Report on the Deliberation Results

November 7, 2019

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	Corectim Ointment 0.5%
Non-proprietary Name	Delgocitinib (JAN*)
Applicant	Japan Tobacco Inc.
Date of Application	January 31, 2019

Results of Deliberation

In its meeting held on October 25, 2019, the First 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 substance is classified as a powerful drug, but its drug product is not classified as a poisonous drug or a powerful drug.

Conditions of Approval

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

**Japanese Accepted Name (modified INN)*

Review Report

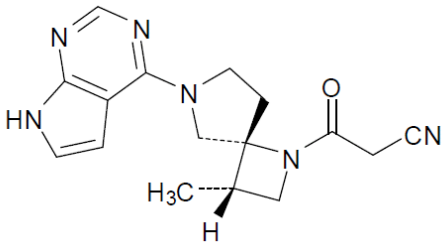
October 10, 2019

Pharmaceuticals and Medical Devices Agency

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

Brand Name	Corectim Ointment 0.5%
Non-proprietary Name	Delgocitinib
Applicant	Japan Tobacco Inc.
Date of Application	January 31, 2019
Dosage Form/Strength	Each gram of ointment contains 5 mg of delgocitinib.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{16}H_{18}N_6O$

Molecular weight: 310.35

Chemical name:

3-[(3*S*,4*R*)-3-Methyl-6-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl]-3-oxopropanenitrile

Items Warranting Special Mention None

Reviewing Office Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of atopic dermatitis, and that the product has acceptable safety in view of its benefits (see Attachment). The safety of the product and the efficacy specification should be further evaluated through post-marketing surveillance in patients with atopic dermatitis who will have received the product.

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions.

Indication	Atopic dermatitis
Dosage and Administration	The following is recommended for adults: Apply an appropriate amount of the ointment to the affected areas twice daily. The dose applied should not exceed 5 g per application.

Conditions of Approval

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

Attachment

Review Report (1)

September 13, 2019

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

Product Submitted for Approval	
Brand Name	Corectim Ointment 0.5%
Non-proprietary Name	Delgocitinib
Applicant	Japan Tobacco Inc.
Date of Application	January 31, 2019
Dosage Form/Strength	Each gram of ointment contains 5 mg of delgocitinib.
Proposed Indication	Atopic dermatitis
Proposed Dosage and Administration	The following is recommended for patients aged 16 years and older: Apply an appropriate amount of the ointment to the affected areas twice daily. The dose applied should not exceed 5 g per application.

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List of Abbreviations

See Appendix.

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

Atopic dermatitis is a skin disease characterized by itching eczematous lesions and a course marked by exacerbations and remissions. The majority of patients with atopic dermatitis have a predisposition[1)] to atopy.

According to the Japanese Guidelines for the Management of Atopic Dermatitis 2018 (hereinafter referred to as "Guidelines for the Management"), the mainstay of pharmacotherapy for atopic dermatitis consists of topical therapy with topical corticosteroids or tacrolimus ointments. However, topical corticosteroids are known to cause local adverse reactions such as skin atrophy, capillary dilatation, steroid acne, and steroid flushing; therefore, as a principle, low- to mid-potency corticosteroids are recommended for use in skin areas such as the face and neck. Tacrolimus is known to induce skin irritation such as a burning sensation, and thus has limitations in use. For example, the application of tacrolimus onto the eroded or ulcerated skin is not allowed because it may result in increased blood concentrations of the drug.

Delgocitinib is a Janus kinase (JAK) inhibitor discovered by the applicant. Delgocitinib was expected to inhibit activation of the JAK/signal transducer and activator of transcription (STAT) pathway, suppressing the activation of immune cells and inflammatory cells induced by various cytokine-mediated stimulation, thereby effectively treating atopic dermatitis. This led to the development of the drug.

An application for marketing approval has been filed based on data from Japanese clinical studies that demonstrated the efficacy and safety of delgocitinib.

As of September 2019, delgocitinib has not been approved in any other country or region outside Japan.

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

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to slightly yellowish red powder, and its appearance/description, solubility, hygroscopicity, melting point, dissociation constant, distribution coefficient, and optical rotation have been determined. Delgocitinib exists in 6 types of [redacted] forms ([redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] crystals), 2 types of [redacted] forms, and 16 types of [redacted]. The [redacted] crystal is used for commercial production.

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

[1)] Family history, medical history (bronchial asthma, allergic rhinitis, allergic conjunctivitis, and atopic dermatitis), or predisposition to the production of IgE antibodies.

2.1.2 Manufacturing process

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

The critical quality attributes (CQAs) identified are shown below. Material attributes and process parameters that may affect CQAs were assessed to develop a drug substance control strategy (Table 1).

Table 1. Outline of the drug substance control strategy

CQA	Method of control
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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

2.1.3 Control of drug substance

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

2.1.4 Stability of drug substance

Table 2 shows the main stability studies for the drug substance. Photostability testing showed that the drug substance is photolabile.

Table 2. Main stability studies for the drug substance

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 pilot-scale batches	25°C	60% RH	Polyethylene bags (double layered) plus polyethylene bottle	24 months
Accelerated	3 pilot-scale batches	40°C	75% RH		6 months

Based on the above, a retest period of 36 months has been proposed for the drug substance when stored in a double polyethylene bag inside a light-protected polyethylene drum at room temperature according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q1E Guidelines “Evaluation of Stability Data.” Long-term testing will be continued for up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an ointment containing delgocitinib 5 mg per gram. The drug product contains white petrolatum, paraffin, and squalane as its excipients.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprising the steps of grinding, dispersion, melting, cooling, mixing, packing, testing, and storage. [redacted] has been defined as a critical step.

The CQAs identified are shown below. Material attributes and process parameters that may affect CQAs were assessed to develop a drug product control strategy (Table 3).

Table 3. Outline of the drug product control strategy

CQA	Method of control
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description (appearance), identification (HPLC), purity (degradation products [HPLC]), microbial limit test, and assay (HPLC).

2.2.4 Stability of drug product

Table 4 shows the main stability studies. Photostability testing showed that the drug product is photostable.

Table 4. Main stability studies of the drug product

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 production batches	25°C	60% RH	Aluminum tube	18 months
Accelerated	3 production batches	40°C	75% RH		6 months

Based on the above, a shelf-life of 24 months has been proposed for the drug product when packed in an aluminum tube and stored at room temperature according to the ICH Q1E Guidelines "Evaluation of Stability Data." Long-term testing will be continued for up to [redacted] months.

2.R Outline of the review conducted by PMDA

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

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

Primary pharmacodynamics studies include *in vitro* studies of JAK inhibition, cytokine signaling inhibition, and effects on immune cells, inflammatory cells, and keratinocytes; and *in vivo* studies of effects on dermatitis and scratching behavior. A secondary pharmacology study investigated effects on enzymes other than JAKs. Safety

pharmacology studies investigated effects on the central nervous system, cardiovascular system, respiratory system, gastrointestinal system, and renal-urological system.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* inhibitory activity against human JAK family members (CTD 4.2.1.1-1, Study [redacted]B052EN01)

The inhibitory activity of delgocitinib against recombinant human JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) was investigated. Delgocitinib inhibited the JAKs with a half maximal inhibitory concentration (IC_{50}) value (mean ± standard error [SE]) of 2.8 ± 0.6 nmol/L for JAK1, 2.6 ± 0.2 nmol/L for JAK2, 12.5 ± 0.3 nmol/L for JAK3, and 57.8 ± 9.4 nmol/L for TYK2.

3.1.2 Inhibition of cytokine signaling (CTD 4.2.1.1-2 and CTD 4.2.1.1-3, Studies [redacted]B052SG01 and [redacted]B052SG01)

The inhibitory effects of delgocitinib at 0.001 to 10 μmol/L on the phosphorylation of STAT induced by stimulation with various cytokines (interleukin [IL]-2, IL-6, IL-23, interferon [IFN]-α, and granulocyte macrophage colony-stimulating factor [GM-CSF]) were investigated using human peripheral blood monocytes. Five pairings of JAKs (JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, JAK2/JAK2, and JAK2/TYK2) associate with specific types of cytokine receptors. The following combinations have been reported: a JAK1/JAK2 paring associates with receptors for IL-6 and other cytokines, JAK1/JAK3 with receptors for IL-2 and other cytokines, JAK1/TYK2 with receptors for Type I IFN receptors (binding receptors for IFN-α), JAK2/JAK2 with receptors for GM-CSF and other cytokines, and JAK2/TYK2 with receptors for IL-23 (*Semin Cell Dev Biol.* 2008;19:311-8).

Delgocitinib inhibited phosphorylation of STAT induced by stimulation with the cytokine studied (IL-2, IL-6, IL-23, IFN-α, and GM-CSF) in a concentration-dependent manner with an IC_{50} value (mean ± SE) of 39.6 ± 9.0 nmol/L for IL-2, 32.5 ± 14.5 nmol/L for IL-6, 84.3 ± 11.3 nmol/L for IL-23, 18.1 ± 2.6 nmol/L for IFN-α, and 304 ± 22 nmol/L for GM-CSF. The results show that delgocitinib inhibits the activation of the JAK-STAT pathway following stimulation with IL-2, IL-6, IL-23, IFN-α, and GM-CSF in human peripheral blood monocytes.

3.1.3 Suppression of T cell activation (CTD 4.2.1.1-4 to 4.2.1.1-6, Studies [redacted]B052HT01, [redacted]B052RT01, and [redacted]B052MT01)

The effects of delgocitinib at 1 to 300 nmol/L on cell proliferation stimulated with IL-2 were investigated using mitogen-pretreated human peripheral blood T cells, mouse splenic T cells, and rat splenic T cells.[2)] Delgocitinib suppressed T cell proliferation stimulated with IL-2 in all of the tested cells in a concentration-dependent manner with an IC_{50} value (mean ± SE) of 8.9 ± 3.6 nmol/L (human peripheral

[2)] Human peripheral blood T cells and mouse splenic T cells were precultured in the presence of phytohemagglutinin (PHA), while rat splenic T cells were precultured in concanavalin A (ConA) and phorbol 12-myristate 13-acetate (PMA). Phytohemagglutinin, ConA, and PMA are mitogens, which enhance T cell response to IL-2.

blood T cells), 10.9 ± 1.5 nmol/L (mouse splenic T cells), and 15.3 ± 5.4 nmol/L (rat splenic T cells). Delgocitinib suppressed IL-2-stimulated activation of human, mouse, and rat T cells.

3.1.4 Suppression of B cell activation (CTD 4.2.1.1-7, Study [redacted]B052HB01)

The effects of delgocitinib at 0.001 to 10 μmol/L on cell proliferation stimulated with IL-21 in the presence of anti-CD 40 antibodies[3)] were investigated using human peripheral blood B cells. Delgocitinib suppressed B cell proliferation stimulated with IL-21 in a concentration-dependent manner with an IC_{50} value (mean ± SE) of 49.2 ± 5.6 nmol/L. Delgocitinib suppressed IL-21-stimulated activation of B cells.

3.1.5 Suppression of mast cell activation (CTD 4.2.1.1-8, Study [redacted]B052HH01)

The effects of delgocitinib at 10 to 1,000 nmol/L on IL-13 production stimulated with IL-4 or IgE cross-linking were investigated using human umbilical cord blood mast cells. Delgocitinib suppressed IL-13 production stimulated with IL-4 or IgE cross-linking in a concentration-dependent manner with an IC_{50} value (mean ± SE) of 135 ± 24 nmol/L. Delgocitinib suppressed mast cell activation stimulated with IL-4 or IgE cross-linking.

3.1.6 Suppression of monocyte activation (CTD 4.2.1.1-9, Study [redacted]B052HM01)

The effects of delgocitinib at 0.001 to 10 μmol/L on inflammatory cytokine production stimulated with GM-CSF in the presence of lipopolysaccharide (LPS)[4)] with TNF-α production as an indicator were investigated using human peripheral blood monocytes. Delgocitinib suppressed TNF-α production stimulated with GM-CSF in a concentration-dependent manner with an IC_{50} value (mean ± SE) of 277 ± 146 nmol/L. Delgocitinib suppressed monocyte activation stimulated with GM-CSF.

3.1.7 Effects on fibroblast proliferation (CTD 4.2.1.1-10, Study [redacted]B052HF01)

The effects of delgocitinib at 0.1 to 10 μmol/L on cell proliferation in the absence of cytokines were investigated using human lung fibroblasts. There were no clear effects of delgocitinib up to the concentration of 10 μmol/L on human lung fibroblasts.

3.1.8 Effects on the expression of skin barrier function-related factors (CTD 4.2.1.1-11, Study [redacted]B052HK01)

The effects of delgocitinib at 0.01 to 1 μmol/L on the levels of mRNA expression of filaggrin[5)] and loricrin[6)] which are reduced by IL-4 and IL-13 stimulation, were investigated using human epidermal keratinocytes. Delgocitinib suppressed the reduction in the mRNA levels of filaggrin and loricrin induced by IL-4 and IL-13 stimulation.

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3) Because CD40-mediated costimulation is required for IL-21 induced B cell proliferation, an anti-CD40 agonist antibody was added for costimulation.

4) Because the presence of a costimulator is necessary to enhance GM-CSF-induced monocyte inflammatory cytokine secretion, LPS was added.

5) A protein involved in keratin filament polymerization within keratinocytes. Filaggrin deficiency and other genetic factors that are involved in skin barrier dysfunction associated with atopic dermatitis have been reported (*J Clin Invest.* 2012;122:440-7, *N Engl J Med.* 2011;365:1315-27). Furthermore, stimulation of cytokines such as IL-4 and IL-13 led to a reduction in filaggrin production, resulting in impaired skin barrier function (*J Allergy Clin Immunol.* 2007;120:150-5).

6) A keratinocyte cell envelope protein. There are reports on increased cytokines such as IL-4 and IL-13 in skin lesions from patients with atopic dermatitis, where expression of skin barrier function-related proteins such as filaggrin and loricrin has been down-regulated. (*J Allergy Clin Immunol*. 2007;120:150-5, *Clin Immunol.* 2008;126:332-7).

3.1.9 Effects on rat models of DNCB-induced dermatitis (CTD 4.2.1.1-12, Study [redacted]B052RH01)

Delgocitinib 0.03%, 0.3%, or 3%, or placebo was administered by percutaneous application onto the ear of rat models[7] of 2, 4-dinitrochlorobenzene (DNCB)-induced dermatitis once daily for 21 days. This study investigated changes from baseline in ear thickness on Days 1, 7, 14, and 19, as well as histopathological changes (acanthosis and intercellular edema in the epidermis, and infiltration of inflammatory cells in the dermis) on Day 21.

The results indicate that delgocitinib suppressed an increase in ear thickness in a concentration-dependent manner, and there was a significant difference in the delgocitinib 0.3% and 3% groups compared with the placebo group on Day 19 (Table 5).

Delgocitinib suppressed histopathological changes of the skin in a concentration-dependent manner.
Acanthosis and intercellular edema in the epidermis were suppressed in the delgocitinib 0.3% and 3% groups, while infiltration of inflammatory cells in the dermis[8] was suppressed in the delgocitinib 3% group (Table 6).

Table 5. Change from baseline in ear thickness in rat models of DNCB-induced dermatitis

Treatment group	Change from baseline in ear thickness at each time point ($\times 10^{-2}$ mm)			
	Day 1	Day 7	Day 14	Day 19
Placebo	0.4 ± 2.4	9.8 ± 7.8	39.2 ± 17.0	40.3 ± 12.9
Delgocitinib 0.03%	0.5 ± 1.2	4.1 ± 3.9	34.8 ± 8.8	34.9 ± 8.1
Delgocitinib 0.3%	−0.7 ± 1.7	3.6 ± 4.0	23.4 ± 9.3*	22.7 ± 9.8**
Delgocitinib 3%	−0.8 ± 1.5	1.2 ± 2.7	9.1 ± 8.2**	7.0 ± 6.5**

n = 9, mean ± standard deviation [SD]
*, $P < 0.05$; **, $P < 0.01$ (vs. placebo by Dunnett's test)

Table 6. Histopathological changes in rat models of DNCB-induced dermatitis

	Score	Placebo (n = 9)	Delgocitinib 0.03% (n = 8)	Delgocitinib 0.3% (n = 9)	Delgocitinib 3% (n = 9)
Acanthosis	0	0	0	0	4
	1	0	0	0	3
	2	4	5	8	2
	3	5	3	1	0
	4	0	0	0	0
Intercellular edema in the epidermis	0	0	0	0	8
	1	1	1	3	0
	2	2	2	3	1
	3	6	5	3	0
	4	0	0	0	0
Infiltration of inflammatory cells in the dermis	0	0	0	0	6
	1	1	0	1	2
	2	5	2	4	0
	3	3	5	3	1
	4	0	1	1	0

Histopathological score (0, normal; 1, slight; 2, mild; 3, moderate; 4, severe)

[7] Rat models of repeated-dose DNCB-induced dermatitis were prepared by applying 0.5% DNCB on both sides of the ears of male rats 3 times weekly for 3 weeks (9 applications in total).
[8] According to the applicant's explanation, unlike the results for acanthosis and intercellular edema in the epidermis, infiltration of inflammatory cells in the dermis tended to improve in the placebo group compared with the non-treated group, and therefore, no clear difference was observed between the placebo group and delgocitinib 0.3% group.

3.1.10 Effects on scratching behavior (CTD 4.2.1.1-13, Study [redacted]B052MI01)

Following administration of a single percutaneous dose of vehicle (5% dimethyl sulfoxide [DMSO] and 95% acetone mixture), delgocitinib 0.03%, 0.3%, or 3% was administered to male mice, and then a single intracutaneous dose of IL-31 was administered to the animals 15 minutes later to induce scratching behavior. The number of scratches (mean ± standard deviation [SD]) within 1 hour of IL-31 administration was 103 ± 49 (vehicle), 89 ± 54 (0.03%), 57 ± 36 (0.3%), and 30 ± 22 (3%), indicating that the number of scratches was significantly reduced in the delgocitinib 0.3% and 3% groups compared with the vehicle control group. The applicant explained that delgocitinib can suppress cytokine-induced itching.

3.2 Secondary pharmacodynamics

3.2.1 Inhibitory effects on receptors and enzymes (CTD 4.2.1.2-1, Study AL-4447-G)

The study investigated the inhibitory effects of delgocitinib at 10 μmol/L on 23 receptors (including ion channels) and 5 enzymes. No inhibitory effects of delgocitinib at 10 μmol/L were noted on any of the receptors or enzymes.

3.3 Safety pharmacology

Of the safety pharmacology studies submitted, the main studies are summarized in Table 7.

Table 7. Summary of results of safety pharmacology studies

Organ system	Species/strain	Test parameter/ method	Delgocitinib dose/ concentration (*in vitro*)	Route of administration	Findings	CTD (Study Identifier)
Central nervous system	Rat (6 males/ group)	Modified Irwin test	3, 10, 30 mg/kg	Single oral dose	No effects were observed up to 30 mg/kg, the maximum dose level. The no-observed-effect level (NOEL) for the central nervous system in rats was determined to be 30 mg/kg.	4.2.1.3-1 (P[redacted]0984)
Cardiovascular system	HEK293 cell (5 specimens each)	hERG current	3, 10, 30 µmol/L	*in vitro*	In the presence of delgocitinib, hERG current was inhibited by 0.5% (3 µmol/L), 4.7% (10 µmol/L), and 10.4% (30 µmol/L) (IC_{50} >30 µmol/L).	4.2.1.3-2 (P[redacted]0986)
	Dog (4 males/ group)	Blood pressure (systolic, diastolic, and mean), heart rate, electrocardiogram	0.3, 1, 3 mg/kg	Single oral dose	In the 3 mg/kg group, transient decrease in blood pressure and increased heart rate were observed. The NOEL for the cardiovascular system in dogs was determined to be 1 mg/kg.	4.2.1.3-3 (P[redacted]0985)
	Rat (6 males/ group)	Blood pressure (systolic, diastolic, and mean), heart rate	3, 10, 30 mg/kg	Single oral dose	In the 30 mg/kg group, decreased blood pressure and increased heart rate were observed. The NOEL for the cardiovascular system in rats was determined to be 10 mg/kg.	4.2.1.3-4 ([redacted]B052SP05)
	Rat Thoracic aorta specimen (5 specimens each)	Phenylephrine (Phe)- and KCl-induced contraction (relaxation of vascular smooth muscle)	1, 3, 10, 30 µmol/L	*in vitro*	Delgocitinib suppressed Phe- and KCl-induced contraction in a concentration-dependent manner with IC_{50} values of 3.6 µmol/L and 3.5 µmol/L, respectively.	4.2.1.3-5 ([redacted]B052SP01)
	Rat Heart specimen (4 specimens each)	Left ventricular pressure (max, end-diastolic pressure, pulse pressure), coronary perfusion flow rate, heart rate, etc.	3, 30 µmol/L	*in vitro*	A significant increase in coronary perfusion flow rate in the 30 µmol/L group.	4.2.1.3-6 ([redacted]B052SP04)
Respiratory system	Dog (4 males/ group)	Respiratory rate, blood gas (pH, oxygen partial pressure, carbon dioxide partial pressure, hemoglobin oxygen saturation)	0.3, 1, 3 mg/kg	Single oral dose	No effects were observed up to 3 mg/kg, the maximum dose level. The NOEL for the respiratory system in dogs was determined to be 3 mg/kg.	4.2.1.3-3 (P[redacted]0985)
Gastrointestinal system	Rat (10 males/ group)	Intestinal charcoal transit in the small intestine	3, 10, 30 mg/kg	Single oral dose	Intestinal charcoal transit decreased significantly in the 30 mg/kg group (decreased by 27% compared with the vehicle control group). The NOEL for the gastrointestinal system in rats was determined to be 10 mg/kg.	4.2.1.3-7 ([redacted]B052SP02) Reference data
Renal-urological system	Rat (6 males/ group)	Urine output, urinary electrolytes (Na^+, K^+, Cl^-) excretion	3, 10, 30 mg/kg	Single oral dose	Urinary K^+ excretion increased in the 30 mg/kg group. The NOEL for the renal urological system in rats was determined to be 10 mg/kg.	4.2.1.3-8 ([redacted]B052SP03) Reference data

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological action

The applicant's explanation about the pharmacological action of delgocitinib:

Immunological abnormalities, skin barrier dysfunction, and other factors are involved in the pathogenesis of atopic dermatitis. In particular, abnormalities in cytokine production play key roles (e.g., *J Clin Invest.* 2004;113:651-7).

The Janus kinase family (JAK1, JAK2, JAK3, and TYK2) is a family of non-receptor tyrosine kinases. JAKs associate with specific cytokine receptor subunits, acting to transduce signals in the cell when the cytokine binds to the receptor (*Semin Cell Dev Biol.* 2008;19:311-8). Five JAK pairings (JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, JAK2/JAK2, and JAK2/TYK2) associate with specific cytokine receptors, and JAK1/JAK3, JAK1/JAK2, JAK2/TYK2, JAK1/TYK2, and JAK2/JAK2 are activated via IL-2, IL-6, IL-23, IFN-α, and GM-CSF stimulations, respectively. Delgocitinib inhibited the activation of all of the JAK/STAT pathways [see Section 3.1.2], and this suggests that delgocitinib inhibits the cytokine-activated JAK/STAT signaling pathways. Furthermore, delgocitinib suppressed the cytokine-stimulated activation of T cells, B cells, mast cells, and monocytes induced [see Sections 3.1.3 through 3.1.6] and inhibited the skin inflammation in rat models of DNCB-induced dermatitis [see Section 3.1.9]. These findings indicate that delgocitinib inhibits the cytokine-activated JAK/STAT signaling pathways and then suppresses the activation of immune cells and inflammatory cells induced by cytokine stimulation, thereby reducing inflammation in atopic dermatitis. Delgocitinib suppressed scratching behavior induced by IL-31 in mice, suggesting that delgocitinib is also an effective treatment for itching.

PMDA's view:
Based on the submitted primary pharmacodynamics data, and the applicant's discussions, delgocitinib is expected to be an effective treatment for atopic dermatitis because the drug blocks JAKs to inhibit the cytokine-activated signaling pathways, thereby suppressing the activation of immune cells and inflammatory cells induced by cytokine stimulation. Delgocitinib is expected to have some efficacy in the treatment of itching associated with atopic dermatitis.

3.R.2 Safety pharmacology studies

The applicant's explanation about the findings obtained in safety pharmacology studies:
There were no significant findings related to the central nervous system or respiratory system.

Findings related to the cardiovascular system included decreased blood pressure and increased heart rate in dogs and rats. Delgocitinib suppressed Phe- and KCl-induced contraction in rat thoracic aorta specimens, indicating that it relaxes vascular smooth muscle. Decreased blood pressure can be attributable to delgocitinib. Increased heart rate is considered to be a secondary response to the decrease in blood pressure. However, given that the safety margin between animal and human exposures to delgocitinib for the cardiovascular system is 632-fold for dogs and 1,241-fold for rats,[9)] delgocitinib is unlikely to affect the cardiovascular system in humans.

Findings related to the gastrointestinal system included decreased intestinal charcoal transit in rats, which may be attributable to decreased gastrointestinal motility due to the relaxing effects of delgocitinib on gastrointestinal smooth muscle. However, given that the safety margin between rat and human exposures to

[9)] The safety margin was calculated as the ratio of delgocitinib exposure in individual animal species at the NOEL (C_{max}) to the exposure in patients with atopic dermatitis who received an application of topical delgocitinib 0.5% ointment 5 g twice daily (C_{max}, 0.86 ng/mL).

delgocitinib for the gastrointestinal system is 1,241-fold,[9)] delgocitinib is unlikely to affect the gastrointestinal system in humans.

Findings related to the renal-urological system included increased urinary K^+ excretion in rats, which may be attributed to increased activity of the renin-angiotensin-aldosterone system as a compensatory reaction to decreased blood pressure following administration of delgocitinib. However, given that the safety margin between rat and human exposures to delgocitinib for the renal-urological system is 1,241-fold,[9)] delgocitinib is unlikely to affect the renal-urological system in humans.

Based on the above findings, delgocitinib is unlikely to affect the central nervous system, cardiovascular system, respiratory system, gastrointestinal system, or renal-urological system in humans.

PMDA accepted the applicant's explanation.

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

The pharmacokinetics following administration of unlabeled or ^{14}C-labeled delgocitinib to rats, dogs, and miniature pigs was investigated. Liquid chromatography-tandem mass spectrometry (LC/MS/MS) was used to measure plasma delgocitinib concentrations with the lower limits of quantitation (LLOQ) being 0.05 ng/mL (percutaneous) or 0.5 ng/mL (oral or intravenous) in rats, and 0.5 ng/mL in dogs and miniature pigs. Radioactivity levels following administration of ^{14}C-labeled delgocitinib were determined by liquid scintillation counting. The ointment base used in each test is the same as that for the proposed formulation.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2-1 and 4.2.2.2-5, Studies JTE052-AD-018/B[redacted]0381 and JTE052-AD-002/B[redacted]1259)

A single dose of delgocitinib was administered percutaneously, orally, or intravenously to male rats. Table 8 shows pharmacokinetic parameters of delgocitinib in the tested animals. The bioavailability of topical delgocitinib 3% ointment percutaneously applied onto intact skin and damaged skin without stratum corneum was 2.6% and 5.4%, respectively, indicating that the percutaneous absorption of topical delgocitinib was low in both skin areas. Following application of topical delgocitinib 3% ointment to the damaged skin of rats, the C_{max} was 7.5 times that of the intact skin, and $AUC_{0\text{-}24h}$ was 4.7 times that of the intact skin, suggesting that the defective stratum corneum can increase percutaneous absorption of topical delgocitinib.

Table 8. Plasma pharmacokinetic parameters following single-dose percutaneous, oral, or intravenous administration of delgocitinib

Species	Route of administration	Skin condition	Dose	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	Bioavailability[a)] (%)
Male rat	Percutaneous	Intact	0.3%	3.4 ± 1.3	96.7 ± 85.4	17.4 ± 13.4 [b)]	NC	16.6 ± 10.0
			1%	9.0 ± 12.8	1.3 ± 0.6	25.2 ± 23.0 [b)]	NC	3.2 ± 2.5
			3%	4.6 ± 1.2	6.0 ± 3.5	59.4 ± 13.3 [b)]	NC	2.6 ± 0.9
		Damaged	3%	34.2 ± 18.9	1.7 ± 0.6	276.1 ± 197.6 [b)]	NC	5.4 ± 2.8
	Oral		0.3 mg/kg	40 ± 6	0.2 ± 0.0	64 ± 12	3.0 ± 1.3	35.5 ± 6.5
			1 mg/kg	126 ± 35	0.3 ± 0.2	270 ± 27	2.5 ± 1.1	44.9 ± 4.6
			3 mg/kg	448 ± 105	0.3 ± 0.2	806 ± 106	2.8 ± 0.8	44.7 ± 5.8
	Intravenous		1 mg/kg	—	—	601 ± 230	2.5 ± 0.7	—

n = 3; mean ± SD; NC, Not calculated

a) Calculated using $AUC_{0-\infty}$ following intravenous administration of delgocitinib at 1 mg/kg; b) AUC_{0-24h}

4.1.2 Repeated-dose studies (CTD 4.2.3.2-8, Study JTE052-TX-037[redacted]057)

Table 9 shows pharmacokinetic parameters after repeated doses of topical delgocitinib at 1%, 3% or 5% ointment were administered percutaneously to male and female miniature pigs once daily for 36 weeks. While inter-individual variation was great, there was no significant sex difference in C_{max} or AUC_{0-24h}. Unchanged delgocitinib was detected in plasma at Week 13 and later. However, after Week 13, plasma concentrations of unchanged delgocitinib were largely consistent, and no accumulation was observed.

Table 9. Plasma pharmacokinetic parameters following 36-week repeated-dose percutaneous administration of delgotinib to miniature pigs

Delgocitinib concentration	Evaluation time point	Male			Female		
		C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (ng·h/mL)
1%	Day 1	BLQ	—	BLQ	BLQ	—	BLQ
	Week 13	1.0 ± 0.5	13 ± 13	10.6 ± 6.8	2.3, 3.6 [b)]	0, 0 [b)]	4.5, 37.5 [b)]
	Week 28	1.5 [a)]	0 [a)]	22.0 [a)]	3.3 [a)]	0 [a)]	36.3 [a)]
	Week 36	3.1 [a)]	0 [a)]	33.3 [a)]	4.9 [a)]	0 [a)]	69.9 [a)]
3%	Day 1	BLQ	—	BLQ	BLQ	—	BLQ
	Week 13	3.3 ± 3.2	0 ± 0	24.4 ± 21.3	2.7 ± 1.4	6 ± 12	26.4 ± 16.6
	Week 28	1.2 ± 0.7	14 ± 12	19.4 ± 14.9	2.5 ± 3.4	1 ± 2	34.2 ± 53.6
	Week 36	5.0 ± 3.8	2 ± 2	83.7 ± 73.3	6.0 ± 6.5	0 ± 0	87.3 ± 95.4
5%	Day 1	0.8, 2.1 [b)]	24, 24 [b)]	6.6, 16.4 [b)]	0.51-0.83 [c)]	24-24 [c)]	4.07-6.63 [c)]
	Week 13	4.3 ± 2.8	12 ± 13	56.1 ± 44.7	3.6 ± 2.4	5 ± 10	39.6 ± 21.1
	Week 28	5.2 ± 7.3	1 ± 2	89.0 ± 149.3	2.9 ± 2.5	5 ± 10	35.7 ± 35.0
	Week 36	9.9 ± 15.7	1 ± 2	149.7 ± 236.1	5.0 ± 4.4	5 ± 9	79.0 ± 81.5

n = 4 [n = 6 only for delgocitinib 5%]; a) n = 1, b) n = 2, c) n = 3); mean ± SD [however, in c), minimum and maximum values of 3 animals are shown.]

4.2 Distribution

4.2.1 Tissue distribution in rats (CTD 4.2.2.3-1 and 4.2.2.2-4, Studies JTE052-AD-017/B[redacted]0379 and JTE052-AD-001/B[redacted]1257)

A single dose of ^{14}C-labeled delgocitinib (delgocitinib 3%) was percutaneously administered by application onto the normal or damaged skin of male rats, and radioactivity levels in tissues[10)] at 1, 24, 96, and 168 hours post-dose were investigated. At 24 hours after percutaneous administration onto the intact skin, apart from

[10)] Radioactivity levels in the following tissues were investigated: plasma, blood, the cerebrum, cerebellum, pituitary gland, eyeball, harderian gland, submandibular gland, mesenteric lymph node, thyroid gland, trachea, thymus, heart, lung, liver, adrenal gland, kidney, spleen, pancreas, prostate gland, testis, epididymis, seminal vesicle, artery, skin, skin of the administration site, skeletal muscle, bone marrow, white adipose tissue, brown adipose tissue, stomach, small intestine, cecum, and large intestine.

the skin at the administration site, radioactivity was detected in the cecum, large intestine, liver, pancreas, and kidney at levels less than 0.01% of the administered radioactivity. After percutaneous administration onto the damaged skin, the maximum radioactivity levels were observed in 1 hour in the majority of tissues. The radioactivity levels at 1 hour post-dose were ≥3 times the radioactivity levels in plasma in the following tissues, apart from the skin at the administration site: the kidney, small intestine, liver, skin, adrenal gland, and prostate gland. The radioactivity levels in tissues decreased over time, and at 168 hours post-dose, radioactivity was not detected in the majority of tissues except for the skin at the administration site. Based on the total urinary and fecal radioactivity excretion rates up to 168 hours post-dose, the percutaneous absorption of delgocitinib was estimated to be 1.4% for the intact skin, and 6.3% for the damaged skin.

A single oral dose of ^{14}C-labeled delgocitinib 1 mg/kg was administered to male rats, and radioactivity levels in tissues[11)] at 0.5, 8, 24, and 168 hours post-dose were investigated. The maximum radioactivity levels were observed at 0.5 hours post-dose in the majority of tissues, and the radioactivity levels at 0.5 hours post-dose were ≥3 times the radioactivity levels in plasma in the following tissues: the stomach, small intestine, kidney, liver, arteries, and adrenal gland. The radioactivity levels in tissues decreased over time, and at 168 hours post-dose, radioactivity was not detected in the majority of tissues.

4.2.2 Tissue distribution in dogs (CTD 4.2.2.2-7, Study JTE052-AD-003/P[redacted]0263)

A single oral dose of ^{14}C-labeled delgocitinib 1 mg/kg was administered to male dogs, and radioactivity levels in tissues at 168 hours post-dose were investigated.[12)] The radioactivity levels in the pigmented skin and eyeball were ≥150 times the radioactivity levels in plasma, and the radioactivity levels in the pigmented skin were approximately 10 times those in the non-pigmented skin. The above findings suggested that delgocitinib has an affinity for melanin. However, given that no eyeball-related toxicity findings have been shown in the repeated-dose toxicity studies [see Section 5.2], and no eye-related adverse events were reported in the Japanese clinical studies, the applicant considers that at this point, delgocitinib is unlikely to have an effect on the eye.

4.2.3 Protein binding (CTD 4.2.2.3-5 and 4.2.2.3-6, Studies JTE052-AD-005/B[redacted]1262 and JTE052-AD-023/B[redacted]0157)

The protein binding of ^{14}C-labeled delgocitinib (0.03 to 100 μg/mL) was studied using mouse, rat, rabbit, dog, miniature pig, and human plasma. The mean protein binding was 28.4% to 29.4% (mouse), 23.5% to 27.1% (rat), 26.1% to 27.5% (rabbit), 17.7% to 22.2% (dog), 20.7% to 23.0% (miniature pig), and 21.8% to 29.1% (human), indicating that protein binding was not concentration dependent within the concentration range studied.

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11) Radioactivity levels in the following tissues were investigated: plasma, blood, the cerebrum, cerebellum, pituitary gland, eyeball, harderian gland, submandibular gland, mesenteric lymph node, thyroid gland, thymus, heart, lung, liver, adrenal gland, kidney, spleen, pancreas, prostate gland, testis, epididymis, seminal vesicle, artery, skin, skeletal muscle, bone marrow, white adipose tissue, brown adipose tissue, stomach, small intestine, cecum, and large intestine.

12) Radioactivity levels in the following tissues were investigated: plasma, blood, the cerebrum, cerebellum, pituitary gland, eyeball, submandibular gland, mesenteric lymph node, thyroid gland, thymus, heart, lung, liver, adrenal gland, kidney, spleen, pancreas, prostate gland, testis, epididymis, artery, pigmented skin, white skin, skeletal muscle, bone marrow, white adipose tissue, brown adipose tissue, gallbladder, stomach, small intestine, cecum, and large intestine.

4.2.4 Distribution in blood cells (CTD 4.2.2.3-7, Study JTE052-AD-006/B[redacted]1261)

The distribution of ^{14}C-labeled delgocitinib (0.03 to 100 μg/mL) in blood cells was investigated using blood from rats, dogs, and humans. The mean distribution in blood cells was 55.3% to 56.0% (rat), 58.5% to 59.6% (dog), and 57.6% to 60.2% (human), indicating that distribution in blood cells was not concentration dependent within the concentration range studied. The blood/plasma concentration ratio was 1.37 to 1.40 (rat), 1.27 to 1.31 (dog), and 1.40 to 1.49 (human), and the applicant explained that there was no notable difference between the plasma and blood concentrations.

4.2.5 Placental transfer and distribution in fetuses in rats (CTD 4.2.2.3-8, Study JTE052-AD-022/B[redacted]0158)

Following a single oral dose of ^{14}C-labeled delgocitinib 1 mg/kg to pregnant rats on gestation day 18, tissue radioactivity levels in dams and fetuses were measured. The maximum radioactivity levels were observed at 0.5 hours post-dose in all tissues of fetuses, and then decreased over time. At 0.5 hours post-dose, only the spleen in fetuses showed a radioactivity level higher than the plasma radioactivity levels in dams, i.e., 3.59 times higher. Radioactivity levels in the remaining fetal tissues were ≤0.68 times the plasma radioactivity levels of the dams. Radioactivity transfer across the placenta to the fetus was ≤0.03% of the total radioactivity. The above findings indicate that following oral administration of delgocitinib, small amounts are transferred across the placenta to the fetus. However, given that exposure following percutaneous administration is lower compared with oral administration, the applicant explained that when delgocitinib is administered percutaneously, transfer across the placenta to the fetus is negligible [see Section 5.R.3 for the effects of delgocitinib on the fetus].

4.3 Metabolism

4.3.1 *In vitro* metabolite studies (CTD 4.2.2.4-7, 4.2.2.4-8, and 4.2.2.4-9, Studies JTE052-AD-009/B[redacted]1263, JTE052-AD-024/B[redacted]0327, and JTE052-AD-010/B[redacted]1264)

The metabolism of ^{14}C-labeled delgocitinib was investigated using mouse, rat, rabbit, dog, and miniature pig hepatocytes. Metabolites M2 and M3, which are oxidized on the pyrrolopyrimidine ring of delgocitinib, were detected. After 4 hours of reaction, unchanged delgocitinib accounted for 97.3% (mouse), 95.5% (rat), 97.7% (rabbit), 96.3% (dog), and 86.5% (miniature pig) of the total radioactivity in the sample, indicating that metabolites represented only a small percentage of the total.

The metabolism of ^{14}C-labeled delgocitinib was investigated using mouse, rat, rabbit, dog, and miniature pig microsomes. In mouse, rat, rabbit, and miniature pig microsomes, M1 (a metabolite which is oxidized on the side chain portion of the azetidine ring of delgocitinib), M2, and M3 were detected, while in dog microsomes, M2 and M3 were detected. After 1 hour of reaction, unchanged delgocitinib accounted for 86.8% (mouse), 90.0% (rat), 85.1% (rabbit), 95.7% (miniature pig), and 57.0% (dog) of the total radioactivity in the sample.

4.3.2 Plasma and urinary metabolites (CTD 4.2.2.4-2, Study JTE052-AD-008/JE052PK012)

The percentages of unchanged delgocitinib and its metabolites in plasma, urine, and feces following single oral administration of ^{14}C-labeled delgocitinib 1 mg/kg to male rats were investigated. At 0.5 hours post-dose,

unchanged delgocitinib accounted for the highest percentage in plasma (92.3% of plasma radioactivity), and metabolite M3 (7.7% of plasma radioactivity) was also detected. Up to 24 hours post-dose, 45.2% of the total radioactivity was detected in urine, and 55.8% of the total radioactivity was detected in feces. In urine, unchanged delgocitinib accounted for the highest percentage (93.1% of urinary radioactivity), and metabolite M3 (7.0% of urinary radioactivity) was also detected by 24 hours post-dose. In feces, unchanged delgocitinib accounted for the highest percentage (75.7% of fecal radioactivity), and a metabolite M3 (6.6% of fecal radioactivity) was also detected by 24 hours post-dose.

The percentages of unchanged delgocitinib and its metabolites in plasma, urine, and feces following single oral administration of ^{14}C-labeled delgocitinib 1 mg/kg to male dogs were investigated. At 2 hours post-dose, unchanged delgocitinib accounted for the highest percentage in plasma (80.9% of plasma radioactivity), and metabolites M2 (2.3% of plasma radioactivity) and M3 (16.8% of plasma radioactivity) were also detected. In urine, 59.6% of the radioactivity administered was detected during the first 24 hours post-dose, and in feces, 35.9% of the radioactivity administered was detected during the first 24 hours post-dose. In urine, up to 24 hours post-dose, unchanged delgocitinib accounted for the highest percentage (53.2% of urinary radioactivity), and metabolites M2 (1.8% of urinary radioactivity) and M3 (33.6% of urinary radioactivity) were also detected. In feces, substances mainly detected during the first 48 hours post-dose were unchanged delgocitinib (25.9% of fecal radioactivity) and M3 (39.6% of fecal radioactivity).

4.4 Excretion

4.4.1 Urinary, fecal, expiratory, and biliary excretion in rats (CTD 4.2.2.3-1 and 4.2.2.2-4, Studies JTE052-AD-017/B[redacted]0379 and JTE052-AD-001/B[redacted]1257)

Urinary and fecal radioactivity excretion was investigated up to 168 hours post-dose following single percutaneous administration of ^{14}C-labeled delgocitinib (topical delgocitinib 3%) onto the intact or damaged skin (10 cm^2) of male rats. At 24 hours post-dose, ^{14}C-labeled delgocitinib (topical delgocitinib 3%) was to be removed. In the intact skin, 96.8% of the radioactivity was detected in the ointment that was removed 24 hours post-dose, and 0.8% and 0.4% of radioactivity administered was excreted in urine and feces, respectively, by 168 hours post-dose. In the damaged skin, 93.2% of the radioactivity was detected in the ointment that was removed 24 hours post-dose, and 4.2% and 1.9% of the radioactivity administered was excreted in urine and feces, respectively, by 168 hours post-dose.

Following single intravenous administration of ^{14}C-labeled delgocitinib 1 mg/kg to male rats, 65.4% was excreted in urine and 30.9% in feces by 168 hours post-dose. Expiratory radioactivity excretion was less than 0.1%. Following single oral administration of ^{14}C-labeled delgocitinib 1 mg/kg to male rats, the mean radioactivity excretion up to 168 hours post-dose was 45.6% in urine, 57.1% in feces, and 0.1% in breath.

Following single intravenous administration of ^{14}C-labeled delgocitinib 1 mg/kg to male rats in which a bile fistula was created, the mean radioactivity excretion up to 48 hours post-dose was 14.1% in bile, 61.7% in urine, and 10.2% in feces. Following single oral administration of ^{14}C-labeled delgocitinib 1 mg/kg to male rats in which a bile fistula was created, the mean radioactivity excretion up to 48 hours post-dose was 10.9%

in bile, 49.0% in urine, and 37.6% in feces.

4.4.2 Urinary and fecal excretion in dogs (CTD 4.2.2.2-7, Study JTE052-AD-003/P[redacted]0263)

Following single intravenous administration of ^{14}C-labeled delgocitinib 1 mg/kg to male dogs, radioactivity excretion up to 168 hours post-dose was 68.6% in urine and 27.5% in feces. Following single oral administration of ^{14}C-labeled delgocitinib 1 mg/kg to male dogs, radioactivity excretion up to 168 hours post-dose was 61.9% in urine and 36.7% in feces.

4.4.3 Excretion in breast milk in rats (CTD 4.2.2.5-5, Study JTE052-AD-021/B[redacted]0159)

Radioactivity levels in breast milk at 0.5, 2, 4, 8, 24, and 48 hours following single oral administration of ^{14}C-labeled delgocitinib 1 mg/kg to female rats on lactation day 12 were investigated. The radioactivity levels in breast milk reached their maximum at 30 minutes post-dose (369 ng eq./mL, 1.68 times the plasma radioactivity level), and then decreased over time. The above findings showed that delgocitinib is excreted in breast milk in rats following oral administration.

4.R Outline of the review conducted by PMDA

4.R.1 Excretion of delgocitinib in breast milk

Because radioactivity was detected in breast milk following oral administration of ^{14}C-labeled delgocitinib to lactating rats [see Section 4.4.3], PMDA asked the applicant to explain the effects on infants when delgocitinib is used in lactating women.

The applicant's explanation:

Excretion of delgocitinib in breast milk after oral administration has been studied, but no studies have been performed with regard to percutaneous administration. However, given that exposure following percutaneous administration is lower compared with oral administration, and that following oral administration of delgocitinib up to 30 mg/kg/day (safety margin, 579-fold[13)]) to lactating dams, no toxicity findings were noted in their F1 live pups in the rat study on prenatal and postnatal development and maternal function [see Section 5.5], delgocitinib is unlikely to be excreted in breast milk following percutaneous administration to lactating women to a degree that would have an impact on infants. Nevertheless, it is not known whether delgocitinib is excreted in human breast milk; therefore, information on the results of the rat study, which demonstrated that excretion in breast milk following oral administration, will be provided. At the same time, cautionary statements to the following effect will be included in the package insert: Physicians should, taking into account the benefits of treatment and other aspects, consider whether breastfeeding mothers continue breastfeeding.

PMDA accepted the applicant's explanation.

[13)] The safety margin was calculated as the ratio of delgocitinib exposure ($AUC_{0\text{-}24}$) in rats at the no-observed-adverse-effect level (NOAEL) to the exposure in patients with atopic dermatitis who received an application of topical delgocitinib 0.5% ointment 5 g twice daily ($AUC_{0\text{-}24}$, 13.9 ng·h/mL).

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant conducted the following toxicity studies of delgocitinib: single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, juvenile animal toxicity studies, local tolerance studies, and other toxicity studies (e.g., skin sensitization study, photosafety studies, and immunotoxicity study). In *in vivo* studies, unless otherwise specified, 0.5% methylcellulose solution was used as a vehicle for oral administration, while an ointment containing [redacted]% white petrolatum, [redacted]% squalane, and [redacted]% paraffin was used as an ointment base for percutaneous administration.

5.1 Single-dose toxicity

Single oral dose toxicity studies were conducted in mice and dogs. Furthermore, based on the results after the initial administration of delgocitinib in the *in vivo* bone marrow chromosome aberration study, the acute toxicity of delgocitinib in rats was evaluated (Table 10). The applicant explained that the deaths which occurred in mice and rats were attributable to excessive decreases in blood pressure due to the vasorelaxation effects caused by delgocitinib.

Table 10. Single-dose toxicity studies

Species/strain	Route of administration	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	CTD
Male mouse (ICR)	Oral	100, 300, and 1,000	Died or sacrificed moribund: 1,000 (9 of 9 animals) ≥100, reddening of the skin, decrease in locomotor activity, eyelid closure ≥300, subnormal temperature, soiled perineal region, prone position	1,000	4.2.3.1-1
Male rat (SD)	Oral	37.5, 75, 150, and 300	Acute toxicity was evaluated in an *in vivo* bone marrow chromosome aberration study. Died or sacrificed moribund: 300 (6 of 12 animals) ≥37.5, reddening of the skin, ≥150, decrease in locomotor activity 300, eyelid closure, irregular respiration, prone position	300	4.2.3.1-2
Male dog (Beagle)	Oral	0.3, 1, 3, and 10	≥3, reddening of the ear and visible mucous membranes (conjunctiva/sclera) 10, swelling of orbit, exposure of nictating membrane, diarrhoea, mucous feces	>10	4.2.3.1-3

5.2 Repeated-dose toxicity

Repeated oral dose toxicity studies were conducted in rats (administered for 2 weeks, 3 months, and 6 months) and dogs (administered for 2 weeks, 3 months, and 9 months), and repeated percutaneous dose studies were conducted in miniature pigs (administered for 1 month and 9 months) (Table 11).

Major findings following oral administration to rats and dogs were low white blood cell count, decreases in red blood cell-related parameters (e.g., red blood cell count, haemoglobin, and reticulocyte count), opportunistic infections (including inflammatory changes), and reddening of the skin. The exposures (AUC) at the no-observed-adverse-effect level (NOAEL) (3 mg/kg/day for male rats, 10 mg/kg/day for female rats; 0.6 mg/kg/day for female dogs) in rats (6 months) and dogs (9 months) were 86-fold (male rats), 309-fold (female rats), 111-fold (male dogs), and 109-fold (female dogs) the exposure at the maximum clinical dose.[13)]

The weight of the pituitary gland was slightly higher in the delgocitinib 5% group following percutaneous administration to miniature pigs.

Table 11. Repeated-dose toxicity studies

Species/strain	Route of administration	Duration of administration	Dose (mg/kg)	Major findings	NOAEL (mg/kg)	CTD
Male/female rat (SD)	Oral	2 weeks (once daily)	0, 3, 10, and 30	≥3, reddening of the skin, decreased white blood cell/lymphocyte count, decreased thymus/splenic weight, decreased lymphocyte count in the thymic cortex and medulla, increased tingible body macrophages in the thymus, increased bone marrow fatty infiltration ≥10, high food consumption, low feeding efficiency, low reticulocyte count ratio, low platelet count, decreased relative weight of the lung, high chlorine in blood, decreased nucleated cells other than bone marrow erythroid/myeloblast cells 30, increased urinary ketones/proteins, increased aspartate aminotransferase (AST), decreased adrenal weight, decreased splenic extramedullary hematopoiesis	30[a)]	4.2.3.2-1
	Oral	3 months (once daily) + 1 month for recovery	0, 3, 10, and 30	≥3, decreased splenic weight, decreased counts of white blood cells/lymphocytes/basophils/large unstained cells, decreased nucleated cells other than bone marrow erythroid/myeloblast cells ≥10, low feeding efficiency, reddening of the skin, suppressed weight gain, decreased eosinophil count, decreased thymic weight, decreased thymic/splenic size, decreased area in the thymic cortex and medulla, decreased density of lymphoid cells in the thymus, decreased area of lymphatic follicle/periarterial lymphatic sheath in the spleen, increased bone marrow fatty infiltration 30, high food consumption, decreased red blood cell count/ hemoglobin concentration/ hematocrit/ neutrophil count/ monocyte count, increased blood total cholesterol/ phospholipid, decreased area of lymphatic follicle/ paracortex in the splenic marginal zone/ mesenteric lymph node, increased bone marrow erythroid cells, decreased bone marrow myeloblast cells, low M/E ratio, decreased weight of the submandibular gland/kidney/adrenal gland Reversibility: reversible	30[a)]	4.2.3.2-2
	Oral	6 months (once daily)	0, 3, 10, and 30	≥3, decreased counts of white blood cells/lymphocytes/basophils/eosinophils, decreased splenic weight, decreased nucleated cells other than bone marrow erythroid/myeloblast cells ≥10, suppressed body weight gain, low feeding efficiency, reddening of the skin, decrease monocyte count, increased blood total cholesterol/ phospholipid/glucose, hypertrophy of adrenal zona glomerulosa, decreased area in the thymic cortex/ medulla/ splenic lymphatic follicle/ periarterial lymphatic sheath/ splenic marginal zone, decreased density/area of lymphatic follicle/ paracortex in mesenteric lymph nodes,	3 (males) 10 (females)[b)]	4.2.3.2-3

				degeneration of epithelial cells in the forestomach border (male), increased bone marrow fatty infiltration 30, decreased red blood cell count/hemoglobin concentration/ hematocrit/ neutrophil count, decreased blood triglyceride, decreased thymus weight, degeneration of epithelial cells in the forestomach border (female), glandular stomach erosion		
Male/female dog (Beagle)	Oral	2 weeks (once daily)	0, 0.3, 1, and 3	≥1, decreased red blood cell count/hemoglobin concentration/ hematocrit/ reticulocyte count, decreased blood total proteins/ albumin/ calcium, suppressed development of germinal center of lymph node, decreased bone marrow erythroid cells (basophilic erythroblast/ polychromatic erythroblast), increased M/E ratio 3, reddening of oral mucosa/ conjunctiva/ skin/ ear, decreased A/G ratio, decreased area of splenic lymphatic follicle	3[a)]	4.2.3.2-4
	Oral	3 months (once daily) + 1 month for recovery	0, 0.3, 1, and 3	≥0.3, increased food consumption ≥1, decreased red blood cell count/ hemoglobin concentration/ hematocrit/ reticulocyte count/ eosinophil count, increased blood CRP/globulin, decreased blood albumin/ A/G ratio, increased α2 globulin/γ globulin fraction 3, reddening of oral mucosa/ conjunctiva/ ear, decreased body weight/ food consumption, increased counts of white blood cells/ neutrophils/monocytes, suppressed development of mesenteric lymph nodes/ Peyer's patch in the ileum/ germinal center of the palatine tonsil Reversibility: reversible	3[a)]	4.2.3.2-5
	Oral	9 months (once daily) + 3 months for recovery	0, 0.1, 0.6, 3/1.5[c)]	Died or sacrificed moribund, 3/1.5 (males, 3/6; females, 4/6), swelling of the skin, decreased body weight/ food consumption, increased body temperature, increased counts of neutrophils/monocytes/platelets, increased blood CRP/globulin/fibrinogen, inflammation of the ileum/ submandibular gland ≥0.1, decreased red blood cell count/ hemoglobin concentration/ hematocrit/ lymphocyte count ≥0.6, decreased eosinophil count, 3/1.5, skin hair loss, pimples, cysts, eruption, wet ulcer in the limbs, pyogenic granuloma (Demodex), lymph node inflammation, inflammatory cell infiltration in the liver, splenic extramedullary hematopoiesis, increased immature myeloid progenitor cells in bone marrow Reversibility: reversible[d)]	0.6	4.2.3.2-6
Male/female miniature pig (Gettingen)	Percutaneous	1 month (once daily)	(as delgocitinib) 0, 0.3, 1, and 3%[e)]	None	12	4.2.3.2-7
	Percutaneous	9 months (once daily) + 1 month for recovery	(as delgocitinib) 0, 1, 3, and 5%[f)]	20, increased pituitary gland weight[g)]	20	4.2.3.2-8

a) The observed findings were determined to be toxicologically less meaningful because they were changes attributable to the pharmacological action of delgocitinib, or the changes were mild in degree, and histopathological findings suggestive of organ toxicity were not observed.
b) The observed findings were determined to be toxicologically less meaningful because they were changes attributable to the pharmacological action of delgocitinib, or the changes were mild in degree, and histopathological findings suggestive of organ toxicity were not observed. This was determined based on suppressed body weight gain, decreased feeding efficiency, and histopathological changes of the stomach.
c) Because serious skin findings were noted at Week 16 or later, the dose level was changed from 3 mg/kg to 1.5 mg/kg at Week 24.
d) All findings were either resolved or improving as a result of withdrawal or the like.

e) Delgocitinib 0.3%, 1%, or 3% was applied onto approximately 10% of the body surface under semi-occlusion, and was removed once daily using soapy water and lukewarm water (corresponding to 1.2, 4, and 12 mg/kg as the dose of delgocitinib).
f) Delgocitinib 1%, 3%, or 5% was applied onto approximately 10% of the body surface under semi-occlusion, and was removed using soapy water and lukewarm water at 20 hours post-dose (corresponding to 4, 12, and 20 mg/kg as the dose of delgocitinib).
g) No histopathological changes were observed in the pituitary gland, and no changes suggesting effects on pituitary gland function were observed, and therefore, this was not considered to be toxicologically meaningful.

5.3 Genotoxicity

In vitro genotoxicity studies consisted of a bacterial reverse mutation assay and a chromosomal aberration assay with human peripheral blood lymphocytes; while *in vivo* genotoxicity studies consisted of a bone marrow chromosome aberration assay in rats, and a micronucleus assay in hairless mice (Table 12). In the chromosomal aberration assay with human peripheral blood lymphocytes, an increase in polyploids was observed. However, because all *in vivo* assays yielded negative results, it was determined that delgocitinib was unlikely to be genotoxic.

Table 12. Genotoxicity studies

Study type		Species/strain	S9 (treatment)	Concentration or dose	Test result	CTD
In vitro	Bacterial reverse mutation assay (Ames)	Salmonella typhimurium: TA98, TA100, TA1535, and TA1537	− / +	0, 313, 625, 1,250, 2,500, and 5,000 µg/plate	Negative	4.2.3.3.1-1
		Escherichia coli: WP2*uvrA*				
	Chromosomal aberration assay with mammalian cell culture	Human peripheral blood lymphocytes	− (3, 24 hours)	3 hours: 0, 31.25, 62.5, 125, 250, 500, 1,000, and 2,000 µg/mL 24 hours: 0, 12.5, 25, 50, 100, and 150 µg/mL	Positive (≥125-fold increase in polyploids compared with 3-hour treatment in the absence of S9; ≥50-fold increase in polyploids compared with 24-hour treatment in the absence of S9)	4.2.3.3.1-2
			+ (3 hours)	0, 62.5, 125, 250, and 500 µg/mL		
In vivo	Chromosomal aberration assay in rodents	Male rat (SD) bone marrow		0, 37.5, 75, 150, and 300 mg/kg/day (oral, single-dose)	Negative	4.2.3.1-2
	Micronucleus assay in rodents	Male hairless mouse skin		0%, 3%, and 5% (percutaneous, 3 days)	Negative	4.2.3.3.2-2 Reference data

5.4 Carcinogenicity

A mouse percutaneous dose carcinogenicity study and a rat oral dose carcinogenicity study were conducted (Table 13).

In the mouse percutaneous dose carcinogenicity study, no neoplastic changes were observed.

In the rat oral dose carcinogenicity study, neoplastic changes, namely, thymoma, Leydig cell tumor, pancreatic acinar cell adenoma, and subcutaneous lipoma were observed. In addition, as preneoplastic changes, hyperplasia was observed in the thymus, Leydig cells, and pancreatic acinar cells. Changes that are considered to be associated with the effects of delgocitinib were observed as follows: thymoma/hyperplasia and Leydig cell tumor/hyperplasia at delgocitinib ≥10 mg/kg and pancreatic acinar cell adenoma/hyperplasia

and lipoma at delgocitinib ≥3 mg/kg.[14)] The exposures (AUC) at 3 mg/kg were greater than 86-fold (male) and 84-fold (female) that of the maximum clinical dose, and the exposures (AUC) at 10 mg/kg were greater than 322-fold (male) and 309-fold (female) that of the maximum clinical dose.[13)]

Table 13. Carcinogenicity studies

Species/ strain	Route of administration	Duration of administration	Main lesion	Sex	Dose (mg/kg)[a)]				Noncarcinogenic (mg/kg)	CTD
					0	6	18	30		
				n	60	60	60	60		
Male/ female mouse (ICR)	Percutaneous	104 weeks (once daily)	Neoplastic lesion	M F	None				30	4.2.3.4.1-3
			Nonneoplastic lesion	M F	Increased number of adipocytes in the sternal/femoral bone marrow, increased adipose tissue in the skin of the administration site/ back/groin area					
Male/ female rat (SD)	Oral	104 weeks (once daily)	Main lesion	Sex	Dose (mg/kg)				<3	4.2.3.4.1-2
					0	3	10	30		
				n	66	66	66	66		
			Thymoma	M	0	1	1	3		
				F	0	0	4*	8*[b)]		
			Thymic hyperplasia	M	1	1	1	0		
				F	0	2	1	6[†]		
			Leydig cell tumor	M	0	2	2	6*		
				F	NA	NA	NA	NA		
			Leydig cell hyperplasia	M	4	9	11*	18*		
				F	NA	NA	NA	NA		
			Pancreatic acinar cell adenoma	M	0	4[#]	4[#]	4[#]		
				F	1	0	0	0		
			Pancreatic acinar cell hyperplasia	M	4	11*	18*	22*		
				F	1	0	2	4		
			Subcutaneous lipoma	M	0	3*	7*	3*		
				F	0	0	0	1		
			Nonneoplastic lesion	M & F	Alveolar proteinosis, inflammation of the cornea, cutaneous/subcutaneous pyogenic granulomatous inflammation, increased adipose tissue in the skin of the groin area, clear cell foci of altered hepatocytes in the liver, seminal vesicle dilatation, intraluminal mineral deposition in the kidney, atrophic change in the spleen/ Peyer's patch/ mesentery/ submandibular lymph node/ thymus					

NA, not applicable

*, It was concluded that the lesion was likely to be associated with delgocitinib for the following reasons: the findings increased statistically significantly compared with the vehicle control group, the findings occurred at a frequency greater than the institutional limits, the frequency/degree of the findings increased, or other reasons.

†, Because thymoma increased statistically significantly in females, and thymic hyperplasia occurred with a relatively higher incidence/degree in females at 30 mg/kg, it was concluded that the lesion was likely to be associated with delgocitinib.

#, While the frequency of the lesion was within the institutional limits in all groups, and no statistically significant increase was noted compared with the vehicle control group, given that the lesion was not observed in the vehicle control group, and that a clear increase in pancreatic acinar cell hyperplasia was observed, it was therefore concluded that the lesion was likely to be associated with delgocitinib.

a) Delgocitinib (1%, 3%, or 5%) 600 mg/kg was percutaneously administered once daily by application onto the hair-removed skin of the back (corresponding to delgocitinib dose of 6, 18, and 30 mg/kg, respectively).

b) Thymoma malignant occurred in 1 of 8 animals.

[14)] The changes were likely to be associated with delgocitinib, based on some reasons including the following: the number of findings statistically significantly increased in the delgocitinib group compared with the vehicle control group, and the findings occurred more frequently than the historical data.

5.5 Reproductive and developmental toxicity

Studies of fertility and early embryonic development to implantation in male and female rats, embryo-fetal development studies in rats and rabbits, and a study on prenatal and postnatal development and maternal function in rats were conducted (Table 14). The study of fertility and early embryonic development to implantation in female rats indicated lower conception rates, fewer implantations, fewer live fetuses, and higher embryonic mortality. The rat and rabbit embryo-fetal development studies indicated lower fetal body weights, fewer live fetuses, higher embryo-fetal mortality, and higher incidences of thymic remnant in neck and skeletal mutation, but no incidence of teratogenicity. The NOAEL for embryo-fetal development was 3 mg/kg/day for both rats and rabbits, with the exposures (AUC) being 64-fold and 103-fold, respectively, that of the maximum clinical dose.[13)]

Table 14. Reproductive and developmental toxicity studies

Study type	Species/ strain	Route of administration	Duration of administration	Dose (mg/kg)	Major findings	NOAEL (mg/kg)	CTD
fertility and early embryonic development to implantation	Male rat (SD)	Oral	Approximately 6 weeks (starting 14 days prior to mating) (once daily)	0, 3, 10, and 30	≥10, reddening of the skin, suppressed body weight gain, low feeding efficiency, smaller thymus 30, high food consumption, smaller spleen No effects on fertility or early embryonic development	Parent animal (general toxicity), fertility, early embryonic development: 30	4.2.3.5.1-1
	Female rat (SD)	Oral	Approximately 4 weeks (starting 14 days prior to mating) (once daily)	0, 3, 10, 30, and 100	≥10, reddening of the skin, higher post-implantation mortality ≥30, fewer live fetuses 100, suppressed body weight gain, decreased food consumption, fewer corpus lutea of pregnancy/ implantations, lower conception rates, higher preimplantation embryo mortality	Dam (general toxicity), fertility: 30 Early embryonic development: 3	4.2.3.5.1-2
Embryo-fetal development	Female rat (SD)	Oral	Gestation day 7 through gestation day 17 (once daily)	0, 3, 10, and 30	Dams: ≥10, reddening of the skin 30, suppressed body weight gain Fetuses: ≥10, lower fetal body weight, higher incidence of wavy ribs, 30, higher post-implantation embryonic-fetal mortality, higher incidences of thymic remnant in neck/ asymmetrical thymus/ splitting of the sternum/ splitting of thoracic spine/ 7th lumbar vertebra formation, fewer parts of the sternum	Dam (general toxicity): 30 Embryo-fetal development: 3	4.2.3.5.2-1
	Female rabbit (NZW)	Oral	Gestation day 6 through gestation day 18 (once daily)	0, 1, 3, and 10	Dams: 10, reddening of the ear, clearly visible blood vessels in the ear Fetuses: 10, higher post-implantation embryonic-fetal mortality, fewer live fetuses, lower fetal body weight	Dam (general toxicity): 10 Embryonic-fetal development: 3	4.2.3.5.2-2
Prenatal and postnatal development and maternal function	Female rat (SD)	Oral	Dam, gestation day 7 through day 20 post-partum (once daily)	0, 3, 10, and 30	Dams: ≥10, reddening of the skin 30, low food consumption, longer gestational period, lower birth rate, fewer live pups, higher number of dead pups, smaller	Dam (general toxicity, reproductivity): 10 Viability/development of F1 live pups: 10	4.2.3.5.3-1

Study type	Species/ strain	Route of administration	Duration of administration	Dose (mg/kg)	Major findings	NOAEL (mg/kg)	CTD
					thymus/spleen F1 live pups: 30, lower 4-day survival rate, lower live pup body weight, smaller spleen	Behavioral development/ reproductivity of F1 pups: 30	

5.6 Toxicity studies in juvenile animals

Toxicity studies were conducted using juvenile rats and juvenile miniature pigs (Table 15). In juvenile rats, no increased toxicity in the findings compared with those in mature rats, and no new toxicity findings were found. In juvenile miniature pigs, no delgocitinib-related findings were noted.

Table 15. Toxicity studies in juvenile animals

Species/strain	Route of administration	Duration of administration	Dose (mg/kg)	Major findings	NOAEL (mg/kg)	CTD
Male/female juvenile rat (SD)	Oral	10 weeks (starting day 21 post-partum) (once daily) + 12-week recovery period	0, 3, 10, and 30	≥3, suppressed body weight gain, lower food consumption, growth suppression in the ulna, lower hemoglobin level, decreased counts of white blood cells/ lymphocytes/ basophils/ eosinophils/ large unstained cells, higher red cell distribution width, higher percentage of erythroblasts, lower percentages of nucleated cells other than erythroblasts/myeloblasts, lower M/E ratio, fewer T cells/ B cells/ NK cells, lower anti-Keyhole limpet hemocyanin (KLH) specific antibody titers, decreased splenic weight, increased bone marrow fatty infiltration ≥10, reddening of the skin, lower monocyte counts, decreased thymic weight, decreased area in the thymic cortex and medulla, decreased density of lymphoid cells in the thymus, decreased area in the periarterial lymphatic sheath in the spleen/ splenic marginal zone 30, decreased neutrophil counts, lower red blood cell counts, and lower hematocrit levels; hypertrophy of adrenal zona glomerulosa Reversibility: reversible	30[a)]	4.2.3.5.4-1
Male/female juvenile miniature pig (Gettingen)	Percutaneous	1 month (starting day 30 post-partum)	0, 12, and 20[b)] (0%, 3%, and 5% as delgocitinib concentration)	None[c)]	20	4.2.3.5.4-2 Reference data

a) The findings were either changes attributable to the pharmacological action of delgocitinib, or the changes were mild in degree, and histopathological findings suggestive of organ toxicity were not observed; therefore, the observed findings were determined to be toxicologically less meaningful.
b) To identical animals, a single intravenous dose of delgocitinib 0.1 mg/kg was administered on Day 1 to investigate toxicokinetics; a single percutaneous dose at 12 mg/kg (topical delgocitinib 3% was applied to about 10% of the body surface under semi-occlusion) on Day 3 to investigate general toxicity; and repeated percutaneous doses at 20 mg/kg (topical delgocitinib 5% was applied to about 10% of the body surface under semi-occlusion) on Days 6 to 33.
c) Histopathological examination was performed only for the skin.

5.7 Local tolerance

Primary skin irritation studies in rabbits and miniature pigs and an eye mucosa primary skin irritation study with isolated bovine cornea were conducted (Table 16). In the rabbit and miniature pig primary skin irritation studies, there were no trends towards an increase in stimulation response in the damaged skin compared with the intact skin. In the rabbit skin primary study, both the ointment base and delgocitinib 3% were determined to be weak irritants; however, the irritability was attributable to white petrolatum contained in the ointment

base, and therefore, delgocitinib was unlikely to cause local irritability when used clinically. Based on the results of the eye mucosa primary skin irritation study using isolated bovine cornea, delgocitinib was determined to be a non-irritant.

Table 16. Local tolerance studies

Study type	Species/strain	Testing method	Major findings	CTD
Primary skin irritation	Male rabbit (Japanese white)	The ointment base or delgocitinib 3% (0.5 g/site) was applied to the intact and damaged skin of the back under occlusion for 24 hours, and the site was observed 24, 48, and 72 hours after the start of application.	The intact skin displayed slight to clear erythema, and the damaged skin displayed slight erythema in both of the animal groups dosed with the ointment base or delgocitinib 3%. The ointment base and delgocitinib 3% were assessed as weak irritants.	4.2.3.6-1
	Male miniature pig (Gettingen)	The ointment base or delgocitinib 1% or 3% (0.5 g/site) was applied to the intact and damaged skin of the back under occlusion for 24 hours, and the site was observed 24, 48, and 72 hours after the start of application.	The ointment base and delgocitinib 1% and 3% were assessed as non-irritants.	4.2.3.6-2
Bovine corneal opacity and permeability (BCOP)	Isolated bovine cornea	The ointment base or delgocitinib 1% or 3% was applied to the cornea to investigate irritability based on corneal opacity and fluorescein permeability	The ointment base and delgocitinib 1% and 3% were assessed as non-irritants.	4.2.3.6-3

5.8 Other studies

5.8.1 Skin sensitization

Based on a skin sensitization study in guinea pigs (Table 17), it was concluded that delgocitinib was not a skin irritant.

Table 17. Skin sensitization study

Study type	Species/strain	Testing method	Major findings	CTD
Skin sensitization (adjuvant and patch test)	Male Guinea pig (Hartley)	Freund's complete adjuvant 50% emulsion 0.1 mL was subcutaneously administered into the interscapular site. After abrasion of the skin at the interscapular site, delgocitinib 3% (100 mg/site) was applied under occlusion (initial induction of sensitization), white petrolatum (250 mg) containing 10% sodium lauryl sulfate was applied without occlusion, and topical delgocitinib 3% (200 mg) was applied under occlusion (second induction of sensitization), followed by application of delgocitinib 0.3%, 1% and 3% at different sites without occlusion as a challenge.	None	4.2.3.6-4

5.8.2 Photosafety

Phototoxicity studies in mice and guinea pigs and a skin sensitization study in guinea pigs were conducted (Table 18), and based on the results, delgocitinib was determined to be non-phototoxic and non-photosensitizing.

Table 18. Photosafety studies

Study type	Species/strain	Testing method	Major findings	CTD
Phototoxicity	Male mouse (Institute of Cancer Research [ICR])	Irradiation of long wavelength ultraviolet rays was performed for approximately 4 hours (21.6 J/cm^2 UVA and 1.4 J/cm^2 UVB) within 30 minutes of single oral dose of delgocitinib 25, 50, or 100 mg/kg, and the site was observed 24 and 48 hours after completion of irradiation.	None	4.2.3.7.7-1
	Male Guinea pig (Hartley)	Irradiation of long wavelength ultraviolet rays was performed for 120 minutes (15 J/cm^2) 30 minutes after application of delgocitinib 0.3%, 1%, or 3% (100 mg/site) onto the skin of the back without occlusion, and the site was observed 24, 48, and 72 hours after completion of irradiation.	None	4.2.3.7.7-2
Skin photosensitization (adjuvant and strip test)	Male Guinea pig (Hartley)	Freund's complete adjuvant 50% emulsion 0.1 mL was subcutaneously administered into the interscapular site. Delgocitinib 3% (100 mg/site) was applied to the site without occlusion, and irradiation of long wavelength ultraviolet rays was performed for 70 minutes (10.2 J/cm^2) to sensitize the skin. Three weeks after the initial day of photosensitization, delgocitinib 0.3%, 1%, or 3% (20 mg/site) was applied without occlusion, and irradiation of long wavelength ultraviolet rays was performed for 70 minutes (10.2 J/cm^2) for induction.	None	4.2.3.6-5

5.8.3 Immunotoxicity

An immunotoxicity study was conducted in rats (Table 19). T cell-dependent antibody responses and all lymphocyte subsets in peripheral blood as well as immature and mature thymocyte counts were low, and these were determined to be changes attributable to the pharmacological action of delgocitinib.

Table 19. Immunotoxicity study

Study type	Species/ strain	Testing method	Major findings	CTD
Immunotoxicity	Male/ female rat (SD)	Repeated oral doses of delgocitinib 0, 3, 10, or 30 mg/kg were administered once daily for 4 weeks, T cell-dependent antibody responses to sheep red blood cells (SRBC), and lymphocyte subsets in peripheral blood and the thymus were measured.	Lower anti-SRBC antibody titer, lower peripheral blood T-cell counts/ CD4$^+$T cell counts/ CD8$^+$T cell counts/ B cell counts/ NK cell counts/ NK cell percentage/CD8$^+$T cell percentage, lower thymic lymphocytes/ CD4$^+$CD8$^-$ cell counts/ CD4$^-$CD8$^+$ cell counts/ CD4$^+$CD8$^+$ cell counts/ CD4$^-$CD8$^-$ cell counts	4.2.3.7.2-1

5.R Outline of the review conducted by PMDA

5.R.1 Toxicological profiles of delgocitinib

The applicant's explanation about the toxicological profiles of delgocitinib:

Following oral administration of delgocitinib to rats and dogs, low white blood cell count, low antibody production, low red blood cell-related parameters (e.g., red blood cell count, hemoglobin, and reticulocyte count), opportunistic infections (including inflammatory changes), and reddening of the skin were observed [see Sections 5.2 and 5.8.3]. All findings seem to be associated with excessive pharmacological action or vasorelaxation caused by systemic exposure to delgocitinib. The AUC-based safety margins[13)] for these findings were 86-fold (male rats), 309-fold (female rats), 111-fold (male dogs), and 109-fold (female dogs), and therefore, these findings are unlikely to cause problems when delgocitinib is used clinically.

- Lower white blood cell counts and lower antibody production are attributable to suppression of lymphocyte activation mediated by inhibition of the JAK/STAT pathway by delgocitinib.
- Lower red blood cell-related parameters (e.g., red blood cell count, hemoglobin, and reticulocyte count) may be attributed to the suppression of signaling pathways downstream of erythropoietin (EPO) receptor

via JAK2 inhibition by delgocitinib rather than reduction in EPO excretion, because no changes in plasma EPO concentrations were noted.
- Opportunistic infections (including inflammatory changes) are attributable to excessive immunosuppressive effects of delgocitinib.
- Reddening of the skin is attributed to the vasorelaxation effects of delgocitinib.

Following percutaneous administration of delgocitinib 5% to miniature pigs, there was a slight increase in the pituitary gland weight [see Section 5.2]. However, given the absence of histopathological changes in the pituitary gland, and pituitary gland function-related changes in a variety of tests including urine analysis and hematology and blood biochemical tests, delgocitinib is unlikely to affect pituitary gland function when used clinically.

Accordingly, the above findings from the toxicity studies are unlikely to cause problems when delgocitinib is administered percutaneously in clinical use.

Based on the submitted data from toxicity studies and the applicant's explanation, PMDA considered that systemic toxicity is unlikely to occur when delgocitinib is percutaneously administered clinically.

5.R.2 Carcinogenicity of delgocitinib

The applicant’s explanation about neoplastic changes observed in the rat oral carcinogenicity study of delgocitinib:

In the rat oral carcinogenicity study, delgocitinib-related neoplastic and pre-neoplastic changes, namely, thymoma/thymic hyperplasia, Leydig cell tumor/hyperplasia, pancreatic acinar cell adenoma/hyperplasia, and subcutaneous lipoma, were observed. Because the genotoxicity study results indicate delgocitinib is unlikely to be genotoxic [see Section 5.3], all neoplastic and pre-neoplastic changes are caused by non-genotoxicity mechanisms.

Thymoma and thymic hyperplasia is inferred to occur as a result of suppression of signaling by the prolactin receptor on thymic epithelial cells via the inhibition of JAK2 by delgocitinib, but their detailed mechanisms of action have not been clarified. However, a significant increase in thymoma was observed at ≥10 mg/kg, and there were no cases of thymoma at 3 mg/kg. The exposure (AUC) at 3 mg/kg is 84-fold[13)] the exposure at the maximum clinical dose; therefore, it is unlikely that patients would develop thymoma or thymic hyperplasia when delgocitinib is used clinically.

Leydig cell tumor and Leydig cell hyperplasia are considered to be induced by downregulation of luteinizing hormone (LH) receptors in Leydig cells and continuous elevation of blood LH levels as a result of decreased blood prolactin through JAK inhibition by delgocitinib. In humans, prolactin receptors are not expressed in the testis in most cases, and Leydig cell hyperplasia does not occur after administration of LH agonists to humans. Because of these and other factors, the results are not necessarily extrapolated to humans (*Toxicol Sci.* 2017;155:148-56).

Pancreatic acinar cell adenoma and pancreatic acinar cell hyperplasia seem to be attributable to increased blood cholecystokinin (CCK) levels following administration of delgocitinib because of the following factors: delgocitinib is a weak trypsin inhibitor[15)]; inhibition of trypsin increases blood CCK levels, which is known to induce pancreatic acinar cell adenoma (*Cancer Res.* 1989;49:2438-41); and the rat oral carcinogenicity study displayed an increase in blood CCK levels. Pancreatic acinar cell adenoma resulting from CCK stimulation is reported to be rat specific, and therefore, the results cannot necessarily be extrapolated to humans (*Pharmacol Toxicol.* 2002;91:333-50, *Gastroenterology*. 2001;121:1380-90).

Subcutaneous lipoma is likely attributable to increased volume of adipose tissue as a result of acceleration of adipocyte proliferation due to JAK inhibition by delgocitinib because it is reported that in adipocytes, cytokine-stimulated or hormone-stimulated signaling are transmitted via JAK1 or JAK2, while some cytokines including IFN-γ suppress adipocyte proliferation, and growth hormone (GH) decreases the volume of adipose tissue (*Trends Endocrinol Metab.* 2011;22:325-32). Additionally, JAK2 has been reported to regulate lipid and glucose metabolism (*Trends Endocrinol Metab.* 2018;29:55-65), and changes in blood glucose and triglyceride levels have been reported in a rat study [see Section 5.2]. Therefore, JAK inhibition by delgocitinib may have accelerated glucose and lipid generation. However, acceleration of glucose and lipid generation in rats was not observed in humans, dogs, or miniature pigs; acceleration of glucose and lipid generation occurred at delgocitinib 1%, but lipoma did not occur in the mouse percutaneous dose carcinogenicity study; therefore, percutaneous administration of delgocitinib is unlikely to affect glucose and lipid metabolism in clinical use, causing a patient to develop lipoma.

Based on the above, the above neoplastic changes are unlikely to occur following administration of delgocitinib in clinical use.

PMDA's view:

The results on Leydig cell tumor and Leydig cell hyperplasia as well as pancreatic acinar cell adenoma and pancreatic acinar cell hyperplasia, which occurred in rats following oral administration of delgocitinib, cannot necessarily be extrapolated to humans, and therefore it is unlikely that, in clinical use, these toxic events will occur after percutaneous administration of delgocitinib. At this point in time, thymoma and thymic hyperplasia is unlikely to occur in clinical use because a safety margin of 84-fold[13)] was achieved, and neither thymoma nor thymic hyperplasia occurred in the clinical studies. It is also unlikely at this point in time that subcutaneous lipoma will occur in clinical use because effects of delgocitinib on glucose and lipid metabolism have not been observed in the clinical studies. However, thymoma, thymic hyperplasia, and lipoma are considered changes associated with delgocitinib as a JAK inhibitor; therefore, information about these changes should be included in the package insert.

[15)] Delgocitinib was found to have weak trypsin inhibitory effect *in vitro* (IC_{50} value of 6.4 mg/mL).

5.R.3 Embryo-fetal effects

Data have suggested that delgocitinib can be transferred across the placenta to the fetus following oral administration to pregnant rats [see Section 4.2.5]. The JAK/STAT pathway is involved in early embryonic development (*Science.* 2002;296:1653-5), and following administration of an oral JAK inhibitor, teratogenic effects which are suspected to be related to the pharmacological action of the drug were observed in multiple animal species (see Review Report "Xeljanz Tablets 5 mg," dated February 28, 2013). PMDA asked the applicant to explain the effects of delgocitinib on reproduction and development.

The applicant's explanation:

In the reproductive and development toxicity studies, no teratogenic effects were observed in animals dosed with oral delgocitinib. However, higher post-implantation embryo-fetal mortality was observed in early embryos. In embryos and fetuses, higher post-implantation embryo-fetal mortality, lower fetal body weights, higher incidences of skeletal mutation and thymic remnant in neck, and other findings were noted. Furthermore, lower survival was noted in live pups.

Given that JAK/STAT3 activation of the intrauterine epithelium is important for implantation of fertilized eggs in the uterus, and that inhibition of JAK/STAT3 activation in the uterus has been reported to decrease implantation rates (*Proc Natl Acad Sci USA.* 2001;98:8680-5, *Proc Natl Acad Sci USA.* 2005;102:8585-90), higher post-implantation embryo-fetal mortality and low survival of live pups may be attributable to the pharmacological action of delgocitinib. Suppression of fetal development by delgocitinib may have affected the higher incidences of skeletal mutation and thymic remnant in neck and other findings in fetuses because these were accompanied by lower body weights.

However, all of the above findings were observed following oral administration of delgocitinib. In contrast, Corectim Ointment is a topical agent, only a small amount is absorbed trans-dermally, and data from clinical studies in patients with atopic dermatitis have demonstrated that systemic exposure is low following percutaneous administration of delgocitinib [see Section 6.R.1]. The safety margin between animal and human exposures to delgocitinib based on the above toxicity findings in the reproductive and developmental studies is 64-fold for rats and 103-fold for rabbits, suggesting that delgocitinib is unlikely to affect reproduction and development in humans.

PMDA's view:

The toxicity findings observed in the reproductive and development toxicity studies may have been caused by the pharmacological action of delgocitinib. However, given that a certain safety margin has been assured, percutaneous administration of topical delgocitinib to humans is unlikely to affect fetuses. Therefore, at this point in time, it is not necessary to restrict the use of topical delgocitinib to women who are or may be pregnant. However, the package insert should provide information about higher post-implantation embryo-fetal mortality after oral administration of delgocitinib.

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 formulation used in clinical studies, from which the evaluation data were submitted for the present application, was identical to the proposed commercial formulation.

In the clinical studies, the concentrations of unchanged delgocitinib in plasma and urine were measured by LC/MS/MS. The LLOQs for unchanged delgocitinib concentrations were 1 ng/mL (plasma) and 25 ng/mL (urine).

6.1.1 *In vitro* studies of metabolites (CTD 4.2.2.4-6, 4.2.2.4-7, 4.2.2.4-9, and 4.2.2.4-10, Studies JTE052-AD-020/B[redacted]0479, JTE052-AD-009/B[redacted]1263, JTE052-AD-010/B[redacted]1264, and JTE052-AD-011/B[redacted]1265)

The metabolism of ^{14}C-labeled delgocitinib was investigated using human skin microsomes. After 1 hour of reaction, 100% of delgocitinib remained unchanged, and no metabolites were observed.

The metabolism of ^{14}C-labeled delgocitinib was investigated using primary human hepatocytes. After 4 hours of reaction, 100% of delgocitinib remained unchanged, and no metabolites were observed. The metabolism of ^{14}C-labeled delgocitinib was investigated using human liver microsomes. Metabolites M1, M2, and M3 were detected, and each metabolite accounted for <5% of radioactivity in the sample. No metabolites unique to humans were observed [see Section 4.3.1].

Delgocitinib (5 μmol/L) was added to recombinant human cytochrome P450 (CYP) isoform expressions (CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5). CYP3A4 was involved in the formation of M1 and M2, and CYP1A1, CYP2C19, CYP2D6, and CYP3A4 were involved in the formation of M3.

Based on the above, the applicant explained that delgocitinib was hardly metabolized following percutaneous administration to humans.

6.1.2 The induction of human liver drug-metabolizing enzyme by delgocitinib (CTD 4.2.2.4-12, Study JTE052-AD-014/[redacted]3147)

Delgocitinib was incubated with human primary hepatocytes to investigate the effect of delgocitinib on the induction of CYP isoforms (CYP1A2, CYP2B6, and CYP3A4). The maximum induction of CYP1A2, CYP2B6, and CYP3A4 mRNA (induction factor of delgocitinib at 30 μmol/L) was 1.82-fold, 1.31-fold, and 2.14-fold, respectively.

Based on the above, the applicant explained that because delgocitinib had no marked effects on the levels of mRNA of each CYP isoform, delgocitinib is unlikely to show CYP induction effects in humans.

6.1.3 Inhibition of human liver drug-metabolizing enzyme by delgocitinib (CTD 4.2.2.4-11, Study JTE052-AD-013/JE052PK021)

Delgocitinib was incubated with human liver microsomes to investigate the inhibitory effect of delgocitinib on the enzyme activity of each of the CYP isoforms[16] (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5). No decreases in enzyme activity were noted for any of the CYP isoforms up to the maximum concentration (30 μmol/L) studied.

6.1.4 Investigation of transporter substrate properties and inhibitory effects (CTD 4.2.2.6-1, Study JTE052-AD-015/GE-1006-G)

P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP)-mediated transport of ^{14}C-labeled delgocitinib (1, 10, and 30 μmol/L) was investigated using human colonic adenocarcinoma cell (Caco)-2 cell monolayers. The results showed that delgocitinib is a substrate for P-gp, but is not a substrate for BCRP.

^{14}C-labeled delgocitinib at 1, 10, and 30 μmol/L was added to HEK293 cell lines expressing organic anion transporter (OAT)1, OAT3, and organic cation transporter (OCT)2. The results showed that delgocitinib is a weak substrate for OAT3 and OCT2, but is not a substrate for OAT1.

Inhibitory effects[17] of delgocitinib were investigated with P-gp-, BCRP-, organic anion transporting polypeptide (OATP)1B1-, and OATP1B3-mediated transports as indices. The results indicated that the IC_{50} of delgocitinib was >30 μmol/L for all the transporters.

Inhibitory effects[18] of delgocitinib were investigated with OAT1-, OAT3-, and OCT2-mediated transports as indices. The results indicated that delgocitinib inhibited OAT1 and OAT3, and the IC_{50} was 1.59 μmol/L for OAT1 and 6.38 μmol/L for OAT3. The IC_{50} of delgocitinib was >30 μmol/L for OCT2.

According to the applicant's explanation, delgocitinib is unlikely to inhibit transporters in clinical use because steady-state C_{max} following administration of topical delgocitinib 0.5% ointment 5 g twice daily was estimated to be 2.76 nmol/L, which is sufficiently lower than the IC_{50}.

6.2 Clinical pharmacology

6.2.1 Japanese phase I cutaneous safety study (CTD 5.3.3.1-2, Study QBX1-1 [[redacted] to [redacted]]

A randomized, double-blind, intra-individual comparison study was conducted in healthy adults (target sample size, 22 subjects) to assess skin irritation, photo-urticaria, and phototoxicity of topical delgocitinib (occlusive patch test and photo patch test).

In this study, approximately 20 mg of placebo, the base ointment for topical delgocitinib (white petrolatum),

[16] The following substances were evaluated as substrates: phenacetin for CYP1A2, coumarin for CYP2A6, bupropion for CYP2B6, amodiaquine for CYP2C8, diclofenac CYP2C9, S-mephenytoin for CYP2C19, bufuralol for CYP2D6, and midazolam and testosterone for CYP 3A4/5.

[17] The following substances were evaluated as substrates: [^{3}H]digoxin for P-gp, [^{3}H]estrone-3-sulfate for BCRP, and [^{3}H]estradiol-17β-D-glucuronide for OATP1B1 and OATP1B3.

[18] The following substances were evaluated as substrates: [^{3}H]p-aminohippuric acid for OAT1, [^{3}H]estrone-3-sulfate for OAT3, and [^{14}C]metformin for OCT2.

or topical delgocitinib 0.03%, 0.1%, 0.3%, 1%, or 3% ointment was applied onto the back using occlusive patches (Finn Chamber). The duration of patch application was 48 hours in the occlusive patch test, and 24 hours in the photo patch test.

All 22 subjects who received the study drug were included in the safety analysis set.

No skin irritation or photo-urticaria was observed at any concentration of topical delgocitinib. As for photo toxicity, at 60 minutes after the removal of the Finn Chamber patch, mild responses were observed at the application sites of placebo, the base ointment (white petrolatum), and topical delgocitinib 0.03%, 0.1%, and 0.3% ointment in 1 subject, and at the application sites of topical delgocitinib 1% and 3% ointment in 2 subjects. However, at 24 hours, there were no responses at any of the application sites, indicating that the phototoxicity of topical delgocitinib was low.

6.2.2 Japanese phase I single-dose and repeated-dose administration study (CTD 5.3.3.2-1, Study QBX1-2 [[redacted] to [redacted]])

Single percutaneous application

A placebo-controlled, randomized, single-blind study was conducted in healthy adults (target sample size, 8 subjects; n = 2 [placebo] and n = 6 [delgocitinib]), and patients with atopic dermatitis (target sample size, 16 subjects; n = 4 [placebo] and n = 6/group [delgocitinib]) to assess the pharmacokinetics and safety of topical delgocitinib following single percutaneous application. In this study, a single application of placebo or topical delgocitinib 3% ointment 5 g was administered to healthy adults, and a single application of of placebo or topical delgocitinib 1% or 3% ointment 5 g was administered to patients with atopic dermatitis, and then removed at 24 hour post-application.

All 24 subjects who received the study drug (8 healthy adults and 16 patients with atopic dermatitis) were included in the safety analysis set. One subject in the delgocitinib 3% group discontinued the study when violation of the exclusion criteria was found after receiving the study drug, and the remaining 23 subjects (8 healthy adults and 15 patients with atopic dermatitis) were included in the pharmacokinetics analysis.

Plasma unchanged delgocitinib concentrations were less than the LLOQ (1 ng/mL) in all 6 subjects who received topical delgocitinib 3%, and the urinary excretion of unchanged delgocitinib was 0.02% of the administered amount at 48 hours post-application.

Of the patients with atopic dermatitis who received topical delgocitinib, all 6 subjects in the delgocitinib 1% group had plasma delgocitinib concentrations below the LLOQ. In the delgocitinib 3% group, plasma delgocitinib was detected in 1 subject (C_{max}, 7.4 ng/mL), and delgocitinib concentrations were below the LLOQ in the other 4 subjects. Urinary excretion at 48 hours post-application was 0.38% in the delgocitinib 1% group and 0.41% in the delgocitinib 3% group. While the percutaneous absorption of delgocitinib in patients with atopic dermatitis is slightly higher than that in healthy adults, systemic exposure was limited.

In healthy adults, an adverse event (white blood cell count decreased) occurred in 1 of 6 subjects (16.7%) in the delgocitinib 3% group, while in patients with atopic dermatitis, an adverse event (white blood cell count decreased) occurred in 1 of 6 subjects (16.7%) in the delgocitinib 3% group. A causal relationship to delgocitinib was ruled out for the both events. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation in any of the groups.

Repeated percutaneous applications

The pharmacokinetics and safety of delgocitinib following repeated percutaneous applicationswas investigated in patients with atopic dermatitis aged ≥18 years and <65 years (target sample size, 20 subjects; n = 4 [placebo], and n = 8/group [delgocitinib]).

In the study, placebo or topical delgocitinib 1% or 3% ointment 5 g was applied twice daily for 7 days.

All 20 subjects who received the study drug were included in the safety analysis set. Of the 20 subjects, 1 subject in the delgocitinib 3% group was discontinued from the study at the subject's request, and the remaining 19 subjects were included in the pharmacokinetic analysis set.

Plasma delgocitinib was detected in 2 of 8 subjects in the delgocitinib 1% group. Plasma delgocitinib concentrations in these patients were 1.0 to 1.5 ng/mL. In the delgocitinib 3% group, the C_{max} was 3.7 ng/mL for the first application on Day 1 and 2.9 ng/mL for the first application on Day 7, while the AUC_{tau} was 30.4 ng·h/mL (Day 1) and 25.2 ng·h/mL (Day 7), suggesting that repeated applications did not cause accumulation. Urinary excretion up to 12 hours after the first application on Day 7 was 0.19% at delgocitinib 1% and 0.29% at delgocitinib 3%.

Adverse events occurred in 2 of 8 subjects (25.0%) in the delgocitinib 1% group (erysipelas and dermatitis atopic) and 1 of 8 subjects (12.5%) in the delgocitinib 3% group (dermatitis atopic). An adverse drug reaction occurred in 1 of 8 subjects (12.5%) in the delgocitinib 1% group (erysipelas). There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation in any of the groups.

6.2.3 Japanese phase II study in patients with atopic dermatitis (CTD 5.3.5.1-1, Study QBA2-1 [to])

This study investigated plasma unchanged delgocitinib concentrations following repeated percutaneous applications of topical delgocitinib to patients aged ≥16 years and <65 years with atopic dermatitis (target sample size, 300 subjects).

In this study, topical delgocitinib 0.25%, 0.5%, 1%, or 3% ointment was applied at a maximum of 5 g per application twice daily for 4 weeks [see Section 7.1 for the outline of study, and the results of efficacy and safety].

Table 20 shows the percentage of patients in whom plasma delgocitinib was detected at Weeks 2 and 4, and the plasma unchanged delgocitinib concentrations. Plasma delgocitinib was more frequently detectable in patients at delgocitinib 1% and 3% than in those at other delgocitinib concentrations. On the other hand, unchanged delgocitinib concentrations (mean) in patients in whom plasma delgocitinib was detected were close to the LLOQ (1 ng/mL) in all groups.

Table 20. Plasma unchanged delgocitinib concentrations after 4-week percutaneous administration of delgocitinib to patients with atopic dermatitis (ng/mL)

Delgocitinib		Week 2	Week 4
0.25%	Percentage of patients with plasma delgocitinib detected (Number of patients detected / number of patients tested)	10.4% (7/67)	12.1% (8/66)
	Mean ± SD[a)]	1.67 ± 0.72	1.76 ± 0.75
0.5%	Percentage of patients with plasma delgocitinib detected (Number of patients detected / number of patients tested)	6.3% (4/64)	7.9% (5/63)
	Mean ± SD[a)]	3.30 ± 2.40	2.22 ± 0.94
1%	Percentage of patients with plasma delgocitinib detected (Number of patients detected / number of patients tested)	23.4% (15/64)	25.4% (16/63)
	Mean ± SD[a)]	1.96 ± 1.10	2.62 ± 2.66
3%	Percentage of patients with plasma delgocitinib detected (Number of patients detected / number of patients tested)	51.6% (33/64)	41.3% (26/63)
	Mean ± SD[a)]	2.55 ± 2.52	3.13 ± 2.50

a) Mean ± SD of plasma unchanged delgocitinib concentrations in patients in whom plasma delgocitinib was detected

6.2.4 Japanese phase III study in patients with atopic dermatitis (CTD 5.3.5.1-2, Study QBA4-1 [to])

This study investigated plasma unchanged delgocitinib concentrations following repeated percutaneous administration of topical delgocitinib to patients aged ≥16 years with atopic dermatitis (target sample size, 150 subjects; 50 subjects [placebo] and 100 subjects [delgocitinib]).

In this study, placebo or topical delgocitinib 0.5% ointment was applied at a maximum of 5 g per application twice daily for 4 weeks [see Section 7.2.1 for the outline of study, and the results of efficacy and safety].

The percentage of patients in whom plasma delgocitinib was detected at Week 4 was 8.2% (8 of 98 subjects). The plasma unchanged delgocitinib concentration in patients in whom plasma delgocitinib was detected at Week 4 was 2.36 ± 1.03 ng/mL (mean ± SD). The above results demonstrated that systemic exposure following 4-week percutaneous administration of topical delgocitinib 0.5% twice daily was low.

6.2.5 Japanese long-term study in patients with atopic dermatitis (CTD 5.3.5.2-1, Study QBA4-2 [to]

This study investigated plasma unchanged delgocitinib concentrations following repeated percutaneous administration of topical delgocitinib to patients aged ≥16 years with atopic dermatitis (target sample size, 330 subjects).

In this study, topical delgocitinib 0.5% ointment was applied at a maximum of 5 g per application twice daily for 52 weeks [see Section 7.2.2 for the outline of study, and the results of efficacy and safety].

Table 21 shows plasma unchanged delgocitinib concentrations. The percentage of patients in whom plasma delgocitinib was detected, and the plasma unchanged delgocitinib concentrations remained constant at and after Week 4 and did not tend to increase with increasing treatment period.

Table 21. Plasma unchanged delgocitinib concentrations during 52-week percutaneous administration of delgocitinib to patients with atopic dermatitis (ng/mL)

		Week 4	Week 12	Week 28	Week 52
Delgocitinib 0.5%	Percentage of patients with plasma delgocitinib detected (Number of patients detected / number of patients tested)	13.6% (45/330)	16.2% (50/308)	13.8% (39/282)	11.5% (30/262)
	Mean ± SD[a)]	2.55 ± 1.82	2.52 ± 2.41	2.37 ± 2.17	2.24 ± 1.65

a) Mean ± SD of unchanged delgocitinib concentrations in the plasma of patients in whom plasma delgocitinib was detected

6.R Outline of the review conducted by PMDA

6.R.1 Pharmacokinetics of delgocitinib following percutaneous administration

The applicant's explanation about the pharmacokinetics following percutaneous administration of delgocitinib:

Data on patients treated with topical delgocitinib 0.5% from the phase II, phase III comparative, and long-term studies were pooled for analysis (the data were hereinafter referred collectively to as "pooled data from the 3 studies"). In the pooled data from the 3 studies, the percentage of patients in whom plasma delgocitinib was detected up to Week 52 was 11.5% to 15.8%, indicating that plasma delgocitinib was detectable in only limited patients. The mean plasma unchanged delgocitinib concentrations in patients in whom plasma delgocitinib was detected was 2.2 to 2.5 ng/mL, which was close to the LLOQ (1 ng/mL), indicating that only a small amount of delgocitinib was distributed in blood (Table 22). Because the percutaneous absorption following percutaneous administration of topical delgocitinib 0.5% twice daily was low, systemic exposure was very limited.

Table 22. Plasma unchanged delgocitinib concentrations following repeated percutaneous administration of topical delgocitinib by Investigator's Global Assessment (IGA) score at baseline (ng/mL) (Pooled data from the 3 studies)

IGA score at baseline		Week 2	Week 4	Week 12	Week 28	Week 52
Total	Percentage of patients with plasma delgocitinib detected (Number of patients detected / number of patients tested)	12.9% (22/170)	11.9% (59/494)	15.8% (65/411)	14.2% (54/380)	11.5% (30/262)
	Mean ± SD[a)]	2.3 ± 1.5	2.5 ± 1.7	2.4 ± 2.2	2.4 ± 2.2	2.2 ± 1.6
2 (Mild)	Percentage of patients with plasma delgocitinib detected (Number of patients detected / number of patients tested)	—	10.4% (11/106)	11.9% (12/101)	8.3% (8/96)	4.5% (4/89)
	Mean ± SD[a)]	—	1.8 ± 0.8	3.3 ± 3.3	1.6 ± 0.8	2.0 ± 1.2
3 (Moderate)	Percentage of patients with plasma delgocitinib detected (Number of patients detected / number of patients tested)	7.8% (10/128)	11.1% (36/323)	16.2% (41/253)	15.2% (35/231)	11.7% (18/154)
	Mean ± SD[a)]	2.3 ± 1.6	2.4 ± 1.4	1.9 ± 1.3	2.0 ± 1.2	2.0 ± 1.0
4 (Severe)	Percentage of patients with plasma delgocitinib detected (Number of patients detected / number of patients tested)	28.6% (12/42)	18.5% (12/65)	21.1% (12/57)	20.8% (11/53)	42.1% (8/19)
	Mean ± SD[a)]	2.4 ± 1.4	3.4 ± 2.6	3.2 ± 3.0	4.0 ± 4.0	3.0 ± 2.7

a) Mean ± SD of plasma unchanged delgocitinib concentrations in patients in whom plasma delgocitinib was detected

Because the percutaneous absorption of delgocitinib tended to be higher in the skin with defective stratum corneum [see Section 4.1.1], plasma delgocitinib concentrations in relation to the severity of atopic dermatitis (Investigator's Global Assessment [IGA] score at baseline; score 2 to 4) were investigated. The percentage of patients in whom plasma delgocitinib was detected, and the plasma delgocitinib concentrations tended to be higher in patients with higher IGA scores (Table 22). However, in the long-term treatment (pooled data from the Japanese phase III comparative study and the long-term study), the incidence of adverse events by IGA score among patients in whom plasma delgocitinib was detected was as follows: 63.0% (17 of 27 subjects) for IGA score 2; 69.0% (69 of 100 subjects) for IGA score 3; and 73.0% (27 of 37 subjects) for IGA score 4. There were no trends towards an increase in the incidence of adverse events with increasing severity of atopic dermatitis. Furthermore, there was no significant difference in the trend of the incidence of systemic adverse events by severity.

Based on the above, there would appear to be no concerns about systemic delgocitinib exposure in patients with severe atopic dermatitis.

PMDA confirmed that systemic exposure was very limited following repeated percutaneous administration of topical delgocitinib 0.5% twice daily. Systemic delgocitinib exposure is unlikely to affect safety in patients with severe atopic dermatitis.

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

The applicant submitted efficacy and safety evaluation data, in the form of results from 3 Japanese clinical studies (Table 23).

Table 23. Japanese clinical studies on efficacy and safety

Phase	Study title Purpose	Design	Group (number of subjects)	Duration of study	Percentage change from baseline in Modified Eczema Area and Severity Index (mEASI) score (%) [95% CI]
II	QBA2-1 Dose finding	Single-blind (evaluator-blinded)	Placebo (31) Topical delgocitinib 0.25% (69) Topical delgocitinib 0.5% (65) Topical delgocitinib 1% (66) Topical delgocitinib 3% (65) Tacrolimus 0.1% (30)	4 weeks	Last administration (Week 4 or at the time of discontinuation) Placebo: −12.7 [−30.3, 4.8] Topical delgocitinib 0.25%: −41.5 [−52.8, −30.1] Topical delgocitinib 0.5%: −57.5 [−66.1, −48.9] Topical delgocitinib 1%: −54.1 [−64.3, −43.8] Topical delgocitinib 3%: −73.3 [−79.6, −67.1] Tacrolimus 0.1%:−62.0 [−76.1, −47.9]
III	QBA4-1 Confirmatory and extension	Confirmatory phase Double-blind	Placebo (52) Topical delgocitinib (106)	4 weeks	Last administration (Week 4 or at the time of discontinuation) Placebo: 1.7 [−9.0, 12.5] Topical delgocitinib: −44.3 [−51.8, −36.8]
		Extension phase Open-label	Newly treated subjects (48) Continuously treated subjects (106)	24 weeks	Last administration (Week 24 or at the time of discontinuation) Newly treated subjects: −52.7 [-65.0, −40.4] Continuously treated subjects: −52.3 [−60.1, −44.5]
III	QBA4-2 Long-term	Open-label	Topical delgocitinib (352)	52 weeks	Last administration (Week 52 or at the time of discontinuation) −12.8 [−22.3, −3.4]

Table 24 shows Eczema Area and Severity Index (EASI) and modified EASI (mEASI) scoring systems used for the efficacy evaluation in the submitted clinical study. Table 25 shows the IGA scoring system used for overall evaluation of rash.

Table 24. EASI and mEASI scoring systems

EASI score = A + B + C + D **mEASI score = B + C + D** **Head and neck: A = 0.1 × (erythema score + edema/papulation score + excoriation score + lichenification score) × region score** **Upper extremities: B = 0.2 × (erythema score + edema/papulation score + excoriation score + lichenification score) × region score** **Trunk: C = 0.3 × (erythema score + edema/papulation score + excoriation score + lichenification score) × region score** **Lower extremities: D = 0.4 × (erythema score + edema/papulation score + excoriation score + lichenification score) × region score**	
Skin signs	**The severity of erythema, edema/papulation, excoriation, and lichenification for each body region (head and neck, upper extremities, trunk, and lower extremities) is rated using the 7-point scale shown below.** **0: none** **0.5: somewhere between none and mild** **1: mild** **1.5: somewhere between mild and moderate** **2: moderate** **2.5: somewhere between moderate and severe** **3: severe**
Region score	**The percentage of involvement of inflammatory rashes, except for dry skin, in each body region (head and neck, upper extremities, trunk, and lower extremities) is rated using the 7-point scale shown below.** **0: no lesion** **1: 1% to 9%** **2: 10% to 29%** **3: 30% to 49%** **4: 50% to 69%** **5: 70% to 89%** **6: 90% to 100%**

Table 25. IGA scoring system

The severity of systemic inflammatory rashes was rated using the following 6-point scale by the investigator according to the "Criteria for severity" published by the study group of research funded by the Health and Labour Sciences Research Grant. **0: no symptoms** **1: almost no symptoms** **2: mild** **3: moderate** **4: severe** **5: very severe**
"Criteria for severity" **Mild: only mild rashes* are observed regardless of the affected area.** **Moderate: intense inflammatory rashes** are observed in <10% of the body surface area.** **Severe: intense inflammatory rashes are observed in ≥10% and <30% of the body surface area.** **Very severe: intense inflammatory rashes are observed in ≥30% of the body surface area.** *** Mild rashes: lesions primarily consisting of mild erythema, dry skin, and desquamation** **** Intense inflammatory rashes: lesions accompanied by erythema, papulation, erosion, edema, and lichenification**

7.1 Phase II studies

7.1.1 Japanese dose-finding study (CTD 5.3.5.1-1, Study QBA2-1 [[redacted] to [redacted]])

A multicenter, randomized, evaluator-blinded, placebo-controlled, parallel-group study (the tacrolimus group was unblinded) was conducted at 38 study centers in Japan to investigate the efficacy, safety, and dose of topical delgocitinib in patients aged ≥16 years and <65 years with atopic dermatitis (Table 26) (target sample size, 300 subjects; 60 subjects/group [delgocitinib], 30 subjects [placebo], and 30 subjects [tacrolimus]).

Table 26. Main inclusion and exclusion criteria

Main inclusion criteria **• Patients with mEASI score of ≥10.** **• Patients with an IGA score of ≥3 (moderate).** **• Patients with inflammatory rashes except for dry skin (e.g., erythema, edema/papulation, excoriation, lichenification) affecting ≥10% and <30% of the body surface area.**
Main exclusion criteria **• Patients with active infection at the planned sites of study drug application.** **• Patients who received biologics (e.g., cytokine products and antibody products) within 24 weeks prior to the start of study drug administration.** **• Patients who received the following therapies within 28 days prior to the start of study drug administration:** **Systemic corticosteroid preparations, topical corticosteroids (strongest or very strong),** **Systemic immunosuppressants, live vaccines, phototherapies (e.g., UVB [broadband and narrow band], psoralens plus UVA [PUVA]), desensitization therapies.** **• Patients who used an agent (or agents) listed below within 7 days prior to the start of study drug administration:** **Tacrolimus ointment, topical corticosteroids (strong, medium, or weak),** **Topical analgesics, antipruritics, and anti-inflammatory agents (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]) used for the study drug application sites,** **Agents intended for the treatment of atopic dermatitis (including traditional herbal medicines)**

In this study, an appropriate amount of placebo, topical delgocitinib 0.25%, 0.5%, 1%, or 3%, or tacrolimus ointment was applied twice daily for 4 weeks to the sites of inflammatory rashes except for dry skin (excluding scalp, palms, and plantar regions of the foot). The maximum amount was 5 g per application (10 g per day).

All 327 subjects who were randomly assigned (32 subjects [placebo], 69 subjects [delgocitinib 0.25%], 65 subjects [delgocitinib 0.5%], 66 subjects [delgocitinib 1%], 65 subjects [delgocitinib 3%], and 30 subjects [tacrolimus]) received the study drug, and were included in the safety analysis set. Of the 327 subjects receiving the study drug, 1 subject in the placebo group was excluded due to lack of efficacy evaluation, and the remaining 326 subjects were included in the full analysis set (FAS), which was used for the primary efficacy analysis. Eighteen subjects discontinued treatment (6 subjects [placebo], 3 subjects [delgocitinib 0.25%], 2 subjects [0.5%], 3 subjects [1%], 2 subjects [3%], and 2 subjects [tacrolimus]) because of "worsening of primary disease" in 5 subjects (3 subjects [placebo], 1 subject [delgocitinib 0.25%], and 1 subject [1%]), "adverse events" in 4 subjects (1 subject [delgocitinib 0.25%], 1 subject [0.5%], 1 subject [1%], and 1 subject [tacrolimus]), "lost to follow-up" in 4 subjects (2 subjects [placebo], 1 subject [delgocitinib 0.25%], and 1 subject [3%]), "at the subject's request" in 2 subjects (1 subject [placebo], and [delgocitinib 1%]), "pregnancy" in 2 subjects (1 subject [delgocitinib 0.5%] and 1 subject [tacrolimus]), and "investigator's decision" in 1 subject (delgocitinib 3%).

Table 27 shows the percentage change from baseline in the mEASI score at the final evaluation point (Week 4 or at the time of discontinuation) (FAS), the primary endpoint. The results indicated that there were statistically significant differences between any of the delgocitinib groups and the placebo group ($p = 0.0004$ [0.25%], $p < 0.0001$ [0.5%, 1%, and 3%]; Williams' test, one-tailed significance level of 2.5%).

Table 27. Percentage change from baseline in the mEASI score at the final evaluation point (Week 4 or at the time of discontinuation) (FAS)

	Placebo (N = 31)	0.25% (N = 69)	0.5% (N = 65)	1% (N = 66)	3% (N = 65)	Tacrolimus (N = 30)
mEASI score at baseline (mean ± SD)	14.8 ± 4.0	15.6 ± 4.3	15.0 ± 4.4	16.2 ± 4.3	14.9 ± 3.8	15.3 ± 4.9
mEASI score at the final evaluation point (mean ± SD)	13.4 ± 9.0	9.4 ± 8.8	6.3 ± 5.2	7.8 ± 7.4	4.0 ± 3.9	6.3 ± 7.8
Percentage change from baseline in the mEASI score at the final evaluation point [95% CI] (%)	−12.7 [−30.3, 4.8]	−41.5 [−52.8, −30.1]	−57.5 [−66.1, −48.9]	−54.1 [−64.3, −43.8]	−73.3 [−79.6, −67.1]	−62.0 [−76.1, −47.9]
P-value[a)]		0.0004	<0.0001	<0.0001	<0.0001	

a) Williams' test for the placebo group, one-tailed significance level of 2.5%

The incidence of adverse events was 15.6% (5 of 32 subjects) in the placebo group, 18.8% (13 of 69 subjects) in the delgocitinib 0.25% group, 18.5% (12 of 65 subjects) in the 0.5% group, 21.2% (14 of 66 subjects) in the 1% group, 18.5% (12 of 65 subjects) in the 3% group, and 43.3% (13 of 30 subjects) in the tacrolimus group. No adverse drug reactions occurred in the placebo group. The incidence of adverse drug reactions was 4.3% (3 of 69 subjects) in the 0.25% group, 6.2% (4 of 65 subjects) in the 0.5% group, 9.1% (6 of 66 subjects) in the 1% group, 4.6% (3 of 65 subjects) in the 3% group, and 16.7% (5 of 30 subjects) in the tacrolimus group. Tables 28 and 29 show adverse events that occurred in ≥2 subjects in at least 1 group, and adverse drug reactions that occurred in ≥2 subjects in at least 1 group, respectively.

Table 28. Adverse events that occurred in ≥2 subjects in at least 1 group

	Placebo (N = 32)	0.25% (N = 69)	0.5% (N = 65)	1% (N = 66)	3% (N = 65)	Tacrolimus (N = 30)
Adverse events total	15.6 (5)	18.8 (13)	18.5 (12)	21.2 (14)	18.5 (12)	43.3 (13)
Acne	0 (0)	1.4 (1)	0 (0)	0 (0)	4.6 (3)	3.3 (1)
Nasopharyngitis	6.3 (2)	2.9 (2)	4.6 (3)	3.0 (2)	3.1 (2)	0 (0)
Folliculitis	0 (0)	0 (0)	1.5 (1)	0 (0)	3.1 (2)	0 (0)
Furuncle	0 (0)	0 (0)	3.1 (2)	1.5 (1)	1.5 (1)	3.3 (1)
Application site acne	0 (0)	0 (0)	0 (0)	3.0 (2)	1.5 (1)	0 (0)
C-reactive protein increased	0 (0)	1.4 (1)	0 (0)	3.0 (2)	0 (0)	0 (0)
Kaposi's varicelliform eruption	0 (0)	1.4 (1)	0 (0)	3.0 (2)	0 (0)	0 (0)
Pharyngitis	0 (0)	2.9 (2)	0 (0)	1.5 (1)	0 (0)	3.3 (1)
Application site pain	0 (0)	0 (0)	0 (0)	1.5 (1)	0 (0)	10.0 (3)
Application site irritation	0 (0)	0 (0)	1.5 (1)	0 (0)	0 (0)	6.7 (2)
Contusion	0 (0)	4.3 (3)	0 (0)	0 (0)	0 (0)	0 (0)

Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J ver.) 18.0
Incidence, % (n)

Table 29. Adverse drug reactions that occurred in ≥2 subjects in at least 1 group

	Placebo (N = 32)	0.25% (N = 69)	0.5% (N = 65)	1% (N = 66)	3% (N = 65)	Tacrolimus (N = 30)
Adverse drug reactions total	0 (0)	4.3 (3)	6.2 (4)	9.1 (6)	4.6 (3)	16.7 (5)
Acne	0 (0)	0 (0)	0 (0)	0 (0)	3.1 (2)	0 (0)
Application site acne	0 (0)	0 (0)	0 (0)	3.0 (2)	1.5 (1)	0 (0)
Furuncle	0 (0)	0 (0)	3.1 (2)	1.5 (1)	0 (0)	0 (0)
Application site pain	0 (0)	0 (0)	0 (0)	1.5 (1)	0 (0)	10.0 (3)
Application site irritation	0 (0)	0 (0)	1.5 (1)	0 (0)	0 (0)	6.7 (2)

MedDRA/J ver.18.0
Incidence, % (n)

No deaths or serious adverse events occurred. No adverse events in the placebo and delgocitinib 3% group led to treatment discontinuation. The incidence of adverse events leading to treatment discontinuation was 1.4% (1 of 69 subjects; dermatitis contact) in the delgocitinib 0.25% group, 1.5% (1 of 65 subjects; application site irritation) in the 0.5% group, 1.5% (1 of 66 subjects; Kaposi's varicelliform eruption) in the 1% group, and 3.3% (1 of 30 subjects; application site irritation) in the tacrolimus group. With the exception of Kaposi's varicelliform eruption in the 1% group, all these adverse events were classified as adverse drug reactions; however, these were mild or moderate in severity, and the outcome was reported as "resolved."

7.2 Phase III studies

7.2.1 Japanese phase III comparative study (CTD 5.3.5.1-2, Study QBA4-1 [[redacted] to [redacted]])

A multicenter, randomized, double-blind, placebo-controlled, parallel-group comparative study was conducted at 24 study centers in Japan to investigate the efficacy and safety of topical delgocitinib in patients aged ≥16 years with atopic dermatitis (Table 30) (target sample size, 150 subjects; 50 subjects [placebo] and 100 subjects [delgocitinib]).

Table 30. Main inclusion and exclusion criteria

Confirmatory phase: start of treatment to Week 4
Main inclusion criteria
• Patients with mEASI score of ≥10.
• Patients with an IGA score of 3 (moderate) or 4 (severe).
• Patients with inflammatory rashes except for dry skin (erythema, edema/papulation, excoriation, lichenification) affecting ≥10% and <30% of the body surface area.
Main exclusion criteria
• Patients with active infection at the planned sites of study drug application.
• Patients who received biologics (e.g., cytokines and antibody drugs) within 24 weeks prior to the start of study drug administration.
• Patients who received the following therapies within 28 days prior to the start of study drug administration.
Systemic corticosteroid preparations, topical corticosteroids (strongest or very strong),
Systemic immunosuppressants, live vaccines, phototherapies (e.g., UVB [broadband and narrow band], PUVA), desensitization therapies
• Patients who used an agent (or agents) listed below within 7 days prior to the start of study drug administration:
Tacrolimus ointment, topical corticosteroids (strong, medium, or weak),
Topical analgesics, antipruritics, and anti-inflammatory agents (e.g., NSAIDs) used for the study drug application sites,
Agents intended for the treatment of atopic dermatitis.
Use of antihistamines, antiallergic agents, moisturizers, and skin protective agents (e.g., heparinoids, urea preparations, petrolatum, zinc oxide ointments) is acceptable.
Extension phase: Week >4 through Week 28
Main inclusion criteria
• Patients who gave their consent to continuing participation in the study.
• Patients with an IGA score of ≤4 (severe).
Main exclusion criteria
• Patients who withdrew from the study or experienced serious adverse events during the confirmatory phase (in the case of worsening of primary disease, the patient may be allowed to enter the extension phase)

In this study, an appropriate amount of topical delgocitinib 0.5% or placebo was applied twice daily for 4 weeks to the sites (excluding scalp, palms, and plantar regions of the foot) of inflammatory rashes except for dry skin (confirmatory phase). At Week 4, patients meeting the criteria shown in Table 30 were to enter the extension phase, in which patients were to receive topical delgocitinib 0.5% twice daily for 24 weeks. The amount to be applied was 5 g per application at maximum (10 g per day). Application was optional if the EASI skin sign score (Table 24) was 0 at any of the sites (head and neck, upper extremities, trunk, and lower extremities). If the EASI skin sign score was 0 at all of the sites, the reduced number of applications or the interruption of applications was possible. Application was to be resumed in the event of relapse of rash. The

use of concomitant topical corticosteroids was prohibited in the confirmatory phase. In the extension phase, in principle, the use of concomitant topical corticosteroids was prohibited; however, the minimal use of topical corticosteroids was allowed only for cases where the use was unavoidable due to exacerbation of primary disease or for treatment of adverse events.

All 158 randomized subjects (52 subjects [placebo] and 106 subjects [delgocitinib]) received the study drug and were included in the safety analysis set and FAS, and the FAS was used for the primary efficacy analysis. Three subjects (all in the placebo group) discontinued treatment because of "worsening of primary disease" in 2 subjects and "at the subject's request" in 1 subject.

Of the 127 subjects who completed the confirmatory phase (29 subjects [placebo] and 98 subjects [delgocitinib]), 1 subject in the placebo group was excluded because entry into the extension phase was not allowed by "investigator's decision," and the remaining 126 subjects (28 subjects [placebo] and 98 subjects [delgocitinib]) entered the extension phase. Additionally, 28 subjects (20 subjects [placebo] and 8 subjects [delgocitinib]) who were judged by the investigator as unfit to continue the study in the confirmatory phase due to worsening of primary disease, and also met the criteria for the extension phase entered the extension phase, which meant a total number of 154 subjects (48 subjects [placebo] and 106 subjects [delgocitinib]) in the extension phase. Sixteen subjects discontinued treatment (6 subjects on placebo in the confirmatory phase [newly treated subjects], and 10 subjects on delgocitinib in the confirmatory phase [continuously treated subjects]) because of "worsening of primary disease" in 11 subjects (5 newly treated subjects and 6 continuously treated subjects), "at the subject's request" in 3 subjects (1 newly treated subject and 2 continuously treated subjects), "adverse events" in 1 continuously treated subject, and "lost to follow-up" in 1 continuously treated subject.

Table 31 shows the percentage change from baseline in the mEASI score at the final evaluation point (Week 4 or at the time of discontinuation) (FAS), the primary endpoint. The results demonstrated the superiority of delgocitinib over placebo ($P < 0.0001$, analysis of covariance based on the mixed effect linear models, one-tailed significance level of 2.5%).

Table 31. Percentage change from baseline in the mEASI score at the final evaluation point (Week 4 or at the time of discontinuation) (FAS)

	Placebo (N = 52)	**Delgocitinib (N = 106)**
mEASI score at baseline (mean ± SD)	**14.5 ± 3.8**	**14.2 ± 3.5**
mEASI score at the final evaluation point (mean ± SD)	**15.3 ± 7.8**	**8.1 ± 6.5**
Percentage change from baseline in the mEASI score at the final evaluation point (least squares mean) [95% CI] (%)[a)]	**1.7 [−9.0, 12.5]**	**−44.3 [−51.8, −36.8]**
Between-group difference in the percentage change from baseline in the mEASI score (delgocitinib group minus placebo group) [95% CI] (%)[a)]	**−46.0 [−59.2, −32.9]**	
***P*-value[a)]**	**<0.0001**	

a) An analysis of covariance based on the mixed effect linear models with percentage change from baseline in the mEASI score as a response variable, treatment group as a fixed effect, the baseline mEASI score as a covariate, and study center as a random effect; one-tailed significance level of 2.5%.

In the confirmatory phase, the incidence of adverse events was 11.5% (6 of 52 subjects) in the placebo group and 21.7% (23 of 106 subjects) in the delgocitinib group. Table 32 shows adverse events that occurred in ≥2 subjects in at least 1 group. The incidence of adverse drug reactions was 1.9% in the placebo group (1 of 52 subjects; 1 subject developed both application site pruritus and application site folliculitis) and 4.7% in the delgocitinib group (5 of 106 subjects; application site rash [1], application site folliculitis [1], herpes simplex [1], hordeolum [1], and Kaposi's varicelliform eruption [1]). There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

Table 32. Adverse events occurring in ≥2 subjects in either group (confirmatory phase)

	Placebo (N = 52)	Delgocitinib (N = 106)
Adverse events total	11.5 (6)	21.7 (23)
Nasopharyngitis	3.8 (2)	5.7 (6)
Pyrexia	1.9 (1)	1.9 (2)
Dental caries	0 (0)	1.9 (2)
Kaposi's varicelliform eruption	0 (0)	1.9 (2)

MedDRA/J ver.19.1
Incidence, % (n)

In the extension phase, adverse events occurred in 24 of 48 newly treated subjects (50.0%) and 54 of 106 continuously treated subjects (50.9%). Table 33 shows adverse events that occurred in ≥2.0% of the overall population. Adverse drug reactions occurred in 2 of 48 newly treated subjects (4.2%; eosinophil count increased [1 subject] and urticaria [1]) and 7 of 106 continuously treated subjects (6.6%; Kaposi's varicelliform eruption [3 subjects], application site acne [1 subject], application site rash [1], paradoxical drug reaction [1], application site folliculitis [1], herpes simplex [1], hordeolum [1], blood lactate dehydrogenase increased [1], and dermatitis acneiform [1]; including duplicates). There were no adverse drug reactions with an incidence of ≥2.0% in all subjects.

Table 33. Adverse events occurring in ≥2.0% of the overall population (Extension period)

	Newly treated (N = 48)	Continuously treated (N = 106)	Overall population (N = 154)
Adverse events total	50.0 (24)	50.9 (54)	50.6 (78)
Nasopharyngitis	12.5 (6)	22.6 (24)	19.5 (30)
Kaposi's varicelliform eruption	0 (0)	5.7 (6)	3.9 (6)
Acne	2.1 (1)	3.8 (4)	3.2 (5)
Dental caries	0 (0)	3.8 (4)	2.6 (4)
Paronychia	0 (0)	3.8 (4)	2.6 (4)
Pyrexia	4.2 (2)	1.9 (2)	2.6 (4)

MedDRA/J ver.19.1
Incidence, % (n)

No deaths or serious adverse events occurred. Adverse events leading to treatment discontinuation occurred in 1 continuously treated subject (blood lactate dehydrogenase increased and paradoxical drug reaction). Both events were classified as adverse drug reactions; however, these were moderate in severity, and the outcome was reported as "resolved" and "resolving."

7.2.2 Japanese long-term study (CTD 5.3.5.2-1, Study QBA4-2 [[redacted] to [redacted]])

A multicenter, open-label, uncontrolled study was conducted at 47 study centers in Japan to investigate the safety and efficacy of long-term treatment with topical delgocitinib in patients aged ≥16 years with atopic dermatitis (Table 34) (target sample size, 330 subjects).

Table 34. Main inclusion and exclusion criteria

Main inclusion criteria **• Patients with an IGA score of ≥2 (mild) and <4 (severe).** **• Patients with inflammatory rashes except for dry skin (erythema, edma/papulation, excoriation, lichenification) affecting ≥5% and <30% of the body surface area.** **Main exclusion criteria** **• Patients with active infection at the planned sites of study drug application.** **• Patients who received biologics (e.g., cytokines and antibody drugs) within 24 weeks prior to the start of study drug administration.** **• Patients who received the following therapies within 28 days prior to the start of study drug administration.** **Systemic corticosteroid preparations, systemic immunosuppressants, live vaccines,** **Phototherapies (e.g., UVB [broadband and narrow band], PUVA), desensitization therapies** **• Patients who received strongest or very strong topical corticosteroids within 14 days prior to the start of study drug administration.**

In this study, an appropriate amount of topical delgocitinib 0.5% was applied twice daily for 52 weeks to the sites (excluding scalp) of inflammatory rashes except for dry skin. The amount to be applied was 5 g per application at maximum (10 g per day). Application was optional if the EASI skin sign score (Table 24) was 0 at any of the sites (head and neck, upper extremities, trunk, and lower extremities). If the EASI skin sign score was 0 at all of the sites, the reduced number of applications or the interruption of applications was possible. Application was to be resumed in the event of relapse of rash. In principle, the use of concomitant topical corticosteroids was prohibited; however, the minimal use of topical corticosteroids was allowed only for cases where the use was unavoidable due to exacerbation of primary disease or for treatment of adverse events.

All 352 subjects enrolled in the study received the study drug and were included in the efficacy and safety analysis set. Ninety subjects discontinued treatment because of “worsening of primary disease” in 45 subjects, “at the subject's request” in 23 subjects, “occurrence of adverse events” in 16 subjects, “investigator's decision” in 3 subjects, “lost to follow-up” in 2 subjects, and “ineligible for enrollment in the study” in 1 subject.

Table 35 shows the percentage change from baseline in the mEASI score at the final evaluation point (Week 52 or at the time of discontinuation) (FAS).

Table 35. Percentage change from baseline in the mEASI score at the final evaluation point (Week 52 or at the time of discontinuation) (FAS)

	Delgocitinib (N = 352)
mEASI score at baseline (mean ± SD)	**8.8 ± 4.9**
mEASI score at the final evaluation point (mean ± SD)	**7.5 ± 8.0**
Percentage change from baseline in the mEASI score at the final evaluation point [95% CI] (%)	**−12.8 [−22.3, −3.4]**

The incidence of adverse events was 77.0% (271 of 352 subjects). Table 36 shows adverse events with an incidence of ≥2.0%. The incidence of adverse drug reactions was 19.6% (69 of 352 subjects). Table 37 shows adverse drug reactions that occurred in ≥2 subjects.

Table 36. Adverse events with an incidence of ≥2.0%

Adverse event	Delgocitinib (N = 352)	Adverse event	Delgocitinib (N = 352)
Adverse events total	77.0 (271)	Eczema	2.6 (9)
Nasopharyngitis	28.7 (101)	Seasonal allergy	2.6 (9)
Dermatitis contact	5.7 (20)	Somnolence	2.6 (9)
Acne	4.8 (17)	Conjunctivitis allergic	2.3 (8)
Influenza	4.8 (17)	Dyshidrotic eczema	2.3 (8)
Application site folliculitis	4.3 (15)	Otitis externa	2.3 (8)
Application site acne	4.0 (14)	Application site erythema	2.0 (7)
Herpes simplex	3.4 (12)	Dental caries	2.0 (7)
Kaposi's varicelliform eruption	3.1 (11)	Herpes zoster	2.0 (7)
Folliculitis	2.8 (10)	Hordeolum	2.0 (7)
Gastroenteritis	2.8 (10)	Impetigo	2.0 (7)
Oral herpes	2.8 (10)	Paronychia	2.0 (7)
Application site irritation	2.6 (9)		

MedDRA/J ver.19.1
Incidence, % (n)

Table 37. Adverse drug reactions in ≥2 subjects

Adverse drug reaction	Delgocitinib (N = 352)
Adverse drug reactions total	19.6 (69)
Application site folliculitis	3.1 (11)
Application site acne	2.8 (10)
Application site irritation	2.6 (9)
Application site erythema	2.0 (7)
Dermatitis contact	1.7 (6)
Kaposi's varicelliform eruption	1.4 (5)
Oral herpes	1.1 (4)
Herpes zoster	0.9 (3)
Application site pruritus	0.9 (3)
Application site warmth	0.6 (2)
Application site cellulitis	0.6 (2)
Furuncle	0.6 (2)
Herpes simplex	0.6 (2)
Impetigo	0.6 (2)

MedDRA/J ver.19.1
Incidence, % (n)

No deaths occurred. The incidence of serious adverse events was 2.0% (7 of 352 subjects; nephrolithiasis [1], rectal cancer [1], pyogenic granuloma [1], Kaposi’s varicelliform eruption [1], pneumonia [1], inguinal hernia [1], and enterocolitis [1]). Of these serious adverse events, Kaposi’s varicelliform eruption was classified as an adverse drug reaction, with the outcome reported as "resolved." Non-serious adverse events that led to treatment discontinuation occurred in 14 of 352 subjects (4.0%; dermatitis contact [5 subjects]; application site irritation [2]; asthma [2]; application site irritation, application site eczema, and application site erythema [1]; hypersensitivity [1]; urticaria [1]; skin irritation [1]; and skin depigmentation [1]). Except for asthma in 2 subjects and skin depigmentation in 1 subject, these events were classified as adverse drug

reactions; however, these were mild or moderate in severity, and the outcome was reported as “resolved” or “resolving.”

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

Based on the discussions in Sections 7.R.1.1 through 7.R.1.5, PMDA considers that the efficacy of topical delgocitinib in the treatment of atopic dermatitis has been demonstrated.

7.R.1.1 Primary endpoint

The applicant’s explanation about the rationale for selecting the primary endpoint and the results of the primary endpoint in the phase III comparative study:

The EASI is a scoring system that provides indices according to the severity and extent of the area affected by skin signs (erythema, edema/papulation, excoriation, and lichenification) at the body region (head and neck, upper extremities, trunk, and lower extremities) of inflammatory rashes, and has been commonly used in many countries including Japan for evaluation of the severity of atopic dermatitis (*Exp Dermatol*.2001; 10:11-8). Topical delgocitinib is an ointment and is difficult to apply to areas of scalp covered with hair; therefore, its use on the head was limited in the clinical studies (topical delgocitinib was not to be applied to the scalp while it could be applied to the face and neck). It was therefore decided that the mEASI score, which is obtained by subtracting the head and neck score from the EASI score, was to be used as the evaluation index for the primary endpoint in the phase III comparative study (Table 24). Based on the results of the phase II study, Week 4 was selected as an evaluation point for the primary endpoint to obtain a period sufficient to evaluate the percentage change from baseline in the mEASI score.

In the phase III comparative study, placebo was selected as a control because topical tacrolimus, an approved agent, causes skin irritation including a burning sensation, and therefore it is difficult to maintain blindness.

Table 31 shows the percentage change from baseline in the mEASI score (FAS) at the final evaluation point (Week 4 or at the time of discontinuation), the primary endpoint for the phase III comparative study, and the results demonstrated the superiority of delgocitinib over placebo ($P < 0.0001$, analysis of covariance based on the mixed effect linear models, one-tailed significance level of 2.5%). Table 38 shows the results of sensitivity analysis on the per protocol set (PPS), indicating that the results are similar to those of the primary analysis.

Table 38. Percentage change from baseline in the mEASI score at the final evaluation point (Week 4 or at the time of discontinuation) (phase III comparative study, PPS; sensitivity analysis)

	Placebo (N = 48)	Delgocitinib (N = 104)
mEASI score at baseline (mean ± SD)	14.5 ± 3.7	14.2 ± 3.5
mEASI score at the final evaluation point (mean ± SD)	15.1 ± 7.6	8.1 ± 6.5
Percentage change from baseline in the mEASI score at the final evaluation point (least squares mean) [95% CI] (%)[a)]	1.1 [−10.2, 12.4]	−44.2 [−51.9, −36.6]
Between-group difference in percentage change from baseline in the mEASI score (delgocitinib group minus placebo group) [95% CI] (%)[a)]	−45.3% [−59.0, −31.7]	
P-value[a)]	<0.0001	

a) An analysis of covariance based on the mixed effect linear models with the percentage change from baseline in the mEASI score as a response variable, treatment group as a fixed effect, the baseline mEASI score as a covariate, and study center as a random effect; one-tailed significance level of 2.5%

PMDA's view:

The results for the percentage change from baseline in the mEASI score at the final evaluation point (Week 4 or at the time of discontinuation), the primary endpoint for the phase III comparative study, demonstrated the superiority of delgocitinib over placebo; therefore, the efficacy of topical delgocitinib has been demonstrated. PMDA also confirmed that the analysis on the PPS produced similar results as the primary analysis.

7.R.1.2 Key secondary endpoints

Table 39 shows the results of the key secondary endpoints for the phase III comparative study. PMDA confirmed that for all the endpoints, the results indicate the trends towards greater improvement in the delgocitinib group compared with the placebo group.

Table 39. Results of key secondary endpoint (phase III comparative study; FAS)

	Placebo (N = 52)	Delgocitinib (N = 106)
Dropout rate up to Week 4 due to worsening of primary disease	42.3% (22 subjects)	7.5% (8 subjects)
IGA score complete response rate at the final evaluation point[a)]	3.8% (2 subjects)	10.4% (11 subjects)
Change in daytime numeric rating score (NRS) at the final evaluation point[b)] (mean ± SD)	0.3 ± 2.6	−1.4 ± 2.1
Change in nighttime NRS score at the final evaluation point[b)] (mean ± SD)	0.6 ± 2.6	−1.6 ± 1.9

a) Complete response: IGA score of 0 (no symptoms), or 1 (almost no symptoms).

b) Itch sensation was rated on an 11-point scale, with 0 being "not itchy" and 10 being "most itchy" (the worst itch ever experienced caused by atopic dermatitis). Average of itching condition in daytime (being awake) and nighttime (sleeping) is recorded twice daily (before bedtime and after waking up) in the patient diary.

7.R.1.3 Efficacy at different areas of the body

Table 40 shows the percentage change from baseline in the EASI score at different body regions (head and neck, upper extremities, trunk, and lower extremities) in the phase III study. PMDA confirmed that there were trends towards greater improvement in all body regions in the delgocitinib group compared with the placebo group.

Table 40. Percentage change from baseline in the EASI score by body region at the final evaluation point (phase III comparative study, FAS)

		Placebo (N = 52)	Delgocitinib (N = 106)
Head and neck	Percentage change from baseline in the EASI score at the final evaluation point (least squares mean) [95% CI] (%)[a)]	32.4 [10.8, 54.0]	−52.5 [−67.7, −37.4]
	Between-group difference in the percentage change from baseline in the EASI score (delgocitinib group minus placebo group) [95% CI] (%)[a)]	−84.9 [−111.3, −58.5]	
Upper extremities	Percentage change from baseline in the EASI score at the final evaluation point (least squares mean) [95% CI] (%)[a)]	15.3 [0.2, 30.4]	−42.5 [−53.1, −31.8]
	Between-group difference in the percentage change from baseline in the EASI score (delgocitinib group minus placebo group) [95% CI] (%)[a)]	−57.8 [−76.3, −39.3]	
Trunk	Percentage change from baseline in the EASI score at the final evaluation point (least squares mean) [95% CI] (%)[a)]	13.6 [−1.4, 28.6]	−42.8 [−53.4, −32.3]
	Between-group difference in the percentage change from baseline in the EASI score (delgocitinib group minus placebo group) [95% CI] (%)[a)]	−56.4 [−74.7, −38.1]	
Lower extremities	Percentage change from baseline in the EASI score at the final evaluation point (least squares mean) [95% CI] (%)[a)]	−1.0 [−15.9, 14.0]	−41.2 [−51.7, −30.7]
	Between-group difference in the percentage change from baseline in the EASI score (delgocitinib group minus placebo group) [95% CI] (%)[a)]	−40.2 [−58.5, −21.9]	

a) An analysis of covariance using the mixed effect linear models on the percentage change from baseline in the EASI score (%) at the final evaluation point (Week 4 of treatment or at the time of discontinuation). The EASI score at each body region was calculated by "(erythema + edema/papulation + excoriation + lichenification) score × area score" (it is not multiplied by the factor for each body region).

7.R.1.4 Efficacy by patient characteristics

Table 41 shows the percentage change from baseline in the mEASI score by patient characteristics at the final evaluation point (Week 4 or at the time of discontinuation) in the phase III comparative study. PMDA considers that while it should be noted that strict evaluation is difficult for subpopulations consisting of only a few subjects, there were trends towards greater improvement in the delgocitinib group compared with the placebo group.

Table 41. Percentage change from baseline in mEASI score by patient characteristics at the final evaluation point (phase III comparative study, FAS)

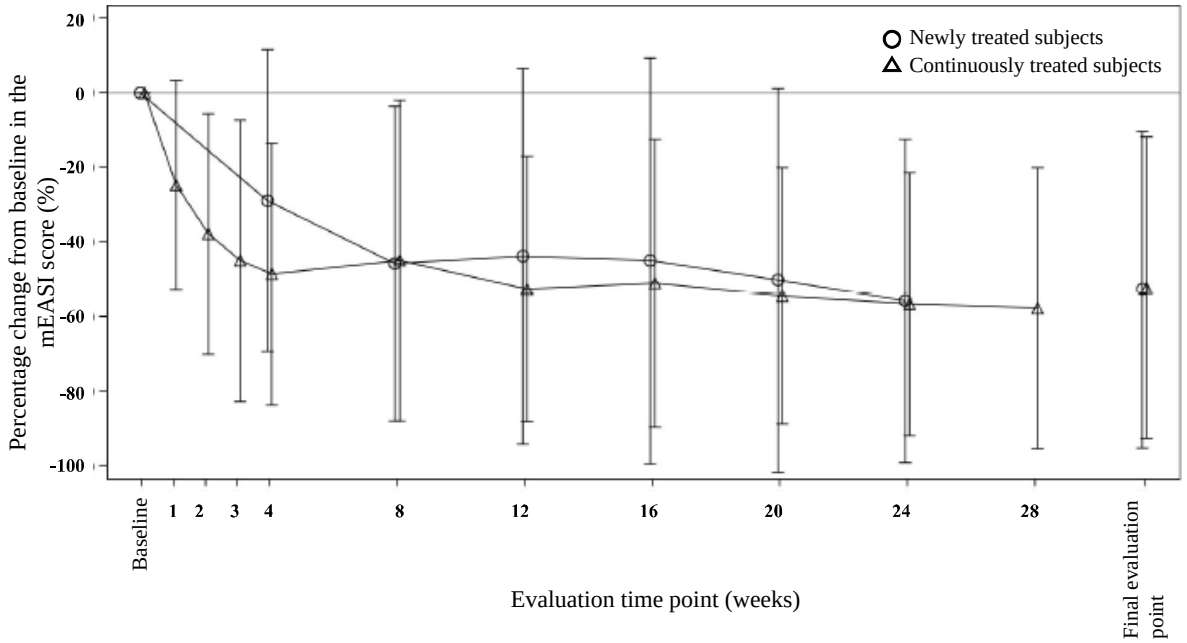
		Placebo (N = 52)	Delgocitinib (N = 106)
Sex	Male	−0.8 [−20.2, 18.7] (34 subjects)	−40.9 [−58.4, −23.5] (64 subjects)
	Female	1.5 [−15.4, 18.4] (18 subjects)	−54.9 [−65.9, −43.8] (42 subjects)
Age[a)]	≥16 years and <20 years	50.1 [−8.7, 108.8] (2 subjects)	−36.1 [−63.7, −8.5] (9 subjects)
	≥20 years and <30 years	−0.1 [−17.8, 17.5] (22 subjects)	−37.2 [−49.7, −24.8] (44 subjects)
	≥30 years and <45 years	4.9 [−9.7, 19.5] (22 subjects)	−51.1 [−61.5, −40.6] (43 subjects)
	≥45 years and <65 years	−7.2 [−49.5, 35.1] (5 subjects)	−58.2 [−87.5, −28.9] (10 subjects)
Baseline mEASI score	≥10 and <15	−10.4 [−24.3, 3.5] (30 subjects)	−48.2 [−57.3, −39.0] (69 subjects)
	≥15	14.5 [−10.6, 39.5] (22 subjects)	−40.5 [−62.0, −19.0] (37 subjects)
Baseline IGA score	3 (moderate)	−7.4 [−19.5, 4.7] (36 subjects)	−51.4 [−59.9, −42.9] (73 subjects)
	4 (severe)	23.6 [2.0, 45.3] (16 subjects)	−29.2 [−44.2, −14.2] (33 subjects)
Disease duration	≤10 years	−22.0 [−62.1, 18.0] (6 subjects)	−53.0 [−84.0, −22.0] (10 subjects)
	≥11 years and ≤20 years	16.6 [−9.0, 42.2] (14 subjects)	−29.5 [−47.6, −11.4] (28 subjects)
	≥21 years and ≤30 years	−7.6 [−35.0, 19.9] (17 subjects)	−47.2 [−72.4, −22.1] (37 subjects)
	≥31 years and ≤40 years	7.1 [−14.7, 28.9] (10 subjects)	−52.9 [−66.4, −39.5] (26 subjects)
	≥41 years	−12.5 [−51.3, 26.4] (5 subjects)	−76.6 [−117.3, −35.8] (5 subjects)
Prior treatment	Topical corticosteroids	5.9 [−6.4, 18.2] (46 subjects)	−42.1 [−51.2, −33.0] (93 subjects)
	Tacrolimus ointment	7.5 [−14.8, 29.7] (13 subjects)	−42.9 [−59.6, −26.1] (23 subjects)

Least squares mean [95% CI] (n)

a) Since there was only 1 subject aged ≥65 years in the placebo group, the "≥65 years group" is not shown in the table.

7.R.1.5 Long-term efficacy

Figure 1 shows the percentage change from baseline in the mEASI score following administration of topical delgocitinib in the phase III comparative study (newly treated subjects, the extension phase; continuously treated subjects, the confirmatory + extension phases). The percentage change from baseline in the mEASI score in newly treated subjects decreased over time up to Week 8, and remained roughly constant thereafter up to Week 24. The percentage change from baseline in the mEASI score in continuously treated subjects decreased over time up to Week 4, and remained roughly constant thereafter up to Week 28. The percentage change from baseline[19] in the mEASI score at the last administration of topical delgocitinib (mean ± SD) was −52.7% ± 42.3% for newly treated subjects (48 subjects; Week 24 or at the time of discontinuation), and −52.3% ± 40.4% in continuously treated subjects (106 subjects; Week 28 or at the time of discontinuation).



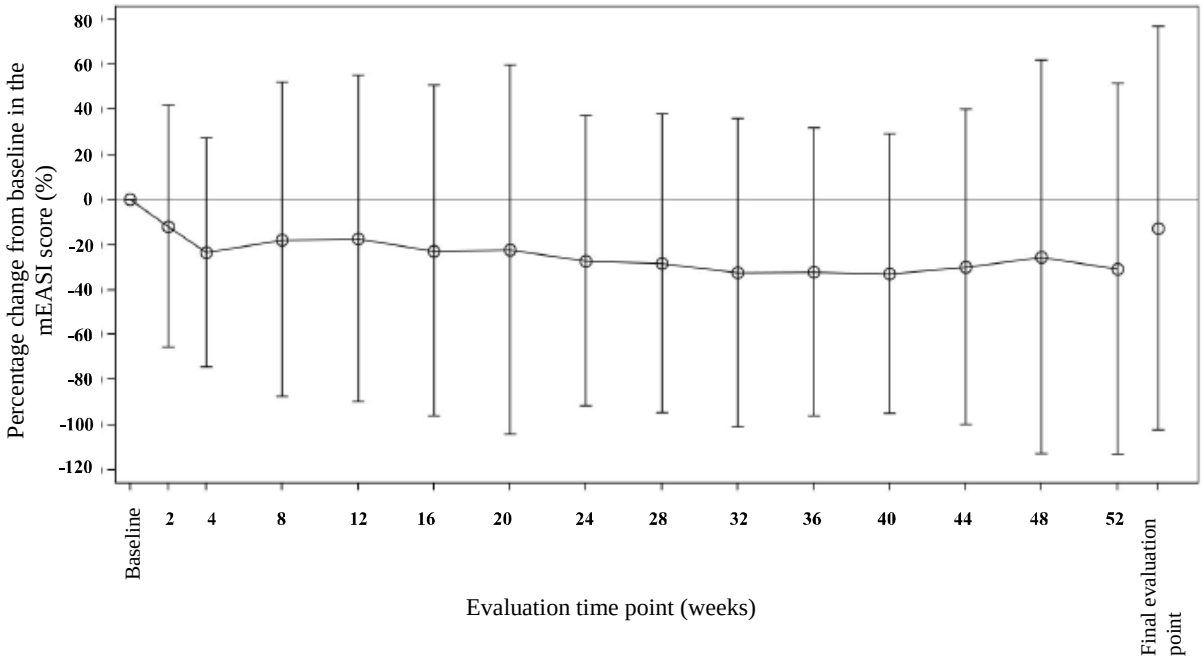
Evaluation point (week)		Baseline	1	2	3	4	8	12	16	20	24	28	Final evaluation point
n	Newly treated subjects	48	-	-	-	47	47	45	43	42	42	-	48
	Continuously treated subjects	106	106	102	100	102	103	101	100	98	95	94	106

Figure 1. Time-course diagram of percentage change from baseline in the mEASI score (mean ± SD) (phase III comparative study, FAS)

Figure 2 shows the percentage change from baseline in the mEASI score in the long-term study. The percentage change from baseline in the mEASI score decreased over time up to Week, and remained almost constant thereafter up to Week 52. While the percentage change from baseline in the mEASI score at Week 4 was −44.6% in the delgocitinib group in the phase III study (confirmatory phase), it was −23.4% in the long-term study. The applicant explained the reasons as follows.

[19] Baseline values in newly treated subjects: data at 4 weeks of placebo in the confirmatory phase, or data obtained during the run-in period before the start of topical delgocitinib treatment in the extension phase
Baseline values in continuously treated subjects: data at the start of topical delgocitinib treatment in the confirmatory phase

In the long-term study, patients with mild symptoms (IGA score 2), which did not meet the inclusion criteria in the phase III comparative study, were also included in the phase III comparative study, and the baseline mEASI score (mean) was 8.8, lower than the figure of 14.2 obtained in the phase III comparative study. On the other hand, the mEASI score at Week 4 was 7.4 in the phase III comparative study and 6.3 in the long-term study, indicating similar improvement in the both studies. The above results suggest that the difference in the percentage change from baseline in the mEASI score between the phase III comparative and long-term studies at Week 4 can be attributed to the difference in baseline patient characteristics.



Evaluation point (week)	Baseline	2	4	8	12	16	20	24	28	32	36	40	44	48	52	Final evaluation point
n	346	338	324	314	303	294	283	282	278	276	270	266	263	260	258	346

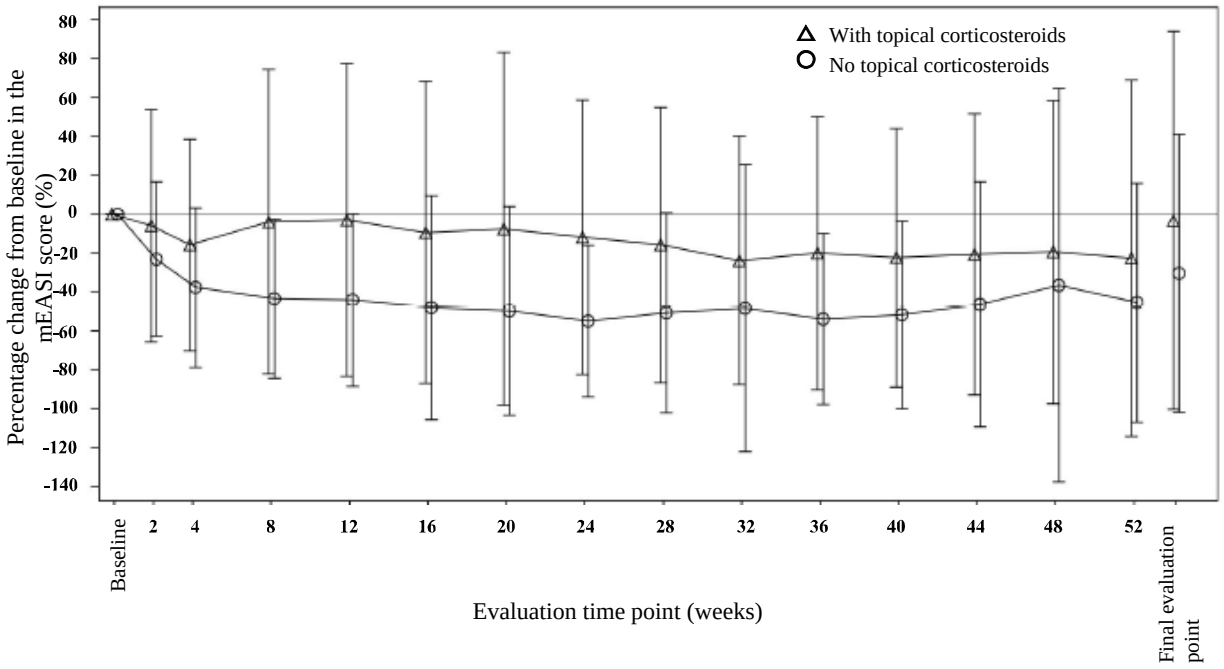
Figure 2. Time-course diagram of percentage change (mean ± SD) from baseline in the mEASI score (long-term study, FAS)

The applicant's explanation attributing the percentage difference in the mEASI score at Week 4 between the phase III comparative and long-term studies to the difference in baseline patient characteristics is understandable. Given that the mEASI score at Week 4 was similar between the two studies, PMDA considered that both the phase III comparative study and long-term study indicate similar trends in terms of the efficacy of delgocitinib.

In the long-term study, topical corticosteroids could be used when necessary for the treatment of worsening atopic dermatitis or adverse events.[20)] Figure 3 shows the percentage change from baseline in the mEASI score with or without the use of topical corticosteroids. In the group of patients who did not use topical

[20)] When worsening of atopic dermatitis occurred at the application sites of topical delgocitinib, a topical corticosteroid was to be applied to the rashes instead of topical delgocitinib (in the areas where no worsening occurred, delgocitinib was continuously used. Topical delgocitinib and a topical corticosteroid were not to be applied together in layers in the same area.)

corticosteroids (labeled as “no topical corticosteroids”), the percentage change from bassline in the mEASI score decreased up to 4 weeks post-dose, and remained almost constant thereafter up to Week 52. In contrast, in the group consisting of patients who had used topical corticosteroids at least once (labeled as “with topical corticosteroids”), the percentage change from bassline in the mEASI score decreased to a lesser extent compared with that in the no topical corticosteroid group.



Evaluation point (week)		Baseline	2	4	8	12	16	20	24	28	32	36	40	44	48	52	Final evaluation point
n	With topical corticosteroids	221	218	209	202	196	191	182	181	178	176	172	169	167	166	164	221
	Without topical corticosteroids	125	120	115	112	107	103	101	101	100	100	98	97	96	94	94	125

Figure 3. Time-course diagram of percentage change (mean ± SD) from baseline in the mEASI score with/without topical corticosteroids (long-term study, FAS)

The applicant’s explanation about the difference in change from baseline in the mEASI score between patients who used corticosteroids and those who did not during the study period:

The proportion of patients who used topical corticosteroids due to worsening of atopic dermatitis was 63.6% (224 of 352 subjects) with the number of days to the initiation of topical corticosteroid therapy after the start of treatment with delgocitinib being 106.3 ± 86.1 days (mean ± SD). The percentage of patients with moderate or severe diseases as rated by IGA at baseline was higher in the group consisting of patients who used concomitant topical corticosteroids than in the group consisting of patients who did not (72.8% of concomitant corticosteroid-treated patients [163 of 224 subjects] and 61.7% of non-corticosteroid treated patients [79 of 128 subjects]). In addition, a higher percentage of patients used higher-potency topical corticosteroids (strongest or very strong) as prior treatments (66.5% of concomitant corticosteroid-treated patients [149 of 224 subjects] and 48.4% of non-corticosteroid treated patients [62 of 128 subjects]). It was

suggested that atopic dermatitis was more likely to be exacerbated in patients who had used higher-potency topical corticosteroids as prior treatment, and therefore the percentage change from baseline in the mEASI score was smaller.

PMDA's view:
Based on the results from the phase III comparative study and long-term study, the mEASI score tended to decrease up to Week 4 of topical delgocitinib treatment, and remained almost constant thereafter. In the long-term study, about 60% of patients used topical corticosteroids due to worsening of atopic dermatitis, suggesting that a certain proportion of patients had an inadequate response to topical delgocitinib alone and needed to use concomitant agents or switch to another therapy. The use of topical delgocitinib in combination with other agents will be discussed in Section 7.R.5.2.

7.R.2 Safety

Based on the results in Sections 7.R.2.1 through 7.R.2.6, the safety of topical delgocitinib is acceptable in the treatment of atopic dermatitis. However, caution should be exercised in cases where the skin at the application sites is infected, and information should be continuously gathered in post-marketing surveillance.

7.R.2.1 Summary of safety in the clinical studies

The applicant's explanation about the safety of topical delgocitinib:
In the phase II study, there were no significant differences in the incidence of adverse events between the delgocitinib 0.5% group and the placebo group (Table 28). In the phase III comparative study, the incidence of adverse events was higher in the delgocitinib group compared with the placebo group up to Week 4 (Table 32); however, adverse events observed in the delgocitinib group were mild to moderate in severity, in addition, no serious adverse events occurred, suggesting that these adverse events would be unlikely to cause significant clinical problems.

Data for delgocitinib-treated patients from the phase III comparative study (28 weeks of treatment at maximum) and long-term study, in which topical delgocitinib was administered for ≥6 months, were pooled and analyzed. Table 42 shows the summary of adverse events in the pooled analysis data for delgocitinib-treated patients from these studies (hereinafter referred to as "pooled analysis data from the phase III studies"). The incidence of adverse drug reactions was 15.4% (78 of 506 subjects). Adverse drug reactions that occurred with an incidence of ≥2.0% were application site folliculitis (2.4%; 12 of 506 subjects) and application site acne (2.2%; 11 of 506 subjects). While many adverse drug reactions were observed at the application sites, they were mild to moderate in severity.

Table 42. Summary of adverse events (pooled analysis data from the phase III studies)

	Pooled analysis data from the phase III studies (N = 506)
Adverse events total	69.0 (349)
Adverse drug reactions total	15.4 (78)
Deaths	0 (0)
Serious adverse events	1.4 (7)
Serious adverse drug reactions	0.2 (1)
Adverse events leading to treatment discontinuation	3.0 (15)
Adverse drug reactions leading to treatment discontinuation	2.4 (12)
Adverse events with an incidence of ≥2.0%	
Nasopharyngitis	25.9 (131)
Dermatitis contact	4.5 (23)
Acne	4.3 (22)
Application site folliculitis	3.6 (18)
Kaposi's varicelliform eruption	3.4 (17)
Influenza	3.4 (17)
Application site acne	3.2 (16)
Herpes simplex	3.0 (15)
Folliculitis	2.4 (12)
Gastroenteritis	2.4 (12)
Paronychia	2.2 (11)
Conjunctivitis allergic	2.2 (11)
Dental caries	2.2 (11)
Eczema	2.0 (10)
Oral herpes	2.0 (10)
Seasonal allergy	2.0 (10)

MedDRA/J ver.21.0
Incidence, % (n)

No deaths occurred. Serious adverse events occurred in 7 subjects (enterocolitis, inguinal hernia, Kaposi's varicelliform eruption, pneumonia, pyogenic granuloma, rectal cancer, and nephrolithiasis in 1 subject each). Among these serious adverse events, Kaposi's varicelliform eruption was classified as an adverse drug reaction, with the outcome being reported as "resolved."

Based on the above, relatively many application site-related adverse events were observed at the application sites of delgocitinib; however, there were no trends of particular concern in other events.

Given that the incidence of application site-related adverse events was higher in the delgocitinib group than in the placebo group, and that as a serious adverse drug reaction, Kaposi's varicelliform eruption occurred, it is considered necessary to exercise caution regarding application site infections. PMDA also confirmed that except for application site-related adverse events, there were no trends of particular clinical concern in other events. Safety at application sites and skin infections will be discussed in Section 7.R.2.4 and Section 7.R.2.5, respectively.

7.R.2.2 Safety by patient characteristics

The applicant's explanation about safety by patient characteristics:

Table 43 shows the incidence of adverse events by patient characteristics in the pooled analysis data from the phase III studies. Although there were only a limited number of subjects aged ≥65 years, which makes strict

evaluation difficult, there were no trends towards an increase in the incidence of adverse events in specific groups.

Table 43. Incidence of adverse events by patient characteristics (pooled analysis data from the phase III studies)

		Pooled analysis data from the phase III studies (N = 506)
Sex	Male	66.4 (211/318)
	Female	73.4 (138/188)
Age	≥16 years and <20 years	64.5 (20/31)
	≥20 years and <30 years	68.1 (147/216)
	≥30 years and <45 years	72.3 (128/177)
	≥45 years and <65 years	64.6 (51/79)
	≥65 years	100 (3/3)
Baseline mEASI score	<10	75.7 (171/226)
	≥10 and <15	63.6 (117/184)
	≥15	64.1 (59/92)
Baseline IGA score	2 (mild)	75.5 (83/110)
	3 (moderate)	68.7 (222/323)
	4 (severe)	60.3 (44/73)
Disease duration	≤10 years	73.6 (53/72)
	≥11 years and ≤20 years	64.1 (84/131)
	≥21 years and ≤30 years	66.9 (105/157)
	≥31 years and ≤40 years	76.7 (79/103)
	≥41 years	65.1 (28/43)
Prior treatment type	Topical corticosteroids	69.1 (313/453)
	Tacrolimus ointment	68.8 (108/157)

MedDRA/J ver.21.0
Incidence, % (n/N)

In the extension phase of the phase III comparatives study and the long-term study, the use of concomitant topical corticosteroids was allowed when it was necessary for the treatment of atopic dermatitis and adverse events. Accordingly, the incidence of adverse events was analyzed for subgroups with or without concomitant corticosteroids (Table 44). In the pooled analysis data from the phase III studies, there were no significant differences in the incidence of adverse events or adverse drug reactions between subjects who used concomitant corticosteroids and those who did not.

Table 44. Incidence of adverse events with and without use of topical corticosteroids (pooled analysis data from the phase III studies)

	With topical corticosteroids (N = 288)	Without topical corticosteroids (N = 218)
Adverse events total	74.0 (213)	62.4 (136)
Adverse drug reactions total	16.7 (48)	13.8 (30)
Adverse events with an incidence of ≥2.0% in at least 1 group		
Nasopharyngitis	28.8 (83)	22.0 (48)
Dermatitis contact	5.2 (15)	3.7 (8)
Application site folliculitis	4.9 (14)	1.8 (4)
Application site acne	4.9 (14)	0.9 (2)
Acne	4.5 (13)	4.1 (9)
Herpes simplex	3.5 (10)	2.3 (5)
Influenza	3.1 (9)	3.7 (8)
Kaposi's varicelliform eruption	3.1 (9)	3.7 (8)
Somnolence	3.1 (9)	0 (0)
Gastroenteritis	2.8 (8)	1.8 (4)
Folliculitis	2.4 (7)	2.3 (5)
Conjunctivitis allergic	2.4 (7)	1.8 (4)
Paronychia	2.4 (7)	1.8 (4)
Otitis externa	2.4 (7)	0.9 (2)
Oral herpes	2.1 (6)	1.8 (4)
Eczema	2.1 (6)	1.8 (4)
Impetigo	2.1 (6)	0.9 (2)
Headache	2.1 (6)	0.5 (1)
Dental caries	1.7 (5)	2.8 (6)
Seasonal allergy	1.7 (5)	2.3 (5)
Application site irritation	1.4 (4)	2.3 (5)

MedDRA/J ver.21.0
Incidence, % (n)

PMDA confirmed that there were no specific groups in which the incidence of adverse events could cause clinical problems.

7.R.2.3 Long-term safety

The applicant's explanation about the long-term safety of topical delgocitinib:

Table 45 shows the incidence of adverse events by treatment period in the pooled analysis data from the phase III studies. There were no trends towards an increase in the incidence of adverse events with increasing treatment duration.

Table 45. Incidence of adverse events by treatment period (pooled analysis data from the phase III studies)

	Weeks 1 to 12 (N = 506)	Weeks 13 to 24 (N = 456)	Weeks 25 to 36 (N = 387)	Weeks 37 to 52 (N = 275)	Overall period (N = 506)
Adverse events	44.5 (225)	33.8 (154)	32.0 (124)	34.5 (95)	69.0 (349)
Adverse drug reactions	9.7 (49)	3.9 (18)	2.6 (10)	6.2 (17)	15.4 (78)
Serious adverse events	1.0 (5)	0 (0)	0.5 (2)	0 (0)	1.4 (7)
Adverse events leading to treatment discontinuation	2.8 (14)	0.4 (2)	0.3 (1)	0 (0)	3.4 (17)
Adverse events with an incidence of ≥2.0% in overall period					
Nasopharyngitis	10.7 (54)	11.4 (52)	11.1 (43)	8.4 (23)	25.9 (131)
Dermatitis contact	2.2 (11)	1.8 (8)	0.8 (3)	1.8 (5)	4.5 (23)
Acne	2.2 (11)	1.1 (5)	1.3 (5)	1.8 (5)	4.3 (22)
Application site folliculitis	1.2 (6)	1.3 (6)	0.5 (2)	1.8 (5)	3.6 (18)
Kaposi's varicelliform eruption	2.0 (10)	0.4 (2)	1.3 (5)	0.7 (2)	3.4 (17)
Application site acne	2.2 (11)	0.7 (3)	0.3 (1)	1.5 (4)	3.2 (16)
Herpes simplex	1.8 (9)	0.9 (4)	0.5 (2)	1.8 (5)	3.0 (15)
Folliculitis	1.0 (5)	1.1 (5)	0 (0)	0.7 (2)	2.4 (12)

Incidence, % (n)

PMDA confirmed that there were no trends regarding the incidence of adverse events in relation to treatment duration that could be a cause of concern.

7.R.2.4 Safety at application sites

The applicant's explanation about the safety of topical delgocitinib at application sites:

Among the adverse drug reactions of tacrolimus ointment, skin irritation occurred at a relatively high frequency (the package insert of "Protopic Ointment 0.1%" 18th version); in contrast, the incidence of skin irritation-related adverse events of topical delgocitinib (application site irritation, application site pain, application site pruritus, and application site warmth) was low (Tables 28, 32, and 36) and the level of severity was mild. In the pooled analysis data from the phase III studies, adverse events occurring at application sites in ≥2 subjects are shown in Table 46. Adverse events with an incidence of ≥2.0% were application site folliculitis, application site acne, Kaposi's varicelliform eruption, and dermatitis contact, and these events were either mild or moderate in severity.

Table 46. Adverse events occurring at study drug application sites in ≥2 subjects (pooled analysis data from the phase III studies)

Adverse events SOC/PT	Pooled analysis data from the phase III studies (N = 506)	
	Adverse events	Adverse drug reactions
Total	**26.7 (135)**	**13.0 (66)**
Administration site conditions	**8.1 (41)**	**6.3 (32)**
Application site acne	**3.2 (16)**	**2.2 (11)**
Application site irritation	**1.8 (9)**	**1.8 (9)**
Application site erythema	**1.4 (7)**	**1.4 (7)**
Application site urticaria	**1.2 (6)**	**0.2 (1)**
Application site pruritus	**0.6 (3)**	**0.6 (3)**
Application site eczema	**0.4 (2)**	**0.2 (1)**
Application site erosion	**0.4 (2)**	**0.2 (1)**
Application site warmth	**0.4 (2)**	**0.4 (2)**
Infections and infestations	**11.9 (60)**	**6.1 (31)**
Application site folliculitis	**3.6 (18)**	**2.4 (12)**
Kaposi's varicelliform eruption	**2.2 (11)**	**1.4 (7)**
Herpes simplex	**1.6 (8)**	**0.4 (2)**
Application site cellulitis	**1.2 (6)**	**0.4 (2)**
Herpes zoster	**1.0 (5)**	**0.4 (2)**
Furuncle	**0.4 (2)**	**0.4 (2)**
Impetigo	**0.8 (4)**	**0.4 (2)**
Hand-foot-and-mouth disease	**0.4 (2)**	**0 (0)**
Injury, poisoning and procedural complications	**1.4 (7)**	**0 (0)**
Skin abrasion	**1.0 (5)**	**0 (0)**
Skin and subcutaneous tissue disorders	**7.9 (40)**	**2.4 (12)**
Dermatitis contact	**2.0 (10)**	**1.2 (6)**
Urticaria	**1.2 (6)**	**0.4 (2)**
Acne	**1.0 (5)**	**0 (0)**
Miliaria	**1.0 (5)**	**0 (0)**
Eczema	**0.6 (3)**	**0.2 (1)**
Dyshidrotic eczema	**0.4 (2)**	**0 (0)**
Toxic skin eruption	**0.4 (2)**	**0 (0)**

MedDRA/J ver. 21.0
Incidence, % (n)

Based on the above, topical delgocitinib has acceptable safety at application sites given that no severe adverse events occurred at the sites where topical delgocitinib was applied, and that observed skin

irritation-related adverse events were all mild and well tolerated. However, as delgocitinib has immunosuppressive activity, the application sites should be carefully observed for infections. Furthermore, given that patients with active infections at application sites were excluded from the clinical studies, cautionary statements should be included in the package insert to the effect that application of topical delgocitinib at sites where the skin is infected should be avoided.

Because no severe adverse events occurred at the application sites of topical delgocitinib, topical delgocitinib has acceptable safety at application sites. Taking into account delgocitinib's mechanism of action, patients should be carefully observed for development of skin infections. Skin infections will be discussed separately [see Section 7.R.2.5].

7.R.2.5 Skin infections

Because of the immunosuppressive activity of delgocitinib, patients should be monitored closely for skin infections. The applicant's explanation about the incidence of skin infections in the pooled analysis data from the phase III studies:

Of the adverse events classified under the System Organ Class (SOC) "Infections and infestations" in the Medical Dictionary for Regulatory Activities (MedDRA), skin-related events were retrieved and analyzed.

In the pooled analysis data from the phase III studies, skin infection-related adverse events occurred in 122 of 506 subjects (24.1%). Adverse events that occurred at an incidence of ≥2.0% were application site folliculitis (3.6%; 18 of 506 subjects), Kaposi's varicelliform eruption (3.4%; 17 of 506 subjects), herpes simplex (3.0%; 15 of 506 subjects), folliculitis (2.4%; 12 of 506 subjects), paronychia (2.2%; 11 of 506 subjects), and oral herpes (2.0%; 10 of 506 subjects). Of these adverse events, application site folliculitis (12), Kaposi's varicelliform eruption (8), oral herpes (4), and herpes simplex (3) were classified as adverse drug reactions, but were either mild or moderate in severity. The majority of the skin infection-related adverse events resolved or were resolving after being treated with appropriate agents such as antibacterials, antivirals, or antifungals.

Due to impaired skin barrier function and cutaneous immune activity, patients with atopic dermatitis are prone to developing bacterial, fungal, or viral infections. Kaposi's varicelliform eruption is one of the common viral infections (Guidelines for the Management). The incidence of Kaposi's varicelliform eruption in Japanese clinical studies was reviewed. In the phase II study, the incidence of Kaposi's varicelliform eruption was 1.4% (1 of 69 subjects) in the delgocitinib 0.25% group, and 3.0% (2 of 66 subjects) in the 1% group, whereas there were no cases in the placebo group (Table 28). Also, in the confirmatory phase of the phase III comparative study, there were no cases in the placebo group, in contrast to an incidence of 1.9% (2 of 106 subjects) in the delgocitinib group (Table 32). Since Kaposi's varicelliform eruption is caused by primary or reactivation of herpes simplex virus infection, of the adverse events classified under the MedDRA SOC "Infections and infestations," herpes infection-related adverse events were retrieved from the pooled analysis data from the phase III studies for analysis. Table 47 shows the incidence of herpes infection-related adverse events in the pooled analysis data from the phase III studies. One patient in the pooled analysis data

from the phase III studies with Kaposi's varicelliform eruption, which was classified as a serious adverse drug reaction, withdrew from the study; however, the outcome was reported as "resolved" after being treated appropriately with antibacterial, antiviral, or antifungal agents.

Table 47. Herpes infection-related adverse events (pooled analysis data from the phase III studies)

Adverse events SOC/PT	Pooled analysis data from the phase III studies (N = 506)	
	Adverse events	Adverse drug reactions
Infections and infestations total	49.8 (252)	7.9 (40)
Herpes-related adverse events	9.3 (47)	3.8 (19)
Kaposi's varicelliform eruption	3.4 (17)	1.6 (8)
Herpes simplex	3.0 (15)	0.6 (3)
Oral herpes	2.0 (10)	0.8 (4)
Herpes zoster	1.4 (7)	0.6 (3)
Ophthalmic herpes simplex	0.4 (2)	0.2 (1)
Varicella	0.2 (1)	0 (0)

MedDRA/J ver. 21.0
Incidence, % (n)

The incidence of Kaposi's varicelliform eruption events, classified as adverse drug reactions in the clinical studies and post-marketing surveillance of tacrolimus ointment, was 2.1% (26 of 1,230 subjects) in the clinical studies and 1.2% (65 of 5,383 subjects) in the post-marketing surveillance (the Interview Form "Protopic Ointment 0.1%" 19th version), suggesting that the risk of Kaposi's varicelliform eruption associated with the use of topical delgocitinib is not higher than it is with tacrolimus ointment.

As shown above, skin infections including herpes infections reported in the Japanese clinical studies resolved or were resolving after being treated appropriately with agents such as antibacterials, antivirals, or antifungals. In addition, the incidence of Kaposi's varicelliform eruption associated with the use of topical delgocitinib is not higher than that of tacrolimus ointment, and therefore the risk of topical delgocitinib for skin infections including herpes infections can be managed. However, because of the immunosuppressive activity of delgocitinib, cautionary statements should be included in the package insert to the effect that topical delgocitinib should not be applied to the sites where there is skin infection.

PMDA's view:
Although it is difficult to strictly compare topical delgocitinib with drugs already available on the market in terms of the risk for Kaposi's varicelliform eruption, at this point in time, there seems to be no clear evidence suggesting that topical delgocitinib tends to pose a higher risk for Kaposi's varicelliform eruption than the drugs already being marketed. However, given that the incidence of Kaposi's varicelliform eruption was higher in the delgocitinib group than in the placebo group in the phase II and phase III studies (Tables 28 and 32), and that a serious adverse drug reaction occurred in 1 subject, potential occurrence of skin infections, including Kaposi's varicelliform eruption, should be monitored during the treatment with topical delgocitinib. It is necessary to provide cautionary statements in the package insert to the effect that the development of skin infections at the application sites needs to be closely monitored, in addition to avoiding application of the ointment onto the sites where skin infections are present.

7.R.2.6 Malignancies

Malignancies such as lymphoma and solid cancers have been reported in association with the use of approved oral JAK inhibitors (e.g., Review Report "Xeljanz Tablets 5 mg," dated February 28, 2013). The applicant's explanation about the incidence of malignancies associated with topical delgocitinib:

In the pooled analysis data from the phase III studies, adverse events classified under "Neoplasms benign, malignant and unspecified (incl cysts and polyps)" occurred in 11 of 506 subjects (2.2%; skin papilloma [6], acrochordon [2], pyogenic granuloma [2], rectal cancer [1], and uterine leiomyoma [1]; including duplicates), of which only rectal cancer was malignant. A causal relationship to topical delgocitinib was ruled out for all the events. Given that the systemic exposure is limited [see Section 6.R.1], it is unlikely that the use of topical delgocitinib would cause malignancies.

PMDA's view:

Based on the results of the clinical studies showing no particular concerns regarding the incidence of malignancies, together with the level of exposure following application of topical delgocitinib, the risk of malignancies is not considered to be high at this point in time, however, post-marketing information should be gathered continuously.

7.R.3 Clinical positioning

The applicant's explanation about clinical positioning:

Atopic dermatitis is disease with multiple pathogenic factors including genetic predisposition. The standard therapies include pharmacotherapy, skin care with topical moisturizers, and searching for and removal of exacerbating factors according to the patient's condition. After a definitive diagnosis and evaluation of severity, treatment should be given by combining appropriate therapies depending on the status of rashes as well as the patient's characteristics (Guidelines for the Management of Atopic Dermatitis 2018). Except for patients with very severe or refractory atopic dermatitis, basic treatment consists of appropriate selection and combination of topical corticosteroids and tacrolimus ointment.

Topical corticosteroids are the mainstay of atopic dermatitis treatment. The use of an optimum grade is recommended depending on the severity of cutaneous symptoms, the sites affected, and age; however, the long-term use of corticosteroids is associated with adverse drug reactions such as steroid flushing and skin atrophy. Tacrolimus ointment interferes with T cell activation by blocking calcineurin activity, thereby suppressing inflammation, and has been established as a useful agent to treat atopic dermatitis rashes, which are difficult to treat with topical corticosteroids, especially rashes on the face and neck. However, there are certain limitations to the use of tacrolimus ointment. Unlike topical corticosteroids, tacrolimus ointment is contraindicated on ulcerated skin or clearly eroded skin sites forming a plaque, and in patients with severe renal impairment, hyperkalemia, or other conditions. In addition, topical tacrolimus is known to cause skin irritation such as a burning sensation.

Topical delgocitinib is a JAK inhibitor and a novel topical agent with mechanism of action that is different from that of other topical agents already being marketed. The clinical studies demonstrated the efficacy of

topical delgocitinib, and that it has acceptable safety. Therefore, topical delgocitinib offers a new treatment option for atopic dermatitis.

Based on the efficacy [see Section 7.R.1] and safety [see Section 7.R.2] of topical delgocitinib, PMDA considers that it will provide a new topical treatment option for patients with atopic dermatitis.

7.R.4 Indication

The applicant's explanation about the indication of topical delgocitinib:
Similarly to other topical agents, the main patient population for which topical delgocitinib is expected to be used in routine clinical practice consists of patients with mild to severe atopic dermatitis. The eligible population in the phase III comparative study was composed of patients with moderate to severe atopic dermatitis, while that in the long-term study was composed of patients with mild to severe atopic dermatitis. Data from the phase III comparative study suggested no significant differences between subpopulations with different severity levels that could affect the efficacy or safety of delgocitinib [see Sections 7.R.1.4 and 7.R.2.2]. In the long-term study, there were no problems in relation to efficacy or safety in patients with mild atopic dermatitis.

Based on the above, the efficacy of topical delgocitinib in patients with mild to severe atopic dermatitis has been demonstrated, and it was considered appropriate to specify the indication as atopic dermatitis.

The results of Japanese clinical studies in patients with mild to severe atopic dermatitis demonstrated the efficacy of topical delgocitinib [see Section 7.R.1], and its safety is acceptable [see Section 7.R.2]; therefore, PMDA considers it is acceptable to specify the indication of topical delgocitinib as "atopic dermatitis."

7.R.5 Dosage and administration

7.R.5.1 Dosage and administration of topical delgocitinib

The applicant's explanation about the dosage regimen of topical delgocitinib:
In the phase III comparative study and long-term study, the dosage regimens were selected based on the results of the phase II study.

In Study QBX1-2, a Japanese phase I study conducted in patients with atopic dermatitis, topical delgocitinib 1% and 3% were well tolerated [see Section 6.2.2], and in rat models of DNCB-induced dermatitis, delgocitinib showed an anti-inflammatory effect at ≥0.3% [see Section 3.1.9]. On the basis of these findings, topical delgocitinib concentrations of 0.25%, 0.5%, 1%, and 3% were selected in the phase II study. The efficacy results of the study demonstrated that the mEASI score decreased significantly in all delgocitinib groups compared with the placebo group. Patients in whom plasma delgocitinib was detected accounted for a higher percentage at delgocitinib 1% and 3% compared with those at other delgocitinib concentrations [see Section 6.2.3]. There were no significant differences in the incidence of adverse events across the groups at 0.25% to 3% of topical delgocitinib [see Section 7.1.1]. Because of the inhibitory activity of delgocitinib against JAKs involved in immune responses, a high level of absorption into the body would raise safety

concerns; therefore, it was considered that doses that ensure low systemic exposure and safe use while promoting local activity should be selected. Based on the above, taking into account the results on efficacy, pharmacokinetics, and safety, a clinical concentration of 0.5% of topical delgocitinib would appear to be the appropriate recommended dose.

It was considered desirable, after consulting with a medical expert, that the maximum amount per application could cover up to 30% of the body surface, as a topical agent for atopic dermatitis. Taking into account the safety of topical delgocitinib 5g demonstrated in the Japanese phase I study (Study QBX1-2), together with the extensibility of topical delgocitinib, a maximum amount of 5 g per application would be sufficient to allow topical delgocitinib to be applied to up to 30% of the body surface. For this reason, in the phase II, phase III comparative, and long-term studies, topical delgocitinib was applied at a maximum of 5 g (1 tube) per application twice daily to patients with inflammatory rashes covering <30% of the body surface. The results of the phase III comparative study demonstrated the efficacy of delgocitinib [see Section 7.R.1], its safety was acceptable [see Section 7.R.2], and therefore it was considered that topical delgocitinib 0.5% twice daily (maximum of 5 g per application) would be appropriate.

The use of topical delgocitinib should be stopped if the symptoms do not improve after treatment, and a cautionary statement to this effect will be included in the package insert.

PMDA's view:
There should be no problem in specifying the proposed dosage and administration for topical delgocitinib based on the dosage regimen employed in the phase III studies. However, it is necessary to advise caution in the package insert that if a response is not achieved, the use of topical delgocitinib should be stopped, and that if symptoms improve, the necessity of continuing treatment should be reviewed not to keep using topical delgocitinib for a prolonged period in the absence of a clear treatment strategy.

7.R.5.2 Use of topical delgocitinib in combination with other therapies

The applicant's explanation about the use of topical delgocitinib in combination with other therapies for atopic dermatitis:
In the clinical studies of topical delgocitinib, subjects were allowed to use moisturizers. In the phase III comparative study (extension phase) and long-term study, use of topical corticosteroids was allowed if necessary. The results indicated no safety-related problems (Table 44). Because the use of tacrolimus ointment was prohibited in the clinical studies, no data on its use in combination with topical delgocitinib are available. However, given that systemic exposure is low after application of topical delgocitinib to rash sites, and because it is unlikely to cause systemic effects, the use of topical delgocitinib in combination with tacrolimus ointment is unlikely to affect the efficacy or safety of either agent. Therefore, it would not be necessary to limit the use of topical delgocitinib in combination with tacrolimus ointment.

When the use of existing therapies such as topical agents do not achieve an adequate response, systemic therapies, such as ciclosporin and biologics (dupilumab, anti-IL-4/13 receptor human monoclonal antibody)

are used in the treatment of atopic dermatitis. While data on the efficacy and safety of topical delgocitinib in combination with ciclosporin or dupilumab have not been obtained, their mechanism of action suggests that concomitant use of the agents may result in intensified immunosuppressive effects. In terms of efficacy, the anti-inflammatory effect may be intensified at the application site of delgocitinib. In terms of safety, the risk of local infections at the application sites of topical delgocitinib may increase; however, folliculitis is the only local infection reported in association with ciclosporin, and folliculitis is an adverse drug reaction that has been reported following administration of topical delgocitinib alone. Given that the general advice in the package insert is that dupilumab should be used in conjunction with anti-inflammatory topical agents (e.g. topical corticosteroids and tacrolimus ointment), and that there are no clear trends indicating higher safety risks for topical delgocitinib compared with the drugs already available on the market [see Section 7.R.2], it is unlikely that the use of topical delgocitinib in combination with dupilumab would cause safety-related problems compared with other commonly available topical agents. Therefore, it is not necessary to limit the use of topical delgocitinib in combination with ciclosporin or dupilumab.

In some cases, phototherapies are used in the treatment of atopic dermatitis. Although the use of topical delgocitinib in combination with phototherapies was prohibited in the clinical studies of topical delgocitinib, the non-clinical photosafety study and the phase I cutaneous safety study showed no safety concerns in terms of phototoxicity [see Sections 5.8.2 and 6.2.1]; therefore, it is not necessary to limit the use of topical delgocitinib in combination with phototherapies.

PMDA's view:
Based on the applicant's explanation above, it is not necessary to limit the use of topical delgocitinib in combination with topical corticosteroids or tacrolimus ointment. However, given that no clinical study data on the use of concomitant tacrolimus ointment are available, and that the importance of concomitant use of such agents and the local safety of the agents used concomitantly for prolonged periods are not clear, there is only a limited rationale for recommending the use of topical delgocitinib in combination with topical corticosteroids or tacrolimus ointment. Taken together, the use of topical delgocitinib in combination with tacrolimus ointment should be decided by the physician only after careful consideration of the patient's condition, such as selecting treatment on an individual lesion basis.

Ciclosporin and dupilumab are systemic therapies which are used when an adequate response cannot be achieved with topical agents such as corticosteroids or tacrolimus and, in principle, they are used in combination with other topical agents available on the market. In the clinical studies of topical delgocitinib, the use of ciclosporin and dupilumab was not prohibited, and therefore no data on the use of topical delgocitinib in combination with these agents are available. However, based on the safety of topical delgocitinib, the use of topical delgocitinib in combination with ciclosporin/dupilumab is unlikely to cause safety concerns greater than those associated with other commonly available topical agents used in combination with ciclosporin/dupilumab. Therefore, it is not necessary to limit the use of topical delgocitinib in combination with ciclosporin or dupilumab at this point in time, provided that precautions about the use of ciclosporin or dupilumab are followed.

There are no data from studies evaluating the efficacy and safety of topical delgocitinib in combination with phototherapies. However, because the results of non-clinical studies and the phase I study did not indicate any safety concern over phototoxicity, it is not necessary to limit the use of topical delgocitinib in combination with phototherapies.

Based on the above, it is not necessary to limit the use of topical delgocitinib in combination with conventional drugs or therapies for atopic dermatitis at this point in time, provided that the precautions about the use of each therapy are followed. However, it is desirable that the use of topical delgocitinib in combination with tacrolimus ointment be decided only after careful consideration by the physician. With the exception of topical corticosteroids, no data from studies on concomitant use of the agents are available; therefore, data should be continuously collected and analyzed on the safety of topical delgocitinib in combination with other agents or therapies in post-marketing surveillance or other surveys.

7.R.6 Clinical development for pediatric patients

The applicant's explanation about the clinical development of topical delgocitinib for pediatric patients:
Since there are many pediatric patients with atopic dermatitis, the clinical development of topical delgocitinib for children aged ≥2 years with atopic dermatitis is ongoing. Currently, a phase III Japanese clinical study is underway.

PMDA accepted the applicant's explanation.

7.R.7 Post-marketing investigations

The applicant has planned to conduct a post-marketing general use-results survey as shown in Table 48.

Table 48. Outline of general use-results survey (draft)

Objective	**To assess the safety, efficacy, and other aspects of topical delgocitinib in patients with atopic dermatitis in routine clinical practice**
Survey method	**Central registry**
Population	**Patients with atopic dermatitis**
Planned sample size	**300 patients**
Observation period	**6 months**
Main survey items	• **Patient characteristics (e.g., age, sex, disease duration, severity, complications, past medical history)** • **Status of delgocitinib treatment (treatment duration and dose)** • **Prior treatments and concomitant medication (e.g., presence of prior treatments and concomitant medication, names of agents, route of administration)** • **Efficacy** • **Adverse events (e.g., onset date, seriousness, outcome, discontinuation of topical delgocitinib, a causal relationship to topical delgocitinib)**

PMDA considers that information on the following issues should be collected and investigated. The details of the post-marketing surveillance plans will be finalized taking into account the comments from the Expert Discussion.

- Incidence of skin infections

- The safety and efficacy of topical delgocitinib in combination with other drugs or therapies for atopic dermatitis

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

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

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

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

The new drug application data (CTD 5.3.5.1-2 and CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of 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 Corectim Ointment 0.5% has efficacy in the treatment of atopic dermatitis, and that the product has acceptable safety in view of its benefits.

PMDA has concluded that Corectim Ointment 0.5% may be approved if it is not considered to have any particular problems regarding the issues of efficacy, safety, indication, dosage and administration, and post-marketing investigation based on comments from the Expert Discussion.

Review Report (2)

October 9, 2019

Product Submitted for Approval

Brand Name	Corectim Ointment 0.5%
Non-proprietary Name	Delgocitinib
Applicant	Japan Tobacco Inc.
Date of Application	January 31, 2019

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 Safety

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in Section "7.R.2 Safety" in the Review Report (1). The following comments were made by the expert advisors:

- In the clinical study of topical delgocitinib, the application of the drug onto eroded or ulcerated skin surfaces was prohibited because such treatment was likely to increase penetration of delgocitinib into the blood. Nevertheless, delgocitinib was detected in the plasma of some patients. In clinical practice, topical delgocitinib applied onto eroded or ulcerated skin surfaces may penetrate into the blood and then increase blood delgocitinib levels, resulting in the enhanced systemic action of delgocitinib which may increase the risk of adverse events. For this reason, it is necessary to provide precautionary advice against the application of topical delgocitinib onto eroded/ulcerated skin surfaces, and to investigate the risk of adverse events caused by the systemic action of delgocitinib.

PMDA's view:

In the repeated oral toxicity studies, the safety margins of delgocitinib based on the systemic toxicity findings were 86-fold (male rats), 309-fold (female rats), 111-fold (male dogs), and 109-fold (female dogs) (the safety margin was calculated as the ratio of the exposure [$AUC_{0\text{-}24}$] in animals receiving oral delgocitinib at the NOAEL to the estimated exposure in patients with atopic dermatitis receiving application of topical delgocitinib [0.5%] ointoment 5 g per application twice daily [$AUC_{0\text{-}24}$, 13.9 ng·h/mL]) [see Section 5.2]. Following application of topical delgocitinib 3% to the damaged skin of rats, $AUC_{0\text{-}24}$ was 4.7-fold that following application of topical delgocitinib 3% to the intact skin [see Section 4.1.1]. Based on these data, even if topical delgocitinib 0.5% is administered to patients with atopic dermatitis and then delgocitinib enters the bloodstream, such treatment is unlikely to pose the risk of systemic adverse events.

The percentage of patients in whom plasma delgocitinib was detected, and the plasma delgocitinib concentrations, tended to be higher in patients with higher IGA scores. However, when the long-term treatment data (pooled analysis data from the Japanese phase III comparative study and the long-term study) were analyzed for the incidence of adverse events by IGA score among patients in whom plasma delgocitinib was detected, there were no trends toward an increase in the incidence of adverse events with increasing severity of atopic dermatitis. Furthermore, there was no significant difference in the trend of the incidence of systemic adverse events by severity [see Section 6.R.1].

Even after assessment of the individual data of plasma delgocitinib concentrations in patients in whom plasma delgocitinib was detected in long-term treatment (pooled analysis data from the Japanese phase III comparative study and the long-term study), percutaneous application of topical delgocitinib is unlikely to pose the risk of systemic adverse events. However, given that application of topical delgocitinib onto eroded or ulcerated skin surfaces was prohibited in the clinical studies, and that following percutaneous administration of topical delgocitinib, plasma delgocitinib was detected in some patients (11.5% to 15.8%; pooled data from the 3 studies), PMDA instructed the applicant to include a cautionary statement to the effect that topical delgocitinib should not be applied onto eroded or ulcerated skin surfaces. The applicant agreed to take such action.

1.2 Efficacy, indication, and dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in Sections "7.R.1 Efficacy," "7.R.4 Indication," and "7.R.5 Dosage and Administration" in the "Review Report (1)."

Based on the discussions at the Expert Discussion and other information, PMDA concluded that the indication should be specified without modifying the proposed indication. In addition, PMDA requested the applicant to modify the contents of the "Dosage and Administration" section and "Precautions for Dosage and Administration" section of the package insert as shown below. The applicant took such actions, and PMDA accepted the response.

Indication

Atopic dermatitis

Dosage and Administration

The following is recommended for adults:

Apply an appropriate amount of the ointment to the affected areas twice daily. The dose applied should not exceed 5 g per application.

Precautions for dosage and administration

1. Stop using the product if the rash does not improve within 4 weeks of treatment.
2. If symptoms improve, consider whether to continue treatment. Do not keep using Corectim Ointment injudiciously for a prolonged period.

1.3 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusion on the issues presented in Section "7.R.7 Post-marketing investigations." The following comments were made by the expert advisors:

- In the clinical studies of topical delgocitinib, the use of concomitant systemic therapies and topical agents including tacrolimus hydrate was prohibited; however, in clinical settings, the use topical delgocitinib in combination with various drugs available on the market is anticipated. When topical delgocitinib is used concomitantly with immunosuppressants available on the market, the immunosuppressive effect will be intensified, thus the risk for skin infections may be higher than indicated by the results of the clinical studies. Furthermore, topical delgocitinib is used in patients with various forms and severity of atopic dermatitis in clinical practice. Therefore, it is necessary to investigate the risk of skin infections associated with the use of topical delgocitinib in as many patients as possible in post-marketing surveillance to ensure the safety in patients with a range of characteristics.
- Malignancies such as lymphoma and solid cancers have been reported in association with the use of approved oral JAK inhibitors. The long-term use of topical delgocitinib may potentially increase the risk of malignancies, accordingly, in post-marketing surveillance, the applicant should collect information on the incidence of malignancies in cases where the product has been used for a prolonged period.

Based on the deliberations at the Expert Discussion and other information, PMDA concluded that it is necessary to collect data on the long-term safety of topical delgocitinib in post-marketing surveillance in a greater number of patients than planned at the time of regulatory submission, and requested the applicant to review the post-marketing surveillance plan. The applicant responded as shown below, and PMDA accepted the plan.

- The planned sample size will be increased to 3,000 patients. An observation period of 6 months is specified (up to 3 years for patients receiving topical delgocitinib for >6 months).

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for delgocitinib should include the following safety and efficacy specifications presented in Table 49, the applicant should perform the additional pharmacovigilance actions and risk minimization actions presented in Table 50 and the general use-results survey presented in Table 51.

Table 49. Safety and efficacy specification for the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Skin infections	• Malignancies	• None
Efficacy specification		
• None		

Table 50. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • General use-results survey	• Disseminate data gathered during early post-marketing phase vigilance

Table 51. Outline of general use-results survey (draft)

Objective	To assess the safety, efficacy and other aspects of topical delgocitinib in patients with atopic dermatitis in routine clinical practice
Survey method	Central registry
Population	Patients with atopic dermatitis
Planned sample size	3,000 patients
Observation period	6 months (up to 3 years for patients receiving topical delgocitinib for >6 months)
Main survey items	• Patient characteristics (e.g., age, sex, disease duration, severity, complications, medical history) • Status of topical delgocitinib treatment (treatment duration and dose) • Prior treatments and concomitant medications (e.g., presence of prior treatments and concomitant medications, names of agents, and route of administration) • Efficacy • Adverse events (e.g., onset date, seriousness, outcome, discontinuation of topical delgocitinib [if discontinued], and causal relationship to topical delgocitinib)

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. Since 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 substance is classified as a poisonous drug, but its drug product is not classified as a poisonous drug or a powerful drug.

Indication

Atopic dermatitis

Dosage and Administration

The following is recommended for adults:

Apply an appropriate amount of the ointment to the affected areas twice daily. The dose applied should not exceed 5 g per application.

Conditions of Approval

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

Appendix

List of Abbreviations

A/G ratio	Albumin/globulin ratio
Adverse drug reaction	An adverse event for which a causal relationship to the study drug cannot be ruled out
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration-versus-time curve
BCRP	Breast cancer resistance protein
^{14}C	Carbon-14
Caco-2 cell	Human colonic adenocarcinoma cell
CCK	Cholecystokinin
CD40	Cluster of differentiation 40
C_{max}	Maximum concentration
ConA	Concanavalin A
CQA	Critical quality attribute
CRP	C-reactive protein
CTD	Common technical document
CYP	Cytochrome P450
DMSO	Dimethyl sulfoxide
DNCB	2, 4-dinitrochlorobenzene
Dupilumab	Dupilumab (Genetical Recombination)
EASI	Eczema Area and Severity Index
EPO	Erythropoietin
FAS	Full analysis set
GC	Gas chromatography
GCP	Good clinical practice
GH	Growth hormone
GLP	Good laboratory practice
GM-CSF	Granulocyte macrophage colony-stimulating factor
Guidelines for the Management	"Guidelines for the Management of Atopic Dermatitis 2018," [in Japanese], the Japanese Dermatological Association, and Japanese Society of Allergology: Preparation Committee for the Guidelines for the Management of Atopic Dermatitis, [The Japanese Journal of Dermatology. 2018; 128: 2431-502])
HEK293	Human embryonic kidney cell line 293
hERG	Human ether-a-go-go related gene
HPLC	High performance liquid chromatography
IC_{50}	Half maximal inhibitory concentration
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use
ICH Q1E Guidelines	"Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
ICR	Institute of Cancer Research
IFN	Interferon
Ig	Immunoglobulin
IGA	Investigator's Global Assessment
IL	Interleukin
IR	Infrared absorption spectrum
JAK	Janus kinase
KCl	Potassium chloride

Ki	Inhibition constant
KLH	Keyhole limpet hemocyanin
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
LH	Luteinizing hormone
Long-term study	Japanese long-term study in patients with atopic dermatitis (CTD 5.3.5.2-1, Study QBA4-2)
LPS	Lipopolysaccharide
M/E ratio	Myeloid/erythroid ratio
M1	A metabolite of delgocitinib
M2	A metabolite of delgocitinib
M3	A metabolite of delgocitinib
mEASI	modified Eczema Area and Severity Index
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
mRNA	Messenger ribonucleic acid
MS	Mass spectrometry
NA	Not applicable
NC	Not calculated
NK cell	Natural killer cell
NMR	Nuclear magnetic resonance spectrum
NZW	New Zealand White
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
^{33}P	Phosphorus-33
P-gp	P-glycoprotein
PHA	Phytohemagglutinin
Phase II study	Japanese dose-finding study in patients with atopic dermatitis (CTD 5.3.5.1-1, Study QBA2-1)
Phase III comparative study	Japanese phase III study in patients with atopic dermatitis (CTD 5.3.5.1-2, Study QBA4-1)
Phe	Phenylephrine
PMA	Phorbol 12-myristate 13-acetate
PMDA	Pharmaceuticals and Medical Devices Agency
Pooled data from the 3 studies	Pooled analysis data for topical delgocitinib 0.5% from the phase II, phase III comparative, and long-term studies
Pooled analysis data from the phase III studies	Pooled analysis data from the phase III comparative study and the long-term study
PPK	Population Pharmacokinetics
PPS	Per protocol set
PT	Preferred Term in the Medical Dictionary for Regulatory Activities
PTP	Press through packaging
PUVA	Psoralens plus UVA
RH	Relative humidity
SD	Sprague-Dawley
SOC	System Organ Class in the Medical Dictionary for Regulatory Activities
SRBC	Sheep red blood cell
STAT	Signal transducer and activator of transcription
$t_{1/2}$	Elimination half life
Tacrolimus	Tacrolimus hydrate
t_{max}	Time to reach maximum concentration
TNF-α	Tumor necrosis factor-α
TYK2	Tyrosine kinase 2
UV/VIS	Ultraviolet-visible absorption spectroscopy

UVA	Ultraviolet A
UVB	Ultraviolet B