (9/50)	30.6 (15/49)	38.0 (19/50)	1.7 (1/58)
	Europe	17.4 (4/23)	12.5 (3/24)	16.0 (4/25)	24.1 (7/29)	0 (0/29)
	Asia	7.4 (2/27)	40.9 (9/22)	19.4 (6/31)	29.6 (8/27)	4.5 (1/22)
	Rest of World	12.0 (3/25)	24.0 (6/25)	21.1 (4/19)	22.2 (4/18)	0 (0/21)
Disease type	Common type	24.3 (9/37)	41.7 (15/36)	37.5 (18/48)	45.5 (20/44)	0 (0/44)
	Alopecia totalis	7.7 (2/26)	9.7 (3/31)	7.4 (2/27)	20.8 (5/24)	0 (0/24)
	Alopecia universalis	8.0 (2/25)	9.5 (2/21)	9.1 (2/22)	4.2 (1/24)	0 (0/34)
	Alopecia ophiasis	0 (0/7)	0 (0/3)	33.3 (2/6)	37.5 (3/8)	0 (0/4)
Duration since AA diagnosis	<6.9 years	14.3 (10/70)	22.2 (12/54)	31.3 (20/64)	29.0 (18/62)	1.6 (1/61)
	≥6.9 years	14.3 (7/49)	22.4 (15/67)	15.0 (9/60)	32.3 (20/62)	1.4 (1/69)
Duration of current AA episode	<2.5 years	24.5 (13/53)	21.8 (12/55)	29.9 (20/67)	34.8 (23/66)	3.1 (2/65)
	≥2.5 years	6.1 (4/66)	22.7 (15/66)	15.8 (9/57)	25.9 (15/58)	0 (0/65)
Drug therapy for AA	Yes	13.4 (11/82)	23.0 (17/74)	28.1 (27/96)	34.8 (31/89)	0 (0/95)
	No	16.2 (6/37)	21.3 (10/47)	7.1 (2/28)	20.0 (7/35)	5.7 (2/35)

% (n)

PMDA's view:

In Study B7981015 in AA patients with extensive scalp hair loss, pairwise comparisons between ritlecitinib and placebo showed statistically significant differences in the primary endpoint of the SALT ≤20 response rate at Week 24, except for the 10 mg group, which was included only to support the characterization of the exposure response. The study demonstrated the superiority of ritlecitinib (excluding the 10 mg group) to placebo in the primary endpoint and showed a greater improvement in the ritlecitinib groups (excluding the 10 mg group) than in the placebo group also for other efficacy endpoints. Thus, the efficacy of ritlecitinib in the treatment of AA was demonstrated. The results in the Japanese subgroup also showed a similar trend to those in the overall population, and the efficacy of ritlecitinib in Japanese patients with AA is expected.

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

7.R.3 Safety

7.R.3.1 Summary of safety

The applicant's explanation about the safety of ritlecitinib based on the results of analyses of the pooled data from the placebo-controlled periods (24 weeks) of 3 clinical studies in AA patients[53)] (the PCPAA pool) and the pooled data from 4 clinical studies in AA patients[54)] (the All Exposure Pool [AEP]), etc.:

Table 57 shows a summary of safety of ritlecitinib in the PCPAA pool and the AEP, and there were no evident differences among the treatment groups including the placebo group. There were no clear differences between the Japanese subgroup and the overall population.

[53)] Studies B7931005, B7981015, and B7981037

[54)] Studies B7931005, B7981015, B7981037, and B7981032 (data cutoff date of May 30, 2022)

Table 57. Summary of safety of ritlecitinib (Safety analysis set)

Safety pool	PCPAA						AEP	
Treatment group/Treated subjects	10 mg	30 mg	200/30 mg	50 mg	200/50 mg	Placebo	50 mg	All 50 mg [a)]
Overall population								
N	62	132	129	130	215	213	191	1,228
Total drug exposure (patient-years)	27.7	56.3	58.4	58.3	96.1	95.0	339.1	2,053.7
All adverse events	43 (69.4) 316.9	95 (72.0) 363.3	91 (70.5) 338.3	98 (75.4) 393.9	151 (70.2) 331.2	148 (69.5) 326.9	179 (93.7) 239.3	989 (80.5) 149.7
Serious adverse events	2 (3.2) 7.3	1 (0.8) 1.8	0	0	4 (1.9) 4.2	4 (1.9) 4.2	10 (5.2) 3.0	52 (4.2) 2.6
Death	0	0	0	0	0	0	0	2 (0.2) 0.1
Adverse events leading to treatment discontinuation	2 (3.2) 7.3	4 (3.0) 7.1	0	2 (1.5) 3.4	6 (2.8) 6.3	5 (2.3) 5.3	19 (9.9) 5.6	68 (5.5) 3.3
Adverse drug reactions	19 (30.6) 84.9	45 (34.1) 106.9	46 (35.7) 107.3	47 (36.2) 106.8	71 (33.0) 99.7	68 (31.9) 95.1	100 (52.4) 48.6	451 (36.7) 30.9
Japanese subgroup								
N	5	8	8	9	8	9	15	77
Total drug exposure (patient-years)	1.9	3.7	3.8	4.2	3.3	4.2	35.0	164.4
All adverse events	3 (60.0) 304.4	7 (87.5) 554.6	8 (100) 796.2	5 (55.6) 208.0	5 (62.5) 247.8	6 (66.7) 241.1	15 (100) 188.5	68 (88.3) 148.2
Serious adverse events	0	0	0	0	0	0	1 (6.7) 3.0	3 (3.9) 1.9
Death	0	0	0	0	0	0	0	0
Adverse events leading to treatment discontinuation	1 (20.0) 53.7	0	0	0	1 (12.5) 30.6	0	0	1 (1.3) 0.6
Adverse drug reactions	1 (20.0) 53.7	2 (25.0) 66.5	4 (50.0) 180.2	5 (55.6) 199.8	3 (37.5) 119.9	2 (22.2) 59.1	12 (80.0) 92.9	41 (53.2) 42.5

Upper row, n (%); Lower row, Exposure[b)]-adjusted incidence rate per 100 patient-years

a) Pooled data from subjects who received 50 or 200/50 mg (including the data after subjects switched from placebo to ritlecitinib) and subjects who received 10, 30, or 200/30 mg in Study B7981015 and then 50 mg in Study B7981032 (the data after they started the 50 mg dose)

b) Sum across all subjects, the total time to first event or total exposure if no event (years)

Tables 58, 59, and 60 show the main adverse events in the PCPAA pool or the AEP.

Table 58. Adverse events occurring in ≥3% of subjects in any group (Safety analysis set)

Safety pool	PCPAA (Overall population)					
Treatment group	10 mg (N = 62)	30 mg (N = 132)	200/30 mg (N = 129)	50 mg (N = 130)	200/50 mg (N = 215)	Placebo (N = 213)
Nasopharyngitis	6 (9.7)	16 (12.1)	18 (14.0)	13 (10.0)	21 (9.8)	15 (7.0)
Upper respiratory tract infection	2 (3.2)	11 (8.3)	10 (7.8)	8 (6.2)	21 (9.8)	16 (7.5)
Headache	11 (17.7)	20 (15.2)	10 (7.8)	12 (9.2)	20 (9.3)	17 (8.0)
Diarrhoea	0	6 (4.5)	4 (3.1)	12 (9.2)	14 (6.5)	8 (3.8)
Acne	3 (4.8)	7 (5.3)	7 (5.4)	8 (6.2)	12 (5.6)	10 (4.7)
Nausea	3 (4.8)	10 (7.6)	2 (1.6)	3 (2.3)	12 (5.6)	15 (7.0)
Folliculitis	2 (3.2)	3 (2.3)	8 (6.2)	4 (3.1)	12 (5.6)	4 (1.9)
Dizziness	1 (1.6)	3 (2.3)	7 (5.4)	3 (2.3)	11 (5.1)	3 (1.4)
Urticaria	1 (1.6)	4 (3.0)	6 (4.7)	6 (4.6)	11 (5.1)	3 (1.4)
Urinary tract infection	0	5 (3.8)	2 (1.6)	0	8 (3.7)	6 (2.8)
Blood CPK increased	2 (3.2)	3 (2.3)	3 (2.3)	2 (1.5)	7 (3.3)	0
Influenza	2 (3.2)	1 (0.8)	0	2 (1.5)	6 (2.8)	3 (1.4)
Myalgia	5 (8.1)	5 (3.8)	1 (0.8)	1 (0.8)	5 (2.3)	3 (1.4)
Pruritus	1 (1.6)	2 (1.5)	6 (4.7)	1 (0.8)	4 (1.9)	5 (2.3)
Pyrexia	1 (1.6)	3 (2.3)	0	4 (3.1)	4 (1.9)	0
Gastroenteritis	2 (3.2)	0	3 (2.3)	2 (1.5)	3 (1.4)	0
Oropharyngeal pain	0	1 (0.8)	6 (4.7)	4 (3.1)	3 (1.4)	6 (2.8)
Back pain	2 (3.2)	2 (1.5)	2 (1.6)	2 (1.5)	3 (1.4)	0
Rash	0	1 (0.8)	3 (2.3)	5 (3.8)	3 (1.4)	2 (0.9)
Acneiform dermatitis	0	1 (0.8)	4 (3.1)	1 (0.8)	2 (0.9)	0
Arthralgia	2 (3.2)	3 (2.3)	3 (2.3)	1 (0.8)	2 (0.9)	6 (2.8)
Upper abdominal pain	0	2 (1.5)	3 (2.3)	4 (3.1)	1 (0.5)	2 (0.9)
Contact dermatitis	3 (4.8)	3 (2.3)	0	0	1 (0.5)	2 (0.9)
Fall	2 (3.2)	0	1 (0.8)	2 (1.5)	1 (0.5)	2 (0.9)
Fatigue	2 (3.2)	6 (4.5)	6 (4.7)	4 (3.1)	1 (0.5)	5 (2.3)
Constipation	0	5 (3.8)	0	0	1 (0.5)	3 (1.4)
SARS-CoV-2 test positive	0	4 (3.0)	0	4 (3.1)	0	1 (0.5)
Laryngitis	2 (3.2)	0	0	0	0	1 (0.5)

n (%) MedDRA ver.25.0 (MedDRA/J ver.25.0)

Table 59. Adverse events occurring in ≥2 subjects in any group (Safety analysis set)

Safety pool	PCPAA (Japanese subgroup)					
Treatment group	10 mg (N = 5)	30 mg (N = 8)	200/30 mg (N = 8)	50 mg (N = 9)	200/50 mg (N = 8)	Placebo (N = 9)
Nasopharyngitis	2 (40.0)	1 (12.5)	4 (50.0)	1 (11.1)	2 (25.0)	1 (11.1)
Lymphocyte count decreased	0	0	2 (25.0)	0	1 (12.5)	1 (11.1)
Urticaria	0	2 (25.0)	2 (25.0)	0	1 (12.5)	1 (11.1)
Pharyngitis	0	0	2 (25.0)	0	0	1 (11.1)
Stomatitis	0	0	0	2 (22.2)	0	0

n (%) MedDRA ver.25.0 (MedDRA/J ver.25.0)

Table 60. Main adverse events observed in the AEP (Safety analysis set)

Safety pool	AEP				Safety pool	AEP			
	Overall population		Japanese subgroup			Overall population		Japanese subgroup	
Treated subjects	50 mg (N = 191)	All 50 mg [a] (N = 1,228)	50 mg (N = 15)	All 50 mg [a] (N = 77)	Treated subjects	50 mg (N = 191)	All 50 mg [a] (N = 1,228)	50 mg (N = 15)	All 50 mg [a] (N = 77)
SARS-CoV-2 test positive	37 (19.4)	192 (15.6)	1 (6.7)	3 (3.9)	Upper abdominal pain	6 (3.1)	25 (2.0)	1 (6.7)	3 (3.9)
Headache	32 (16.8)	186 (15.1)	2 (13.3)	8 (10.4)	Rash	8 (4.2)	25 (2.0)	0	1 (1.3)
Nasopharyngitis	21 (11.0)	117 (9.5)	1 (6.7)	14 (18.2)	Abdominal pain	8 (4.2)	25 (2.0)	1 (6.7)	3 (3.9)
Acne	22 (11.5)	111 (9.0)	4 (26.7)	12 (15.6)	ALT increased	8 (4.2)	24 (2.0)	0	2 (2.6)
Upper respiratory tract infection	22 (11.5)	104 (8.5)	0	1 (1.3)	Rhinitis	6 (3.1)	23 (1.9)	0	0
Cough	20 (10.5)	93 (7.6)	2 (13.3)	5 (6.5)	Eczema	5 (2.6)	22 (1.8)	0	5 (6.5)
Pyrexia	18 (9.4)	93 (7.6)	5 (33.3)	15 (19.5)	Atopic dermatitis	5 (2.6)	21 (1.7)	1 (6.7)	7 (9.1)
Fatigue	15 (7.9)	77 (6.3)	1 (6.7)	2 (2.6)	Gastroenteritis	6 (3.1)	21 (1.7)	1 (6.7)	4 (5.2)
Oropharyngeal pain	21 (11.0)	74 (6.0)	0	0	Contusion	5 (2.6)	21 (1.7)	1 (6.7)	5 (6.5)
Urticaria	15 (7.9)	74 (6.0)	3 (20.0)	10 (13.0)	COVID-19	9 (4.7)	20 (1.6)	0	0
Folliculitis	16 (8.4)	63 (5.1)	3 (20.0)	7 (9.1)	Gastrooesophageal reflux disease	3 (1.6)	20 (1.6)	1 (6.7)	3 (3.9)
Urinary tract infection	7 (3.7)	62 (5.0)	0	0	Contact dermatitis	5 (2.6)	19 (1.5)	2 (13.3)	9 (11.7)
Diarrhoea	13 (6.8)	58 (4.7)	1 (6.7)	2 (2.6)	Neurosensory deafness	3 (1.6)	18 (1.5)	0	3 (3.9)
Nausea	7 (3.7)	53 (4.3)	1 (6.7)	3 (3.9)	Lymphocyte count decreased	2 (1.0)	16 (1.3)	0	6 (7.8)
Myalgia	5 (2.6)	45 (3.7)	0	1 (1.3)	Herpes zoster	6 (3.1)	16 (1.3)	1 (6.7)	4 (5.2)
Back pain	12 (6.3)	45 (3.7)	1 (6.7)	4 (5.2)	Skin papilloma	1 (0.5)	14 (1.1)	1 (6.7)	3 (3.9)
Arthralgia	11 (5.8)	43 (3.5)	0	2 (2.6)	Lymphopenia	3 (1.6)	13 (1.1)	2 (13.3)	3 (3.9)
Blood CPK increased	13 (6.8)	40 (3.3)	0	1 (1.3)	Constipation	3 (1.6)	13 (1.1)	2 (13.3)	5 (6.5)
Fall	8 (4.2)	36 (2.9)	1 (6.7)	5 (6.5)	Cystitis	4 (2.1)	10 (0.8)	2 (13.3)	2 (2.6)
Nasal congestion	7 (3.7)	33 (2.7)	0	0	Iron deficiency anaemia	1 (0.5)	8 (0.7)	0	3 (3.9)
Tinnitus	6 (3.1)	32 (2.6)	0	0	Gingivitis	2 (1.0)	4 (0.3)	1 (6.7)	3 (3.9)
Dizziness	6 (3.1)	32 (2.6)	0	0	Stomatitis	2 (1.0)	3 (0.2)	2 (13.3)	3 (3.9)
Pain in extremity	5 (2.6)	31 (2.5)	1 (6.7)	3 (3.9)					

MedDRA ver.25.0 (MedDRA/J ver.25.0)

n (%)
Events meeting the following criteria in any treatment group are listed as the main events.
The 50 mg group (Overall population), the All 50 mg group (Overall population), and the All 50 mg group (Japanese subgroup): ≥3%
The 50 mg group (Japanese subgroup): ≥2 subjects
a) Pooled data from subjects who received 50 or 200/50 mg (including the data after subjects switched from placebo to ritlecitinib) and subjects who received 10, 30, or 200/30 mg in Study B7981015 and then 50 mg in Study B7981032 (the data after they started the 50 mg dose)

Two deaths occurred in the AEP All 50 mg group (acute respiratory failure and cardio-respiratory arrest; and breast cancer [1 subject each]), but a causal relationship to study drug was denied for both cases.

Serious adverse events occurred in 52 subjects in the AEP All 50 mg group (appendicitis [4 subjects]; spontaneous abortion; and breast cancer [3 subjects each]; COVID-19; and intervertebral disc protrusion [2 subjects each]; and invasive lobular breast carcinoma; empyema and sepsis; pulmonary embolism; cholelithiasis; staphylococcal sepsis; suicidal ideation and bipolar disorder; malignant melanoma; urinary calculus; acute respiratory failure and cardio-respiratory arrest; syncope; ileus; aortic aneurysm; pyelonephritis and flank pain; joint dislocation and ligament rupture; anaphylactic reaction; tendon rupture; subdural haematoma; Bell's palsy; basal cell carcinoma; cervical polyp; COVID-19 pneumonia and acute respiratory failure; thermal burn; acute myocardial infarction; hypersensitivity; retinal artery occlusion; major depression; bipolar I disorder; vulval abscess; COVID-19 pneumonia, acute respiratory failure, septic shock, and delirium; upper gastrointestinal haemorrhage; varicose vein; testis cancer; foot deformity; cervical

dysplasia; cyst rupture; papillary thyroid cancer; meniscus injury; and Takayasu's arteritis [1 subject each]), and a causal relationship to study drug could not be ruled out for spontaneous abortion; and breast cancer (2 subjects each); and empyema and sepsis; malignant melanoma; pyelonephritis; hypersensitivity; and testis cancer (1 subject each).

Taking account of the pharmacological effects of ritlecitinib, the occurrence of adverse events in clinical studies, the safety profile reported with the currently approved JAK and BTK inhibitors, etc., PMDA reviewed the following specific adverse events in details.

7.R.3.2 Infections

The applicant's explanation about the occurrence of adverse events related to infections following administration of ritlecitinib:

Tables 61 and 62 show the occurrence of adverse events related to infections by safety pool.

Table 61. Occurrence of adverse events related to infections (Safety analysis set, Overall population)

Safety pool	PCPAA						AEP	
Treatment group/Treated subjects	10 mg	30 mg	200/30 mg	50 mg	200/50 mg	Placebo	50 mg	All 50 mg[a)]
N	62	132	129	130	215	213	191	1,228
Total drug exposure (patient-years)	27.7	56.3	58.4	58.3	96.1	95.0	339.1	2,053.7
Infections	20 (32.3) 91.5	48 (36.4) 110.2	48 (37.2) 110.1	43 (33.1) 94.8	88 (40.9) 121.6	66 (31.0) 85.4	100 (52.4) 50.7	559 (45.5) 40.6
Category								
Serious infections	0	1 (0.8) 1.8	0	0	2 (0.9) 2.1	0	2 (1.0) 0.6	12 (1.0) 0.6
Tuberculosis	0	0	0	0	0	0	4 (2.1) 1.2	27 (2.2) 1.3
Pneumonia	0	0	0	0	0	0	0	2 (0.2) 0.1
Pneumocystis pneumonia	0	0	0	0	0	0	0	0
Sepsis	0	0	0	0	1 (0.5) 1.0	0	1 (0.5) 0.3	2 (0.2) 0.1
Opportunistic infections	0	0	0	0	1 (0.5) 1.0	0	0	1 (0.1) 0.05
Herpes zoster	0	0	2 (1.6) 3.4	2 (1.5) 3.5	1 (0.5) 1.0	0	7 (3.7) 2.1	18 (1.5) 0.9
Main events (PT)								
Nasopharyngitis	6 (9.7) 23.6	16 (12.1) 30.8	18 (14.0) 34.0	13 (10.0) 24.2	21 (9.8) 23.0	15 (7.0) 16.4	21 (11.0) 6.9	117 (9.5) 6.1
Upper respiratory tract infection	2 (3.2) 7.4	11 (8.3) 20.2	10 (7.8) 18.0	8 (6.2) 14.4	21 (9.8) 23.3	16 (7.5) 17.6	22 (11.5) 7.0	104 (8.5) 5.4
Folliculitis	2 (3.2) 7.2	3 (2.3) 5.4	8 (6.2) 14.4	4 (3.1) 7.0	12 (5.6) 12.9	4 (1.9) 4.3	16 (8.4) 5.0	63 (5.1) 3.2
Urinary tract infection	0	5 (3.8) 9.0	2 (1.6) 3.5	0	8 (3.7) 8.5	6 (2.8) 6.4	7 (3.7) 2.1	62 (5.0) 3.1
Influenza	2 (3.2) 7.4	1 (0.8) 1.8	0	2 (1.5) 3.5	6 (2.8) 6.4	3 (1.4) 3.2	3 (1.6) 0.9	25 (2.0) 1.2
Sinusitis	0	2 (1.5) 3.6	2 (1.6) 3.4	1 (0.8) 1.7	3 (1.4) 3.2	3 (1.4) 3.2	3 (1.6) 0.9	24 (2.0) 1.2
Rhinitis	0	3 (2.3) 5.4	0	0	0	2 (0.9) 2.1	6 (3.1) 1.8	23 (1.9) 1.1
Gastroenteritis	2 (3.2) 7.4	0	3 (2.3) 5.2	2 (1.5) 3.5	3 (1.4) 3.2	0	6 (3.1) 1.8	21 (1.7) 1.0
COVID-19	0	2 (1.5) 3.6	0	3 (2.3) 5.2	1 (0.5) 1.0	2 (0.9) 2.1	9 (4.7) 2.7	20 (1.6) 1.0
Viral reactivation	1 (1.6) 3.7	5 (3.8) 9.1	5 (3.9) 8.7	4 (3.1) 7.0	2 (0.9) 2.1	5 (2.3) 5.4	12 (6.3) 3.7	45 (3.7) 2.3
Category								
HBV reactivation	0	0	0	0	0	0	0	0
Main events (PT)								
Oral herpes	0	1 (0.8) 1.8	1 (0.8) 1.7	0	1 (0.5) 1.1	0	1 (0.5) 0.3	17 (1.4) 0.8
Herpes zoster	0	0	2 (1.6) 3.4	2 (1.5) 3.5	0	0	6 (3.1) 1.8	16 (1.3) 0.8
Herpes simplex	1 (1.6) 3.7	3 (2.3) 5.4	2 (1.6) 3.5	2 (1.5) 3.5	0	4 (1.9) 4.3	3 (1.6) 0.9	9 (0.7) 0.4

Upper row, n (%); Lower row, Exposure[b)]-adjusted incidence rate per 100 patient-years; See Section 10 for the definitions of events.
MedDRA ver.25.0 (MedDRA/J ver.25.0)
a) Pooled data from subjects who received 50 or 200/50 mg (including the data after subjects switched from placebo to ritlecitinib) and subjects who received 10, 30, or 200/30 mg in Study B7981015 and then 50 mg in Study B7981032 (the data after they started the 50 mg dose)
b) Sum across all subjects, the total time to first event or total exposure if no event (years)

Table 62. Occurrence of adverse events related to infections (Safety analysis set, Japanese subgroup)

Safety pool	PCPAA						AEP	
Treatment group/Treated subjects	10 mg	30 mg	200/30 mg	50 mg	200/50 mg	Placebo	50 mg	All 50 mg[a)]
N Total drug exposure (patient-years)	5 1.9	8 3.7	8 3.8	9 4.2	8 3.3	9 4.2	15 35.0	77 164.4
Infections	2 (40.0) 184.9	2 (25.0) 62.2	6 (75.0) 352.9	3 (33.3) 90.9	3 (37.5) 116.9	3 (33.3) 88.2	9 (60.0) 42.7	43 (55.8) 40.9
Category								
Serious infections, tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, opportunistic infections	0	0	0	0	0	0	0	0
Herpes zoster	0	0	0	0	0	0	1 (6.7) 3.1	4 (5.2) 2.5
Main events (PT)								
Nasopharyngitis	2 (40.0) 184.9	1 (12.5) 29.7	4 (50.0) 150.8	1 (11.1) 25.5	2 (25.0) 68.3	1 (11.1) 26.5	1 (6.7) 3.1	14 (18.2) 9.8
Folliculitis	1 (20.0) 52.2	1 (12.5) 28.1	1 (12.5) 29.9	0	0	0	3 (20.0) 9.8	7 (9.1) 4.5
Gastroenteritis	0	0	0	0	0	0	1 (6.7) 2.9	4 (5.2) 2.5
Herpes zoster	0	0	0	0	0	0	1 (6.7) 3.1	4 (5.2) 2.5
Gingivitis	0	0	0	1 (11.1) 24.2	0	0	1 (6.7) 3.1	3 (3.9) 1.9
Paronychia	0	0	0	0	1 (12.5) 34.0	0	1 (6.7) 3.0	2 (2.6) 1.3
Hordeolum	0	0	0	0	0	0	0	2 (2.6) 1.2
Tonsillitis	0	0	1 (12.5) 28.5	0	0	0	0	2 (2.6) 1.2
Cystitis	0	0	0	1 (11.1) 25.4	0	0	2 (13.3) 6.2	2 (2.6) 1.2
Viral reactivation	0	0	0	1 (11.1) 26.5	0	0	2 (13.3) 6.5	6 (7.8) 3.8
Category								
HBV reactivation	0	0	0	0	0	0	0	0
Reported events (PT)								
Herpes zoster	0	0	0	0	0	0	1 (6.7) 3.1	4 (5.2) 2.5
Oral herpes	0	0	0	0	0	0	0	1 (1.3) 0.6
Herpes simplex	0	0	0	1 (11.1) 26.5	0	0	1 (6.7) 3.0	1 (1.3) 0.6

Upper row, n (%); Lower row, Exposure[b)]-adjusted incidence rate per 100 patient-years; See Section 10 for the definitions of events.
MedDRA ver.25.0 (MedDRA/J ver.25.0)
a) Pooled data from subjects who received 50 or 200/50 mg (including the data after subjects switched from placebo to ritlecitinib) and subjects who received 10, 30, or 200/30 mg in Study B7981015 and then 50 mg in Study B7981032 (the data after they started the 50 mg dose)
b) Sum across all subjects, the total time to first event or total exposure if no event (years)

In the PCPAA pool, although there were no clear differences in the incidences of infections and viral reactivation between the ritlecitinib and placebo groups, when analyzed by category, serious infection, sepsis, opportunistic infection, and herpes zoster occurred in the ritlecitinib group only. Serious infections occurred in 12 subjects in the AEP All 50 mg group (appendicitis [4 subjects]; COVID-19 [2 subjects]; and empyema and sepsis; staphylococcal sepsis; pyelonephritis; vulval abscess; COVID-19 pneumonia; and COVID-19 pneumonia and septic shock [1 subject each]), and a causal relationship to study drug could not be ruled out for empyema and sepsis; and pyelonephritis (1 subject each).

Tuberculosis occurred in 27 subjects in the AEP All 50 mg group, but all of these cases were determined not to meet the criteria for active tuberculosis.

The event adjudicated as an opportunistic infection was non-serious multi-dermatomal herpes zoster.

Though comparisons across different clinical studies have limitations, the incidence rates of infections, serious infections, herpes zoster, and viral reactivation (40.6, 0.6, 0.9, and 2.3/100 patient-years, respectively) in the AEP All 50 mg group were similar to those in patients treated with baricitinib 4 mg according to the pooled data from baricitinib clinical studies in AA patients (44.4, 0.7, 1.5, and 1.8/100 patient-years, respectively [Review Report on Olumiant tablets 2 mg/4 mg as of May 12, 2022]). The incidence rates of serious infections and herpes zoster [95% CI] in external cohorts, which are similar to subjects in Study B7981015, are as follows: 1.15 [0.95, 1.39] and 0.55 [0.42, 0.73]/100 patient-years, respectively, in a retrospective cohort study using a US healthcare claims database (CTD 5.3.5.4.3) and 1.80 [1.61, 2.00] and 1.14 [0.99, 1.30]/100 patient-years, respectively, in a retrospective cohort study using the Danish National Populations Health Registry (CTD 5.3.5.4.2). The incidence rates of these events in the AEP All 50 mg group did not far exceed those in the external cohorts.

There were no clear differences in the occurrence of adverse events related to infections between the Japanese subgroup and the overall population.

Based on the above results, the immunosuppressive effect of ritlecitinib may increase the risk of infections. Thus, the package insert will include warnings/precautions about infections and viral reactivation, and information on the occurrence of serious infections etc. in clinical practice will be collected via post-marketing surveillance etc.

PMDA's view:
Ritlecitinib inhibits JAK3 that is involved in immune responses. Also in clinical studies, serious infections, tuberculosis, pneumonia, sepsis, an opportunistic infection, and herpes zoster were reported. Thus, the package insert should include warnings/precautions about the risk of serious infections etc. following administration of ritlecitinib and advise to take appropriate measures, e.g., screening for tuberculosis before starting ritlecitinib and monitoring during treatment with ritlecitinib.

As to viral reactivation, since reactivation of herpesvirus etc. was reported in clinical studies, the package insert should include warnings/precautions about reactivation of herpesvirus, hepatitis virus, etc.

Moreover, since the number of Japanese patients with AA evaluated in the clinical studies is limited, the occurrence of serious infections etc. following administration of ritlecitinib should be investigated via post-marketing surveillance etc. [for post-marketing surveillance etc., see Section 7.R.7].

7.R.3.3 Thromboembolic events

The applicant's explanation about the occurrence of thromboembolic events following administration of ritlecitinib:

Table 63 shows the occurrence of thromboembolic events by safety pool.

Table 63. Occurrence of thromboembolic events (Safety analysis set, Overall population)

Safety pool	PCPAA						AEP	
Treatment group/Treated subjects	10 mg	30 mg	200/30 mg	50 mg	200/50 mg	Placebo	50 mg	All 50 mg[a)]
N	62	132	129	130	215	213	191	1,228
Total drug exposure (patient-years)	27.7	56.3	58.4	58.3	96.1	95.0	339.1	2,053.7
Thromboembolic events	0	0	0	0	0	0	1 (0.5) 0.3	3 (0.2) 0.2
Reported events (PT)								
Acute myocardial infarction	0	0	0	0	0	0	0	1 (0.1) 0.05
Pulmonary embolism	0	0	0	0	0	0	1 (0.5) 0.3	1 (0.1) 0.05
Retinal artery occlusion	0	0	0	0	0	0	0	1 (0.1) 0.05

Upper row, n (%); Lower row, Exposure[b)]-adjusted incidence rate per 100 patient-years; See Section 10 for the definitions of events.
MedDRA ver.25.0 (MedDRA/J ver.25.0)
a) Pooled data from subjects who received 50 or 200/50 mg (including the data after subjects switched from placebo to ritlecitinib) and subjects who received 10, 30, or 200/30 mg in Study B7981015 and then 50 mg in Study B7981032 (the data after they started the 50 mg dose)
b) Sum across all subjects, the total time to first event or total exposure if no event (years)

A venous thromboembolic event occurred in 1 subject (pulmonary embolism) and arterial thromboembolic events occurred in 2 subjects (retinal artery occlusion; and acute myocardial infarction [1 subject each]) in the AEP All 50 mg group, but a causal relationship to study drug was denied for all those events.[55)] All those subjects had risk factors for thromboembolic events.[56)] The incidence rates of pulmonary embolism (a venous thromboembolic event) and arterial thromboembolic events reported in the AEP All 50 mg group were 0.05 and 0.10/100 patient-years, respectively, which were similar to the incidence rates of pulmonary embolism and arterial thromboembolic events [95% CI] in external cohorts, which are similar to subjects in Study B7981015 (0.07 [0.03, 0.14] and 0.05 [0.02, 0.13]/100 patient-years, respectively, in a retrospective cohort study using a US healthcare claims database, 0.04 [0.01, 0.07] and 0.02 [0.01, 0.05]/100 patient-years, respectively, in a retrospective cohort study using the Danish National Populations Health Registry).

No thromboembolic events were reported in the Japanese subgroup of the PCPAA pool or the AEP.

Based on the above, although an increased risk of thromboembolic events associated with ritlecitinib has not been suggested at present, as thromboembolic events were reported in patients receiving ritlecitinib, and venous thromboembolism is a known safety risk associated with the currently approved JAK inhibitors, the package insert will include a warning/precaution about thromboembolism, and the risk of thromboembolism associated with ritlecitinib will be investigated via post-marketing surveillance etc.

PMDA's view:
Given the occurrence of venous thromboembolism with the currently approved JAK inhibitors and a relevant warning/precaution in their package inserts, and taking into account that thromboembolism was reported in

[55)] The event of pulmonary embolism was considered by the investigator as unrelated to study drug, but was considered by the sponsor as related to study drug.
[56)] The subjects had the following risk factors:
The subject with pulmonary embolism had obesity. The subject with acute myocardial infarction had hyperlipidemia and diabetes mellitus and was a current smoker. The subject with retinal artery occlusion had congenital arterial malformation and antiphospholipid syndrome.

patients receiving ritlecitinib in clinical studies, as with the currently approved JAK inhibitors, the package insert should include a warning/precaution about the risk of venous thromboembolism, and it is necessary to collect post-marketing information on the occurrence of thromboembolism, including published literature, and appropriately provide the obtained information to healthcare professionals in clinical practice.

7.R.3.4 Malignancies

The applicant's explanation about the occurrence of malignancies following administration of ritlecitinib:

Table 64 shows the occurrence of malignancies by safety pool.

Table 64. Occurrence of malignancies (Safety analysis set, Overall population)

Safety pool	PCPAA						AEP	
Treatment group/Treated subjects	10 mg	30 mg	200/30 mg	50 mg	200/50 mg	Placebo	50 mg	All 50 mg [a)]
N	62	132	129	130	215	213	191	1,228
Total drug exposure (patient-years)	27.7	56.3	58.4	58.3	96.1	95.0	339.1	2,053.7
Malignancies	0	0	0	0	1 (0.5) 1.0	0	2 (1.0) 0.6	10 (0.8) 0.5
Category								
NMSC	0	0	0	0	0	0	0	3 (0.2) 0.2
Malignancies (excluding NMSC)	0	0	0	0	1 (0.5) 1.0	0	2 (1.0) 0.6	7 (0.6) 0.3
Lymphoma	0	0	0	0	0	0	0	0
Reported events (PT)								
Breast cancer	0	0	0	0	0	0	2 (1.0) 0.6	3 (0.2) 0.2
Basal cell carcinoma	0	0	0	0	0	0	0	2 (0.2) 0.1
Bowen's disease	0	0	0	0	0	0	0	1 (0.1) 0.05
Malignant melanoma	0	0	0	0	0	0	0	1 (0.1) 0.05
Papillary thyroid cancer	0	0	0	0	0	0	0	1 (0.1) 0.05
Testis cancer	0	0	0	0	0	0	0	1 (0.1) 0.05
Invasive lobular breast carcinoma	0	0	0	0	1 (0.5) 1.0	0	0	1 (0.1) 0.05

Upper row, n (%); Lower row, Exposure[b)]-adjusted incidence rate per 100 patient-years; See Section 10 for the definitions of events.
MedDRA ver.25.0 (MedDRA/J ver.25.0)
a) Pooled data from subjects who received 50 or 200/50 mg (including the data after subjects switched from placebo to ritlecitinib) and subjects who received 10, 30, or 200/30 mg in Study B7981015 and then 50 mg in Study B7981032 (the data after they started the 50 mg dose)
b) Sum across all subjects, the total time to first event or total exposure if no event (years)

In the AEP All 50 mg group, malignancies (excluding non-melanoma skin cancer [NMSC]) occurred in 7 subjects (breast cancer [3 subjects]; and invasive lobular breast carcinoma; papillary thyroid cancer; testis cancer; and malignant melanoma [1 subject each]), and NMSC occurred in 3 subjects (basal cell carcinoma [2 subjects]; and Bowen's disease [1 subject]). A causal relationship to study drug could not be ruled out for breast cancer (2 subjects); and testis cancer; and malignant melanoma (1 subject each).

The incidence rates of malignancies (excluding NMSC) and NMSC in the AEP All 50 mg group were 0.3 and 0.2/100 patient-years, respectively, which were similar to those according to the pooled data from clinical studies of baricitinib in AA patients (the incidence rates of malignancies [excluding NMSC] were 0.3/100 patient-years in the 4 mg group and zero in the 2 mg group; the incidence rates of NMSC were zero in the 4 mg group and 0.2/100 patient-years in the 2 mg group [Review Report on Olumiant tablets 2 mg/4 mg as of

May 12, 2022]). The incidence rates of malignancies (excluding NMSC) [95% CI] in external cohorts, which are similar to subjects in Study B7981015, were 1.00 [0.82, 1.23]/100 patient-years in a retrospective cohort study using a US healthcare claims database and 0.56 [0.46, 0.68]/100 patient-years in a retrospective cohort study using the Danish National Populations Health Registry. The incidence rate in the AEP All 50 mg group did not exceed those in the external cohorts.

No malignancies were reported in the Japanese subgroup of the PCPAA pool or the AEP.

Based on the above, although the effect of ritlecitinib on the occurrence of malignancies is unclear, as the possibility that the immunosuppressive effect of ritlecitinib affects the immune surveillance of malignancies cannot be ruled out, the package insert will include a warning/precaution about malignancies, and the risk of malignancies associated with ritlecitinib will be investigated via post-marketing surveillance etc.

PMDA's view:
Malignancies generally occur infrequently and take some time to develop. It is thus difficult to reach a conclusion on the risk of malignancies associated with ritlecitinib, based on the currently available limited clinical study data. However, the pharmacological effects of ritlecitinib, the possibility that chronic immunosuppression caused by ritlecitinib increases the carcinogenic risk cannot be ruled out. In clinical studies, patients treated with ritlecitinib also showed a similar rate of malignancies to patients treated with baricitinib. Given these outcomes, as with the currently approved JAK inhibitors, the package insert should include a warning etc. about the risk of malignancies associated with ritlecitinib. Also, information on the occurrence of malignancies with ritlecitinib, including the long-term treatment with ritlecitinib, must be further collected via post-marketing surveillance etc. and appropriately provided to healthcare professionals.

7.R.3.5 Cardiovascular events and arrhythmia

The applicant's explanation about the occurrence of cardiovascular events and arrhythmia following administration of ritlecitinib:
Table 65 shows the occurrence of cardiovascular events and arrhythmia by safety pool.

Table 65. Occurrence of cardiovascular events and arrhythmia (Safety analysis set, Overall population)

Safety pool	PCPAA						AEP	
Treatment group/Treated subjects	10 mg	30 mg	200/30 mg	50 mg	200/50 mg	Placebo	50 mg	All 50 mg[a)]
N	62	132	129	130	215	213	191	1,228
Total drug exposure (patient-years)	27.7	56.3	58.4	58.3	96.1	95.0	339.1	2,053.7
Cardiovascular events	2 (3.2) 7.4	4 (3.0) 7.3	2 (1.6) 3.5	6 (4.6) 10.7	5 (2.3) 5.3	4 (1.9) 4.3	13 (6.8) 4.1	67 (5.5) 3.4
Category								
MACE	0	0	0	0	0	0	0	3 (0.2) 0.2
Main events (PT)								
Hypertension	1 (1.6) 3.6	0	0	1 (0.8) 1.7	1 (0.5) 1.0	1 (0.5) 1.1	4 (2.1) 1.2	18 (1.5) 0.9
Palpitations	0	1 (0.8) 1.8	0	1 (0.8) 1.7	1 (0.5) 1.1	1 (0.5) 1.1	3 (1.6) 0.9	12 (1.0) 0.6
Raynaud's phenomenon	0	0	0	0	0	0	0	5 (0.4) 0.2
Atrioventricular block first degree	1 (1.6) 3.7	1 (0.8) 1.8	0	1 (0.8) 1.7	0	0	1 (0.5) 0.3	4 (0.3) 0.2
Sinus bradycardia	0	0	0	1 (0.8) 1.7	1 (0.5) 1.1	1 (0.5) 1.1	2 (1.0) 0.6	4 (0.3) 0.2
Varicose vein	0	0	0	0	0	0	1 (0.5) 0.3	3 (0.2) 0.2
Peripheral venous disease	0	0	0	0	0	0	0	3 (0.2) 0.2
Peripheral coldness	0	0	0	0	0	0	1 (0.5) 0.3	3 (0.2) 0.2
Arrhythmia	0	0	1 (0.8) 1.7	0	0	1 (0.5) 1.1	1 (0.5) 0.3	2 (0.2) 0.1
Reported events (PT)								
Supraventricular tachycardia	0	0	0	0	0	0	0	1 (0.1) 0.05
Sinus tachycardia	0	0	0	0	0	1 (0.5) 1.1	1 (0.5) 0.3	1 (0.1) 0.05
Atrial tachycardia	0	0	1 (0.8) 1.7	0	0	0	0	0

Upper row, n (%); Lower row, Exposure[b)]-adjusted incidence rate per 100 patient-years; See Section 10 for the definitions of events.
MedDRA ver.25.0 (MedDRA/J ver.25.0)
a) Pooled data from subjects who received 50 or 200/50 mg (including the data after subjects switched from placebo to ritlecitinib) and subjects who received 10, 30, or 200/30 mg in Study B7981015 and then 50 mg in Study B7981032 (the data after they started the 50 mg dose)
b) Sum across all subjects, the total time to first event or total exposure if no event (years)

Major adverse cardiovascular events (MACE) occurred in 3 subjects (acute respiratory failure and cardio-respiratory arrest; acute myocardial infarction; and retinal artery occlusion [1 subject each]) in the AEP All 50 mg group, but a causal relationship to study drug was denied for all those events. None of these subjects experienced lipid parameter changes above the normal range, but they had risk factors for cardiovascular events.[57)] The incidence rate of MACE in the AEP All 50 mg group was 0.2/100 patient-years, which was similar to that in the baricitinib 2 mg group according to the pooled data from clinical studies of baricitinib in AA patients (0.2/100 patient-years [zero in the 4 mg group] [Review Report on Olumiant tablets 2 mg/4 mg as of May 12, 2022]). The incidence rates of MACE [95% CI] in external cohorts, which are similar to subjects in Study B7981015, were 1.20 [0.99, 1.45]/100 patient-years in a retrospective cohort study using a US healthcare claims database and 0.58 [0.44, 0.74]/100 patient-years in a retrospective cohort study using the Danish National Populations Health Registry. The incidence rate in the AEP All 50 mg group did not exceed the incidence rates in the external cohorts.

[57)] The subjects had the following risk factors: The subject with acute respiratory failure and cardio-respiratory arrest had a history of smoking. The subject with acute myocardial infarction had hyperlipidemia and diabetes mellitus and was a current smoker. The subject with retinal artery occlusion had congenital arterial malformation and antiphospholipid syndrome.

As arrhythmia is an adverse reaction to some of the currently approved BTK inhibitors, the risk of arrhythmia associated with ritlecitinib was examined. In the AEP All 50 mg group, arrhythmia occurred in 2 subjects (supraventricular tachycardia; and sinus tachycardia [1 subject each]), and a causal relationship to study drug could not be ruled out for sinus tachycardia. However, both events were non-serious and mild in severity and did not lead to study drug interruption or discontinuation, with an outcome of "resolved."

In the Japanese subgroup, a cardiovascular event observed in the AEP All 50 mg group was palpitations (1 subject), and MACE or arrhythmia was not reported.

PMDA's view:
Based on the currently available clinical study data, the causal relationship between ritlecitinib and cardiovascular events is unclear. Given that MACE occurred in subjects treated with ritlecitinib in clinical studies, and that there is a concern about the risk of cardiovascular events associated with the currently approved JAK inhibitors, as with the currently approved JAK inhibitors, the package insert for ritlecitinib should also include a warning/precaution about cardiovascular events. Since cardiovascular events may be related to dyslipidemia, the need for cautionary advice about dyslipidemia should be determined taking account of the clinical study results [see Section 7.R.3.10].

Arrhythmia observed in the clinical studies of ritlecitinib were non-serious and mild in severity and resolved without study drug interruption. Supraventricular tachycardia and sinus tachycardia observed in the clinical studies are arrhythmias with a mechanism different from that of atrial fibrillation, which is mainly listed in the precautions and warnings section of the package inserts for some currently approved BTK inhibitors. A warning/precaution about arrhythmia in the package insert is limited to some of the currently approved BTK inhibitors. Given these points, no clear relationship between ritlecitinib and arrhythmia has been suggested at present.

Post-marketing information should be further collected on the occurrence of both cardiovascular events and arrhythmia following administration of ritlecitinib, including published literature, and appropriately provided to healthcare professionals.

7.R.3.6 Effects on hematological parameters

The applicant's explanation about the effects of ritlecitinib on hematological parameters:
Table 66 shows the occurrence of changes in hematological parameters etc. by safety pool. Patients with low values of these hematological parameters were excluded from the clinical studies.[58)]

[58)] The exclusion criteria as to hematological parameters for the clinical studies included in the AEP are as follows: Study B7931005 [neutrophil count <2,500/mm^3, hemoglobin <10.0 g/dL, hematocrit <30%, platelet count below the lower limit of normal, lymphocyte count <800/mm^3] and other studies [neutrophil count <1,200/mm^3, hemoglobin <11.0 g/dL, hematocrit <33%, platelet count <150,000/mm^3, lymphocyte count <800/mm^3]

Table 66. Occurrence of changes in hematological parameters etc. (Safety analysis set)

Safety pool	PCPAA						AEP	
Treatment group/Treated subjects	10 mg	30 mg	200/30 mg	50 mg	200/50 mg	Placebo	50 mg	All 50 mg [a)]
Overall population								
N	62	132	129	130	215	213	191	1,228
Total drug exposure (patient-years)	27.7	56.3	58.4	58.3	96.1	95.0	339.1	2,053.7
Anaemia	0	0	2 (1.6) 3.5	0	1 (0.5) 1.0	1 (0.5) 1.1	1 (0.5) 0.3	12 (1.0) 0.6
Haemoglobin decreased	0	0	0	0	0	0	2 (1.0) 0.6	9 (0.7) 0.4
Neutrophil count decreased	0	1 (0.8) 1.8	0	0	0	1 (0.5) 1.1	1 (0.5) 0.3	5 (0.4) 0.2
Lymphocyte count decreased	0	1 (0.8) 1.8	2 (1.6) 3.5	2 (1.5) 3.5	6 (2.8) 6.4	2 (0.9) 2.1	4 (2.1) 1.2	24 (2.0) 1.2
Platelet count decreased	0	3 (2.3) 5.4	1 (0.8) 1.7	1 (0.8) 1.7	0	0	1 (0.5) 0.3	3 (0.2) 0.2
Japanese subgroup								
N	5	8	8	9	8	9	15	77
Total drug exposure (patient-years)	1.9	3.7	3.8	4.2	3.3	4.2	35.0	164.4
Anaemia	0	0	0	0	0	0	0	2 (2.6) 1.2
Neutrophil count decreased	0	1 (12.5) 29.9	0	0	0	0	0	0
Lymphocyte count decreased	0	0	2 (25.0) 67.9	0	1 (12.5) 34.8	1 (11.1) 26.3	0	6 (7.8) 3.9
Haemoglobin decreased, Platelet count decreased	0	0	0	0	0	0	0	0

Upper row, n (%); Lower row, Exposure[b)]-adjusted incidence rate per 100 patient-years; See Section 10 for the definitions of events.
MedDRA ver.25.0 (MedDRA/J ver.25.0)
a) Pooled data from subjects who received 50 or 200/50 mg (including the data after subjects switched from placebo to ritlecitinib) and subjects who received 10, 30, or 200/30 mg in Study B7981015 and then 50 mg in Study B7981032 (the data after they started the 50 mg dose)
b) Sum across all subjects, the total time to first event or total exposure if no event (years)

In the PCPAA pool, the incidence of lymphocyte count decreased was higher in the ritlecitinib group than in the placebo group, and platelet count decreased occurred in the ritlecitinib group only. Thus, the package insert will include a warning/precaution about the risk of lymphocyte count decreased and platelet count decreased associated with ritlecitinib. Since there were no marked differences in the incidences of anaemia, haemoglobin decreased, and neutrophil count decreased between the placebo and ritlecitinib groups, and CTCAE grade ≥3 haemoglobin decreased (<8.0 g/dL) or neutrophil count decreased (<1,000/mm^3) did not occur in any treatment group, the risk of these events should be low.

PMDA's view:

As explained by the applicant, an effect of treatment with ritlecitinib was suggested for lymphocyte count decreased and platelet count decreased. Haemoglobin decreased and neutrophil count decreased were reported in subjects treated with ritlecitinib in clinical studies. Non-clinical studies showed effects on red blood cell parameters [see Section 5.R.1.3]. and the package inserts for the currently approved JAK inhibitors contain warnings/precautions about haemoglobin decreased and neutrophil count decreased. Given these points, the risk of haemoglobin decreased and neutrophil count decreased associated with ritlecitinib cannot be ruled out.

Thus, as with the currently approved JAK inhibitors, the package insert should advise the following points in order to minimize the risk of lymphocyte count decreased, platelet count decreased, haemoglobin decreased, and neutrophil count decreased: screening prior to starting ritlecitinib and regular monitoring during treatment with ritlecitinib; and the use of ritlecitinib should be avoided in patients with low values of these parameters.

7.R.3.7 Muscle disorder-related events

The applicant's explanation about the occurrence of muscle disorder-related events following administration of ritlecitinib:

Table 67 shows the occurrence of muscle disorder-related events by safety pool.

Table 67. Occurrence of muscle disorder-related events (Safety analysis set)

Safety pool	PCPAA						AEP	
Treatment group/Treated subjects	10 mg	30 mg	200/30 mg	50 mg	200/50 mg	Placebo	50 mg	All 50 mg [a)]
Overall population								
N	62	132	129	130	215	213	191	1,228
Total drug exposure (patient-years)	27.7	56.3	58.4	58.3	96.1	95.0	339.1	2,053.7
Muscle disorder-related events (rhabdomyolysis/myopathy)	7 (11.3) 27.5	9 (6.8) 16.7	5 (3.9) 8.8	4 (3.1) 7.0	11 (5.1) 11.7	4 (1.9) 4.3	18 (9.4) 5.6	86 (7.0) 4.4
Reported events (PT)								
Myalgia	5 (8.1) 19.3	5 (3.8) 9.1	1 (0.8) 1.7	1 (0.8) 1.7	5 (2.3) 5.3	3 (1.4) 3.2	5 (2.6) 1.5	45 (3.7) 2.2
Blood CPK increased	2 (3.2) 7.4	3 (2.3) 5.4	3 (2.3) 5.2	2 (1.5) 3.5	7 (3.3) 7.4	0	13 (6.8) 4.0	40 (3.3) 2.0
Musculoskeletal pain	0	0	0	1 (0.8) 1.7	0	0	1 (0.5) 0.3	2 (0.2) 0.1
Muscular weakness	0	1 (0.8) 1.8	1 (0.8) 1.7	0	0	1 (0.5) 1.1	0	2 (0.2) 0.1
Muscle rupture	0	0	0	0	0	0	0	1 (0.1) 0.05
Japanese subgroup								
N	5	8	8	9	8	9	15	77
Total drug exposure (patient-years)	1.9	3.7	3.8	4.2	3.3	4.2	35.0	164.4
Muscle disorder-related events (rhabdomyolysis/myopathy)	0	1 (12.5) 30.9	0	0	0	0	0	2 (2.6) 1.2
Reported events (PT)								
Myalgia	0	1 (12.5) 30.9	0	0	0	0	0	1 (1.3) 0.6
Blood CPK increased	0	0	0	0	0	0	0	1 (1.3) 0.6

Upper row, n (%); Lower row, Exposure[b)]-adjusted incidence rate per 100 patient-years; See Section 10 for the definitions of events.
MedDRA ver.25.0 (MedDRA/J ver.25.0)
a) Pooled data from subjects who received 50 or 200/50 mg (including the data after subjects switched from placebo to ritlecitinib) and subjects who received 10, 30, or 200/30 mg in Study B7981015 and then 50 mg in Study B7981032 (the data after they started the 50 mg dose)
b) Sum across all subjects, the total time to first event or total exposure if no event (years)

In the PCPAA pool, the incidence of muscle disorder-related events tended to be higher in the ritlecitinib group than in the placebo group, and 25 subjects treated with ritlecitinib experienced CTCAE grade ≥3 CPK increased. However, most of the muscle disorder-related events observed in the AEP All 50 mg group were myalgia and blood CPK increased, and no subjects experienced rhabdomyolysis or myopathy. Thus, ritlecitinib is unlikely to increase the risk of rhabdomyolysis and myopathy.

PMDA's view:

Although rhabdomyolysis or myopathy was not reported in the clinical studies, blood CPK increased occurred in the ritlecitinib group only in the PCPAA pool. Blood CPK increased is indicative of skeletal muscle or cardiac muscle damage, etc., and muscular effects of persistent increase in CPK following long-term treatment with ritlecitinib are unclear. Thus, as with the currently approved JAK inhibitors, the package insert should include a warning/precaution about muscle disorder-related events, and it is necessary to collect information

on the occurrence of muscle disorder-related events in clinical practice, including published literature, and appropriately provide the obtained information to healthcare professionals in clinical practice.

7.R.3.8 Bleeding events

Bleeding has been reported as an adverse reaction to the currently approved BTK inhibitors.

The applicant's explanation about the occurrence of bleeding events following administration of ritlecitinib:

Table 68 shows the occurrence of bleeding events by safety pool.

Table 68. Occurrence of bleeding events (Safety analysis set)

Safety pool	PCPAA						AEP	
Treatment group/Treated subjects	10 mg	30 mg	200/30 mg	50 mg	200/50 mg	Placebo	50 mg	All 50 mg [a)]
Overall population								
N	62	132	129	130	215	213	191	1,228
Total drug exposure (patient-years)	27.7	56.3	58.4	58.3	96.1	95.0	339.1	2,053.7
Bleeding events	1 (1.6) 3.7	5 (3.8) 9.1	8 (6.2) 14.4	7 (5.4) 12.5	9 (4.2) 9.6	4 (1.9) 4.3	16 (8.4) 5.0	85 (6.9) 4.4
Main events (PT)								
Contusion	0	1 (0.8) 1.8	2 (1.6) 3.5	2 (1.5) 3.5	3 (1.4) 3.2	0	5 (2.6) 1.5	21 (1.7) 1.0
Epistaxis	1 (1.6) 3.7	0	1 (0.8) 1.7	1 (0.8) 1.7	2 (0.9) 2.1	1 (0.5) 1.1	2 (1.0) 0.6	21 (1.7) 1.0
Heavy menstrual bleeding	0	1 (0.8) 1.8	0	0	1 (0.5) 1.0	1 (0.5) 1.1	1 (0.5) 0.3	8 (0.7) 0.4
Haematuria	0	0	1 (0.8) 1.7	0	0	0	0	4 (0.3) 0.2
Intermenstrual bleeding	0	0	0	1 (0.8) 1.7	0	0	1 (0.5) 0.3	4 (0.3) 0.2
Conjunctival haemorrhage	0	0	1 (0.8) 1.7	0	0	0	1 (0.5) 0.3	3 (0.2) 0.2
Blood urine present	0	0	0	0	0	0	1 (0.5) 0.3	3 (0.2) 0.2
Vaginal haemorrhage	0	0	0	0	0	0	0	3 (0.2) 0.2
Japanese subgroup								
N	5	8	8	9	8	9	15	77
Total drug exposure (patient-years)	1.9	3.7	3.8	4.2	3.3	4.2	35.0	164.4
Bleeding events	0	0	0	1 (11.1) 25.1	0	0	2 (13.3) 6.1	7 (9.1) 4.5
Reported events (PT)								
Contusion	0	0	0	1 (11.1) 25.1	0	0	1 (6.7) 3.0	5 (6.5) 3.2
Subdural haematoma	0	0	0	0	0	0	0	1 (1.3) 0.6
Subcutaneous haemorrhage	0	0	0	0	0	0	0	1 (1.3) 0.6
Epistaxis	0	0	0	0	0	0	1 (6.7) 2.9	1 (1.3) 0.6
Vaginal haemorrhage	0	0	0	0	0	0	0	1 (1.3) 0.6

Upper row, n (%); Lower row, Exposure[b)]-adjusted incidence rate per 100 patient-years; See Section 10 for the definitions of events.
MedDRA ver.25.0 (MedDRA/J ver.25.0)
a) Pooled data from subjects who received 50 or 200/50 mg (including the data after subjects switched from placebo to ritlecitinib) and subjects who received 10, 30, or 200/30 mg in Study B7981015 and then 50 mg in Study B7981032 (the data after they started the 50 mg dose)
b) Sum across all subjects, the total time to first event or total exposure if no event (years)

In the PCPAA pool, though the incidence of bleeding events was higher in the ritlecitinib group than in the placebo group, there was no dose-dependent increase, and the finding was not considered clinically significant. Bleeding events occurred in 85 subjects in the AEP All 50 mg group, but the majority of the events were non-serious and mild in severity, with an outcome of “resolved.” Although serious events occurred in 2 subjects

(subdural haematoma [caused by bruise of the head due to fall]; and upper gastrointestinal haemorrhage), the platelet count immediately before the onset of the event was above the lower limit of normal in both subjects, and a causal relationship to study drug was denied for both events.

Although the mechanism underlying bleedings following administration of BTK inhibitors is not completely understood, it is well-known that B-lymphoid neoplasms, for which the currently approved BTK inhibitors are indicated, can suppress the formation of essentially all components of the hematopoietic system, and the combination of the suppressed hematopoiesis caused by the tumor burden and the pharmacological effects of BTK inhibitors could be responsible for bleedings (*Front Cell Dev Biol.* 2021; 9: 630942). Thus, bleedings caused by BTK inhibitors cannot only be associated with BTK inhibition.

Based on the above, given the reported bleeding events in the clinical studies of ritlecitinib, ritlecitinib is unlikely to increase the risk of bleeding events.

PMDA's view:
The incidence of bleeding events tended to be higher in the ritlecitinib group than in the placebo group in the PCPAA pool. Although the mechanism underlying bleedings following administration of BTK inhibitors including ritlecitinib is unknown, BTK inhibition is considered to contribute to bleeding risk to some extent. Given these points, as with the currently approved BTK inhibitors, the package insert should include a warning/precaution about the risk of bleeding associated with ritlecitinib, and it is necessary to collect post-marketing information on the occurrence of bleeding events, including published literature, and appropriately provide the obtained information to healthcare professionals in clinical practice.

7.R.3.9 Audiological and neurological events

The applicant's explanation about the occurrence of audiological and neurological events following administration of ritlecitinib:
Tables 69 and 70 show the occurrence of audiological and neurological events by safety pool.

Table 69. Occurrence of audiological and neurological events (Safety analysis set, Overall population)

Safety pool	PCPAA						AEP	
Treatment group/Treated subjects	10 mg	30 mg	200/30 mg	50 mg	200/50 mg	Placebo	50 mg	All 50 mg [a)]
N	62	132	129	130	215	213	191	1,228
Total drug exposure (patient-years)	27.7	56.3	58.4	58.3	96.1	95.0	339.1	2,053.7
Audiological events	0	1 (0.8) 1.8	0	1 (0.8) 1.7	0	0	2 (1.0) 0.6	12 (1.0) 0.6
Reported events (PT)								
Neurosensory deafness	0	1 (0.8) 1.8	0	1 (0.8) 1.7	0	0	1 (0.5) 0.3	7 (0.6) 0.3
Hypoacusis	0	0	0	0	0	0	1 (0.5) 0.3	3 (0.2) 0.2
Deafness	0	0	0	0	0	0	0	2 (0.2) 0.1
Abnormal audiogram	0	0	0	0	0	0	1 (0.5) 0.3	1 (0.1) 0.05
Unilateral deafness	0	0	0	0	0	0	0	1 (0.1) 0.05
Neurological events	4 (6.5) 15.0	7 (5.3) 12.6	5 (3.9) 8.9	2 (1.5) 3.5	6 (2.8) 6.3	9 (4.2) 9.7	13 (6.8) 4.0	67 (5.5) 3.4
Main events (PT)								
Paraesthesia	0	0	1 (0.8) 1.7	0	1 (0.5) 1.0	1 (0.5) 1.1	1 (0.5) 0.3	11 (0.9) 0.5
Headache	0	3 (2.3) 5.4	1 (0.8) 1.7	0	1 (0.5) 1.0	2 (0.9) 2.1	1 (0.5) 0.3	9 (0.7) 0.4
Hypoaesthesia	0	2 (1.5) 3.6	2 (1.6) 3.5	2 (1.5) 3.5	1 (0.5) 1.0	2 (0.9) 2.1	3 (1.6) 0.9	8 (0.7) 0.4
Migraine	0	0	0	0	0	0	1 (0.5) 0.3	4 (0.3) 0.2
Somnolence	1 (1.6) 3.7	0	0	0	0	1 (0.5) 1.1	1 (0.5) 0.3	3 (0.2) 0.2
Sciatica	0	0	0	0	0	0	0	3 (0.2) 0.2
Syncope	1 (1.6) 3.6	0	0	0	1 (0.5) 1.0	3 (1.4) 3.2	0	3 (0.2) 0.2
Dysgeusia	0	0	0	0	0	0	1 (0.5) 0.3	3 (0.2) 0.2

Upper row, n (%); Lower row, Exposure[b)]-adjusted incidence rate per 100 patient-years; See Section 10 for the definitions of events.
MedDRA ver.25.0 (MedDRA/J ver.25.0)
a) Pooled data from subjects who received 50 or 200/50 mg (including the data after subjects switched from placebo to ritlecitinib) and subjects who received 10, 30, or 200/30 mg in Study B7981015 and then 50 mg in Study B7981032 (the data after they started the 50 mg dose)
b) Sum across all subjects, the total time to first event or total exposure if no event (years)

Table 70. Occurrence of audiological and neurological events (Safety analysis set, Japanese subgroup)

Safety pool	PCPAA						AEP	
Treatment group/Treated subjects	10 mg	30 mg	200/30 mg	50 mg	200/50 mg	Placebo	50 mg	All 50 mg [a)]
N	5	8	8	9	8	9	15	77
Total drug exposure (patient-years)	1.9	3.7	3.8	4.2	3.3	4.2	35.0	164.4
Audiological events	0	0	0	0	0	0	0	1 (1.3) 0.6
Reported events (PT)								
Neurosensory deafness	0	0	0	0	0	0	0	1 (1.3) 0.6
Neurological events	1 (20.0) 53.7	0	0	0	0	0	3 (20.0) 9.6	7 (9.1) 4.6
Reported events (PT)								
Bell's palsy	0	0	0	0	0	0	1 (6.7) 3.0	1 (1.3) 0.6
Eyelid myokymia	0	0	0	0	0	0	0	1 (1.3) 0.6
Eyelid ptosis	0	0	0	0	0	0	1 (6.7) 2.9	1 (1.3) 0.6
Cervical radiculopathy	0	0	0	0	0	0	0	1 (1.3) 0.6
Positional vertigo	0	0	0	0	0	0	0	1 (1.3) 0.6
Headache	0	0	0	0	0	0	0	1 (1.3) 0.6
Dysgeusia	0	0	0	0	0	0	1 (6.7) 3.0	1 (1.3) 0.6
Syncope	1 (20.0) 53.7	0	0	0	0	0	0	0

Upper row, n (%); Lower row, Exposure[b)]-adjusted incidence rate per 100 patient-years; See Section 10 for the definitions of events.
MedDRA ver.25.0 (MedDRA/J ver.25.0)
a) Pooled data from subjects who received 50 or 200/50 mg (including the data after subjects switched from placebo to ritlecitinib) and subjects who received 10, 30, or 200/30 mg in Study B7981015 and then 50 mg in Study B7981032 (the data after they started the 50 mg dose)
b) Sum across all subjects, the total time to first event or total exposure if no event (years)

In the PCPAA pool, audiological events occurred in the ritlecitinib group only. There were no clear differences in the incidence of neurological events between the placebo and ritlecitinib groups.

Although audiological events occurred in 12 subjects and neurological events occurred in 67 subjects in the AEP All 50 mg group, all those events, except for Bell's palsy and syncope (both neurological events), were non-serious, and a causal relationship to study drug was denied also for Bell's palsy and syncope.

The incidence rates of neurosensory deafness, paraesthesia/dysaesthesia, and peripheral neuropathy in the AEP All 50 mg group were 0.6, 1.0, and 0.2/100 patient-years, respectively. The incidence rates of these events [95% CI] in external cohorts, which are similar to subjects in Study B7981015, were as follows: The incidence rates of neurosensory deafness, paraesthesia/dysaesthesia, and peripheral neuropathy were 2.72 [2.40, 3.09], 3.2 [2.9, 3.6], and 4.9 [4.4, 5.3]/100 patient-years, respectively, in a retrospective cohort study using a US healthcare claims database, and the incidence rate of neurosensory deafness was 0.32 [0.24, 0.41]/100 patient-years in a retrospective cohort study using the Danish National Populations Health Registry. The incidence rates of all those events in the AEP All 50 mg group did not far exceed those in the external cohorts.

A phase II, neuro-audiology safety study of ritlecitinib (Study B7981037[59)]) showed no clear effects of ritlecitinib on BAEP results and intraepidermal nerve fiber density/axonal swelling.

Based on the above, ritlecitinib is unlikely to increase the risk of audiological and neurological events.

PMDA's view:
Axonal dystrophies in the central and peripheral nervous systems of unknown relevance to humans were reported in the non-clinical studies of ritlecitinib [see Section 5.2]. Audiological and neurological events for which a causal relationship to study drug could not be ruled out were reported with certain frequencies in the AEP All 50 mg group.[60)] Given these findings, the possibility that audiological and neurological events occur following administration of ritlecitinib cannot be ruled out. Thus, the package insert should contain information on the occurrence of audiological events such as deafness and neurological events such as paraesthesia and headache in the clinical studies. Taking into account that hearing-related events occurred in the ritlecitinib group only and considering the effect of the possible occurrence of more severe hearing-related events, hearing-related events should be listed as an important potential risk, and it is necessary to continue to watch for the occurrence of hearing-related events. It is also necessary to collect post-marketing information on the occurrence of audiological and neurological events, including published literature, and appropriately provide the obtained information to healthcare professionals in clinical practice.

7.R.3.10 Other events

The applicant's explanation about the occurrence of hypersensitivity, renal dysfunction, psychiatric events, hepatic dysfunction, gastrointestinal perforation, interstitial lung disease, and dyslipidemia following administration of ritlecitinib:
Table 71 shows the occurrence of hypersensitivity, renal dysfunction, psychiatric events, hepatic dysfunction, gastrointestinal perforation, interstitial lung disease, and dyslipidemia by safety pool. There were no cases of hepatic dysfunction meeting Hy’s Law criteria.

[59)] CTD 5.3.5.1.3 (Reference data): A foreign study in AA patients aged 18-50 years. Ritlecitinib (200 mg during a 4-week induction phase followed by 50 mg) or placebo was to be administered orally once daily for 9 months, and then all subjects were to receive ritlecitinib 50 mg (subjects on placebo were to be treated with 200 mg during the first 4 weeks) orally once daily for 15 months.
[60)] Among the reported audiological events, a causal relationship to study drug could not be ruled out for hypoacusis; and neurosensory deafness (2 subjects each); and deafness; and neurosensory deafness and unilateral deafness (1 subject each). Among the reported neurological events, a causal relationship to study drug could not be ruled out for headache (5 subjects); hypoaesthesia; and paraesthesia (3 subjects each); dysgeusia; and tinnitus (2 subjects each); and dysaesthesia; paraesthesia, myoclonus, and dyskinesia; hypoaesthesia and paraesthesia; migraine and headache; taste disorder; disturbance in attention; somnolence; and paraesthesia and peripheral neuropathy (1 subject each).

Table 71. Occurrence of other adverse events of special interest (Safety analysis set)

Safety pool	PCPAA						AEP	
Treatment group/Treated subjects	10 mg	30 mg	200/30 mg	50 mg	200/50 mg	Placebo	50 mg	All 50 mg [a)]
Overall population								
N	62	132	129	130	215	213	191	1,228
Total drug exposure (patient-years)	27.7	56.3	58.4	58.3	96.1	95.0	339.1	2,053.7
Hypersensitivity	8 (12.9) 31.4	20 (15.2) 40.1	23 (17.8) 45.0	28 (21.5) 54.7	32 (14.9) 36.4	34 (16.0) 40.2	58 (30.4) 21.2	247 (20.1) 14.1
Category								
Serious hypersensitivity	1 (1.6) 3.6	0	0	0	0	0	0	5 (0.4) 0.2
Renal dysfunction	0	0	0	0	0	0	1 (0.5) 0.3	3 (0.2) 0.2
Psychiatric events	2 (3.2) 7.4	4 (3.0) 7.2	2 (1.6) 3.4	2 (1.5) 3.5	9 (4.2) 9.6	13 (6.1) 14.2	14 (7.3) 4.3	92 (7.5) 4.7
Hepatic dysfunction	2 (3.2) 7.4	2 (1.5) 3.6	4 (3.1) 7.0	1 (0.8) 1.7	6 (2.8) 6.3	1 (0.5) 1.1	12 (6.3) 3.6	51 (4.2) 2.6
Gastrointestinal perforation	0	0	0	0	0	0	0	1 (0.1) 0.05
Interstitial lung disease	0	0	0	0	0	0	0	0
Dyslipidemia	3 (4.8) 11.2	1 (0.8) 1.8	2 (1.6) 3.5	1 (0.8) 1.7	1 (0.5) 1.0	1 (0.5) 1.1	3 (1.6) 0.9	22 (1.8) 1.1
Japanese subgroup								
N	5	8	8	9	8	9	15	77
Total drug exposure (patient-years)	1.9	3.7	3.8	4.2	3.3	4.2	35.0	164.4
Hypersensitivity	1 (20.0) 67.8	3 (37.5) 110.0	3 (37.5) 113.7	3 (33.3) 84.8	1 (12.5) 30.6	2 (22.2) 53.2	6 (40.0) 23.5	32 (41.6) 27.0
Category								
Serious hypersensitivity	0	0	0	0	0	0	0	0
Psychiatric events	0	0	0	0	0	0	0	4 (5.2) 2.5
Hepatic dysfunction	0	0	0	0	0	0	0	2 (2.6) 1.3
Renal dysfunction, gastrointestinal perforation, interstitial lung disease, dyslipidemia	0	0	0	0	0	0	0	0

Upper row, n (%); Lower row, Exposure[b)]-adjusted incidence rate per 100 patient-years; See Section 10 for the definitions of events.
MedDRA ver.25.0 (MedDRA/J ver.25.0)
a) Pooled data from subjects who received 50 or 200/50 mg (including the data after subjects switched from placebo to ritlecitinib) and subjects who received 10, 30, or 200/30 mg in Study B7981015 and then 50 mg in Study B7981032 (the data after they started the 50 mg dose)
b) Sum across all subjects, the total time to first event or total exposure if no event (years)

PMDA's view:

As to hypersensitivity, renal dysfunction, and psychiatric events in the PCPAA pool, the incidence was similar between the placebo and ritlecitinib groups, or no events were reported in any of the treatment groups. No clear relationship between ritlecitinib and hypersensitivity/renal dysfunction/psychiatric events has been suggested at present.

Given that the incidence of hepatic dysfunction tended to be higher in the ritlecitinib group than in the placebo group in the PCPAA pool, and that there is a concern about the risk of hepatic dysfunction associated with the currently approved JAK inhibitors, as with the currently approved JAK inhibitors, the package insert for ritlecitinib should also include a warning/precaution about hepatic dysfunction.

Gastrointestinal perforation or interstitial lung disease did not occur in any of the treatment groups in the PCPAA pool. Also in the AEP All 50 mg group, only 1 subject experienced duodenal ulcer/erosive duodenitis as gastrointestinal perforation-related events. Although the risk of gastrointestinal perforation and interstitial

lung disease associated with ritlecitinib is unclear at present, there is a concern about the risk of gastrointestinal perforation and interstitial lung disease associated with the currently approved JAK inhibitors. Gastrointestinal perforation or interstitial lung disease does not occur at a high frequency, and it is considered difficult to rule out the risk of these events based on their frequencies in the clinical studies of ritlecitinib. Thus, gastrointestinal perforation and interstitial lung disease should be listed as important potential risks, and post-marketing information should be collected.

Although the incidence of dyslipidemia was similar between the placebo and ritlecitinib groups in the PCPAA pool, as lipid parameters were elevated after administration of ritlecitinib,[61)] the package insert should include a warning/precaution about the occurrence of dyslipidemia following administration of ritlecitinib and advise regular monitoring of lipid parameters during treatment with ritlecitinib, etc.

7.R.3.11 Safety in adolescents

The applicant's explanation about the safety of ritlecitinib in adolescent (≥12 and <18 years of age) AA patients: Table 72 shows a summary of safety of ritlecitinib in the adult and adolescent subgroups by safety pool. There were no clear differences in the summary of safety between the adult and adolescent subgroups.

[61)] The mean changes from baseline in lipid parameters ± SD (N) in the 50 mg and placebo groups in the PCPAA pool are as follows (at Weeks 4, 12, and 24]): [Total cholesterol] [−0.4 ± 22.1 (114), 7.5 ± 20.6 (106), 5.6 ± 22.1 (97)] in the 50 mg group, [−2.7 ± 21.6 (118), 0.4 ± 22.4 (113), −2.1 ± 22.3 (134)] in the placebo group; [HDL cholesterol] [0.0 ± 6.8 (114), 0.1 ± 7.6 (106), −0.2 ± 8.1 (97)] in the 50 mg group, [0.3 ± 7.3 (118), 0.2 ± 8.3 (113), −0.1 ± 9.5 (134)] in the placebo group; [LDL cholesterol] [−2.2 ± 18.2 (111), 4.2 ± 18.9 (102), 3.5 ± 18.3 (95)] in the 50 mg group, [−3.9 ± 18.0 (116), −0.4 ± 19.4 (113), −0.8 ± 17.8 (134)] in the placebo group; [Triglycerides] [6.2 ± 33.7 (112), 15.6 ± 36.6 (103), 11.5 ± 37.5 (95)] in the 50 mg group, [2.9 ± 45.9 (117), 2.8 ± 36.2 (113), −6.5 ± 47.7 (134)] in the placebo group

Table 72. Summary of safety of ritlecitinib (Safety analysis set)

Safety pool	PCPAA						AEP	
Treatment group/Treated subjects	10 mg	30 mg	200/30 mg	50 mg	200/50 mg	Placebo	50 mg	All 50 mg[a)]
Adult subgroup (≥18 years)								
N	53	112	110	112	195	194	164	1,056
Total drug exposure (patient-years)	23.5	47.0	49.5	50.3	86.9	86.1	292.8	1,762.9
All adverse events	37 (69.8) 324.6	82 (73.2) 384.3	77 (70.0) 338.6	83 (74.1) 372.8	136 (69.7) 330.3	133 (68.6) 323.2	153 (93.3) 224.0	854 (80.9) 152.7
Serious adverse events	0	1 (0.9) 2.1	0	0	4 (2.1) 4.6	4 (2.1) 4.7	9 (5.5) 3.1	48 (4.5) 2.8
Death	0	0	0	0	0	0	0	2 (0.2) 0.1
Adverse events leading to treatment discontinuation	1 (1.9) 4.3	4 (3.6) 8.5	0	1 (0.9) 2.0	6 (3.1) 6.9	5 (2.6) 5.8	16 (9.8) 5.5	60 (5.7) 3.4
Adverse drug reactions	14 (26.4) 72.0	39 (34.8) 111.4	39 (35.5) 107.7	39 (34.8) 102.2	65 (33.3) 101.1	62 (32.0) 96.0	87 (53.0) 48.5	389 (36.8) 31.1
Adolescent subgroup (≥12 and <18 years)								
N	9	20	19	18	20	19	27	172
Total drug exposure (patient-years)	4.1	9.3	8.9	8.0	9.3	8.9	46.3	290.8
All adverse events	6 (66.7) 276.7	13 (65.0) 270.3	14 (73.7) 336.4	15 (83.3) 572.5	15 (75.0) 339.7	15 (78.9) 364.5	26 (96.3) 401.2	135 (78.5) 133.0
Serious adverse events	2 (22.2) 49.9	0	0	0	0	0	1 (3.7) 2.2	4 (2.3) 1.4
Death	0	0	0	0	0	0	0	0
Adverse events leading to treatment discontinuation	1 (11.1) 24.2	0	0	1 (5.6) 12.5	0	0	3 (11.1) 6.5	8 (4.7) 2.8
Adverse drug reactions	5 (55.6) 170.2	6 (30.0) 84.4	7 (36.8) 105.2	8 (44.4) 137.2	6 (30.0) 86.5	6 (31.6) 86.5	13 (48.1) 49.9	62 (36.0) 29.8

Upper row, n (%); Lower row, Exposure[b)]-adjusted incidence rate per 100 patient-years

a) Pooled data from subjects who received 50 or 200/50 mg (including the data after subjects switched from placebo to ritlecitinib) and subjects who received 10, 30, or 200/30 mg in Study B7981015 and then 50 mg in Study B7981032 (the data after they started the 50 mg dose)

b) Sum across all subjects, the total time to first event or total exposure if no event (years)

With respect to the main adverse events in the AEP All 50 mg group, the events reported at a higher incidence in the adolescent subgroup than in the adult subgroup (a ≥5% incidence and a >5% higher incidence in the adolescent subgroup than in the adult subgroup) were acne (16.9% [29 of 172 subjects] in the adolescent subgroup, 7.8% [82 of 1,056 subjects] in the adult subgroup) only, and there were no clear differences in the reported events between the adult and adolescent subgroups. Also as to the occurrence of the events analyzed in Sections 7.R.3.2 to 7.R.3.10, there were no clear differences between the adult and adolescent subgroups.

As to growth-related events, given the following points, no effects of ritlecitinib on growth have been suggested.

- The incidence of fractures was 1.7% (3 of 172 subjects [tibia fracture; clavicle fracture and radius fracture; and hand fracture (1 subject each)]) and the incidence rate of fractures was 1.1/100 patient-years in the adolescent subgroup in the AEP All 50 mg group, which were similar to the incidence of fractures in the adult subgroup (1.6% [17 of 1,056 subjects]) and the incidence rate of fractures in the general adolescent population (1.33/100 person-years).[62)] All of the events observed in the adolescent subgroup were fractures caused by exercise, and their causal relationship to study drug was denied.
- There were no adverse events related to growth disturbance[63)] in the adolescent subgroup in the AEP All 50 mg group.

62) *J Bone Miner Res.* 2004; 19: 1976-81

63) Growth disorder (PT), growth failure (PT), growth retardation (PT), body height below normal (PT), body height abnormal (PT), and body height decreased (PT)

- For adolescent subjects in the AEP, growth curves and growth velocity curves by gender and treatment group (50 mg group and All 50 mg group) were created and visually evaluated. Adolescent subjects in the overall population largely grew according to the standard growth curves and growth velocity curves. A similar trend was observed also in the Japanese subgroup.

Based on the above, no safety concerns about ritlecitinib unique to adolescent AA patients have been suggested.

PMDA's view:
The currently available clinical study results have suggested no safety concerns about ritlecitinib unique to adolescent AA patients. However, as safety evaluation in Japanese adolescent AA patients in clinical studies was very limited, it is necessary to continue to collect information on the safety of ritlecitinib (including the effect of ritlecitinib on growth) in adolescent AA patients, including published literature, and appropriately provide the obtained information to healthcare professionals in clinical practice.

PMDA's view on the safety of ritlecitinib, including the above considerations in Sections 7.R.3.1 to 11:
Given the submitted clinical study results, the pharmacological effects of ritlecitinib, etc., no serious safety concerns about ritlecitinib in patients with AA have been identified. Thus, the reported adverse events can be managed by providing precaution/warning information described so far and advising that ritlecitinib should be used under the supervision of a physician with adequate knowledge of ritlecitinib and knowledge of and experience in the treatment of AA, etc., as with the currently approved JAK inhibitors. However, serious adverse events including serious infections were also reported in clinical studies, and the risk of malignancies etc. associated with the long-term treatment with ritlecitinib is unclear at present. In addition to the risks associated with the currently approved JAK inhibitors, the risks related to bleeding and hearing are anticipated. Given these points, it is necessary to continue to collect information via post-marketing surveillance etc. and published literature, and appropriately provide the obtained information to healthcare professionals in clinical practice.

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

7.R.4 Clinical positioning

The applicant's explanation about the intended population for ritlecitinib:
AA is divided into the acute phase (approximately 6 months) during which the hair loss rapidly spreads after becoming aware of its symptoms, and the fixed phase during which alopecia persists beyond the acute phase. AA is treated, taking account of disease type, severity, age, disease activity, etc. Since patients who present acutely with a few circular patches of scalp hair loss often recover within 1 year, these patients may be followed without treatment. On the other hand, contact immunotherapy, ultraviolet phototherapy, etc., should be considered for severe AA in the fixed phase (the Japanese clinical practice guidelines).

Under such treatment paradigm for AA, Study B7981015 in adult and adolescent (aged ≥12 years) AA patients

with ≥50% scalp hair loss (SALT score ≥50) without evidence of terminal scalp hair regrowth within the previous 6 months (the fixed phase) showed a trend towards a greater improvement with ritlecitinib compared with placebo for the primary endpoint of the SALT ≤20 response rate and other efficacy endpoints, and this trend towards an improvement was observed regardless of age, disease type, prior treatment, etc. Thus, ritlecitinib is considered to have efficacy [see Section 7.R.2] and acceptable safety [see Section 7.R.3] in AA patients with extensive hair loss. Since Study B7981015 enrolled AA patients with a current episode of hair loss ≤10 years [see Sections 7.2.1 and 7.R.1], the efficacy of ritlecitinib in AA patients with a current episode of hair loss >10 years was not studied. However, given that tofacitinib was effective even in AA patients with a current episode of hair loss >10 years (*JCI Insight*. 2016; 1: e89776), there is no need to restrict the use of ritlecitinib to shorter duration disease.

In the clinical studies of ritlecitinib, the concomitant use of topical corticosteroids etc., intralesional steroid injection, contact immunotherapy, systemic corticosteroids, JAK inhibitors, etc. was prohibited, and there are no data on the concomitant use of ritlecitinib with these treatments. However, topical corticosteroids could be applied to areas other than those under assessment, and there were no safety concerns about its concomitant use. Intralesional steroid injection and contact immunotherapy are used only locally, and according to the AA expert consensus statements (*J Am Acad Dermatol*. 2020; 83: 123-30), systemic corticosteroids and other topical agents may be used in combination with other treatments including JAK inhibitors. Given these points, there should be no particular safety concerns about their concomitant use with ritlecitinib. On the other hand, the concomitant use of ritlecitinib with immunomodulatory biologics, other JAK inhibitors, or potent immunosuppressants such as cyclosporine is expected to increase the risk of infection. Thus, the package insert will advise against the concomitant use of ritlecitinib with these agents.

Based on the above, ritlecitinib will become a new treatment for AA patients with extensive hair loss aged ≥12 years.

PMDA's conclusion:
Given the submitted clinical study results and the treatment paradigm for AA, ritlecitinib can become a new treatment option for AA patients with extensive hair loss aged ≥12 years. In light of the safety profile of ritlecitinib, etc., it is important that prior to the use of ritlecitinib, physicians who are familiar with the diagnosis and treatment of AA carefully balance the expected risks and benefits for individual patients, with an understanding of the clinical study results including the study population, and carefully decide the use of ritlecitinib or the concomitant use of ritlecitinib with other drugs etc., referring to the updated information, e.g., the clinical practice guidelines. The clinical positioning of ritlecitinib is expected to be discussed at the relevant academic societies etc., taking also account of post-marketing information etc.

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

7.R.5 Indication

PMDA's view:

Given the submitted data and the considerations in Sections 7.R.2, 7.R.3, and 7.R.4, AA patients eligible for ritlecitinib should be intractable patients with extensive hair loss, without evidence of spontaneous hair regrowth within a specified period, as with the currently approved JAK inhibitors. Thus, the appropriate indication should be "alopecia areata (limited to intractable cases involving extensive hair loss)," and taking account of the patient population of Study B7981015, the following statements should be included in the PRECAUTIONS CONCERNING INDICATION section of the package insert.

- Ritlecitinib should be used in patients with appropriately ≥50% scalp hair loss at the start of treatment, without evidence of spontaneous hair regrowth within the previous 6 months.
- Ritlecitinib is not indicated for other types of alopecia.

Prior to the use of ritlecitinib, it is important to select eligible patients, with an understanding of the clinical study results including the study population. Thus, the package insert etc. should provide information on the study population and clinical study results.

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

7.R.6 Dosage and administration

The applicant's explanation:

Given the following points, the proposed dosage and administration statement is "The usual dosage for adults and adolescents aged 12 years and older is 50 mg of ritlecitinib administered orally once daily."

- In Study B7981015, pairwise comparisons between ritlecitinib and placebo showed statistically significant differences in the primary endpoint of the SALT ≤20 response rate at Week 24, except for the 10 mg group, which was included only to support the characterization of the exposure response. The study demonstrated the superiority of ritlecitinib (excluding the 10 mg group) to placebo (Table 43).
- With regard to the results of the key efficacy endpoints for Study B7981015, there was a trend towards a greater improvement in the 50 mg group than in the 30 mg group at all time points. On the other hand, there was a trend towards a greater improvement in the 200/50 mg group than in the 50 mg group up to Week 24, but the response rate was similar between the two groups at Week 48, and the effect of a 200 mg loading dose did not tend to be sustained over longer duration of treatment [see Section 7.R.2].
- There were no clear differences in safety among the 30 mg, 50 mg, and 200/50 mg groups in the PCPAA pool [see Section 7.R.3], whereas an exposure-response analysis suggested an increased risk of infection and rash with increasing ritlecitinib exposure and the possibility that the risk of infection and rash is increased during the early phase of treatment with a 200 mg loading dose [see Section 6.4].
- No safety concerns unique to adolescent patients with AA were suggested [see Section 7.R.3.11].

PMDA accepted the applicant's explanation and concluded from the submitted data and the considerations in Sections 7.R.2 and 7.R.3 that the proposed dosage and administration statement of "The usual dosage for adults and adolescents aged 12 years and older is 50 mg of ritlecitinib administered orally once daily." is acceptable.

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

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

The applicant plans to conduct a specified use-results survey to assess the safety and efficacy of ritlecitinib, including the long-term treatment with ritlecitinib, in clinical practice, and to collect information on the occurrence of serious infections, malignancies, etc.

PMDA's view:

As discussed in Section 7.R.3, ritlecitinib is considered to have the risks associated with the currently approved JAK inhibitors and the risks related to bleeding and hearing. Thus, for the management of these risks, ritlecitinib should be used under the supervision of a physician with adequate knowledge of ritlecitinib and knowledge of and experience in the treatment of AA, and serious infections etc. should be managed in cooperation with other departments/medical institutions, as needed. In addition to these safety measures for the currently approved JAK inhibitors, it is necessary to adequately alert physicians to the risks related to bleeding and hearing, also utilizing information materials etc. Then, since ritlecitinib is intended to be administered for long periods, the effect of irreversible inhibition of JAK3 and the TEC family kinases over a long period is unclear, and the number of Japanese patients with AA included in the clinical studies was limited etc., the long-term safety and efficacy of ritlecitinib in Japanese patients with AA should be further investigated in clinical practice via post-marketing surveillance etc.

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 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 5.3.5.1.2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals

and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that ritlecitinib has efficacy in the treatment of intractable AA with extensive hair loss, and that ritlecitinib has acceptable safety in view of its benefits. Ritlecitinib is clinically meaningful because it offers a new treatment option for patients with intractable AA with extensive hair loss. The long-term safety etc. of ritlecitinib in Japanese AA patients should be further investigated in clinical practice via post-marketing surveillance etc.

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

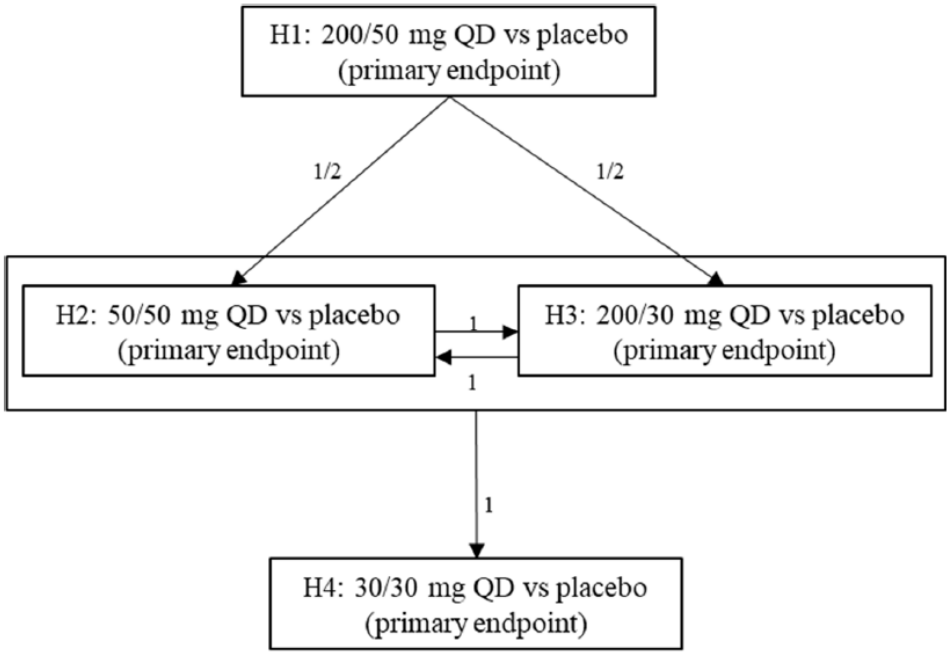
10. Others

The method of efficacy assessment and the definitions of endpoints in clinical studies of ritlecitinib are shown below.

Endpoint	Definition
SALT score	The percentage of hair loss (visual assessment) in each of the 4 areas of the scalp (the top, the back, the right side of the scalp, the left side of the scalp) (0%-100%) is determined and is multiplied by the percentage of scalp covered by that area (the top = 40%, the back = 24%, the right side = 18%, the left side = 18%). The total sum of the 4 products of each area will give the SALT score. Only terminal hair is included in the SALT; vellus hair or any fine downy hair is not taken into account in the SALT scoring process. A SALT score of 0 indicates “no scalp hair loss” and a SALT score of 100 indicates “complete scalp hair loss.”
SALT ≤10 response rate SALT ≤20 response rate	The proportion of subjects achieving a SALT score of ≤10 or ≤20
SALT50/75/90/100 response rate	The proportion of subjects achieving a ≥50%/≥75%/≥90%/100% improvement from baseline in SALT score
EBA score	A 4-point (0-3) numeric rating scale to characterize eyebrow hair loss. The EBA is rated by the investigator. 0: None (No eyebrow hair) 1: Minimal Eyebrow ● Normal or decreased density of one or both eyebrows with large gap(s), OR ● Severely decreased density of one or both eyebrows with or without gap(s). 2: Moderate Eyebrow ● Normal density of both eyebrows with short gap(s) that does not significantly distort the appearance of the eyebrows, OR ● Mildly decreased density of eyebrows with or without short gap(s), OR ● Moderately decreased density of eyebrows without short gap(s). There is visual definition of eyebrows at a distance of 3 feet (approximately 1 m). 3: Normal Eyebrow (Normal density of both right and left eyebrows spanning usual length (i.e., from glabella to near temple) and width. There are no gap(s).)
ELA score	A 4-point (0-3) numeric rating scale to characterize eyelash hair loss. The ELA is rated by the investigator. 0: None (No eyelashes of both right and left upper and lower eyelashes) 1: Minimal Eyelash (Modestly or severely decreased density of and/or large gap(s) in one or both upper eyelashes.) 2: Moderate Eyelash ● Normal density of both upper eyelashes without gap(s), and decreased density or gap(s) is present in one or both lower eyelashes, OR ● Normal density of both upper eyelashes with short gap(s), OR ● Mildly decreased density of one or both upper eyelashes with or without short gap(s). 3: Normal Eyelash (Normal density of both right and left upper and lower eyelashes from near medial canthus to near lateral canthus without any gap(s).)
Proportion of subjects with EBA response	The proportion of subjects with at least a 2-grade improvement from baseline or a score of 3 in the EBA scale among subjects with eyebrow involvement at baseline (an EBA score of ≤2)
Proportion of subjects with ELA response	The proportion of subjects with at least a 2-grade improvement from baseline or a score of 3 in the ELA scale among subjects with eyelash involvement at baseline (an ELA score of ≤2)
PGI-C response rate	PGI-C is a patient-reported outcome measure asking the subject to evaluate the improvement or worsening of their AA as compared to the start of the study using a scale of 7 responses: "greatly worsened," "moderately worsened," "slightly worsened," "not changed," "slightly improved," "moderately improved, "greatly improved." The PGI-C response rate is defined as the proportion of subjects with a PGI-C score of “moderately improved” or “greatly improved.”
Proportion of P-Sat responders	P-Sat assesses patient satisfaction with hair regrowth since the start of the study in 3 domains: “amount,” “quality,” and “overall.” Subjects will select one of 7 responses: "very dissatisfied," "moderately dissatisfied," "slightly dissatisfied," "neither satisfied nor dissatisfied, "slightly satisfied," "moderately satisfied," "very satisfied." The proportion of P-Sat item responders is defined as the proportion of subjects with P-Sat responses of "slightly," "moderately," or "very” satisfied for each domain.
AAPPO	AAPPO is an 11-item questionnaire to assess hair loss (the scalp, eyebrows, eyelashes, and body [4 items]) and its impacts on emotional symptoms (4 items) and activity limitations (3 items). [Hair loss] Subjects will describe the amount of hair loss using a 5-point response scale: "no hair loss," "a little hair loss," "moderate hair loss," "a great deal of hair loss," "complete hair loss" [Impacts on emotional symptoms and activity limitations] The questions are listed below. Subjects will rate the impact of AA using a 5-point response scale: "0: Never/Not at all," "1: Rarely/A little," "2: Sometimes/Moderately," "3: Often/A great deal," "4: Always/Completely" [Impact on emotional symptoms] ● Over the past week, how often did you feel self-conscious about your hair loss? ● Over the past week, how often did you feel embarrassed about your hair loss? ● Over the past week, how often did you feel sad about your hair loss? ● Over the past week, how often did you feel frustrated about your hair loss? [Impact on activity limitations] ● Over the past week, how much did you limit your participation in outdoor activities because of your hair loss? ● Over the past week, how much did you limit your exercise or other physical activity because of your hair loss? ● Over the past week, how much did you limit your interactions with others because of your hair loss? The proportion of subjects with improvement on hair loss items: The proportion of subjects with moderate, a great deal of, or complete hair loss at baseline who achieved "no hair loss" or "a little hair loss" Emotional symptoms score and activity limitations score: the mean of emotional symptoms or activity limitations items

For the analysis of the primary endpoint for a global phase II/III study (Study B7981015), graphical approach was used to adjust for multiplicity. The details of graphical approach are shown in the figure below.

[Study B7981015]



If both the H2 and H3 tests are rejected, then H4 can be tested.

The definitions of events listed in Section 7.R.3 are shown below.

Event	Definition
Infections	PTs in "infections and infestations (SOC)"
Serious infections	Infections reported as serious adverse events
Tuberculosis	Events identified by the following PTs. adrenal gland tuberculosis, bone tuberculosis, bovine tuberculosis, choroid tubercles, congenital tuberculosis, mammary tuberculosis, tuberculous tenosynovitis, oesophageal tuberculosis, oral tuberculosis, pericarditis tuberculous, tuberculosis of eye, tuberculosis of genitourinary system, tuberculosis of intrathoracic lymph nodes, tuberculosis of peripheral lymph nodes, tuberculosis ureter, conjunctivitis tuberculous, cutaneous tuberculosis, disseminated Bacillus Calmette-Guerin infection, disseminated tuberculosis, ear tuberculosis, epididymitis tuberculous, erythema induratum, extrapulmonary tuberculosis, female genital tract tuberculosis, immune reconstitution inflammatory syndrome associated tuberculosis, intestinal tuberculosis, joint tuberculosis, latent tuberculosis, lupus vulgaris, lymph node tuberculosis, male genital tract tuberculosis, peritoneal tuberculosis, prostatitis tuberculous, pulmonary tuberculoma, pulmonary tuberculosis, renal tuberculosis, salpingitis tuberculous, silicotuberculosis, spleen tuberculosis, thyroid tuberculosis, tuberculoma of central nervous system, tuberculosis, tuberculosis bladder, tuberculosis gastrointestinal, tuberculosis liver, tuberculosis of central nervous system, tuberculous endometritis, tuberculous laryngitis, tuberculous pleurisy, meningitis tuberculous, mycobacterium tuberculosis complex test, mycobacterium tuberculosis complex test positive, tuberculin test, tuberculin test false positive, tuberculin test positive, interferon gamma release assay, interferon gamma release assay positive, atypical mycobacterium test positive, seroconversion test, seroconversion test positive, false positive tuberculosis test
Opportunistic infections	Events adjudicated by an external adjudication committee
Herpes zoster	Events identified by the following PTs. herpes zoster, genital herpes zoster, herpes zoster cutaneous disseminated, herpes zoster infection neurological, herpes zoster meningitis, herpes zoster meningoencephalitis, herpes zoster meningomyelitis, herpes zoster meningoradiculitis, herpes zoster necrotising retinopathy, herpes zoster oticus, herpes zoster pharyngitis, herpes zoster reactivation, ophthalmic herpes zoster, varicella zoster gastritis, varicella zoster oesophagitis, varicella zoster pneumonia, varicella zoster sepsis, varicella zoster virus infection, post herpetic neuralgia
Viral reactivation	PTs in HLTs "herpes viral infections," "cytomegaloviral infections," "Epstein-Barr viral infections," "parvoviral infections," "polyomavirus infections," and "adenoviral infections"
Thromboembolic events	Including arterial and venous thromboembolism. Arterial thromboembolism: Events identified by the following PT.

Event	Definition
	acute myocardial infarction, amaurosis, amaurosis fugax, aortic embolus, aortic thrombosis, arterial occlusive disease, arterial thrombosis, basal ganglia infarction, basilar artery occlusion, basilar artery thrombosis, blindness transient, brachiocephalic artery occlusion, capsular warning syndrome, carotid arterial embolus, carotid artery occlusion, carotid artery thrombosis, cerebellar artery occlusion, cerebellar artery thrombosis, cerebral artery occlusion, cerebral artery embolism, cerebral artery thrombosis, cerebral hypoperfusion, cerebrovascular stenosis, coeliac artery occlusion, coronary artery embolism, coronary artery occlusion, coronary artery thrombosis, embolism arterial, femoral artery embolism, hepatic artery embolism, hepatic artery occlusion, hepatic artery thrombosis, iliac artery embolism, iliac artery occlusion, ischaemic cerebral infarction, ischaemic stroke, lacunar infarction, leriche syndrome, mesenteric arterial occlusion, mesenteric artery embolism, mesenteric artery stenosis, mesenteric artery thrombosis, myocardial infarction, myocardial necrosis, papillary muscle infarction, penile artery occlusion, peripheral arterial occlusive disease, peripheral artery occlusion, peripheral artery thrombosis, peripheral embolism, post procedural myocardial infarction, postinfarction angina, precerebral artery occlusion, precerebral artery thrombosis, pulmonary artery occlusion, pulmonary artery thrombosis, renal artery occlusion, renal artery thrombosis, renal embolism, retinal artery embolism, retinal artery occlusion, retinal artery thrombosis, silent myocardial infarction, spinal artery embolism, spinal artery thrombosis, splenic artery thrombosis, splenic embolism, subclavian artery embolism, subclavian artery occlusion, subclavian artery thrombosis, transient ischaemic attack, truncus coeliacus thrombosis, vertebral artery occlusion, vertebral artery thrombosis Venous thromboembolism: Events specified by an external adjudication committee
NMSC	Events adjudicated by an external adjudication committee
Malignancies excluding NMSC	Events adjudicated by an external adjudication committee
Cardiovascular events	PTs in "cardiac disorders (SOC)" and "vascular disorders (SOC)"
MACE	Events adjudicated by an external adjudication committee
Arrhythmia	PTs in "supraventricular tachyarrhythmias (SMQ)" (narrow) and "tachyarrhythmia terms, nonspecific (SMQ)" (narrow)
Lymphocyte count decreased	Events identified by the following PTs. "lymphocyte count decreased," "B-lymphocyte count decreased," "CD4 lymphocytes decreased," "CD8 lymphocytes decreased," "natural killer cell count decreased," "T-lymphocyte count decreased"
Rhabdomyolysis/Myopathy	PTs in "rhabdomyolysis/myopathy (SMQ)" (narrow and broad)
Bleeding events	PTs in "haemorrhages (SMQ)" (narrow)
Audiological events	Events adjudicated by an external adjudication committee
Neurological events	Events adjudicated by an external adjudication committee
Hypersensitivity	PTs in "hypersensitivity (SMQ)" (narrow and broad)
Serious hypersensitivity	Hypersensitivity reported as serious events
Renal dysfunction	PTs in "renal disorders (excl nephropathies) (HLGT)" and "nephropathies (HLGT)"
Psychiatric events	PTs in "psychiatric disorders (SOC)"
Hepatic dysfunction	PTs in "hepatic disorders (SMQ)" (narrow and broad)
Gastrointestinal perforation	PTs in "gastrointestinal ulceration and perforation (HLGT)"
Interstitial lung disease	PTs in "interstitial lung disease (SMQ)" (narrow and broad)
Dyslipidaemia	PTs in "dyslipidaemia (SMQ)" (narrow)

Review Report (2)

May 16, 2023

Product Submitted for Approval

Brand Name	Litfulo Capsules 50 mg
Non-proprietary Name	Ritlecitinib Tosilate
Applicant	Pfizer Japan Inc.
Date of Application	August 25, 2022

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 ritlecitinib presented in the Review Report (1) and made the following comment.

- The expert advisors support PMDA's conclusion on the efficacy of ritlecitinib drawn on the basis of the results of Study B7981015 etc. Meanwhile, as to the handling of missing data in the primary analysis of Study B7981015, subjects with missing data due to COVID-19 related reasons were excluded from the analysis, which was not appropriate based on the intention-to-treat (ITT) principle.

1.2 Safety, post-marketing investigations and safety measures, and risk management plan (draft)

At the Exert Discussion, the expert advisors supported PMDA's conclusions concerning the safety of ritlecitinib, post-marketing investigations and safety measures presented in the Review Report (1) and made the following comment.

- No serious safety concerns about ritlecitinib have been suggested at present. However, despite that ritlecitinib is intended for long-term administration, the duration of treatment and the number of Japanese patients enrolled in the clinical studies were limited. Audiological adverse events etc. associated with ritlecitinib have been reported. Given these points, the applicant should collect information on long-term

safety of ritlecitinib in Japanese patients with AA via post-marketing surveillance etc. and assess the safety of ritlecitinib in clinical practice.

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, PMDA has concluded that the risk management plan (draft) for ritlecitinib should include the safety specification presented in Table 73, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 74. PMDA instructed the applicant to conduct post-marketing surveillance etc. that cover these issues.

Table 73. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
· Serious infections (including tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, and opportunistic infections) · Herpes zoster · Venous thromboembolism · Hepatic dysfunction · Reactivation of hepatitis B virus · Decreased neutrophil count, decreased lymphocyte count, decreased hemoglobin, decreased platelet count · Bleeding	· Malignancies · Gastrointestinal perforation · Interstitial pneumonia · Rhabdomyolysis, Myopathy · Cardiovascular events · Hearing loss/Hypoacusis	None
Efficacy specification		
None		

Table 74. 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 · Specified use-results survey	None	· Disseminate data gathered during early post-marketing phase vigilance · Develop information materials (a proper use guide) to be distributed to healthcare professionals · Develop information materials (a brochure for patients and their families) to be distributed to patients

The applicant's explanation:

As shown in Table 75, a specified use-results survey will be conducted in adult AA patients and adolescent AA patients aged ≥12 years to investigate the long-term safety and efficacy of ritlecitinib in clinical practice, with an observation period of 3 years and a target sample size of 800 patients.

Table 75. Outline of specified use-results survey (draft)

Objective	Assessment of long-term safety and efficacy of ritlecitinib in clinical practice
Survey method	Central registry system
Population	Patients with intractable AA with extensive hair loss
Observation period	3 years (or until treatment discontinuation)
Planned sample size	800 patients (for the safety analysis)
Main survey items	· Safety specification: Important identified risks and important potential risks presented in Table 73 · Patient characteristics · Disease duration · Use of ritlecitinib · Previous treatments for AA · Concomitant medications/therapies · Adverse events · Efficacy assessments

PMDA accepted these measures and considers that the collected information needs to be provided 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

Alopecia areata ~~in patients who are eligible for systemic therapy~~ (~~including alopecia totalis and alopecia universalis~~ limited to intractable cases involving extensive hair loss)

(The strikethrough words are deleted from the proposed text,
and the underlined words are added to the proposed text.)

Dosage and Administration

The usual dosage for adults and adolescents aged 12 years and older is 50 mg of ritlecitinib administered orally once daily.

(No change from the proposed text.)

Approval Condition

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

List of Abbreviations

AA	Alopecia areata
AAPPO	Alopecia areata patient priority outcome
Abl	Abelson tyrosine protein kinase
AIDS	Acquired immunodeficiency syndrome
A/G	Albumin/globulin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration versus time curve
AUC_{0-t}	AUC from zero to t hours
AUC_{inf}	AUC from zero to infinity
AUC_{last}	AUC from zero to time of last measurable concentration
AUC_{tau}	AUC over dosing interval tau
BAEP	Brainstem auditory evoked potentials
BSA	Bovine serum albumin
BCRP	Breast cancer resistance protein
BSEP	Bile salt export pump
BLK	B lymphoid tyrosine kinase
BMI	Body mass index
BMX	Bone marrow tyrosine kinase gene in chromosome X
BTK	Bruton's tyrosine kinase
C_{avg}	Averaged plasma concentration at steady-state
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance
C_{max}	Maximum observed plasma concentration
CPK	Creatine phosphokinase
DMSO	Dimethyl sulfoxide
DSS	Dextran sulfate sodium
EAE	Experimental autoimmune encephalomyelitis
EBA	Eyebrow assessment
EGFR	Epidermal growth factor receptor
eGFR	Estimated glomerular filtration rate
ELA	Eyelash assessment
EPO	Erythropoietin
F	Bioavailability
FAS	Full analysis set
FGR	Tyrosine protein kinase encoded by the *FGR* gene
FLT3	FMS-like tyrosine kinase 3
FM	Farrington and manning
FOB	Functional observational battery
GALT	Gut-associated lymphoid tissue
GST	Glutathione-S-transferase
HBV	Hepatitis B virus
HEK	Human embryonic kidney
HER2/HER4	Human epidermal growth factor receptor2/4
hERG	Human ether-a-go-go related gene
HPLC	High performance liquid chromatography

IC_{50}	50% inhibitory concentration
ICH Q1E guideline	"Guideline on Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3, 2003)
IFN	Interferon
IL	Interleukin
IR	Infrared absorption spectrum
ITK	Interleukin-2 inducible T cell kinase
JAK	Janus kinase
Japanese clinical practice guidelines 2017	The Japanese Dermatological Association's guidelines for the management of alopecia areata 2017 (*The Japanese Journal of Dermatology*. 2017; 127: 2741-62)
k_a	First-order absorption rate constant
K_I	Concentration at half-maximal rate of inactivation
k_{inact}	Maximal inactivation rate
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
MACE	Major adverse cardiovascular event
MAM	Mouse allergy model
MAP2K7	Mitogen-activated protein kinase kinase 7
MATE	Multidrug and toxin extrusion
MCV	Mean corpuscular Volume
MDCK	Madin-darby canine kidney
MedDRA/J	Medical dictionary for regulatory activities Japanese version
MMF	Mycophenolate mofetil
MMRM	Mixed-effect models repeated measures
MN	Miettinen and Nurminen
mRNA	Messenger ribonucleic acid
MTX	Methotrexate
NAP	Nitrosation assay procedure
NK	Natural killer
NMR	Nuclear magnetic resonance spectrum
NMSC	Non-melanoma skin cancer
NRI	Non-responder imputation
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OC	Observed case
OCT	Organic cation transporter
P450	Cytochrome P450
PBMC	Peripheral blood mononuclear cell
peficitinib	Peficitinib Hydrobromide [Brand name: Smyraf Tablets 50 mg/100 mg]
PGI-C	Patient global impression of change
P-gp	P-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
P-Sat	Patient satisfaction with hair growth
Q/F	Apparent inter-compartmental clearance
QT	Time from the beginning of the QRS complex to the end of the T wave
RA	Rheumatoid arthritis
RH	Relative humidity
ritlecitinib	Ritlecitinib tosilate
RLK	Resting lymphocyte kinase
RNA-seq	RNA sequencing
SALT	Severity of alopecia tool
SLK	Ste20-like kinase

STAT	Signal transducer and activator of transcription
SULT	Sulfotransferase
$t_{1/2}$	Terminal phase half-life
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroids
TEC	Tyrosine kinase expressed in hepatocellular carcinoma
The product	Litfulo Capsules 50 mg
t_{max}	Time to maximum observed concentration
TNBS	2, 4, 6-trinitrobenzene sulfonic acid
TNF	Tumor necrosis factor
tofacitinib	Tofacitinib Citrate [Brand name: Xeljanz Tablets 5 mg]
TPO	Thrombopoietin
TR-FRET	Time-resolved fluorescence resonance energy transfer
TXK	Tyrosine protein kinase encoded by the TXK gene
TYK2	Tyrosine kinase 2
UC	Ulcerative colitis
UGT	Uridine 5’ diphospho glucuronosyltransferase
UV	Ultra violet
VEGFR2	Vascular endothelial growth factor receptor 2
V_c/F	Apparent central volume of distribution
V_p/F	Apparent peripheral volume of distribution
V_{ss}	Volume of distribution at steady state
V_z/F	Apparent volume of distribution, estimated from terminal phase, for extravascular dosing
WHO	World Health Organization