Report on the Deliberation Results

September 7, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Moizerto Ointment 0.3% Moizerto Ointment 1%
Non-proprietary Name	Difamilast (JAN*)
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	September 28, 2020

Results of Deliberation

In its meeting held on August 30, 2021, 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. The drug product is not classified as a poisonous drug or a powerful drug.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

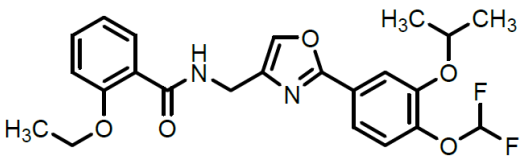
Review Report

August 4, 2021
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Moizerto Ointment 0.3% Moizerto Ointment 1%
Non-proprietary Name	Difamilast
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	September 28, 2020
Dosage Form/Strength	Ointment: Each gram contains 3 mg or 10 mg of difamilast.
Application Classification	Prescription drug, (1) Drugs with a new active ingredient

Chemical Structure



Molecular formula: $C_{23}H_{24}F_2N_2O_5$

Molecular weight: 446.44

Chemical name: *N*-({2-[4-(Difluoromethoxy)-3-(propan-2-yloxy)phenyl]-1,3-oxazol-4-yl}methyl)-2-ethoxybenzamide

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).

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 approval condition.

Indication

Atopic dermatitis

Dosage and Administration

The usual adult dosage is an appropriate amount of the 1% product applied to the affected area twice daily.

The usual pediatric dosage is an appropriate amount of the 0.3% product applied to the affected area twice daily. According to the patient's condition, an appropriate amount of the 1% product may be applied to the affected area twice daily.

Approval Condition

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

Attachment

Review Report (1)

June 29, 2021

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

Product Submitted for Approval

Brand Name	Moizerto Ointment 0.3% Moizerto Ointment 1%
Non-proprietary Name	Difamilast
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	September 28, 2020
Dosage Form/Strength	Ointment: Each gram contains 3 mg or 10 mg of difamilast.

Proposed Indication

Atopic dermatitis

Proposed Dosage and Administration

The usual adult dosage is an appropriate amount of the 1% ointment applied to the affected area twice daily.

The usual pediatric dosage is an appropriate amount of the 0.3% ointment applied to the affected area twice daily. To a severely affected area or an area with inadequate response, an appropriate amount of the 1% ointment may be applied twice daily.

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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 disease characterized by pruritic eczema and a course marked by exacerbations and remissions. The majority of patients with atopic dermatitis have a predisposition[1)] to atopy.

According to the "Guidelines for the Management of Atopic Dermatitis 2018 [in Japanese]" edited by the Japanese Dermatological Association, the Japanese Society of Allergology, and Committee for Guidelines for the Management of Atopic Dermatitis *(The Japanese Journal of Dermatology.* 2018;128:2431-502), the drug treatment of atopic dermatitis basically consist of topical agents, including moisturizers, topical corticosteroids, or tacrolimus ointments. Topical corticosteroids, however, are known to cause local adverse drug reactions such as skin atrophy, capillarectasia, steroidal acne, and steroid flushing. As a principle, low- to mid-potency topical corticosteroids are recommended for use in skin area such as the face and neck. Tacrolimus ointment is known to induce skin irritation such as 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. In 2020, ointment containing delgocitinib, a Janus kinase (JAK) inhibitor, was approved as a topical agent for treatment of atopic dermatitis with a new mechanism of action in Japan.

Difamilast is a phosphodiesterase 4 (PDE4) inhibitor discovered by the applicant, thereby increasing a cyclic adenosine 3',5'-monophosphate (cAMP) concentration and consequently suppressing production of inflammatory cytokines, which was expected to exert effects in treatment of atopic dermatitis. This led to the development of the drug.

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

As of June 2021, difamilast 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 occurs as white to pale yellow-white crystals or crystalline powder. Its description, solubility, hygroscopicity, melting point, partition coefficient, and optical rotation have been determined. During the development, the drug substance was produced in at least 2 types of crystalline forms ([redacted] and [redacted]), but the commercial-scale manufacturing process produces only the drug substance in [redacted] form, which is stable at room temperature.

The chemical structure of the drug substance has been elucidated by [redacted], ultraviolet-visible absorption spectroscopy (UV/VIS), infrared absorption spectroscopy (IR), [redacted], and [redacted].

1) Family history, medical history (bronchial asthma, allergic rhinitis and conjunctivitis, and atopic dermatitis) or predisposition to IgE antibody production

2.1.2 Manufacturing process

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

In view of the quality target product profile (QTPP) and critical quality attributes (CQAs) of the drug product, CQAs of the drug substance were identified, and process parameters were evaluated according to the quality risk assessment and design of experiment to construct the quality control strategy (Table 1).

Table 1. Outline of control strategy of drug substance

Potential CQA for drug substance	Control method
Content	[redacted]
Description	[redacted]
Identification	[redacted]
Melting point	[redacted]
Purity (related substances, residual solvents, mutagenic impurities, and residue on ignition)	[redacted]
Water content	[redacted]
Particle size	[redacted]
Crystalline form	[redacted]
Optical activity	[redacted]
Microbial limit	[redacted]

Steps for reaction and purification have been defined as critical steps. In addition, [redacted] and the crude drug substance are controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (UV/VIS and IR), melting point, purity (related substances [liquid chromatography (LC)] and residual solvents [gas chromatography (GC)]), water content (coulometric titration), residue on ignition, and assay (LC).

2.1.4 Stability of drug substance

Table 2 shows main stability studies of the drug substance. The results showed that the drug substance is stable. In addition, the photostability testing showed that the drug substance is unstable to light.

Table 2. Main stability studies of drug substance

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	3 pilot-scale batches	30 ± 2°C	65 ± 5%RH	Double-layer polyethylene bags + fiber drum	[redacted] months
Accelerated	3 pilot-scale batches	40 ± 2°C	75 ± 5%RH		6 months

Based on the above, a retest period of [redacted] months has been proposed for the drug substance stored in a double-layered polyethylene bag placed inside a light-protected fiber drum at ≤30°C in accordance with the ICH Q1E guideline. Long-term testing will be continued up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is ointment containing 3 mg or 10 mg of difamilast per gram. The drug product contains white petrolatum, liquid paraffin, white beeswax, paraffin, and propylene carbonate as its excipients.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of [redacted], [redacted], [redacted], filling, and packaging/labeling/storage/testing. [redacted], [redacted], and [redacted] have been defined as critical steps. The process control items and process control values have been established for [redacted] and [redacted].

For the drug product, CQAs were identified, and process parameters were evaluated according to the quality risk assessment to construct the control strategy (Table 3).

Table 3. Outline of control strategy of drug product

CQA	Control method
Strength	[redacted]
Description	
Identification	
Viscosity	
Purity	
Droplet size	
Crystallinity	
Filled amount	
Release profile	

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description (appearance), identification (LC and UV), viscosity, purity (related substances [LC]), and assay (LC).

2.2.4 Stability of drug product

Table 4 shows main stability studies conducted on the drug product. The results showed that the drug product is stable. The photostability testing showed that the drug product is unstable to light.

Table 4. Main stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	3 commercial-scale batches	25 ± 2°C	60 ± 5%RH	Aluminum tube/ carton	[redacted] months
Accelerated	3 commercial-scale batches	40 ± 2°C	75 ± 5%RH		6 months

Based on the above, a shelf life of 30 months has been proposed for the drug product packaged in an aluminum tube placed inside a carton, stored at room temperature, in accordance with the ICH Q1E guideline. Long-term testing will be continued 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 product is appropriately controlled.

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

Studies for primary pharmacodynamics evaluated difamilast in terms of inhibition against PDE4, increase of cAMP concentration, suppression against cytokine production, and improvement of dermatitis. Studies for secondary pharmacodynamics evaluated difamilast in terms of effects on non-PDE4 enzymes and receptors as well as on skin atrophy. Studies for safety pharmacology evaluated difamilast in terms of effects on central nervous, cardiovascular, and respiratory systems.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Inhibitory activity against PDE4 (CTD 4.2.1.1-01 to 4.2.1.1-05)

The inhibitory activity of difamilast against 4 types of PDE4 isoforms (PDE4A, PDE4B, PDE4C, and PDE4D) was investigated. Difamilast inhibited all the isoforms with the half maximal inhibitory concentration (IC_{50}) values of 0.08, 0.01, 0.25, and 0.07 μmol/L, respectively.

The inhibitory activity against 10 types of PDE isozymes (PDE1A, PDE2A, PDE3A, PDE5A, PDE6AB, PDE7B, PDE8A, PDE9A, PDE10A, and PDE11A) was investigated. Difamilast inhibited PDE5A and PDE10A with the IC_{50} values of 4.79 and 1.43 μmol/L, respectively, and the IC_{50} values of difamilast for the other isozymes were >10 μmol/L.

3.1.1.2 Increase of cAMP concentration (CTD 4.2.1.1-06)

Difamilast at 0.001 to 10 μmol/L was added to human histiocytic lymphoma-derived U937 cells, and intracellular concentration of cAMP induced by stimulation with PGE1 was measured. The intracellular concentration of cAMP increased with an increasing concentration of difamilast ≥0.01 μmol/L, and the 200% effective concentration (EC_{200}) was 0.009 μmol/L.

3.1.1.3 Suppression against cytokine production (CTD 4.2.1.1-07 to 4.2.1.1-09)

Difamilast at 0.0001 to 10 μmol/L was added to human peripheral blood mononuclear cells (PBMCs), and concentrations of cytokines (interleukin [IL]-1β, IL-6, IL-8, IL-10, granulocyte-macrophage colony-stimulating factor [GM-CSF], macrophage inflammatory protein [MIP]-1α, MIP-1β, and tumor necrosis factor [TNF]-α) induced by stimulation with lipopolysaccharide (LPS) were measured. Difamilast inhibited production of GM-CSF, MIP-1α, MIP-1β, and TNF-α with the IC_{50} values of 7.78, >10, 9.15, and 0.52 μmol/L, respectively. On the other hand, difamilast enhanced production of IL-6 and IL-10 with the EC_{200} values of 5.81 and 0.18 μmol/L, respectively. Difamilast did not have any impact on production of IL-1β and IL-8.

Difamilast at 0.003 to 3 μmol/L was added to human PBMCs, and concentrations of cytokines of IL-2, IL-4, IL-5, IL-10, IL-13, IL-22, interferon (IFN)-γ, GM-CSF, substance regulated on activation normal T cell expressed and secreted (RANTES), and TNF-α induced by stimulation with anti-CD3 and

anti-CD28 antibodies were measured. Difamilast suppressed production of all the cytokines with the IC_{50} values of 0.35, 0.21, 0.16, 0.58, 0.54, 0.48, 0.07, 1.18, 0.42, and 0.66 μmol/L, respectively.

3.1.2 *In vivo* studies

3.1.2.1 Improvement of dermatitis in chronic contact hypersensitivity mouse model (CTD 4.2.1.1-13 to 4.2.1.1-15)

Chronic contact hypersensitivity mouse models[2)] (n = 6-8/group) percutaneously received difamilast 0% (base), 0.03%, 0.1%, 0.3%, 1%, and 3% once daily for 28 days, and ear thickness and contents of cytokines (MIP-1α, MIP-2, IL-4, IFN-γ, and TNF-α) in the affected ear tissue were evaluated. The ear thickness increased and concentrations of MIP-1α and MIP-2 decreased with an increasing concentration of difamilast ≥0.03%.

Chronic contact hypersensitivity mouse models[3)] (n = 6/group) percutaneously received difamilast 0% (base), 1%, and 3% once daily for 29 days, and inflammatory cell count in the right ear and serum IgE concentration were evaluated. Both infiltrating inflammatory cell count and serum IgE concentration were lower in the difamilast ≥1% groups than in the base group.

3.1.2.2 Improvement of dermatitis in scratching-induced chronic dermatitis mouse model (CTD 4.2.1.1-17)

Scratching-induced chronic dermatitis mouse models[4)] (n = 9/group) percutaneously received difamilast 0% (vehicle[5)]), 1%, and 3% once daily for 6 weeks, and skin score,[6)] number of scratching behaviors, and contents of cytokines (MIP-1α and MIP-2) in the affected skin were evaluated. The skin score and contents of MIP-1α and MIP-2 were lower in the difamilast ≥1% groups than in the vehicle group. The number of scratching behaviors, on the other hand, remained unaffected by difamilast.

3.1.2.3 Improvement of dermatitis in contact hypersensitivity mouse models (CTD 4.2.1.1-18)

Contact hypersensitivity mouse models[7)] (n = 10/group) percutaneously received a single dose of difamilast 0% (base) or 3%, and ear-swelling response[8)] and IFN-γ concentration in the ear tissue were evaluated. The ear-swelling response and IFN-γ concentration in the ear tissue were lower in the difamilast 3% group than in the base group.

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2) Both sides of the right ear in male mice were percutaneously treated with 1% 2,4,6-trinitro-1-chlorobenzene every other day for 51 days to induce chronic contact hypersensitivity. Difamilast was started 24 days after start of 2,4,6-trinitro-1-chlorobenzene treatment.

3) Both sides of the right ear in male mice were percutaneously treated with 1% 2,4,6-trinitro-1-chlorobenzene every other day for 53 days to induce chronic contact hypersensitivity. Difamilast was started 24 days after start of 2,4,6-trinitro-1-chlorobenzene treatment.

4) Both sides of the right ear in male mice were percutaneously treated with 1% 2,4,6-trinitro-1-chlorobenzene 3 times a week for 16 weeks, and mice were individually housed until chronic dermatitis was induced in both ears.

5) A mixture of acetone and methanol (1:1) was used.

6) Severity of dermatitis was assessed on the basis of the skin area damaged by scratching with findings such as ulcer, excoriation, erosion, minor hemorrhage, and crust.

7) Both sides of the left ear in male mice were percutaneously treated with 1% 2,4,6-trinitro-1-chlorobenzene as a single dose, and 7 days later both sides of the right ear were percutaneously treated with 1% 2,4,6-trinitro-1-chlorobenzene as a single dose to induce contact hypersensitivity.

8) It was evaluated on the basis of a difference between ear thicknesses before treatment with 2,4,6-trinitro-1-chlorobenzene and after 24 hours of the treatment.

3.2 Secondary pharmacodynamics

3.2.1 Effects on receptors, ion channels, and transporters (CTD 4.2.1.2-01)

Effects of difamilast on 90 types of receptors, ion channels, and transporters were investigated. Difamilast 10 μmol/L inhibited human adenosine transporter by 87.6%. While difamilast inhibited rabbit monoamine transporter by 85.5%, it inhibited human monoamine transporter by 21.5%.

If difamilast inhibits the adenosine transporter, the cardiovascular, respiratory, and coagulation systems would be affected. Safety pharmacology [see Section 3.3] and toxicity [see Section 5.2] studies, however, did not show any effect of difamilast on these systems. At the no observed effect level (NOEL) (30 mg/kg) in a study for safety pharmacology and the dose (3 mg/kg) without any effect on the coagulation system in a toxicity study in dogs, C_{max} (1,409 and 443.9 ng/mL) were 83 and 26 times the estimated C_{max} (16.9 ng/mL[9)]) at steady state in humans receiving difamilast at the maximum clinical recommended dose.

Based on the above, the applicant explained that difamilast is unlikely to affect these transporters in clinical settings.

3.2.2 Effect on skin atrophy (CTD 4.2.1.2-02)

The right ear of male mice (n = 6/group) was percutaneously treated with difamilast 0% (vehicle[5)]), 1%, and 3% once daily for 1 week, and measurement of ear thickness and histological evaluation were performed. Difamilast neither affected the ear thickness nor caused histological changes.

3.3 Safety pharmacology

Table 5 shows an outline of results from safety pharmacology studies.

Table 5. Outline of results from safety pharmacology studies

Item	Test system	Evaluation items and methods	Dose of difamilast	Route of administration	Findings	Attached document CTD
Central nervous system	Rat (6 males/group)	Modified Irwin procedure	30, 100, 200 mg/kg[a)]	Single dose Subcutaneous	≥100 mg/kg: Loose stool 200 mg/kg: Salivation	4.2.1.3-01
Cardiovascular system	CHO-K1 cells (5 preparations/ group)	hERG current	0.1, 1, 10 μmol/L	*In vitro*	≥1 μmol/L: Inhibited hERG current (IC_{50} value = 2.54 μmol/L)	4.2.1.3-03
	Guinea pig isolated right ventricular papillary muscle (5 preparations/ group)	Action potential	0.2, 1, 5 μmol/L	*In vitro*	≥1 μmol/L: Shortened APD	4.2.1.3-04
Cardiovascular system Respiratory system	Dog (4 males/group)	Blood pressure, heart rate, electrocardiogram, respiratory rate, and blood gas	3, 10, 30 mg/kg[a)]	Single dose Subcutaneous	No effects	4.2.1.3-02

a) Corn oil was used as a vehicle.

9) It was estimated from exposures in patients with atopic dermatitis aged ≥2 and <12 years in whom difamilast 1% was applied to ≥35% body surface area twice daily for 15 days and in those patients aged ≥12 and ≤17 years in whom difamilast 1% was applied to ≥25% body surface area twice daily for 15 days.

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological effects

The applicant's explanation about pharmacological effects of difamilast:
Difamilast inhibits PDE4 which is involved in degradation of cAMP. In a body, cAMP acts as one of the second messengers intracellularly produced in response to external stimulation and suppresses production of inflammatory cytokines and chemokines by activating protein kinase A.

PDE4 is expressed in a wide range of immune cells, and peripheral leukocytes in patients with atopic dermatitis show increased PDE activity and decreased intracellular cAMP concentration, indicating that PDE4 is involved in pathology of chronic inflammatory diseases such as atopic dermatitis (*J Invest Dermatol*. 1985;85:161-4). Difamilast is considered to exert therapeutic effects on atopic dermatitis by inhibiting PDE4 and thereby increasing intracellular cAMP concentration, which leads to suppressed inflammatory response.

Because the studies for primary pharmacodynamics showed that difamilast inhibited PDE4 and increased intracellular cAMP concentration as well as improved dermatitis in murine chronic inflammatory skin disease models, difamilast is expected to exert therapeutic effects on atopic dermatitis.

PMDA accepted the applicant's explanation.

3.R.2 Safety pharmacology

The applicant's explanation about findings in studies for safety pharmacology:
No findings in the respiratory system were presented in the studies for safety pharmacology.

As findings in the central nervous system, loose stool and salivation were presented in rats. The findings of loose stool and salivation are considered attributable to inhibitory effect of difamilast against PDE4 according to the literature reporting that the increased intracellular cAMP due to inhibition against PDE4 activated the cystic fibrosis transmembrane conductance regulator on the intestinal pouch, leading to intestinal fluid secretion, which induced diarrhea (*Am J Respir Cell Mol Biol.* 2014;50:549-58); and that the increased intracellular cAMP in the parotid and submandibular glands enhanced production of amylase and mucin (*J Physiol.* 1976;260:351-70, *Biochim Biophys Acta.* 1983;762:215-20). At 10 mg/kg lower than the NOEL (30 mg/kg) for loose stool and NOEL (100 mg/kg) for salivation in a study for safety pharmacology in rats, C_{max} (362.3 and 4,420 ng/mL) were 21 and 262 times the estimated C_{max} (16.9 ng/mL) at steady state in humans receiving difamilast at the maximum clinical recommended dose.

As a finding in the cardiovascular system, difamilast inhibited human ether-a-go-go related gene (hERG) current. In addition, difamilast shortened the action potential duration (APD) in the guinea pig isolated right ventricular papillary muscle. The increased intracellular cAMP concentration elevated slowly activating potassium ion channel current, leading to shortened APD (*Folia Pharmacologica Japonica.* 2005;126:273-9), and the shortened APD is considered as an inhibitory effect of difamilast against PDE4. The IC_{50} value of difamilast against hERG current was 2.54 μmol/L (1,134 ng/mL) and

NOEL of difamilast for shortened APD was 0.2 μmol/L (89.3 ng/mL), which are 22,367 and 1,761 times the blood concentration of free difamilast calculated from the estimated C_{max} (16.9 ng/mL) at steady state in humans receiving difamilast at the maximum clinical recommended dose and blood protein binding (99.7%).

Based on the above, difamilast is considered unlikely to affect the respiratory, central nervous, and cardiovascular systems in clinical use.

PMDA accepted the applicant's explanation.

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

Unlabeled difamilast or ^{14}C-difamilast was administered to rats for investigation of the pharmacokinetics. Plasma difamilast concentrations were determined by liquid chromatography-tandem mass spectrometry (LC/MS/MS), and the lower limit of quantitation was 0.05 ng/mL. When ^{14}C-difamilast was used, the radioactivity was determined with a liquid scintillation counter. The base of all the formulations used in studies was the same as that of the proposed formulation.

4.1 Absorption

4.1.1 Single-dose study (CTD 4.2.2.2-01)

Table 6 shows the plasma pharmacokinetic parameters following a single percutaneous, oral, or intravenous administration of difamilast to female and male rats. When intact skin and damaged skin without corneum of male rats were percutaneously treated with difamilast 3 mg/kg, the bioavailability was 21.7% and 34.7%, respectively. When intact skin of female rats was percutaneously treated with difamilast 3 mg/kg, the bioavailability was 30.4%. C_{max} and $AUC_{0-\infty}$after percutaneous treatment on damaged skin of male rats with difamilast 3 mg/kg were 2.0 and 1.6 times those after percutaneous treatment on intact skin, suggesting that removal of corneum would increase percutaneous absorption of difamilast.

Table 6. Plasma pharmacokinetic parameters in rats after single percutaneous, oral, or intravenous treatment with difamilast

Route of administration	Skin condition	Sex	Dose of difamilast	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng•h/mL)	$t_{1/2}$ (h)	Bioavailability[a)] (%)
Percutaneous	Intact skin	Male	0.3 mg/kg	3.0	8	80	9.8	30.0
			0.9 mg/kg	8.2	16	235	9.6	29.3
			3 mg/kg	17.8	8	579	17.1	21.7
			9 mg/kg	17.6	28	688	11.0	8.6
		Female	3 mg/kg	52.6	8	1,418	8.9	30.4
	Damaged skin	Male	3 mg/kg	35.1	8	926	8.6	34.7
Oral		Male	3 mg/kg	64	6	446	5.1	16.7
Intravenous		Male	0.3 mg/kg	224	-	267	3.7	-
		Female	0.3 mg/kg	172	-	467	6.7	-

Mean value in 3 animals at each timepoint

a) Calculated using $AUC_{0-\infty}$ after intravenous administration of 0.3 mg/kg

4.1.2 Repeated-dose study (CTD 4.2.2.2-07)

Table 7 shows the blood pharmacokinetic parameters following percutaneous administration of ^{14}C-difamilast to male rats once daily for 21 days.

Table 7. Blood pharmacokinetic parameters after repeated percutaneous administration for 21 days.

Dose of difamilast	Measurement timepoint	C_{max} (ng eq./mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng eq.•h/mL)	$t_{1/2}$ (h)
3 mg/kg	Day 1	62 ± 8	24 ± 0	985 ± 156	-
	Day 21	234 ± 55	19 ± 12	4,787 ± 1,006	139 ± 11

n = 3, Mean ± standard deviation (SD)

4.2 Distribution

4.2.1 Tissue distribution in rats (CTD 4.2.2.2-02 and 4.2.2.3-02)

A single dose of ^{14}C-difamilast 3 mg/kg was percutaneously administered to female and male rats, and the radioactivity concentrations in tissues[10)] at 4, 8, 24, 48, 72, 96, and 168 hours were determined. In male rats, radioactivity concentrations in tissues reached the maxima at 24 hours and then decreased with time. In female rats, radioactivity concentrations in tissues other than the skin of the administration site reached maxima at 8 hours and then decreased with time. The radioactivity concentration at the skin of the administration site reached a maximum at 24 hours and then tended to decrease with time.

A single dose of ^{14}C-difamilast 3 mg/kg was subcutaneous administered to male pigmented rats, and the radioactivity concentrations in tissues[11)] at 1, 4, 8, 24, 48, 72, and 168 hours were determined. C_{max} of radioactivity in the non-pigmented skin and pigmented skin was 625.3 and 474.6 ng eq./g, respectively, and $t_{1/2}$ was 46.2 and 50.2 hours, respectively. The radioactivity concentration in the eyeball reached a maximum at 8 hours and was lower than the plasma radioactivity concentration. The $t_{1/2}$ of radioactivity concentrations in the eyeball of albino rats and pigmented rats after administration of the same dose were 70.9 and 74.9 hours, respectively. Based on the above, difamilast is considered unlikely to bind to melanin.

4.2.2 Protein binding (CTD 4.2.2.3-03)

Binding of ^{14}C-difamilast (0.03-3 μg/mL) to protein was investigated using serum specimens from mice, rats, rabbits, dogs, miniature swine, and humans. The mean protein binding was 99.9%, 99.7% to 99.8%, 99.3% to 99.4%, 99.9%, 99.6% to 99.7%, and 99.7%, respectively. Within a range of concentrations investigated, the protein binding was not dependent on the concentration.

4.2.3 Distribution in blood cells (CTD 4.2.2.2-03 and 4.2.2.2-05)

A single dose of ^{14}C-difamilast 3 mg/kg was subcutaneously administered to female and male rats and male dogs, and its distribution in blood cells at 1, 4, 8, and 24 hours was investigated. The mean percentage of the radioactivity distributed in blood cells was 4.1% to 10.8% in male rats, 1.3% to 6.1% in female rats, and 2.6% to 5.5% in male dogs.

10) Blood, plasma, cerebrum, cerebellum, eyeball, heart, lung, liver, adrenal gland, kidney, skin, and skin of the administration site
11) Blood, plasma, eyeball, lung, liver, adrenal gland, kidney, pigmented skin, non-pigmented skin, skeletal muscle, white fat, brown fat, and small intestine

4.2.4 Placental transfer and distribution in fetal in rats (CTD 4.2.2.3-01)

A single dose of ^{14}C-difamilast 3 mg/kg was subcutaneously administered to pregnant rats on Gestation Day 18, and radioactivity concentrations in maternal and fetal tissues[12)] were determined. Radioactivity concentrations in fetal tissues reached maxima at 8 or 24 hours and then decreased with time. Fetal tissues with the radioactivity concentration higher than the maternal blood radioactivity concentration at 8 or 24 hours were blood, lung, liver, and kidney. The concentrations in these tissues were 1.87 to 2.15, 1.49 to 1.54, 1.59 to 1.86, and 1.42 to 2.69 times, respectively, the maternal blood concentration. The radioactivity concentrations in the other fetal tissues (brain and heart) were ≤0.83 times the maternal blood radioactivity concentration. The above results indicated that subcutaneously administered difamilast was transferred via circulating blood across the placenta and distributed in fetuses. In addition, the applicant explained that difamilast, when percutaneously administered to humans, might be absorbed through the skin, transferred via circulating blood across the placenta, and distributed in fetus [for effects of difamilast on fetuses, see Section 5.R.2].

4.3 Metabolism

4.3.1 *In vitro* metabolite studies (CTD 4.2.2.4-06)

Metabolism of ^{14}C-difamilast was investigated using human liver microsomes. The most abundant metabolite was MAP-15485 (de-*O*-ethyl form), and the others included MAP-15497 (hydroxide form).

When ^{14}C-difamilast was added to recombinant human cytochrome P450 (CYP) isoform expression systems (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5), the CYP3A4 expression system generated MAP-15485 and CYP1A2 expression system generated MAP-15497.

4.3.2 Metabolites in the skin of the administration site, urine, and feces (CTD 4.2.2.4-03 and 4.2.2.4-04)

A single dose of ^{14}C-difamilast 3 mg/kg was percutaneously administered to female and male rats, and proportions of unchanged difamilast and its metabolites in the skin of the administration site, urine, and feces were investigated. The most abundant radioactive substance in the skin of the administration site at 24 hours was unchanged difamilast (90.8%/93.1% of the total radioactivity in the skin of the administration site [females/males]), and the others included MAP-15484 (de-ethenzamide carboxylic acid form, 0.6%/0.3% of the total radioactivity in the skin of the administration site [females/males]), MAP-15485 (0.9%/1.0% of the total radioactivity in the skin of the administration site [females/males]), and MAP-15497 (0.8%/0.8% of the total radioactivity in the skin of the administration site [females/males]). The most abundant radioactive substance in urine up to 48 hours post-dose was MAP-15484 (0.8%/0.7% of the radioactivity in urine [females/males]). The most abundant radioactive substance in feces up to 48 hours post-dose was MAP-15485 (7.7%/3.8% of the radioactivity in feces [females/males]).

12) For maternal bodies, blood, cerebrum, cerebellum, medulla oblongata, pituitary gland, eyeball, Harderian gland, submandibular gland, thyroid, thymus, heart, lung, liver, adrenal gland, kidney, spleen, pancreas, skin, skeletal muscle, bone, bone marrow, white fat, brown fat, stomach, small intestine, large intestine, ovary, uterus, mammary gland, amniotic fluid, and placenta. For fetuses, blood, brain, heart, lung, liver, and kidney

4.4 Excretion

4.4.1 Excretion into urine, feces, expired air, and bile (CTD 4.2.2.2-02 and 4.2.2.2-03)

A single dose of ^{14}C-difamilast 3 mg/kg was percutaneously administered to intact skin of female and male rats and damaged skin of male rats, and the radioactivity excreted into urine, feces, and expired air up to 168 hours post-dose was determined. The remaining ^{14}C-difamilast on the skin was to be removed at 24 hours. In the ^{14}C-difamilast removed from the intact skin of female and male rats at 24 hours, 63.3% and 67.5% of the radioactivity administered were detected, and in urine, feces, and expired air up to 168 hours post-dose, 4.9% and 3.6%, 25.0% and 16.9%, and 0.4% and 0.3%, respectively, of the radioactivity administered were excreted. In the ^{14}C-difamilast removed from the damaged skin at 24 hours, 63.7% of the radioactivity administered was detected, and in urine, feces, and expired air up to 168 hours post-dose, 4.1%, 18.6%, and 0.4%, respectively, of the radioactivity administered were excreted.

A single dose of ^{14}C-difamilast 3 mg/kg was subcutaneously administered to bile-duct-cannulated female and male rats, and in bile, urine, and feces up to 72 hours post-dose, 64.6% and 71.4%, 3.4% and 6.4%, and 8.4% and 6.5%, respectively, of the radioactivity were excreted.

4.4.2 Excretion into milk in rats (CTD 4.2.2.5-01)

A single dose of ^{14}C-difamilast 3 mg/kg was subcutaneously administered to female rats on Lactation Day 15 or 16, and radioactivity concentrations in milk at 1, 2, 4, 8, 12, 24, 48, 72, and 168 hours were determined. The radioactivity concentration in milk reached a maximum at 12 hours (1,914 ng eq./mL, 13.7 times the blood radioactivity concentration) and then decreased with time. The above result indicated that subcutaneously administered difamilast is transferred into milk.

4.5 Pharmacokinetic interactions

4.5.1 Induction effect of difamilast of human hepatic drug-metabolizing enzymes (CTD 5.3.2.2-04)

Human hepatocytes were incubated with difamilast (0.2-20 μmol/L), and induction effect of difamilast of CYP isoforms (CYP1A2, CYP2B6, CYP2C9, and CYP3A4) was investigated. Difamilast increased mRNA expression of CYP1A2, CYP2B6, and CYP3A4 in a concentration-dependent manner, indicating that it induces CYP1A2, CYP2B6, and CYP3A4.

4.5.2 Inhibitory effect of difamilast against human hepatic drug-metabolizing enzymes (CTD 5.3.2.2-01 and 5.3.2.2-02)

Human liver microsomes were incubated with difamilast (0.3-30 μmol/L), and inhibitory effect of difamilast against enzyme activities of CYP isoforms[13)] (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) was investigated. Difamilast inhibited CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 with the IC_{50} values of 1.9, 6.0, 2.5, 2.7, 5.4, and 15.7 μmol/L. The other CYP isoforms were not inhibited by difamilast within a range of concentrations investigated.

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13) The following was used as substrates in the investigation: Phenacetin for CYP1A2, coumarin for CYP2A6, bupropion for CYP2B6, paclitaxel for CYP2C8, diclofenac for CYP2C9, S-mephenytoin for CYP2C19, bufuralol for CYP2D6, chlorzoxazone for CYP2E1, and midazolam and testosterone for CYP3A4.

4.5.3 Assessment of substrate potential and inhibition against transporters (CTD 5.3.2.2-05 to 5.3.2.2-09)

^{14}C-difamilast (1, 10, or 30 μmol/L) was added to multidrug resistance (MDR)1 and breast cancer resistance protein (BCRP)-expressing Martin-Darby canine kidney (MDCK) II cells, and the results indicated that difamilast is a substrate of BCRP but not a substrate of P-glycoprotein (P-gp).

^{14}C-difamilast (0.5-10 μmol/L) was added to organic anion transporting polypeptide (OATP)1B1 and OATP1B3-expressing human embryonic kidney cell line 293 (HEK293) cells, and the results indicated that difamilast is not a substrate of OATP1B1 or OATP1B3.

Inhibitory effect of difamilast[14)] against P-gp was investigated using transportation via P-gp as an indicator, and the result indicated that difamilast inhibits P-gp with the IC_{50} value of 0.80 μmol/L.

Inhibitory effect of difamilast[15)] against BCRP was investigated using transportation via BCRP as an indicator, and the result indicated that difamilast inhibits BCRP with the IC_{50} value of 0.22 μmol/L.

Inhibitory effect of difamilast[16)] was investigated using transportations via OATP1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, OCT2, multidrug and toxin extrusion (MATE)1, and MATE2-K as indicators. The results indicated that difamilast inhibited OATP1B1, OATP1B3, OAT3, OCT1, OCT2, MATE1, and MATE2-K with the IC_{50} values of 1.84, 1.22, 6.13, 1.44, 1.03, 1.00, and 6.43 μmol/L, respectively, and the IC_{50} value of difamilast against OAT1 was >30 μmol/L.

4.R Outline of the review conducted by PMDA

4.R.1 Transfer of difamilast into milk

After subcutaneous administration of ^{14}C-difamilast to lactating rats, radioactivity was detected in milk [see Section 4.4.2]. PMDA therefore asked the applicant to explain effects of difamilast used in lactating women on infants.

The applicant's explanation:

In lactating rats which subcutaneously received a single dose of ^{14}C-difamilast 3 mg/kg, C_{max} of radioactivity in milk was 13.7 times that of radioactivity in plasma, but in a study for pre- and postnatal development in rats, repeated subcutaneous administration of difamilast 3 mg/kg did not affect development of the offspring [see Section 5.5]. However, because subcutaneously administered difamilast is deemed to be transferred via circulating blood into milk, difamilast, when percutaneously administered to humans, can be absorbed through the skin and transferred via circulating blood into milk. The package insert of difamilast will include not only information that subcutaneously administered difamilast in rats was transferred into milk but also cautionary statement for lactating women that whether lactation is continued or discontinued should be considered in view of therapeutic benefits.

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14) Quinidine was used as a substrate of P-gp in the investigation.
15) Prazosin was used as a substrate of BCRP in the investigation.
16) The following was used as substrates in the investigation: Estradiol-17β-D-glucuronide for OATP1B1 and OATP1B3, aminohippuric acid for OAT1, estrone-3-sulfate for OAT3, and metformin for OCT1, OCT2, MATE1, and MATE2-K.

PMDA accepted the applicant's explanation.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted data on toxicity of difamilast from single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, juvenile animal toxicity, local tolerance, skin sensitization, phototoxicity, immunotoxicity, and impurity toxicity studies.

In the control group, white petrolatum (negative control) or ointment base (base control) was used for percutaneous administration, and corn oil was used for subcutaneous administration.

5.1 Single-dose toxicity

Single subcutaneous dose toxicity studies in rats and dogs were conducted (Table 8). The approximate lethal dose in rats was >400 mg/kg, the maximum administrable dose, but the concerned dose in dogs was <200 mg/kg for males and 200 to 400 mg/kg for females.

Table 8. Single-dose toxicity

Test system	Route of administration	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	Attached document CTD
Female and male rats (SD)	Subcutaneous	0, 200, and 400	≥200: Salivation (female), low food consumption and body weight 400: Salivation and loose stool (male), perinasal and perioral smudge	>400	4.2.3.1-01
Female and male dogs (beagles)	Subcutaneous	200 and 400	Death: 200 (1 of 1 male), 400 (1 of 1 female) Findings in animals which died: Mass at the administration site, vomiting, salivation, decreased feces, no-feces, decreased locomotor activity, lateral position, decreases in food consumption and body weight, thrombus in the heart, thymus atrophy, dark red maculae on the gastric mucosa, adrenal gland hypertrophy, residual test article in the subcutaneous tissue, dark red maculae at the administration site	<200 (male) 200-400 (female)	4.2.3.1-02

5.2 Repeated-dose toxicity

Repeated percutaneous dose toxicity studies in rats (up to 26 weeks), rabbits (4 weeks), and miniature swine (up to 39 weeks) as well as repeated subcutaneous dose toxicity studies in rats (4 weeks) and dogs (up to 39 weeks) were conducted (Table 9). In the repeated percutaneous dose toxicity studies, decreased food consumption and low body weight attributable to reduced body weight gain were observed in rats, and worsened general condition and death were observed in rabbits. Difamilast, on the other hand, was adequately tolerated in miniature swine. In the repeated subcutaneous dose toxicity studies, effects on food consumption and body weight as well as their secondary effects were observed in rats and dogs. Furthermore, effects on the intestinal tract and mesenteric artery potentially attributable to the inhibitory effect of difamilast against PDE4 were observed in rats, and vomiting was observed in dogs.

The exposure to difamilast (C_{max} [4.63/16.90 ng/mL (males/females)] and AUC_{24h} [92.79/267.0 ng•h/mL (males/females)]) at no observed adverse effect level (NOAEL) (difamilast 0.3%) in the 26-week repeated percutaneous dose toxicity study in rats were 0.27/1.0 (males/females)

and 0.39/1.1 (males/females) times, respectively, the exposure to difamilast (C_{max} [16.9 ng/mL] and AUC_{24h} [237 ng•h/mL]) at the highest clinical dose (difamilast 1%, twice daily). The exposure to difamilast (C_{max} [525.0/362.8 ng/mL (males/females)] and AUC_{24h} [8,444/5,422 ng•h/mL (males/females)]) at the NOAEL (3 mg/kg) in the 39-week repeated subcutaneous dose toxicity study in dogs were 31.1/21.5 (males/females) and 35.6/22.9 (males/females) times, respectively, the exposure to difamilast at the highest clinical dose. The exposure to difamilast (C_{max} [5.04/3.51 ng/mL (males/females)] and AUC_{24h} [90.24/71.32 ng•h/mL (males/females)]) at the NOAEL (3%) in the 39-week repeated percutaneous dose toxicity study in miniature swine were 0.30/0.21 (males/females) and 0.38/0.30 (males/females) times, respectively, the exposure to difamilast at the highest clinical dose. Although a relatively wide safety margin was presented in dogs, safety margins in rats and miniature swine were suggested to be narrow.

Table 9. Repeated-dose toxicity

Test system	Route of administration	Treatment period	Dose	Major findings	NOAEL	Attached document CTD
Female and male rat (SD)	Percutaneous	4 weeks + 4 weeks for recovery	0%,[a] 0%,[b] 0.1%, 0.3%, 1%, and 3% (corresponding to 1.08, 3.27, 11.02, and 33.56 mg/kg/day for males and 1.25, 3.78, 12.74, and 38.56 mg/kg/day for females)	≥0.3: Low body weight (female) ≥1: Low body weight, low food consumption (male) 3: Low food consumption, low inorganic phosphorus and A/G ratio, low glucose value (male), high β-globulin (female), low thymus and spleen weights Reversible[c]	0.3% (male) 0.1% (female)	4.2.3.2-01
Female and male rat (SD)	Percutaneous	13 weeks	0%,[a] 0%,[b] 0.1%, 0.3%, 1%, and 3% (corresponding to 0.31, 0.92, 3.08, and 9.39 mg/kg/day for males and 0.38, 1.13, 3.75, and 11.47 mg/kg/day for females)	3: Low body weight, low thymus weight	1%	4.2.3.2-02
Female and male rat (SD)	Percutaneous	26 weeks	0%,[a] 0%,[b] 0.3%, 1%, and 3% (corresponding to 0.88, 2.95, and 8.99 mg/kg/day for males and 1.07, 3.67, and 11.00 mg/kg/day for females)	≥1: Low body weight	0.3%	4.2.3.2-03

Female and male rat (SD)	Subcutaneous	4 weeks + 4 weeks for recovery	0, 1, 10, and 100 mg/kg/day	Death[d]: 1 (1 of 19 males), 100 (1 of 24 males and 2 of 24 females) ≥10: Low body weight (male); low Hb (female); high neutrophil count (female); prolonged prothrombin time (female); low A/G ratio, albumin concentration, and glucose; high α2 globulin; high β-globulin (female); low thymus weight (male) 100: Low body weight and food consumption; low red blood cell count, Hb, and Ht; high platelet count and neutrophil count; prolonged prothrombin time; prolonged APTT (female); low inorganic phosphorus; high α1-globulin and β-globulin; low thymus and prostate weights; low pituitary gland and seminal vesicle weight (absolute weight only); dilated ileum and cecum (female); red ileal mucosa (female), hypertrophy of ileal wall (female); small thymus and spleen (female); large adrenal gland (female); inflammation starting in tissues around jejunum and ileum (female); mesenteric arteritis (female); inflammation starting tissues around urinary duct (male); stomach erosion (female); decreased zymogen granule in pancreas (female), decreased lymphocytes in mandibular lymph node paracortex (female), karyorrhexis in mesenteric lymph node and thymus (female); splenic white pulp atrophy (male) Reversible	1 mg/kg/day	4.2.3.2-04
Female and male rabbits (NZW)	Percutaneous	4 weeks + 4 weeks for recovery	0%,[a] 0%,[b] 0.1%, 0.3%, 1%, and 3% (corresponding to 0.44, 1.33, 4.55, and 13.99 mg/kg/day for males and 0.46, 1.32, 4.67, and 13.99 mg/kg/day for females)	Death, 1 (1 of 6 females), 3 (1 of 9 males and 1 of 9 females) ≥0.3: Low body weight and food consumption (male) ≥1: Low body weight and food consumption, prolonged prothrombin time (male), high platelet count (male), low A/G ratio (male), high α2-globulin and cholesterol (male), urinary occult blood (male) 3: Low Hb and Ht (female), high white blood cell count (female), low A/G ratio, low albumin (female), high cholesterol, low urine osmolality (male), high adrenal gland weight (male), gray maculae on the liver (female), vacuolation and necrosis of hepatocytes, atrophy of thymus, duodenal erosion (male), acinar cell hypertrophy of the submandibular gland, zygomatic gland, and lacrimal gland (male), hypertrophy of stomach lacunar epithelial cells and fundic gland chief cells (male), lymphocyte infiltration in the kidney, vacuolation of distal tubular epithelium, hypertrophy of adrenal fasciculata cells (male), degeneration and necrosis of cardiomyocytes (female) Reversible	Male, 0.1% Female, 0.3%	4.2.3.2-05
Female and male dog (beagles)	Subcutaneous	4 weeks + 4 weeks for recovery	0, 3, 10, and 30 mg/kg/day	≥10: Vomiting, low food consumption, high neutrophil count and platelet count (male) 30: Little feces and no-feces; mucous feces; emaciation; decreased locomotor activity; salivation (male); decreased body weight; high neutrophil count and platelet count; low inorganic phosphorus; high cholesterol; low thymus weight; small thymus; increased hematopoietic cells in the bone marrow; atrophy of the splenic white pulp (male); erosion of esophageal mucosa and atrophy of esophageal gland (male); atrophy of salivary gland acinus (male); atrophy of hepatocytes and hypertrophy of Kupffer- cells in the liver (male), degeneration of seminiferous tubular epithelial in the testis; decreased lipid	3 mg/kg/day	4.2.3.2-06

				droplets in adrenocortical cells (male); atrophy of the Peyer's patch (female); atrophy of the thymus Reversible		
Female and male dog (beagles)	Subcutaneous	13 weeks	0, 1, 3, and 10 mg/kg/day	≥3: Vomiting, reduced body weight gain, low food consumption (male) 10: Emaciation (male); decreased body weight; low urinary creatinine; low thymus weight; thin heart (female); decreased adipose tissue (male); atrophy of the thymus; atrophy of splenic periarteriolar lymphoid sheath; hypertrophy of adrenal gland zona fasciculata and zona reticularis; atrophy of mesenteric lymph node follicles (male); erosion of the stomach (male); atrophy of hepatocytes (female); atrophy of cardiac fiber (female); atrophy of skeletal muscle fiber (female)	1 mg/kg/day	4.2.3.2-07
Female and male dog (beagles)	Subcutaneous	39 weeks	0, 0.3, 1, and 3 mg/kg/day	No particular findings	3 mg/kg/day	4.2.3.2-08
Female and male miniature swine (Göttingen)	Percutaneous	4 weeks	0%,[a] 0.3%, and 3% (corresponding to 1.0 and 9.9 mg/kg/day for males and 1.0 and 9.6 mg/kg/day for females) Intact skin/damaged skin	No particular findings	3%	4.2.3.2-09
Female and male miniature swine (Göttingen)	Percutaneous	13 weeks	0%,[a] 0%,[b] 0.3%, 1%, and 3% (corresponding to 0.9, 3.1, 9.2 mg/kg/day for males and 0.9, 3.1, and 9.1 mg/kg/day for females)	No particular findings	3%	4.2.3.2-10
Female and male miniature swine (Göttingen)	Percutaneous	39 weeks	0%,[a] 0%,[b] 1%, and 3% (corresponding to 2.7 and 8.1 mg/kg/day for males and 2.8 and 8.3 mg/kg/day for females)	No particular findings	3%	4.2.3.2-11

a) White petrolatum
b) Ointment base
c) No recovery from low body weight in males in the difamilast 3% group
d) For both deaths, the cause was considered to be pulmonary embolism attributable to corn oil used as a vehicle and thus unrelated to difamilast.

5.3 Genotoxicity

For genotoxicity, *in vitro* studies conducted were bacterial reverse mutation assay and mammalian cell forward mutation assay, and the *in vivo* study conducted was rat bone marrow micronucleus assay (Table 10). All the studies presented negative results, leading to a consideration that difamilast is unlikely to induce genotoxicity in a body.

Table 10. Genotoxicity

Type of study		Test system	S9 (treatment)	Concentration (μg/plate or μmol/L) Dose (mg/kg/day)	Test result	Attached document CTD
In vitro	Bacterial reverse mutation assay	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537, and TA102	-	0,[a] 5, 15, 50, 150,[b] 500,[b] 1,500,[b] and 5,000[b] (1st run) 0,[a] 315,[b] 630,[b] 1,260,[b] 2,520,[b] and 5,040[b] (2nd run)	Negative	4.2.3.3.1-01
			+	0,[a] 5, 15, 50, 150, 500, 1,500,[b] and 5,000[b] (1st run) 0,[a] 315, 630, 1260,[b] 2,520,[b] and 5,040[b] (2nd run)		
	Mammalian cell forward mutation assay	Mouse lymphoma cells L5178Y $Tk^{+/-}$	- (3 hours)	0,[a] 20, 30, 70, 100, 200,[b] 300,[b] 700,[b] 1,000[b]	Negative	4.2.3.3.1-02
			+ (3 hours)	0,[a] 1, 3, 10, 30, 70, 100	Negative	
			- (24 hours)	0,[a] 7, 10, 20, 30, 70, 85	Negative	
In vivo	Rat micronucleus assay	Male rats (SD) bone marrow		0, 100, 200, 400 (subcutaneous, 2 days)	Negative	4.2.3.3.2-01

a) Dimethylsulfoxide (DMSO)
b) Deposition of the test article occurred.

5.4 Carcinogenicity

In mice and rats, 104-week percutaneous dose carcinogenicity studies were conducted (Table 11). In mice, mildly high food consumption was observed during the treatment period, and the survival in females in the difamilast 1% group was significantly low. In rats, low food consumption and reduced body weight gain were observed as with repeated-dose toxicity studies, and at end of the treatment period, body weight was lower in the difamilast groups than the control groups. No increased neoplastic lesions attributable to difamilast were observed in either mice or rats, leading to a consideration that difamilast is not carcinogenic.

The exposure to difamilast (C_{max} [95.03/80.83 ng/mL (males/females)] and AUC_{24h} [1,106/867.6 ng•h/mL (males/females)]) at a non-carcinogenic dose (difamilast 3%) in mice were 5.6/4.8 (males/females) and 4.7/3.7 (males/females) times, respectively, the exposure to difamilast (C_{max} [16.9 ng/mL] and AUC_{24h} [237 ng•h/mL]) at the highest clinical dose (difamilast 1%, twice daily). The exposure to difamilast (C_{max} [42.13/115.6 ng/mL (males/females)] and AUC_{24h} [873/2,419 ng•h/mL (males/females)]) at a non-carcinogenic dose (difamilast 3%) in rats were 2.5/6.8 (males/females) and 3.7/10.2 (males/females) times, respectively, the exposure to difamilast at the highest clinical dose.

Table 11. Carcinogenicity

Test system	Route of administration	Treatment period	Major findings							Noncarcinogenic dose (%)	Attached document CTD
Female and male mouse (ICR)	Percutaneous	104 weeks	Major lesion	Sex	Dose (%)					3	4.2.3.4.1-01
					0[a)]	0[b)]	0.3[c)]	1[c)]	3[c)]		
				n	55	55	55	55	55		
			Neoplastic lesion	Male	-	-	-	-	-		
				Female	-	-	-	-	-		
			Nonneoplastic lesion	Male Female	No particular findings						
Female and male rat (SD)	Percutaneous	104 weeks	Major lesion	Sex	Dose (mg/kg)					3	4.2.3.4.1-02
					0[a)]	0[b)]	0.3[d)]	1[d)]	3[d)]		
				n	55	55	55	55	55		
			Neoplastic lesion	Male	-	-	-	-	-		
				Female	-	-	-	-	-		
			Nonneoplastic lesion	Male Female	No particular findings						

a) Untreated control (only shaved)
b) Ointment base (base control)
c) 0.3%, 1%, and 3% doses corresponding to 5.17, 17.21, and 51.79 mg/kg/day for males and 5.66, 19.24, 56.77 mg/kg/day for females.
d) 0.3%, 1%, and 3% doses corresponding to 0.80, 2.68, and 8.20 mg/kg/day for males and 0.98, 3.33, and 10.20 mg/kg/day for females

5.5 Reproductive and developmental toxicity

Studies for fertility and early embryonic development to implantation in rats, embryo-fetal development in rats and rabbits, and effects on pre- and post-natal development including maternal function in rats were conducted (Table 12).

In a study for fertility and early embryonic development to implantation in rats, decreased mating and conception rates were observed. The changes in female animals were reversible after the recovery period. Administration of difamilast only to male animals resulted in decreased mating and conception rates as well as high preimplantation embryonic loss. In these male animals, the sperm count, spermatozoa progressive motility, and spermatozoa morphology abnormality were affected. In a study for embryo-fetal development in rats, not only findings suggestive of developmental delay and teratogenicity but also high postimplantation embryonic loss, low live fetal count, and low fetal body weight were observed.

In a study for fertility and early embryonic development to implantation in rats, the NOAEL for both reproductive performance and early embryonic development in female and male parent animals was 10 mg/kg/day. The exposure to difamilast (C_{max} [418.3/518.6 ng/mL (males/females)] and AUC_{24h} [4,699/7,179 ng•h/mL (males/females)]) at the NOAEL were 24.8/30.7 (males/females) and 19.8/30.3 (males/females) times, respectively, the exposure to difamilast (C_{max} [16.9 ng/mL] and AUC_{24h} [237 ng•h/mL]) at the highest clinical dose (difamilast 1%, twice daily). In the study for embryo-fetal development in rats, the NOAEL for both reproductive performance and embryo-fetal development in female parent animals was 10 mg/kg/day. The exposure to difamilast (C_{max} [518.6 ng/mL] and AUC_{24h} [7,179 ng•h/mL]) at the NOAEL were 30.7 and 30.3 times, respectively, the exposure to difamilast at the highest clinical dose. In the study for embryo-fetal development in rabbits, the NOAEL for both reproductive performance and embryo-fetal development in female parent animals was 1 mg/kg/day. The exposure to difamilast (C_{max} [35 ng/mL] and AUC_{24h} [700.3 ng•h/mL]) at the NOAEL were 2.1 and 3.0 times, respectively, the exposure to difamilast at the highest clinical dose. In the study for effects on pre- and post-natal development including maternal function in rats, the NOAEL for both reproductive performance in female parent animals and offspring was 3 mg/kg/day. The exposure to

difamilast (C_{max} [149.8 ng/mL] and AUC_{24h} [3,002 ng•h/mL]) at the NOAEL were 8.9 and 12.7 times, respectively, the exposure to difamilast at the highest clinical dose.

Table 12. Reproductive and developmental toxicity

Type of study	Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Fertility and early embryonic development to implantation	Female and male rats (SD)	Subcutaneous	Males, from 2 weeks before mating to necropsy Females, from 2 weeks before mating to Gestation Day 7	0, 1, 10, 100	Parent animals (male): Death, 100 (3 of 20 animals) ≥10: Reduced body weight gain, low food consumption 100: Transiently decreased body weight; decreased locomotor activity; hypothermia; diarrhea; wound; atrophy of the thymus; dark red maculae on glandular stomach mucosa; atrophy of the epididymis, seminal vesicle, and prostate; low sperm count; decreased spermatozoa progressive motility; high spermatozoa morphology abnormality; decreased mating and conception rates Parent animals (female): Death, 100 (4 of 20 animals) 100: Reduced body weight gain, transiently decreased body weight, low food consumption, decreased locomotor activity, hypothermia, abdominal distention, soiled fur, diarrhea, atrophy of the thymus, dark red maculae on glandular stomach mucosa, dilated gastrointestinal tract, irregular estrous cycle, low mating and conception rates (reversible after recovery) Early embryo: 100: High preimplantation embryo loss after administration only to males	Parent animals (male) General toxicity: 1 Reproductive performance: 10 Parent animals (female) General toxicity: 10 Reproductive performance: 10 Early embryonic development: 10	4.2.3.5.1-01
Embryo-fetal development	Female rat (SD)	Subcutaneous	Gestation Day 7 to Gestation Day 17	0, 1, 10, 100	Parent animals: ≥10: Reduced body weight gain, transiently decreased body weight, low food consumption 100: Decreased locomotor activity, vaginal hemorrhage, soiled fur, diarrhea, dark red maculae on glandular stomach mucosa Fetuses: 100: High postimplantation embryonic loss, low live fetal count, low fetal body weight, delayed ossification of sternal segment and metacarpal bone, ventricular membranous septal defect	Parent animals (general toxicity): 1 Parent animals (reproductive performance): 10 Embryo-fetal development: 10	4.2.3.5.2-01

	Female rabbits (NZW)	Subcutaneous	Gestation Day 6 to Gestation Day 18	0, 0.1, 0.3, 1, 3	Parent animals: ≥1: Reduced body weight gain, low food consumption, decreased feces 3: Abortion, transiently decreased body weight Fetuses: 3: Extra lumbar vertebra, extra full rib	Parent animals (general toxicity): 0.3 Parent animals (reproductive performance): 1 Embryo-fetal development: 1	4.2.3.5.2-02
Effects on pre- and post-natal development including maternal function	Female rat (SD)	Subcutaneous	Maternal animals, Gestation Day 7 to Lactation Day 20	0, 0.1, 0.3, 3	Parent animals: 3: Reduced body weight gain, low food consumption F1 offspring: No particular findings	Parent animals (general toxicity): 0.3 Parent animals (reproductive performance): 3 F1 offspring development: 3	4.2.3.5.3-01

5.6 Juvenile animal studies

An 8-week repeated percutaneous dose study in juvenile rats and 10-week repeated subcutaneous dose study in neonatal rats were conducted (Table 13). The findings in these studies were not largely different from those observed in adult animals in terms of nature or severity. The toxicity profile in juvenile animals is considered similar to that in mature animals.

Table 13. Juvenile animal studies

Test system	Route of administration	Treatment period	Dose	Major findings	NOAEL	Attached document CTD
Female and male rat (SD) 25 days of age	Percutaneous	8 weeks + 4 weeks for recovery	0%,[a] 0%,[b] 0.3%, 1%, 3% (corresponding to 3.76, 12.56, and 38.52 mg/kg/day for males and 4.23, 14.32, and 43.83 mg/kg/day for females)	3: Low food consumption (female), decreased grip strength (female), low thymus and spleen weights (female) ≥1: Low body weight (female) Reversible	Male, 3% Female, 0.3%	4.2.3.5.4-01
Female and male rats (SD) 4 days of age	Subcutaneous	10 weeks + 4 weeks for recovery	0, 1, 3, and 10 mg/kg/day	10: Low food consumption, low brain weight (absolute weight),[c] reduced body weight gain (male) ≥3: Reduced body weight gain (female) Reversible[d]	Not calculated	4.2.3.5.4-02

a) Vehicle control (white petrolatum)
b) Vehicle control (base control)
c) It is considered attributable to low body weight, and no relevant findings were observed in central nervous system functions or brain, morphologically or histopathologically.
d) Low brain weight in males remained.

5.7 Local tolerance

Primary skin irritation study in rabbits, primary skin irritation study using the product stored under stress condition, and primary eye irritation study in rabbits were conducted (Table 14). Skin irritation potential of difamilast was also evaluated in repeated percutaneous dose toxicity studies, and there are no findings suggestive of definite irritation.

Table 14. Local tolerance

Test system	Application site	Testing method	Assessment	Attached document CTD
Female rabbits (NZW)	Skin	Occlusive application of difamilast 0%,[a] 0%,[b] 0.1%, 0.3%, 1%, and 3% ointment to intact/damaged skin for 24 hours	Weak irritant (primary irritation index, 0.5)	4.2.3.6-01
	Skin	Occlusive application of difamilast 0%,[b] 0.1%, 0.3%, 1%, and 3% ointment (products stored under stress condition [40°C and 75% RH for 6 months]) to intact/damaged skin for 24 hours	Weak irritant (primary irritation index, 0.5)	4.2.3.6-02
	Eye	Administration of 0.1 mL of difamilast 0%,[b] 0.1%, 0.3%, 1%, and 3% ointment into the conjunctival sac	No primary eye irritation potential	4.2.3.6-03

a) Vehicle control (white petrolatum)
b) Ointment base (base control)

5.8 Other toxicity studies

5.8.1 Skin sensitization

A maximization test in guinea pigs was performed (Table 15). The result was negative.

Table 15. Skin sensitization

Type of study	Test system	Testing method	Major findings	Attached document CTD
Maximization method	Male guinea pigs (Hartley)	Intradermal and percutaneous administration of difamilast 0%,[a] 0%,[b] 0.1%, 0.3%, 1%, and 3% ointment for sensitization followed by application of white petrolatum or difamilast to the skin for 24 hours for induction	None No sensitization potential was indicated.	4.2.3.6-04

a) Vehicle control (white petrolatum)
b) Ointment base (base control)

5.8.2 Phototoxicity

Bacterial photo-reverse mutation assay, phototoxicity assay in BALB/3T3 cells, phototoxicity study in guinea pig, and skin photosensitization study in guinea pig were conducted (Table 16). No findings suggestive of phototoxicity of difamilast were noted in any study.

Table 16. Phototoxicity

Type of study	Test system	Testing method	Result	Attached document CTD
Photo-reverse mutation	Ames	In difamilast at 0 to 5,000 μg/plate, irradiation of simulated sunlight at the UVA of 4.8 to 5.1 J/cm^2 was performed for TA102 strain and at the UVA of 0.8 to 0.85 J/cm^2 for the other strains.	Negative	4.2.3.6-05
In vitro phototoxicity	3T3 NRU method	Cells were treated with difamilast at 0 to 200 μg/mL for 1 hour and exposed to simulated sunlight at the UVA of 5 J/cm^2.	Negative	4.2.3.6-06
In vivo phototoxicity	Male guinea pig (Hartley)	A skin test site was topically treated with difamilast 0%,[a] 0%,[b] 0.1%, 0.3%, 1%, and 3% ointment for 30 minutes and then exposed to simulated sunlight at the UVA of 10 J/cm^2.	Negative	4.2.3.6-07
Skin photosensitization	Male guinea pig (Hartley)	A skin test site was topically treated with difamilast 0%,[a] 0%,[b] 0.1%, 0.3%, 1%, and 3% ointment and then subjected to photosensitization, and another skin test site was topically treated with white petrolatum or difamilast and then subjected to photoinduction. For both photosensitization and photoinduction, the test site was exposed to simulated sunlight at the UVA of 10 J/cm^2.	Negative	4.2.3.6-08

a) Vehicle control (white petrolatum)
b) Ointment base (base control)

5.8.3 Immunotoxicity

Immunotoxicity of difamilast was evaluated in rats. Difamilast was shown to have no effect on production of antibodies against T-cell dependent antigen (Table 17).

Table 17. Immunotoxicity

Type of study	Test system	Testing method	Result	Attached document CTD
In vivo immunotoxicity	Female and male rats (SD) Plaque-forming cell (PFC) assay	After subcutaneous administration of difamilast 0, 1, 3, and 10 mg/kg/day for 4 weeks, sheep red blood cells were intravenously administered, and 4 days later the animals were sacrificed. Using isolated spleen cells, PFC response was evaluated.	Negative	4.2.3.7.2-01

5.8.4 Toxicity of impurities

Impurities of MAP-15487, MAP-15499, and OPA-15577 were found in the drug product at amounts exceeding the qualification threshold defined in "Guideline on Impurities in New Drug Products" (PFSB/ELD Notification No. 0703004 dated July 3, 2006) (ICH Q3B(R2) Guideline). Genotoxicity of difamilast spiked with these impurities was evaluated. The evaluation for 2-ethoxybenzamide (ethenzamide) was conducted on the basis of literature information. In the 13-week subcutaneous dose study in dogs and 13-week percutaneous dose study in miniature swine, the drug substance spiked with MAP-15487, MAP-15499, and OPA-15577 was used, but neither development nor aggravation of toxicity potentially related to the impurities was observed. Ethenzamide was shown to be carcinogenic but non-mutagenic with the adequate safety margin, raising no problems.

Table 18. Toxicity of impurities

Impurities	Type of study	Dose	Study result	Attached document CTD
Drug substance spiked with MAP-15487, MAP-15499, and OPA-15577	Ames test	0-5,000 µg/plate	Negative	4.2.3.7.6-01
	Rat bone marrow micronucleus assay	0, 100, 200, and 400 mg/kg/day	Negative	4.2.3.7.6-02
Ethenzamide	Ames test	0-10,000 µg/plate	Negative	4.3-12
	Mammalian cell chromosomal aberration assay	0.6 mg/mL	Positive	4.3-13
	Mouse carcinogenicity assay	Dietary administration at 0%, 0.4%, and 1.2%	Increased occurrence of hepatocellular tumor in males in the 1.2% group	4.3-14

5.R Outline of the review conducted by PMDA

Findings related to difamilast included gastrointestinal symptoms, low food consumption, and low body weight, which were consequences of PDE4 inhibition, its pharmacological effect, and findings attributable to worsened nutritional status and stress, which were considered as the secondary consequences. In studies for reproductive and developmental toxicity, findings suggestive of teratogenicity and embryo-fetal lethality as well as decreased mating and conception rates were observed. Difamilast tested negative for genotoxicity, carcinogenicity, local tolerance, skin sensitization, phototoxicity, and immunotoxicity. The toxicity profile in juvenile animals is considered similar to that in mature animals.

Based on the submitted data and review in the following sections, PMDA concluded that the applicant's explanation about toxicity of difamilast is acceptable.

5.R.1 Safety margin of difamilast

In repeated-dose toxicity studies of difamilast, the exposure to difamilast at the NOAEL was comparable to or lower than that at the highest clinical dose (difamilast 1%, twice daily), and gastrointestinal symptoms, decreased food consumption, and decreased body weight gain were observed as findings representative of the toxicity in animals considered attributable to the inhibitory effect of difamilast against PDE4. Concerning these results, PMDA asked the applicant to explain a potential of occurrence of these findings in clinical use.

The applicant's explanation:

The exposure (AUC_{24h}) to difamilast at the lowest observed adverse effect level in the repeated-dose toxicity studies such as the 26-week percutaneous dose study in rats and 4-week percutaneous dose study in rabbits was 3.0 to 3.2 and 2.7 to 8.5 times, respectively, the exposure at the highest clinical dose, indicating a substantial safety margin. The finding was limited to reduced body weight gain without structural changes. Adverse events classified as gastrointestinal disorders occurred in clinical studies, but for any of the events, a relationship to difamilast was ruled out, and no adverse events related to body weight changes occurred. The applicant therefore considers it unlikely for findings similar to ones in the repeated-dose toxicity studies to occur in clinical use of difamilast.

PMDA's view:

The safety margin of difamilast is not adequately wide, but gastrointestinal symptoms attributable to difamilast and its effects on body weight would not have clinically relevant problems at present in view of adverse events classified as gastrointestinal disorders and adverse events related to body weight changes that occurred in the clinical studies.

5.R.2 Use of difamilast in women of childbearing potential, pregnant women, or women who may possibly be pregnant

The applicant's explanation about use of difamilast in women of childbearing potential, pregnant women, or women who may possibly be pregnant:

- Use in women of childbearing potential

In the study for fertility and early embryonic development to implantation in rats, irregular estrous cycle, decreased mating and conception rates, and high preimplantation embryonic loss were observed in female animals. The NOAEL for both reproductive performance and early embryonic development in parent animals was 10 mg/kg/day. The exposure to difamilast (C_{max} and AUC_{24h}) at the NOAEL were 30.7 and 30.3 times, respectively, the exposure to difamilast at the highest clinical dose (difamilast 1%, twice daily). The safety concerns about developmental toxicity in humans are considered low. To ensure safe use of difamilast thoroughly, however, the package insert should include a cautionary statement that women of childbearing potential should use appropriate contraception during the treatment with difamilast and a certain post-treatment period.

- Use in pregnant women or women who may possibly be pregnant

In the study for embryo-fetal development in rats, findings suggestive of developmental delay and teratogenicity (ventricular septal defect) were observed, but the NOAEL for reproductive performance and embryo-fetal development in female parent animals was 10 mg/kg/day. The exposure to difamilast

(C_{max} and AUC_{24h}) at the NOAEL were 30.7 and 30.3 times, respectively, the exposure to difamilast at the highest clinical dose. The safety concerns about pre-natal development toxicity are considered low. To ensure safe use of difamilast thoroughly, however, the package insert should include a cautionary statement that difamilast is not recommended for pregnant women or women who may possibly be pregnant.

PMDA accepted the applicant's explanation about cautionary statements for use in women of childbearing potential, pregnant women, or women who may possibly be pregnant.

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 difamilast in plasma and urinary were determined by LC/MS/MS. The lower limit of quantification for unchanged difamilast concentrations was 0.05 ng/mL for plasma specimens and 0.20 ng/mL for urinary specimens.

6.2 Clinical pharmacology

6.2.1 Phase I study (CTD 5.3.3.1-01, Study 271-14-001, January to February 2015)

A randomized, single-blind, placebo-controlled, parallel-group study was conducted to assess the pharmacokinetics and safety of difamilast in healthy Japanese adults (target sample size, 32 subjects [8 per group]) after single and multiple percutaneous administrations.

In this study, 5 g of placebo or difamilast 0.3%, 1%, or 3% ointment was topically administered as a single dose and twice daily for 2 weeks. The topically administered ointment was removed at 12 hours post-dose.

All of the 24 patients who received difamilast were included in the pharmacokinetic analysis population. Tables 19 and 20 show plasma pharmacokinetic parameters of unchanged difamilast after single and multiple administrations.

C_{max} and $AUC_{0-\infty}$after single administration and C_{max} and AUC_{0-12h} after multiple administrations all increased with the increasing dose but the increase was less than dose-proportional; the exposure was not dose-proportional. Urinary concentrations of unchanged difamilast were less than the lower limit of quantification (0.20 ng/mL).

Table 19. Plasma pharmacokinetic parameters of unchanged difamilast after a single percutaneous dose of difamilast

Dose of difamilast	n	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0\text{-}12h}$ (ng•h/mL)	$t_{1/2}$ (h)
0.3%	8	0.508 ± 0.304	8.0 (3.0, 16.0)	3.74 ± 2.32	-
1%	8	0.838 ± 0.531	9.0 (4.0, 24.0)	6.42 ± 4.86	14.4 ± 4.9[b]
3%	8	1.61 ± 0.835	16.0 (3.0, 24.0)	11.2 ± 6.24	17.5 ± 5.7[c]

Mean ± SD; -, Not calculated
a) Median (minimum, maximum)
b) n = 4
c) n = 3

Table 20. Plasma pharmacokinetic parameters of unchanged difamilast after multiple percutaneous administration of difamilast

Dose of difamilast	Sampling timepoint	n	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0\text{-}12h}$ (ng•h/mL)	$t_{1/2}$ (h)
0.3%	Day 17	8	0.506 ± 0.348	4.1 (0.0, 16.0)	4.65 ± 3.07	19.3 ± 7.5[b]
1%	Day 17	8	0.795 ± 0.208	3.6 (0.0, 4.1)	7.84 ± 1.78	19.7 ± 5.8
3%	Day 17	8	1.65 ± 0.462	6.1 (0.0, 10.0)	16.6 ± 4.99	21.0 ± 6.5

Mean ± SD
a) Median (minimum, maximum)
b) n = 3

6.2.2 Phase II study in adults (adult dose-finding study) (CTD 5.3.5.1-01, Study 271-15-001, September 2016 to June 2017)

A multi-center, randomized, double-blind, placebo-controlled, parallel-group study was conducted to evaluate the efficacy, safety, and dose of difamilast in patients with atopic dermatitis aged ≥15 and ≤70 years (target sample size, 180 subjects [60 per group]).

Placebo or difamilast 0.3% or 1% ointment was topically applied twice daily for 8 weeks [for the outline of the study and results on the efficacy and safety, see Section 7.1.1].

For the pharmacokinetics, Table 21 shows plasma trough concentrations (number of patients detected/number of patients tested at each timepoint) at Weeks 1, 4, and 8.

Table 21. Plasma concentrations of unchanged difamilast (ng/mL) after multiple percutaneous administration of difamilast

Dose of difamilast		Week 1	Week 4	Week 8
0.3%	Proportion of patients detected (number of patients detected/number of patients tested)	96.9% (62/64)	90.6% (48/53)	84.8% (39/46)
	Mean ± SD[a]	1.68 ± 1.73	1.95 ± 2.55	1.72 ± 1.75
1%	Proportion of patients detected (number of patients detected/number of patients tested)	98.4% (63/64)	98.2% (56/57)	98.1% (52/53)
	Mean ± SD[a]	4.89 ± 4.67	6.07 ± 6.02	6.13 ± 9.27

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

6.2.3 Pediatric phase II study (pediatric dose-finding study) (CTD 5.3.5.1-02, Study 271-102-00002, January to June 2017)

A multi-center, randomized, double-blind, placebo-controlled, parallel-group study was conducted to evaluate the efficacy, safety, and dose of difamilast in patients with atopic dermatitis aged ≥2 and ≤14 years (target sample size, 60 subjects [20 per group]).

Placebo or difamilast 0.3% or 1% ointment was topically applied twice daily for 4 weeks [for the outline of the study and results on the efficacy and safety, see Section 7.1.2].

For the pharmacokinetics, Table 22 shows plasma trough concentrations (number of patients detected/number of patients tested at each timepoint) at Weeks 1 and 4.

Table 22. Plasma concentrations of unchanged difamilast (ng/mL) after multiple percutaneous administration of difamilast

Dose of difamilast		Week 1	Week 4
0.3%	Proportion of patients detected (number of patients detected/number of patients tested)	100% (24/24)	95.5% (21/22)
	Mean ± SD[a)]	1.08 ± 0.95	0.99 ± 1.12
1%	Proportion of patients detected (number of patients detected/number of patients tested)	96.0% (24/25)	100% (24/24)
	Mean ± SD[a)]	2.88 ± 2.54	2.31 ± 1.86

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

6.R Outline of the review conducted by PMDA

6.R.1 Pharmacokinetics of difamilast after percutaneous administration

The applicant's explanation about pharmacokinetics of difamilast after percutaneous administration:
Tables 21 and 22 show plasma concentrations of unchanged difamilast in patients in whom plasma difamilast was detected in at each timepoint in adult and pediatric phase II studies. Plasma concentrations of difamilast tended to be slightly higher in adult patients than in pediatric patients but there were no clinically relevant differences in safety profile between pediatric and adult patients [see Section 7.R.2.1].

Because percutaneous absorption of difamilast tended to be higher in corneum-removed skin than in intact skin [see Section 4.1.1], plasma difamilast concentrations corrected for the dose applied in relation to severity of atopic dermatitis at baseline (Investigator's global assessment [IGA] Score of 2 or 3) were investigated. The plasma difamilast concentrations corrected for the dose applied in adult patients were similar irrespective of the IGA score (Table 23) but those in pediatric patients tended to be higher in the subgroup with a higher IGA score (Table 24).

For incidences of adverse events by the IGA score in the adult patient population, the incidence of all adverse events in the difamilast 1% group tended to be higher in the IGA score 3 subgroup than in the score 2 subgroup but was similar to that in the placebo group (Table 53). In the pediatric patient population, the incidence of all adverse events in the difamilast 1% group tended to be slightly higher in the IGA score 2 subgroup than in the score 3 subgroup and tended to be higher than that in the score 3 subgroup in the placebo group, but the incidences in the IGA score 2 and 3 subgroups in the difamilast 0.3% groups and in the score 2 subgroup in the difamilast 1% group were similar to that in the placebo group (Table 54).

Based on the above, the increased systemic exposure to difamilast associated with severe atopic dermatitis is considered unlikely to affect the safety of difamilast.

Table 23. Plasma concentrations of unchanged difamilast corrected for the dose applied of difamilast after multiple administrations (ng/mL) (adult phase II study)

Dose of difamilast	Baseline IGA score		Week 1	Week 4	Week 8
0.3%	Overall	Proportion of patients detected (number of patients detected/number of patients tested)	96.9% (62/64)	90.6% (48/53)	84.8% (39/46)
		Mean ± SD[a)]	0.11 ± 0.09	0.12 ± 0.12	0.10 ± 0.10
	2	Proportion of patients detected (number of patients detected/number of patients tested)	100% (19/19)	83.3% (15/18)	81.3% (13/16)
		Mean ± SD[a)]	0.09 ± 0.09	0.10 ± 0.09	0.10 ± 0.06
	3	Proportion of patients detected (number of patients detected/number of patients tested)	95.6% (43/45)	94.3% (33/35)	86.7% (26/30)
		Mean ± SD[a)]	0.13 ± 0.09	0.13 ± 0.13	0.11 ± 0.12
1%	Overall	Proportion of patients detected (number of patients detected/number of patients tested)	98.4% (63/64)	98.2% (56/57)	98.1% (52/53)
		Mean ± SD[a)]	0.11 ± 0.09	0.14 ± 0.14	0.14 ± 0.24
	2	Proportion of patients detected (number of patients detected/number of patients tested)	94.7% (18/19)	94.4% (17/18)	94.1% (16/17)
		Mean ± SD[a)]	0.11 ± 0.07	0.17 ± 0.14	0.17 ± 0.34
	3	Proportion of patients detected (number of patients detected/number of patients tested)	100% (45/45)	100% (39/39)	100% (36/36)
		Mean ± SD[a)]	0.11 ± 0.10	0.13 ± 0.13	0.13 ± 0.18

a) Mean ± SD of plasma concentrations of unchanged difamilast corrected for the dose applied in patients in whom plasma difamilast was detected

Table 24. Plasma concentrations of unchanged difamilast corrected for the dose applied of difamilast after multiple administrations (ng/mL) (pediatric phase II study)

Dose of difamilast	Baseline IGA score		Week 1	Week 4
0.3%	Overall	Proportion of patients detected (number of patients detected/number of patients tested)	100% (24/24)	95.5% (21/22)
		Mean ± SD[a)]	0.19 ± 0.18	0.15 ± 0.11
	2	Proportion of patients detected (number of patients detected/number of patients tested)	100% (4/4)	100% (4/4)
		Mean ± SD[a)]	0.11 ± 0.07	0.13 ± 0.15
	3	Proportion of patients detected (number of patients detected/number of patients tested)	100% (20/20)	94.4% (17/18)
		Mean ± SD[a)]	0.20 ± 0.19	0.16 ± 0.10
1%	Overall	Proportion of patients detected (number of patients detected/number of patients tested)	96.0% (24/25)	100% (24/24)
		Mean ± SD[a)]	0.21 ± 0.16	0.19 ± 0.16
	2	Proportion of patients detected (number of patients detected/number of patients tested)	100% (5/5)	100% (4/4)
		Mean ± SD[a)]	0.11 ± 0.05	0.11 ± 0.13
	3	Proportion of patients detected (number of patients detected/number of patients tested)	95.0% (19/20)	100% (20/20)
		Mean ± SD[a)]	0.24 ± 0.17	0.20 ± 0.17

a) Mean ± SD of plasma concentrations of unchanged difamilast corrected for the dose applied in patients in whom plasma difamilast was detected

PMDA's view:

The systemic exposure increased with increasing severity of atopic dermatitis after twice-daily percutaneous administration of difamilast 0.3% or 1% in the phase II study, however, the systemic exposure to difamilast is unlikely to affect the safety within the dosage regimens studied.

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 5 Japanese clinical studies listed in Table 25.

Table 25. Outline of clinical studies for efficacy and safety

Phase	Study number	Population	Study design	Number of patients
Phase II Adult dose-finding study	271-15-001	Patients with AD aged ≥15 years	Double-blind, placebo-controlled, parallel-group	66 patients for placebo 67 patients for difamilast 0.3% 67 patients for difamilast 1%
Phase II Pediatric dose-finding study	271-102-00002	Patients with AD aged ≥2 and ≤14 years	Double-blind, placebo-controlled, parallel-group	24 patients for placebo 24 patients for difamilast 0.3% 25 patients for difamilast 1%
Phase III Adult confirmatory study	271-102-00007	Patients with AD aged ≥15 years	Double-blind, placebo-controlled, parallel-group	182 patients for placebo 182 patients for difamilast 1%
Phase III Pediatric confirmatory study	271-102-00008	Patients with AD aged ≥2 and ≤14 years	Double-blind, placebo-controlled, parallel-group	83 patients for placebo 83 patients for difamilast 0.3% 85 patients for difamilast 1%
Phase III Long-term treatment study	271-102-00006	Patients with AD aged ≥2 years	Open-label, uncontrolled	200 pediatric patients (aged 2-14 years) 144 patients starting treatment with difamilast 0.3% 56 patients starting treatment with difamilast 1% 166 adult patients (aged ≥15 years)

Table 26 shows the IGA scoring system used for efficacy evaluation in the submitted clinical studies. Table 27 shows the Eczema area and severity index (EASI) scoring system used for overall evaluation of skin eruption.

Table 26. IGA scoring system

Score	Severity	Symptoms
0	No symptoms	No inflammatory signs of atopic dermatitis
1	Almost no symptoms	Barely perceptible erythema or barely perceptible infiltration/papulation
2	Mild	Mild erythema or mild infiltration/papulation
3	Moderate	Moderate erythema or moderate infiltration/papulation
4	Severe or very severe	Severe erythema, severe infiltration/papulation, or severe crusting infiltration/papulation with oozing

* IGA responder rate: Proportion of patients who achieved an IGA score of 0 or 1 and improved the severity by ≥2 grades

Table 27. EASI scoring system

EASI score =A + B + C + D Head/neck: A = (erythema score + edema/papulation score + excoriation score + lichenification score) × region score × 0.1 (× 0.2 for patients aged 2-7 years) Upper extremities: B = (erythema score + edema/papulation score + excoriation score +lichenification score) × region score × 0.2 Trunk: C = (erythema score + edema/papulation score + excoriation score + lichenification score) × region score × 0.3 Lower extremities: D = (erythema score + edema/papulation score + excoriation score + lichenification score) × region score × 0.4 (× 0.3 for patients aged 2-7 years)	
Skin symptom score	Severity of erythema, edema/papulation, excoriation, and lichenification of skin eruption is rated on the 7-grade scale shown below: 0, none; 0.5, slight; 1, mild; 1.5, mild to moderate; 2, moderate; 2.5, severe; 3, very severe
Region score	Percentage of area of involvement with inflammatory skin eruption except dry skin is rated on a scale of 0 to 6, shown below: 0, no eruption; 1, 1%-9%; 2, 10%-29%; 3, 30%-49%; 4, 50%-69%; 5, 70%-89%; 6, 90%-100%

* EASI75 responder rate: Proportion of subjects who improved the EASI score from baseline by ≥75%.

7.1 Phase II studies

7.1.1 Adult phase II study (CTD 5.3.5.1-01, Study 271-15-001, September 2016 to June 2017)

A multi-center, randomized, double-blind, placebo-controlled, parallel-group study was conducted to evaluate the efficacy, safety, and dose of difamilast in patients with atopic dermatitis aged ≥15 and ≤70 years (Table 28) (target sample size, 180 subjects,[17] 60 each in the placebo, difamilast 0.3%, and difamilast 1% groups) at 14 study sites in Japan.

Table 28. Major inclusion and exclusion criteria

Major inclusion criteria
• Patients aged ≥15 and ≤70 years.
• Patients who meet Hanifin and Rajka's diagnostic criteria for atopic dermatitis
• Patients with history of atopic dermatitis for ≥3 years
• Patients with an IGA score of 2 or 3
• Patients with ≥5% and ≤40% of body surface area involved
Major exclusion criteria
• Patients who are unable to stop topical corticosteroids, immunosuppressive drugs, retinoids, or antihistamines 7 days before baseline examination and thereafter
• Patients who are unable to stop systemic antihistamines, cromolyn sodium, tranilast, or suplatast tosilate 7 days before baseline examination and thereafter
• Patients who are unable to stop systemic corticosteroids, immunosuppressive drugs, antimetabolites, retinoids, or biological drugs 28 days before baseline examination and thereafter
• Patients who are unable to stop phototherapy 28 days before baseline examination and thereafter

An appropriate amount[18] of placebo or difamilast 0.3% or 1% ointment was topically applied twice daily for 8 weeks.

All of the randomized 200 patients (66 in the placebo group, 67 in the difamilast 0.3% group, and 67 in the 1% group) received the study drug and were included in the safety analysis population and full analysis set (FAS). The FAS was subjected to the primary efficacy analysis. A total of 55 patients (20 in the placebo group, 21 in the difamilast 0.3% group, and 14 in the 1% group) discontinued the study treatment because of “adverse events” in 37 patients (15 in the placebo group, 15 in the difamilast 0.3% group, and 7 in the 1% group), “request from subject” in 11 patients (4 in the placebo group, 3 in the difamilast 0.3% group, and 4 in the 1% group), “physician’s decision” in 4 patients (2 each in the difamilast 0.3% and 1% groups), “increased affected area (≥40% of the body surface area)” in 2 patients (1 each in the placebo and difamilast 1% groups), and “protocol deviation” in 1 patient (1 in the difamilast 0.3% group).

Table 29 shows results on the IGA responder rate at Week 4 (proportion of subjects who achieved the IGA score of 0 or 1 and improved the severity by ≥2 grades), the primary endpoint, demonstrating superiority of difamilast 1% over placebo (P = 0.03, Cochran-Mantel-Haenszel test, two-sided significance level of 5%).

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[17] In a foreign phase II study, the IGA responder rate was 20.93% in the difamilast 1% group and 2.70% in the placebo group. On the assumption that similar results are obtained, the sample size including 54 patients per group was estimated to provide the study with a power of >80% at a two-sided significance level of 5%. With discontinuation and dropout taken into account, the sample size including 60 patients per group was established.

[18] Topical amount per application (g) = amount per 1% of the body surface area (see the table below) (g) × percentage of the area topically treated (%)

Body surface area of the subject (m^2)	<1.0	≥1.0, <1.3	≥1.3, <1.6	≥1.6, <1.9	≥1.9
Amount per 1% of the body surface area (g)	0.1	0.15	0.2	0.25	0.3

Table 29. IGA responder rate at Week 4 (FAS)

	Placebo (n = 66)	Difamilast 0.3% (n = 67)	Difamilast 1% (n = 67)
IGA responder rate (number of responders) [95% CI] (%)	9.09 (n = 6) [3.41, 18.74]	14.93 (n = 10) [7.40, 25.74]	22.39 (n = 15) [13.11, 34.22]
Difference from placebo [95% CI] (%)		5.78 [-5.03, 16.59]	13.22 [1.36, 25.07]
P value[a)]		0.30	0.03

A missing IGA score was handled as non-improvement.

a) Cochran-Mantel-Haenszel test with stratification by baseline IGA (2 or 3), a two-sided significance level of 5%, tested based on the dose in a descending order.

Adverse events occurred in 40.9% (27 of 66) of patients in the placebo group, 46.3% (31 of 67) of patients in the difamilast 0.3% group, and 29.9% (20 of 67) of patients in the 1% group, and adverse drug reactions occurred in 10.6% (7 of 66) of patients in the placebo group, 11.9% (8 of 67) of patients in the difamilast 0.3% group, and 7.5% (5 of 67) of patients in the 1% group. Tables 30 and 31 show adverse events and adverse drug reactions reported by ≥2 patients in any group.

Table 30. Adverse events reported by ≥2 patients in any group

Adverse event	Placebo (n = 66)	Difamilast 0.3% (n = 67)	Difamilast 1% (n = 67)
All adverse events	40.9 (27)	46.3 (31)	29.9 (20)
Atopic dermatitis	18.2 (12)	16.4 (11)	9.0 (6)
Viral upper respiratory tract infection	10.6 (7)	10.4 (7)	6.0 (4)
Pruritus	6.1 (4)	7.5 (5)	1.5 (1)
Influenza	0	3.0 (2)	1.5 (1)

Medical dictionary for regulatory activities Japanese version (MedDRA/J) ver.20.0, Incidence (%) (number of subjects with the event)

Table 31. Adverse drug reactions reported by ≥2 patients in any group

Adverse event	Placebo (n = 66)	Difamilast 0.3% (n = 67)	Difamilast 1% (n = 67)
All adverse drug reactions	10.6 (7)	11.9 (8)	7.5 (5)
Atopic dermatitis	9.1 (6)	7.5 (5)	7.5 (5)
Pruritus	0	3.0 (2)	0

MedDRA/J ver.20.0, Incidence (%) (number of subjects with the event)

Neither deaths nor serious adverse events occurred. Adverse events leading to treatment discontinuation occurred in 22.7% (15 of 66) of patients in the placebo group (atopic dermatitis in 12 patients and pruritus in 4 patients [some subjects had multiple events]), 22.4% (15 of 67) of patients in the difamilast 0.3% group (atopic dermatitis in 10 patients, pruritus in 5 patients, and application site pain in 1 patient [some subjects had multiple events]), and 10.4% (7 of 67) of patients in the 1% group (atopic dermatitis in 6 patients and pruritus in 1 patient). Of the adverse events leading to treatment discontinuation, atopic dermatitis in 6 patients in the placebo group, atopic dermatitis in 4 patients, pruritus in 2 patients, and application site pain in 1 patient in the difamilast 0.3% group as well as atopic dermatitis in 5 patients in the difamilast 1% group were assessed as adverse drug reactions. For outcome, all these reactions resolved.

7.1.2 Pediatric phase II study (CTD 5.3.5.1-02, Study 271-102-00002, January to June 2017)

A multi-center, randomized, double-blind, placebo-controlled, parallel-group study was conducted to evaluate the efficacy, safety, and dose of difamilast in patients with atopic dermatitis aged ≥2 and ≤14

years (Table 32) (target sample size, 60 subjects[19] [including ≥8 subjects aged 2-6 years], 20 each in the placebo, difamilast 0.3%, and difamilast 1% groups) at 8 study sites in Japan.

Table 32. Major inclusion and exclusion criteria

Major inclusion criteria • Patients aged ≥2 and ≤14 years • Patients who meet Hanifin and Rajka's diagnostic criteria for atopic dermatitis • Patients with an IGA score of 2 or 3 • Patients with ≥5% and ≤40% of body surface area involved Major exclusion criteria • Patient who are unable to stop topical corticosteroids, immunosuppressive drugs, retinoids, or antihistamines 7 days before baseline examination and thereafter • Patients who are unable to continue systemic antihistamines, cromolyn sodium, tranilast, or suplatast tosilate without changing the regimen 7 days before baseline examination and thereafter • Patients who are unable to stop systemic corticosteroids, immunosuppressive drugs, antimetabolites, retinoids, or biological drugs 28 days before baseline examination and thereafter • Patients who are unable to stop phototherapy 28 days before baseline examination and thereafter

An appropriate amount[20] of difamilast 0.3% or 1% ointment or placebo was topically applied twice daily for 4 weeks.

All of the randomized 73 patients (24 in the placebo group, 24 in the difamilast 0.3% group, and 25 in the 1% group) received the study drug and were included in the efficacy and safety analysis populations. A total of 10 patients (7 in the placebo group, 2 in the difamilast 0.3% group, and 1 in the 1% group) discontinued the study treatment because of "adverse events" in 6 patients (4 in the placebo group and 1 each in the difamilast 0.3% and 1% groups), "request from guardian" in 2 patients (1 each in the placebo and difamilast 0.3% groups), "request from subject" in 1 patient (placebo group), and "lack of efficacy" in 1 patient (placebo group).

As shown in Table 33, the IGA responder rate at Week 4 was higher in both difamilast groups than in the placebo group.

Table 33. IGA responder rate at Week 4 (FAS)

	Placebo (n = 24)	Difamilast 0.3% (n = 24)	Difamilast 1% (n = 25)
IGA responder rate (number of responders) [95% CI][a] (%)	8.33 (n = 2) [1.03, 27.00]	37.5 (n = 9) [18.80, 59.41	40.0 (n = 10) [21.13, 61.33]
Difference from placebo [95% CI][b] (%)		30.39 [8.51, 52.27]	31.95 [9.79, 54.11]

a) Estimated by Clopper-Pearson method
b) Estimated by Mantel-Haenszel method

Adverse events occurred in 50.0% (12 of 24) of patients in the placebo group, 45.8% (11 of 24) of patients in the difamilast 0.3% group, and 56.0% (14 of 25) of patients in the 1% group. Adverse drug reactions occurred in 20.8% (5 of 24) of patients in the placebo group, 4.2% (1 of 24) of patients in the difamilast 0.3% group, and 16.0% (4 of 25) of patients in the 1% group. Tables 34 and 35 show adverse events and adverse drug reactions reported by ≥2 patients in any group.

[19] In view of the nature of the study targeting pediatric patients, the minimum sample size required for adequate exploratory evaluation of the efficacy and safety was determined as a total of 60 including 20 per group.
[20] Topical amount per application (g) = body surface area (m^2) × percentage of the area topically treated (%) × 10 (g/m^2)

Table 34. Adverse events reported by ≥2 patients in any group

Adverse event	Placebo (n = 24)	Difamilast 0.3% (n = 24)	Difamilast 1% (n = 25)
All adverse events	50.0 (12)	45.8 (11)	56.0 (14)
Upper respiratory tract inflammation	8.3 (2)	4.2 (1)	24 (6)
Blood ALP increased	0	0	8.0 (2)
Atopic dermatitis	16.7 (4)	8.3 (2)	4.0 (1)
Influenza	0	8.3 (2)	4.0 (1)
Viral upper respiratory tract infection	8.3 (2)	4.2 (1)	0

MedDRA/J ver.20.0, Incidence (%) (number of subjects with the event)

Table 35. Adverse drug reactions reported by ≥2 patients in any group

Adverse event	Placebo (n = 24)	Difamilast 0.3% (n = 24)	Difamilast 1% (n = 25)
All adverse drug reactions	20.8 (5)	4.2 (1)	16.0 (4)
Blood ALP increased	0	0	8.0 (2)
Atopic dermatitis	12.5 (3)	4.2 (1)	4.0 (1)

MedDRA/J ver.20.0, Incidence (%) (number of subjects with the event)

Neither deaths nor serious adverse events occurred. Adverse events leading to treatment discontinuation occurred in 4 patients in the placebo group (atopic dermatitis in 4 patients), 1 patient in the difamilast 0.3% group (atopic dermatitis), and 1 patient in the 1% group (atopic dermatitis). Of the adverse events leading to treatment discontinuation, atopic dermatitis in 3 patients in the placebo group and atopic dermatitis in 1 patient in the difamilast 1% group were assessed as adverse drug reactions. For outcome, all these reactions resolved except 1 reaction in the placebo group which did not resolve.

7.2 Phase III studies

7.2.1 Adult phase III study (CTD 5.3.5.1-03, Study 271-102-00007, March to December 2019)

A multi-center, randomized, double-blind, placebo-controlled, parallel-group study was conducted to evaluate the efficacy and safety of difamilast in patients with atopic dermatitis aged ≥15 and ≤70 years (Table 36) (target sample size, 340 subjects,[21)] 170 each in the placebo and difamilast 1% groups) at 30 study sites in Japan.

[21)] In the adult phase II study, the IGA responder rate was 22.4% in the difamilast 1% group and 9.1% in the placebo group. On the assumption that similar results are obtained, the sample size including 167 patients per group was estimated to provide the study with a power of >90% at a two-sided significance level of 5%. With discontinuation and dropout taken into account, the sample size including 170 patients per group was established.

Table 36. Major inclusion and exclusion criteria

Major inclusion criteria • Patients aged ≥15 and ≤70 years. • Patients who meet diagnostic criteria for atopic dermatitis established by the Japanese Dermatological Association • Patient with history of atopic dermatitis for ≥3 years • Patients with an IGA score of 2 or 3 • Patients with ≥5% and ≤40% of body surface area involved Major exclusion criteria • Patient who are unable to stop topical Very Strong corticosteroids or stronger ones (except for scalp) 21 days before baseline examination and thereafter • Patients who are unable to stop topical Strong corticosteroids (except for scalp) or topical immunosuppressive drugs, retinoids, antihistamines, or nonsteroidal anti-inflammatory drugs (except for scalp) 7 days before baseline examination and thereafter • Patient who are unable to stop topical Medium or Weak corticosteroids (except for scalp) 4 days before baseline examination and thereafter • Patients who are unable to continue systemic antihistamines, cromolyn sodium, tranilast, or suplatast tosilate without changing the regimen 7 days before baseline examination and thereafter • Patients who are unable to stop systemic corticosteroids, immunosuppressive drugs, antimetabolites, retinoids, or biological drugs 28 days before baseline examination and thereafter • Patients who are unable to stop phototherapy 28 days before baseline examination and thereafter

An appropriate amount[20)] of placebo or difamilast 1% ointment was topically applied twice daily for 4 weeks.

All of the randomized 364 patients (182 each in the placebo and difamilast 1% groups) received the study drug and were included in the safety analysis population and FAS. The FAS was subjected to the primary efficacy analysis. A total of 64 patients (47 in the placebo group and 17 in the difamilast 1% group) discontinued the study treatment because of "request from subject" in 31 patients (22 in the placebo group and 9 in the difamilast 1% group), "adverse events" in 28 patients (21 in the placebo group and 7 in the difamilast 1% group), and "physician's decision" in 5 patients (4 in the placebo group and 1 in the difamilast 1% group).

Table 37 shows results on the IGA responder rate at Week 4, the primary endpoint, demonstrating superiority of difamilast 1% over placebo ($P < 0.0001$, Cochran-Mantel-Haenszel test, two-sided significance level of 5%).

Table 37. IGA responder rate at Week 4

	Placebo (n = 182)	Difamilast 1% (n = 182)
IGA responder rate (number of responders) [95% CI] (%)	12.64 (n = 23) [8.18, 18.36]	38.46 (n = 70) [31.36, 45.95]
Difference between groups (difamilast 1% - placebo) [95% CI] (%)	25.93 [17.46, 34.40]	
P value[a)]	<0.0001	

A missing IGA score was handled as non-improvement.
a) Cochran-Mantel-Haenszel test with stratification by baseline IGA (2 or 3), a two-sided significance level of 5%.

Adverse events occurred in 28.0% (51 of 182) of patients in the placebo group and 17.6% (32 of 182) of patients in the difamilast 1% group, and adverse drug reactions occurred in 8.8% (16 of 182) of patients in the placebo group and 0.5% (1 of 182) of patients in the difamilast 1% group. Table 38 shows adverse events reported by ≥2 patients in either group. The adverse drug reaction reported by ≥2 patients in either group was only atopic dermatitis (6.0% [11 of 182] of patients in the placebo group and 0.5% [1 of 182] of patients in the difamilast 1% group).

Table 38. Adverse events reported by ≥2 patients in any group

Adverse event	Placebo (n = 182)	Difamilast 1% (n = 182)
All adverse events	28.0 (51)	17.6 (32)
Nasopharyngitis	3.8 (7)	4.9 (9)
Atopic dermatitis	12.1 (22)	3.8 (7)
Herpes simplex	1.1 (2)	0.5 (1)
Cellulitis	3.8 (2)	0
Acne	1.6 (3)	0
Folliculitis	1.1 (2)	0

MedDRA/J ver.22.1, Incidence (%) (number of subjects with the event)

Neither deaths nor serious adverse events occurred. Adverse events leading to treatment discontinuation occurred in 11.5% (21 of 182) of patients in the placebo group (atopic dermatitis in 17 patients and hypersensitivity, herpes simplex, herpes virus infection, dermatitis acneiform, dermatitis contact, and skin burning sensation in 1 patient each [some subjects had multiple events]) and 3.8% (7 of 182) of patients in the difamilast 1% group (atopic dermatitis in 7 patients). Of the adverse events leading to treatment discontinuation, atopic dermatitis in 8 patients and hypersensitivity, dermatitis acneiform, dermatitis contact, and skin burning sensation in 1 patient each in the placebo group and atopic dermatitis in 1 patient in the difamilast 1% group were assessed as adverse drug reactions. Outcomes of atopic dermatitis and hypersensitivity in 1 patient each in the placebo group were resolved, while those of the other reactions were did not resolve.

7.2.2 Pediatric phase III study (CTD 5.3.5.1-04, Study 271-102-00008, May to December 2019)

A multi-center, randomized, double-blind, placebo-controlled, parallel-group study was conducted to evaluate the efficacy and safety of difamilast in patients with atopic dermatitis aged ≥2 and ≤14 years (Table 39) (target sample size, 240 subjects,[22)] 80 each in the placebo, difamilast 0.3%, and difamilast 1% groups) at 30 study sites in Japan.

Table 39. Major inclusion and exclusion criteria

Major inclusion criteria
• Patients aged ≥2 and ≤14 years
• Patients who meet diagnostic criteria for atopic dermatitis established by the Japanese Dermatological Association
• Patients with an IGA score of 2 or 3
• Patients with ≥5% and ≤40% of body surface area involved (except for scalp)
Major exclusion criteria
• Patients who are unable to stop topical Very Strong corticosteroids or stronger ones (except for scalp) 21 days before baseline examination and thereafter
• Patients who are unable to stop topical Strong corticosteroids (except for scalp), all topical corticosteroids other than ones for skin, or topical immunosuppressive drugs, retinoids, antihistamines, or nonsteroidal anti-inflammatory drugs (except for scalp) 7 days before baseline examination and thereafter
• Patients who are unable to stop topical Medium or Weak corticosteroids (except for scalp) 4 days before baseline examination and thereafter
• Patients who are unable to continue systemic antihistamines, cromolyn sodium, tranilast, or suplatast tosilate without changing the regimen 7 days before baseline examination and thereafter
• Patients who are unable to stop allergen immunotherapy (desensitization therapy) 3 months before informed consent and thereafter
• Patients who are unable to stop systemic corticosteroids, immunosuppressive drugs, antimetabolites, retinoids, or biological drugs 28 days before baseline examination and thereafter
• Patients who are unable to stop phototherapy 28 days before baseline examination and thereafter

22) On the assumption that the IGA responder rate was 36% in the difamilast 1% group and 12% in the placebo group, the sample size including 72 patients per group was estimated to provide the study with a power of >90% at a two-sided significance level of 5%. In view of exploratory investigation of the age category, the sample size of 240 in total including 80 patients per group was established.

An appropriate amount[20] of difamilast 0.3% or 1% ointment or placebo was topically applied twice daily for 4 weeks.

All of the randomized 251 patients (83 in the placebo group, 83 in the difamilast 0.3% group, 85 in the 1% group) received the study drug and were included in the safety analysis population and FAS. The FAS was subjected to the primary efficacy analysis. A total of 41 patients (25 in the placebo group, 7 in the difamilast 0.3% group, and 9 in the 1% group) discontinued the study treatment because of "request from guardian" in 19 patients (11 in the placebo group, 4 in the difamilast 0.3% group, and 4 in the 1% group), "lack of efficacy" in 10 patients (8 in the placebo group, 1 in the difamilast 0.3% group, and 1 in the 1% group), "adverse events" in 8 patients (5 in the placebo group, 1 in the difamilast 0.3% group, and 2 in the 1% group), "request from subject" in 3 patients (1 in the difamilast 0.3% group and 2 in the 1% group), and physician's decision in 1 patient (placebo group).

Table 40 shows results on the IGA responder rate at Week 4, the primary endpoint, demonstrating superiority of both difamilast 0.3% and 1% over placebo ($P = 0.0005$ for difamilast 0.3%, $P < 0.0001$ for difamilast 1%, Cochran-Mantel-Haenszel test, two-sided significance level of 5%).

Table 40. IGA responder rate at Week 4 (FAS)

	Placebo (n = 83)	Difamilast 0.3% (n = 83)	Difamilast 1% (n = 85)
IGA responder rate (number of responders) [95% CI] (%)	18.07 (n = 15) [10.48, 28.05]	44.58 (n = 37) [33.66, 55.90]	47.06 (n = 40) [36.13, 58.19]
Difference from placebo [95% CI] (%)		24.65 [11.27, 38.04]	28.70 [14.96, 42.45]
P value[a)]		0.0005	<0.0001

A missing IGA score was handled as non-improvement.

a) Cochran-Mantel-Haenszel test with stratification by baseline IGA (2 or 3) and age ("2-6 years" or "7-14 years"), a two-sided significance level of 5%, tested based on the dose in a descending order.

Adverse events occurred in 33.7% (28 of 83) of patients in the placebo group, 32.5% (27 of 83) of patients in the difamilast 0.3% group, and 34.1% (29 of 85) of patients in the 1% group, and adverse drug reactions occurred in 4.8% (4 of 83) of patients in the placebo group, 6.0% (5 of 83) of patients in the difamilast 0.3% group, and 3.5% (3 of 85) of patients in the 1% group. Tables 41 and 42 show adverse events and adverse drug reactions reported by ≥2 patients in any group.

Table 41. Adverse events reported by ≥2 patients in any group

Adverse event	Placebo (n = 83)	Difamilast 0.3% (n = 83)	Difamilast 1% (n = 85)
All adverse events	33.7 (28)	32.5 (27)	34.1 (29)
Nasopharyngitis	3.6 (3)	6.0 (5)	8.2 (7)
Atopic dermatitis	4.8 (4)	2.4 (2)	3.5 (3)
Arthropod bite	0	2.4 (2)	3.5 (3)
Skin abrasion	1.2 (1)	0	3.5 (3)
Impetigo	6.0 (5)	7.2 (6)	2.4 (2)
Gastroenteritis	1.2 (1)	2.4 (2)	2.4 (2)
Folliculitis	0	2.4 (2)	2.4 (2)
Molluscum contagiosum	0	0	2.4 (2)
Influenza	2.4 (2)	0	1.2 (1)
Upper respiratory tract infection	2.4 (2)	0	0

MedDRA/J ver.22.1, Incidence (%) (number of subjects with the event)

Table 42. Adverse drug reactions reported by ≥2 patients in any group

Adverse event	Placebo (n = 83)	Difamilast 0.3% (n = 83)	Difamilast 1% (n = 85)
All adverse drug reactions	4.8 (4)	6.0 (5)	3.5 (3)
Atopic dermatitis	3.6 (3)	1.2 (1)	1.2 (1)
Impetigo	0	2.4 (2)	0

MedDRA/J ver.22.1, Incidence (%) (number of subjects with the event)

Neither deaths nor serious adverse events occurred. Adverse events leading to treatment discontinuation occurred in 6.0% (5 of 83) of patients in the placebo group (atopic dermatitis in 4 patients and drug eruption in 1 patient), 1.2% (1 of 83) of patients in the difamilast 0.3% group (atopic dermatitis in 1 patient), and 2.4% (2 of 85) of patients in the 1% group (atopic dermatitis in 2 patients). Of the adverse events leading to treatment discontinuation, atopic dermatitis in 3 patients in the placebo group and atopic dermatitis in 1 patient in the difamilast 1% group were assessed as adverse drug reactions, and outcomes of these reactions were all did not resolve.

7.2.3 Long-term treatment study (CTD 5.3.5.2-01, Study 271-102-00006, May 2019 to November 2020)

A multi-center, open-label, uncontrolled study was conducted to evaluate the safety and efficacy of long-term treatment with difamilast in patients with atopic dermatitis aged ≥2 years (Table 43) (target sample size, 330 subjects; 150 subjects aged ≥15 years, 180 subjects aged ≤14 years [including ≥80 subjects each aged 2-6 years and 7-14 years]) at 37 study sites in Japan.

Table 43. Major inclusion and exclusion criteria

Major inclusion criteria
• Patients aged ≥2 years
• Patients who meet diagnostic criteria for atopic dermatitis established by the Japanese Dermatological Association
• Patients with an IGA score of ≥2
• Patients with ≥5% of body surface area involved (except for scalp)
Major exclusion criteria
• Patients who are unable to stop topical Very Strong corticosteroids or stronger ones (except for scalp) 21 days before baseline examination and thereafter
• Patients who are unable to stop topical Strong corticosteroids (except for scalp), all topical corticosteroids other than ones for skin, or topical immunosuppressive drugs (except for scalp) 7 days before baseline examination and thereafter
• Patients who are unable to stop topical Medium or Weak corticosteroids (except for scalp) 4 days before baseline examination and thereafter
• Patients who are unable to stop systemic corticosteroids, immunosuppressive drugs, or antimetabolites 28 days before baseline examination and thereafter
• Patients who are unable to stop phototherapy 28 days before baseline examination and thereafter for patients aged ≥15 years and at baseline examination and thereafter for patients aged ≤14 years

To (adult) patients aged ≥15 years, an appropriate amount[20)] of difamilast 1% ointment was topically applied twice daily for 52 weeks. When all skin symptoms disappeared, withdrawal of difamilast was allowed at the investigator's discretion, and when these relapsed, its topical application was resumed. To (pediatric) patients aged ≤14 years, an appropriate amount[20)] of difamilast 0.3% ointment was topically applied twice daily for 52 weeks. However, in the case where the investigator considered it necessary in view of severity and involvement of skin eruption, topical application was allowed to start with difamilast 1% ointment. In addition, in the case where topical application of difamilast 0.3% ointment for ≥1 month did not improve the symptoms, switch to difamilast 1% ointment was allowed, but when the symptoms were improved, and thus difamilast 1% ointment was considered unnecessary, dose-reduction by switch to difamilast 0.3% ointment was allowed. When all skin symptoms

disappeared, withdrawal of difamilast was allowed at the investigator's discretion or for continued topical application, if applicable, difamilast 0.3% ointment was used, and when the symptoms relapsed, its topical application was resumed.

All of 366 patients enrolled in the study (166 adult patients and 200 pediatric patients) received the study drug and were included in the safety analysis population and FAS. The FAS was subjected to the primary efficacy analysis. A total of 64 patients (42 adult patients and 22 pediatric patients) discontinued the study treatment because of "adverse events" in 20 patients (13 adult patients and 7 pediatric patients), "request from subject" in 20 patients (17 adult patients and 3 pediatric patients), "request from guardian" in 7 pediatric patients, "physician's decision" in 4 patients (2 adult patients and 2 pediatric patients), "lost to follow-up" in 3 patients (2 adult patients and 1 pediatric patient), "lack of efficacy" in 3 patients (2 adult patients and 1 pediatric patient), and "others" in 7 patients (6 adult patients and 1 pediatric patient).

Table 44 shows the IGA responder rate at the last assessment.

Table 44. IGA responder rate at last assessment (FAS)

	Adults	Children		
	Difamilast 1% (n = 166)	Children starting with difamilast 0.3% (n = 144)	Children starting with difamilast 1% (n = 56)	All children (n = 200)
IGA responder rate (number of responders/ number of subjects analyzed) [95% CI] (%)	22.9 (38/166) [16.7, 30.0]	33.6 (48/143[a)]) [25.9, 41.9]	32.1 (18/56) [20.3, 46.0]	33.2 (66/199) [26.7, 40.2]

a) Not including 1 patient in whom efficacy data after administration of the study drug were not available

Adverse events occurred in 72.3% (120 of 166) of adult patients and 89.0% (178 of 200) of pediatric patients, and adverse drug reactions occurred in 8.4% (14 of 166) of adult patients and 8.0% (16 of 200) of pediatric patients. Table 45 shows adverse events reported by ≥5% of patients in either population. Table 46 shows adverse drug reactions reported by ≥2 patients in either population.

Table 45. Adverse events reported by ≥5% of patients in either population

Adverse event	Adults	Children		
	Difamilast 1% (n = 166)	Children starting with difamilast 0.3% (n = 144)	Children starting with difamilast 1% (n = 56)	All children (n = 200)
All adverse events	72.3 (120)	91.0 (131)	83.9 (47)	89.0 (178)
Atopic dermatitis	21.1 (35)	20.8 (30)	30.4 (17)	23.5 (47)
Nasopharyngitis	14.5 (24)	32.6 (47)	30.4 (17)	32.0 (64)
Folliculitis	6.0 (10)	6.3 (9)	8.9 (5)	7.0 (14)
Urticaria	4.8 (8)	9.7 (14)	5.4 (3)	8.5 (17)
Influenza	3.0 (5)	14.6 (21)	7.1 (4)	12.5 (25)
Conjunctivitis allergic	3.0 (5)	9.7 (14)	12.5 (7)	10.5 (21)
Gastroenteritis	3.0 (5)	7.6 (11)	10.7 (6)	8.5 (17)
Dermatitis contact	3.0 (5)	6.3 (9)	5.4 (3)	6.0 (12)
Skin papilloma	2.4 (4)	4.9 (7)	5.4 (3)	5.0 (10)
Impetigo	1.2 (2)	18.1 (26)	8.9 (5)	15.5 (31)
Bronchitis	0.6 (1)	6.3 (9)	5.4 (3)	6.0 (12)
Pharyngitis	0	4.2 (6)	7.1 (4)	5.0 (10)
Molluscum contagiosum	0	4.9 (7)	5.4 (3)	5.0 (10)

MedDRA/J ver.22.1, Incidence (%) (number of subjects with the event)

Table 46. Adverse drug reactions reported by ≥2 patients in either population

Adverse event	Adults	Children		
	Difamilast 1% (n = 166)	Children starting with difamilast 0.3% (n = 144)	Children starting with difamilast 1% (n = 56)	All children (n = 200)
All adverse drug reactions	8.4 (14)	5.6 (8)	14.3 (8)	8.0 (16)
Atopic dermatitis	1.8 (3)	1.4 (2)	3.6 (2)	2.0 (4)
Acne	1.2 (2)	0	0	0
Pigmentation disorder	0.6 (1)	2.1 (3)	1.8 (1)	2.0 (4)
Folliculitis	0.6 (1)	0.7 (1)	1.8 (1)	1.0 (2)

MedDRA/J ver.22.1, Incidence (%) (number of subjects with the event)

No deaths occurred. Serious adverse events occurred in 1.2% (2 of 166) of adult patients (rhegmatogenous retinal detachment and diffuse large B-cell lymphoma in 1 patient each) and 0.5% (1 of 200) of pediatric patients (pneumonia bacterial). A causal relationship to the study drug was ruled out for any of these events. Adverse events leading to discontinuation of the study drug occurred in 7.8% (13 of 166) of adult patients (atopic dermatitis in 3 patients, dermatitis contact and pruritus in 2 patients each, and malaise, sleep disorder, post inflammatory pigmentation change, erythema, skin burning sensation, and diffuse large B-cell lymphoma in 1 patient each) and 3.5% (7 of 200) of pediatric patients (atopic dermatitis in 5 patients, and pruritus allergic and dermatitis contact in 1 patient each). Of the adverse events leading to treatment discontinuation, atopic dermatitis, dermatitis contact, pruritus, erythema, and skin burning sensation in 1 adult patient each as well as atopic dermatitis in 2 pediatric patients, and pruritus allergic and dermatitis contact in 1 pediatric patient each were assessed as adverse drug reactions. Outcomes of these reactions were all resolved except erythema in an adult patient and atopic dermatitis and dermatitis contact in 1 pediatric patient each, of which outcomes were did not resolve.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

PMDA considers that difamilast has been demonstrated to be effective in treatment of atopic dermatitis according to results from the review in Sections 7.R.1.1 to 7.R.1.4.

7.R.1.1 Primary endpoint in phase III studies

The applicant's explanation about rationale for establishment of the primary endpoint and results on this endpoint in phase III studies in adult and pediatric patients:

IGA is a scoring system that assesses overall severity of general skin symptoms in patients with atopic dermatitis, and its score has been widely used as an indicator of severity of atopic dermatitis in many countries including Japan. In efficacy evaluation of difamilast, clinically meaningful improvement is defined as an "IGA score of 0 or 1 with improvement by ≥2 grades," and proportion of subjects achieving the improvement was assessed as the IGA responder rate. Based on results from phase II studies in adult and pediatric patients, Week 4 was selected as an evaluation point to ensure a period adequate for efficacy evaluation on IGA responder rate.

Tables 37 and 40 show results on the IGA responder rate at Week 4, the primary endpoint, in phase III studies in adult and pediatric patients, respectively, demonstrating superiority of difamilast over placebo.

PMDA considers it acceptable for the applicant to specify the IGA responder rate at Week 4 as the primary endpoint in phase III studies in adult and pediatric patients. PMDA confirmed that both studies demonstrated superiority of difamilast over placebo.

7.R.1.2 Main secondary endpoints in phase III studies

Table 47 shows results on the main secondary endpoints at Week 4 in adult and pediatric phase III studies.

Table 47. Results on main secondary endpoints at Week 4 (adult phase III and pediatric phase III studies, FAS)

Endpoint	Adults		Children		
	Placebo (n = 182)	Difamilast 1% (n = 182)	Placebo (n = 83)	Difamilast 0.3% (n = 83)	Difamilast 1% (n = 85)
EASI75 responder rate (%) (number of responders) [95% CI]	13.2 (n = 24) [8.6, 19.0]	42.9 (n = 78) [35.6, 50.4]	18.1 (n = 15) [10.5, 28.0]	43.4 (n = 36) [32.5, 54.7]	57.6 (n = 49) [46.4, 68.3]
Change from baseline in EASI score (number of subjects analyzed)	0.1 ± 7.7 (n = 180)	-4.0 ± 5.8 (n = 180)	0.4 ± 7.9 (n = 81)	-5.0 ± 7.8 (n = 83)	-6.1 ± 6.5 (n = 85)
Itch VRS[a)] from baseline (number of subjects analyzed)	0.0 ± 0.9 (n = 180)	-0.6 ± 0.9 (n = 180)	-0.2 ± 0.9 (n = 40)	-0.8 ± 0.8 (n = 42)	-0.6 ± 1.0 (n = 43)

Mean ± SD, complemented by last observation carried forward (LOCF)

a) Subjects (aged ≥7 years in the pediatric phase III study) rated degree of itch on their own on a scale of 0 to 3 (0, none; 1, mild; 2, moderate; and 3, severe).

PMDA confirmed that results on any of the endpoints showed an improving trend for difamilast compared with placebo.

7.R.1.3 Efficacy by patient characteristics in phase III studies

The applicant's explanation about efficacy by patient characteristics:

Tables 48 and 49 show IGA responder rates at Week 4 by patient characteristics in adult and pediatric phase III studies, respectively. In a subgroup analysis by prior treatment type, the number of patients who previously received tacrolimus ointment alone were very small in both adult and pediatric phase III studies, indicating limitations in analyzing data in this subgroup. In the other subgroups, the IGA responder rate was higher in the difamilast group than in the placebo group.

Table 48. IGA responder rate at Week 4 by patient characteristics (adult phase III study, FAS)

Patient characteristics		Placebo (n = 182)	Difamilast 1% (n = 182)	Difference between groups [95% CI]
Age	≥15 and <20 years	0 (0/12)	45.5 (5/11)	45.6 [16.3, 75.0]
	≥20 and <30 years	13.3 (10/75)	43.4 (36/83)	29.8 [16.7, 42.9]
	≥30 and <45 years	7.7 (5/65)	32.3 (20/62)	25.6 [12.5, 38.8]
	≥45 and ≤60 years	26.7 (8/30)	34.6 (9/26)	6.9 [-17.4, 31.3]
Sex	Male	11.9 (12/101)	35.4 (34/96)	24.2 [12.9, 35.5]
	Female	13.6 (11/81)	41.9 (36/86)	28.0 [15.2, 40.7]
Baseline IGA score	2 (mild)	3.9 (1/26)	14.8 (4/27)	11.0 [-4.3, 26.3]
	3 (moderate)	14.1 (22/156)	42.6 (66/155)	28.5 [19.0, 38.0]
Baseline EASI score	<15	15.7 (22/140)	42.8 (65/152)	27.0 [17.3, 36.8]
	≥15	2.4 (1/42)	16.7 (5/30)	14.2 [0.1, 28.4]
Baseline involvement	<20%	16.3 (16/98)	51.5 (52102)	35.3 [23.5, 47.0]
	≥20%	8.3 (7/84)	22.2 (18/81)	13.9 [3.0, 24.7]
Duration of disease	<10 years	14.3 (3/21)	50.0 (8/16)	35.3 [6.4, 64.2]
	≥10 and <20 years	4.8 (2/42)	43.2 (16/37)	38.4 [21.2, 55.5]
	≥20 and <30 years	16.1 (9/56)	36.2 (25/69)	22.0 [7.5, 36.6]
	≥30 and <40 years	5.0 (2/40)	35.1 (13/37)	31.1 [14.3, 47.8]
	≥40 years	30.4 (7/23)	34.8 (8/23)	1.6 [-26.8, 30.0]
Prior treatment type	Topical corticosteroids[a)]	13.7 (16/117)	41.4 (55/133)	28.0 [17.7, 38.3]
	Tacrolimus ointment[b)]	50.0 (1/2)	25.0 (1/4)	-40.0 [-95.4, 15.4]
	Topical corticosteroids and tacrolimus ointment	6.67 (3/45)	20.0 (6/30)	13.5 [-2.4, 29.4]

IGA responder rate (%) (number of responders/number of subjects analyzed)
a) Not including subjects concomitantly receiving tacrolimus ointment
b) Not including subjects concomitantly receiving topical corticosteroids

Table 49. IGA responder rate at Week 4 by patient characteristics (pediatric phase III study, FAS)

Patient characteristics		Placebo (n = 83)	Difamilast 0.3% (n = 83)	Difamilast 1% (n = 85)	Difference from placebo [95% CI]	
					Difamilast 0.3%	Difamilast 1%
Age	2-6 years	16.7 (7/42)	46.3 (19/41)	42.9 (18/42)	27.3 [8.5, 46.0]	26.8 [7.2, 46.3]
	7-14 years	19.5 (8/41)	42.9 (18/42)	51.2 (22/43)	22.1 [3.0, 41.2]	30.6 [11.3, 49.9]
Sex	Male	16.3 (8/49)	44.7 (17/38)	43.8 (21/48)	29.1 [11.1, 47.2]	27.6 [9.8, 45.4]
	Female	20.6 (7/34)	44.4 (20/45)	51.4 (19/37)	21.5 [1.1, 41.9]	32.8 [10.7, 54.8]
Baseline IGA score	2 (mild)	16.7 (2/12)	53.9 (7/13)	28.6 (4/14)	27.7 [-4.6, 60.0]	9.7 [-26.3 45.7]
	3 (moderate)	18.3 (13/71)	42.9 (30/70)	50.7 (36/71)	24.1 [9.5, 38.8]	32.0 [17.3, 46.7]
Baseline EASI score	<15	22.2 (14/63)	46.0 (29/63)	54.7 (35/64)	21.7 [5.8, 37.5]	32.5 [16.2, 48.8]
	≥15	5.0 (1/20)	40.0 (8/20)	23.8 (5/21)	34.2 [11.0, 57.5]	18.9 [-1.7, 39.5]
Baseline involvement	<20%	26.3 (10/38)	45.7 (21/46)	63.6 (28/44)	18.9 [-0.6, 38.4]	39.5 [18.8, 60.2]
	≥20%	11.1 (5/45)	43.2 (16/37)	29.3 (12/41)	29.9 [11.0, 48.8]	16.9 [0.0, 33.8]
Prior treatment type	Topical corticosteroids[a)]	19.4 (13/67)	47.8 (37/83)	48.5 (33/68)	25.6 [10.4, 40.8]	28.7 [13.2, 44.1]
	Tacrolimus ointment[b)]	50.0 (1/2)	-	33.3 (1/3)	NE	NE
	Topical corticosteroids and tacrolimus ointment	0 (0/9)	30.0 (3/10)	22.2 (2/9)	29.3 [0.6, 58.1]	40.9 [-2.1, 83.9]

IGA responder rate (%) (number of responders/number of subjects analyzed); -, Not applicable; NE, Not estimable
a) Not including subjects concomitantly receiving tacrolimus ointment
b) Not including subjects concomitantly receiving topical corticosteroids

PMDA confirmed that difamilast achieved a largely improving trend compared with placebo, although it should be noted that subgroups with a very small sample size had limitations in analyses.

7.R.1.4 Long-term efficacy

The applicant's explanation about efficacy of long-term treatment with difamilast:

Table 50 shows the IGA responder rate at each evaluation timepoint in the long-term treatment study.

Table 50. IGA responder rate (long-term treatment study, FAS)

Evaluation point	Adults	Children		
	Difamilast 1% (n = 166)	Children starting with difamilast 0.3% (n = 144)	Children starting with difamilast 1% (n = 56)	All children (n = 200)
Week 4	3.8 (6/158)	11.4 (16/141)	14.6 (8/55)	12.2 (24/196)
Week 12	7.5 (11/147)	16.8 (23/137)	15.1 (8/53)	16.3 (31/190)
Week 24	16.5 (22/133)	21.7 (28/129)	17.3 (9/52)	20.4 (37/181)
Week 36	25.0 (32/128)	18.8 (24/128)	19.6 (10/51)	19.0 (34/179)
Week 48	23.8 (30/126)	23.6 (30/127)	23.5 (12/51)	23.6 (42/178)
Week 52	28.5 (35/123)	34.9 (44/126)	33.3 (17/51)	34.5 (61/177)
Last assessment	22.9 (38/166)	33.6 (48/143[a])	32.1 (18/56)	33.2 (66/199)

IGA responder rate (%) (number of responders/number of subjects analyzed)
a) Not including 1 patient in whom efficacy data after administration of the study drug were not available

In the long-term treatment study, the IGA responder rates at Week 4 in both adult and pediatric patients were lower than the corresponding rates in the phase III studies (Tables 37 and 40). A potential cause for the low rates was that the long-term treatment study allowed enrollment of patients with an IGA score of 4 and patients with >40% of body surface area involved, who had been excluded from the phase III studies, resulting in registration of many patients with severe symptoms (patients with an IGA score of 4 accounted for 7.8% [13 of 166] of adult patients and 7.0% [14 of 200] of pediatric patients; and patients with >40% of body surface area involved accounted for 33.7% [56 of 166] of adult patients and 32.0% [64 of 200] of pediatric patients).

In both adult and pediatric patients, the IGA responder rate at Week 4 and thereafter almost increased with an increasing period of the treatment, showing acceptable efficacy of long-term treatment with difamilast.

With results from the long-term treatment study, PMDA confirmed that the efficacy of difamilast did not tend to decrease with the increasing treatment period in either adult or pediatric patients.

7.R.2 Safety

PMDA's view:

Based on the results in Sections 7.R.2.1 to 7.R.2.6, the safety of difamilast in treatment of atopic dermatitis is acceptable. However, attention should be paid to skin infection at the application site, and information on this event should be continuously collected through post-marketing surveillance.

7.R.2.1 Safety of difamilast compared with placebo

The applicant's explanation about the safety of difamilast compared with placebo:

Adverse events in adult patients and pediatric patients were separately pooled from phase II and III studies and analyzed (Table 51 shows the pooled data in adult patients and Table 52 shows the pooled data in pediatric patients).

Table 51. Incidences of adverse events (pooled data in adult patients)

Adverse event	Placebo (n = 248)	Difamilast 0.3% (n = 67)	Difamilast 1% (n = 249)
All adverse events	31.5 (78)	46.3 (31)	20.9 (52)
All adverse drug reactions	9.3 (23)	11.9 (8)	2.4 (6)
Serious adverse events	0	0	0
Adverse events leading to treatment discontinuation	14.5 (36)	22.4 (15)	5.6 (14)
Adverse events with an incidence of ≥2.0% in any group			
Atopic dermatitis	13.7 (34)	16.4 (11)	5.2 (13)
Nasopharyngitis	5.6 (14)	10.4 (7)	5.2 (13)
Pruritus	2.0 (5)	7.5 (5)	0.4 (1)
Influenza	0	3.0 (2)	0.4 (1)

MedDRA/J ver.22.1, Incidence (%) (number of subjects with the event)

Table 52. Incidence of adverse events (pooled data in pediatric patients)

Adverse event	Placebo (n = 107)	Difamilast 0.3% (n = 107)	Difamilast 1% (n = 110)
All adverse events	37.4 (40)	35.5 (38)	39.1 (43)
All adverse drug reactions	6.8 (22)	5.6 (6)	6.4 (7)
Serious adverse events	0	0	0
Adverse events leading to treatment discontinuation	8.4 (9)	1.9 (2)	2.7 (3)
Adverse events with an incidence of ≥2.0% in any group			
Upper respiratory tract inflammation	1.9 (2)	1.9 (2)	6.4 (7)
Nasopharyngitis	4.7 (5)	5.6 (6)	6.4 (7)
Dermatitis allergic	7.5 (8)	3.7 (4)	3.6 (4)
Impetigo	4.7 (5)	5.6 (6)	2.7 (3)
Arthropod bite	0	1.9 (2)	2.7 (3)
Skin abrasion	0.9 (1)	0	2.7 (3)
Molluscum contagiosum	0	0	2.7 (3)
Folliculitis	0	2.8 (3)	1.8 (2)

MedDRA/J ver.22.1, Incidence (%) (number of subjects with the event)

Neither deaths nor serious adverse events were observed in either pooled data. According to the pooled data in adult patients, adverse drug reactions and adverse events leading to treatment discontinuation tended to occur more frequently in the difamilast 0.3% group than in the placebo group. Potential causes for the above trend were that (a) the treatment period differed between the phase II and III studies (8 weeks vs. 4 weeks) (adult patients received difamilast 0.3% only in the phase II study) and (b) patients receiving difamilast 0.3% experienced many adverse events related to worsening of the primary disease, atopic dermatitis, due to inadequate response (Table 7.1.1-3). In the phase II study, adverse events did not largely differ between the difamilast 0.3% and placebo groups. The difamilast 1% group did not indicate any problematic trend compared with the placebo group. The pooled data in pediatric patients did not indicate any clinically relevant difference between either difamilast 0.3% or 1% group and the placebo group.

With the pooled data in adult patients and in pediatric patients, PMDA confirmed that the safety profile of difamilast did not indicate any clinically relevant trend compared with that of placebo. PMDA separately reviews safety of the long-term treatment in Section 7.R.2.3, safety at the application site in Section 7.R.2.4, and skin infection in Section 7.R.2.5.

7.R.2.2 Safety by patient characteristics

The applicant's explanation about safety by patient characteristics:

For incidences of adverse events by patient characteristics, Tables 53 shows the pooled data in adult patients and Table 54 shows the in pediatric patients. According to the pooled data in pediatric patients, the subgroup with a baseline IGA score of 2 showed that the incidence of adverse events tended to be slightly higher in the difamilast 1% group than in the other groups, but the adverse events in the difamilast 1% group were all mild or moderate and included no specific adverse events of which the incidence tended to be higher. The observed trend is therefore considered clinically non-problematic. Although some subgroups were found to be difficult to evaluate owing to the limited sample size, there were no specific subgroups in which the incidence of adverse events tended to be higher.

Table 53. Incidences of adverse events by patient characteristics (pooled data in adult patients)

		Placebo (n = 248)	Difamilast 0.3% (n = 67)	Difamilast 1% (n = 249)
Age	≥15 and <20 years	43.8 (7/16)	22.2 (2/9)	18.8 (3/16)
	≥20 and <30 years	25.7 (27/105)	50.0 (13/26)	20.2 (23/114)
	≥30 and <45 years	32.2 (28/87)	56.0 (14/25)	20.0 (17/85)
	≥45 and ≤60 years	40.0 (16/40)	28.6 (2/7)	28.1 (9/32)
	>60 years	-	-	0 (0/2)
Sex	Male	28.5 (41/144)	44.4 (20/45)	23.9 (33/138)
	Female	35.6 (37/104)	50.0 (11/22)	17.1 (19/111)
Baseline IGA score	2 (mild)	24.4 (11/45)	36.8 (7/19)	17.4 (8/46)
	3 (moderate)	33.0 (67/203)	50.0 (24/48)	21.7 (44/203)
Baseline EASI score	<15	30.1 (59/196)	43.6 (24/55)	20.4 (43/211)
	≥15	36.5 (19/52)	58.3 (7/12)	23.7 (9/38)
Baseline involvement	<20%	29.7 (41/138)	35.1 (13/37)	19.4 (27/139)
	≥20%	33.6 (37/110)	60.0 (18/30)	22.7 (25/110)
Duration of disease	<10 years	25.0 (6/24)	66.7 (4/6)	26.1 (6/23)
	≥10 and <20 years	31.6 (18/57)	26.7 (4/15)	18.9 (10/53)
	≥20 and <30 years	30.6 (26/85)	47.8 (11/23)	21.5 (20/93)
	≥30 and <40 years	34.0 (18/53)	64.3 (9/14)	17.3 (9/52)
	≥40 years	34.5 (10/29)	33.3 (3/9)	25.0 (7/28)
Prior treatment type	Topical corticosteroids[a)]	31.3 (47/150)	45.0 (18/40)	16.2 (27/167)
	Tacrolimus ointment[b)]	40.0 (2/5)	33.3 (1/3)	33.3 (2/6)
	Topical corticosteroids and tacrolimus ointment	36.9 (24/65)	61.5 (8/13)	31.9 (15/47)

Incidence % (number of subjects with event/number of subjects analyzed); -, Not applicable

a) Not including subjects concomitantly receiving tacrolimus ointment

b) Not including subjects concomitantly receiving topical corticosteroids

Table 54. Incidences of adverse events by patient characteristics (pooled data in pediatric patients)

		Placebo (n = 107)	Difamilast 0.3% (n = 107)	Difamilast 1% (n = 110)
Age	2-6 years	40.8 (20/49)	39.6 (19/48)	44.0 (22/50)
	7-14 years	34.5 (20/58)	32.2 (19/59)	35.0 (21/60)
Sex	Male	33.8 (23/68)	35.7 (20/56)	39.7 (25/63)
	Female	43.6 (17/39)	35.3 (18/51)	38.3 (18/47)
Baseline IGA score	2 (mild)	40.0 (6/15)	35.3 (6/17)	52.6% (10/19)
	3 (moderate)	37.0 (34/92)	35.6 (32/90)	36.3% (33/91)
Baseline EASI score	<15	37.8 (31/82)	35.0 (28/80)	41.9% (36/86)
	≥15	36.0 (9/25)	37.0 (10/27)	29.2% (7/24)
Baseline involvement	<20%	31.5 (17/54)	28.1 (16/57)	41.9 (26/62)
	≥20%	43.4 (23/53)	44.0 (22/50)	35.4 (17/48)
Prior treatment type	Topical corticosteroids[a)]	34.1 (28/82)	36.9 (31/84)	35.4% (29/82)
	Tacrolimus ointment[b)]	50.0 (1/2)	0	25.0 (1/4)
	Topical corticosteroids and tacrolimus ointment	53.3 (8/15)	31.3 (5/16)	57.1 (8/14)

Incidence % (number of subjects with event/number of subjects analyzed)

a) Not including subjects concomitantly receiving tacrolimus ointment

b) Not including subjects concomitantly receiving topical corticosteroids

In the long-term treatment study, concomitant topical corticosteroids and tacrolimus ointment were allowed and used in ≥70% of the patients. Table 55 shows incidences of adverse events in subgroups with or without use of concomitant topical corticosteroids or tacrolimus ointment in the long-term treatment study.

Table 55. Incidences of adverse events in subgroups with or without use of concomitant topical corticosteroids or tacrolimus ointment (long-term treatment study)

Adverse event	Adults		Children	
	Used (n = 125)	Not used (n = 41)	Used (n = 150)	Not used (n = 50)
All adverse events	75.2 (94)	63.4 (26)	94.0 (141)	74.0 (37)
All adverse drug reactions	8.8 (11)	7.3 (3)	8.0 (12)	8.0 (4)
Serious adverse events	1.6 (2)	0	0.7 (1)	0
Adverse events leading to treatment discontinuation	8.0 (10)	7.3 (3)	3.3 (5)	4.0 (2)
Adverse events with an incidence of ≥5% in any subgroup				
Atopic dermatitis	27.2 (34)	2.4 (1)	29.3 (44)	6.0 (3)
Nasopharyngitis	15.2 (19)	12.2 (5)	34.7 (52)	24.0 (12)
Acne	6.4 (8)	0	4.0 (6)	6.0 (3)
Folliculitis	4.8 (6)	9.8 (4)	8.0 (12)	4.0 (2)
Urticaria	4.0 (5)	7.3 (3)	6.7 (10)	14.0 (7)
Conjunctivitis allergic	4.0 (5)	0	12.7 (19)	4.0 (2)
Dermatitis contact	4.0 (5)	0	6.7 (10)	4.0 (2)
Gastroenteritis	3.2 (4)	2.4 (1)	10.7 (16)	2.0 (1)
Skin papilloma	3.2 (4)	0	5.3 (8)	4.0 (2)
Influenza	2.4 (3)	4.9 (2)	14.0 (21)	8.0 (4)
Impetigo	0.8 (1)	2.4 (1)	19.3 (29)	4.0 (2)
Skin abrasion	0	7.3 (3)	4.7 (7)	2.0 (1)
Bronchitis	0	2.4 (1)	6.0 (9)	6.0 (3)
Pharyngitis	0	0	5.3 (8)	4.0 (2)
Molluscum contagiosum	0	0	4.0 (6)	8.0 (4)
Constipation	0	0	0	6.0 (3)

MedDRA/J ver.22.1, Incidence (%) (number of subjects with the event)

Incidences of adverse events were higher in the subgroups with concomitant topical corticosteroids or tacrolimus ointment than in the subgroups without, but adverse events of which an incidence differed between the subgroups with and without concomitant use by ≥10% were limited to atopic dermatitis in adult patients and atopic dermatitis and impetigo in pediatric patients. Potential underlying causes for the high incidences of these events are that (a) the subgroups with concomitant use are supposed to have had a worse condition of atopic dermatitis than the subgroups without; and (b) these concomitant drugs were used to treat the concerned adverse events.

PMDA's view:

With respect to the safety by patient characteristics, PMDA understandable the applicant's explanation that the subgroups with concomitant topical corticosteroids or tacrolimus ointment showed higher incidences of adverse events such as atopic dermatitis than the subgroups without, because of the worse condition of atopic dermatitis. For others, although it should be noted that some subgroups were difficult to evaluate owing to the limited sample size, PMDA confirmed that there are no specific subgroups showing problematic trends.

7.R.2.3 Long-term safety

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

For adverse events by treatment period in the long-term treatment study, Tables 56 shows incidences in adult patients and Table 57 shows the incidences in pediatric patients. The incidences of adverse events did not tend to increase with an increasing period of the treatment.

Table 56. Incidences of adverse events by specified period (long-term treatment study, adult patients)

Adverse event	Weeks 0 to 4 (n = 166)	Weeks 4 to 12 (n = 156)	Weeks 12 to 24 (n = 140)	Weeks 24 to 36 (n = 134)	Weeks 36 to 52 (n = 129)	Overall period (n = 166)
Adverse events	25.9 (43)	30.1 (47)	37.9 (53)	26.1 (35)	31.0 (40)	72.3 (120)
Adverse drug reactions	4.8 (8)	1.9 (3)	1.4 (2)	0.7 (1)	0	8.4 (14)
Serious adverse events	0	0	0.7 (1)	0	0.8 (1)	1.2 (2)
Adverse events leading to treatment discontinuation	4.8 (8)	1.9 (3)	0.7 (1)	0	0.8 (1)	7.8 (13)
Adverse events reported by ≥5.0% of patients in overall period						
Atopic dermatitis	8.4 (14)	9.6 (15)	7.1 (10)	2.2 (3)	2.3 (3)	21.1 (35)
Nasopharyngitis	3.0 (5)	3.8 (6)	10.0 (14)	3.0 (4)	2.3 (3)	14.5 (24)
Folliculitis	0.6 (1)	1.3 (2)	2.9 (4)	1.5 (2)	1.6 (2)	6.0 (10)

MedDRA/J ver.22.1, Incidence (%) (number of subjects with the event)

Table 57. Incidences of adverse events by specified period (long-term treatment study, pediatric patients)

Adverse event	Weeks 0 to 4 (n = 200)	Weeks 4 to 12 (n = 197)	Weeks 12 to 24 (n = 190)	Weeks 24 to 36 (n = 184)	Weeks 36 to 52 (n = 179)	Overall period (n = 200)
Adverse events	40.0 (80)	50.8 (100)	58.4 (111)	46.7 (86)	46.9 (84)	89.0 (178)
Adverse drug reactions	3.5 (7)	2.5 (5)	1.1 (2)	0	1.1 (2)	8.0 (16)
Serious adverse events	0	0	0.5 (1)	0	0	0.5 (1)
Adverse events leading to treatment discontinuation	1.5 (3)	0.5 (1)	1.6 (3)	0	0	3.5 (7)
Adverse events reported by ≥5.0% of patients in overall period						
Nasopharyngitis	8.0 (16)	12.2 (24)	12.6 (24)	6.5 (12)	11.2 (20)	32.0 (64)
Atopic dermatitis	5.5 (11)	10.7 (21)	8.9 (17)	4.3 (8)	2.8 (5)	23.5 (47)
Impetigo	2.5 (5)	4.6 (9)	3.2 (6)	2.2 (4)	7.3 (13)	15.5 (31)
Influenza	0	3.0 (6)	8.4 (16)	2.2 (4)	0	12.5 (25)
Conjunctivitis allergic	0	0.5 (1)	2.1 (4)	6.0 (11)	3.4 (6)	10.5 (21)
Gastroenteritis	0.5 (1)	3.0 (6)	3.7 (7)	1.6 (3)	0.6 (1)	8.5 (17)
Urticaria	2.5 (5)	1.0 (2)	3.7 (7)	2.7 (5)	1.1 (2)	8.5 (17)
Folliculitis	2.5 (5)	2.0 (4)	2.1 (4)	0.5 (1)	1.1 (2)	7.0 (14)
Bronchitis	2.5 (5)	2.0 (4)	2.1 (4)	0.5 (1)	1.1 (2)	6.0 (12)
Dermatitis contact	0.5 (1)	1.0 (2)	1.1 (2)	3.3 (6)	1.1 (2)	6.0 (12)
Molluscum contagiosum	1.5 (3)	0.5 (1)	1.6 (3)	1.6 (3)	0.6 (1)	5.0 (10)
Pharyngitis	1.0 (2)	3.0 (6)	0.5 (1)	0	0.6 (1)	5.0 (10)
Skin papilloma	0	1.0 (2)	0	3.3 (6)	1.7 (3)	5.0 (10)

MedDRA/J ver.22.1, Incidence (%) (number of subjects with the event)

PMDA confirmed that there were no problematic trends between period of treatment with difamilast and incidences of adverse events.

7.R.2.4 Safety at the application site

The applicant's explanation about safety of difamilast at the application site:

For incidences of adverse events at the site applied with the study drug in the pooled data in the phase II and III studies, Tables 58 shows the pooled data in adult patients and Table 59 shows the pooled data in pediatric patients. According to the pooled data in adult patients, the incidence of adverse events at the site applied with the study drug tended to be slightly higher in the difamilast 0.3% group [see Section 7.R.2.1], but no problematic trends were observed in the difamilast 1% group. According to

the pooled data in pediatric patients, adverse events at the site applied with the study drug did not considerably differ between either the difamilast group and the placebo group.

Table 58. Adverse events at the site applied with the study drug reported by ≥2.0% of patients in any group (pooled data in adult patients)

Adverse event	Placebo (n = 248)	Difamilast 0.3% (n = 67)	Difamilast 1% (n = 249)
All adverse events	18.1 (45)	25.4 (17)	6.4 (16)
Atopic dermatitis	12.5 (31)	16.4 (11)	4.8 (12)
Pruritus	2.0 (5)	7.5 (5)	0.4 (1)

MedDRA/J ver.22.1, Incidence (%) (number of subjects with the event)

Table 59. Adverse events at the site applied with the study drug reported by ≥2.0% of patients in any group (pooled data in pediatric patients)

Adverse event	Placebo (n = 107)	Difamilast 0.3% (n = 107)	Difamilast 1% (n = 110)
All adverse events	14.0 (15)	12.1 (13)	9.1 (10)
Atopic dermatitis	7.5 (8)	3.7 (4)	3.6 (4)
Folliculitis	0	2.8 (3)	0.9 (1)
Impetigo	1.9 (2)	4.7 (5)	0

MedDRA/J ver.22.1, Incidence (%) (number of subjects with the event)

Table 60 shows incidences of adverse events at the site applied with the study drug reported by ≥2 patients in the adult or pediatric patient population in the long-term treatment study. In the adult patient population, adverse drug reactions occurred in 7.8% (13 of 166) of patients, and adverse drug reactions reported by ≥2 patients were atopic dermatitis in 1.8% (3 of 166) of patients and acne in 1.2% (2 of 166) of patients. In the pediatric patient population, adverse drug reactions occurred in 4.9% (7 of 144) of patients starting with difamilast 0.3%, 14.3% (8 of 56) of patients starting with difamilast 1%, and 7.5% (15 of 200) of pediatric patients overall, and adverse drug reactions reported by ≥2 pediatric patients overall were pigmentation disorder in 2.0% (4 of 200) of patients, atopic dermatitis in 2.0% (4 of 200) of patients, and folliculitis in 1.0% (2 of 200) of patients.

Table 60. Adverse events at the site applied with the study drug reported by ≥2 patients in the adult or pediatric patient population (long-term treatment study)

Adverse event	Adults	Children		
	Difamilast 1% (n = 166)	Children starting with difamilast 0.3% (n = 144)	Children starting with difamilast 1% (n = 56)	All children (n = 200)
All adverse events	39.2 (65)	50.7 (73)	55.4 (31)	52.0 (104)
Atopic dermatitis	20.5 (34)	20.8 (30)	30.4 (17)	23.5 (47)
Urticaria	4.2 (7)	7.6 (11)	3.6 (2)	6.5 (13)
Folliculitis	4.2 (7)	4.2 (6)	5.4 (3)	4.5 (9)
Acne	1.8 (3)	0	3.6 (2)	1.0 (2)
Pruritus	1.8 (3)	0	1.8 (1)	0.5 (1)
Dermatitis contact	1.8 (3)	2.8 (4)	3.6 (2)	3.0 (6)
Pigmentation disorder	1.2 (2)	4.2 (6)	1.8 (1)	3.5 (7)
Impetigo	0.6 (1)	13.9 (20)	5.4 (3)	11.5 (23)
Skin abrasion	0.6 (1)	2.8 (4)	1.8 (1)	2.5 (5)
Skin papilloma	0.6 (1)	1.4 (2)	0	1.0 (2)
Molluscum contagiosum	0	4.2 (6)	5.4 (3)	4.5 (9)
Rash	0	2.1 (3)	0	1.5 (3)
Herpes simplex	0	0.7 (1)	3.6 (2)	1.5 (3)
Kaposi's varicelliform eruption	0	1.4 (2)	1.8 (1)	1.5 (3)
Application site pain	0	0	3.6 (2)	1.0 (2)
Miliaria	0	0	3.6 (2)	1.0 (2)
Furuncle	0	1.4 (2)	0	1.0 (2)
Hand-foot-and-mouth disease	0	1.4 (2)	0	1.0 (2)
Dermatitis allergic	0	1.4 (2)	0	1.0 (2)

MedDRA/J ver.22.1, Incidence (%) (number of subjects with the event)

In the long-term treatment study, no severe adverse events occurred at the site applied with the study drug. The applicant considers the safety of difamilast at the site applied with difamilast acceptable.

PMDA's view:
The safety of difamilast at the application site acceptable because no clinically problematic differences were observed in adverse events at the site applied with the study drug between the difamilast and placebo groups; and no severe adverse events occurred at the site applied with difamilast even in the long-term treatment study.

7.R.2.5 Skin infection

The applicant's explanation about skin infection:
Difamilast suppresses activation of immune cells associated with inflammation by inhibiting intracellular PDE4. Based on the finding in a non-clinical pharmacology study using human PBMC that difamilast suppressed production of IL-2 and IFN-γ [see Section 3.1.1.3], difamilast is considered to suppress activation of Th1 cells. Of skin barrier functions, an immune barrier function is provided by cell-mediated immunity of Th1 cells, and thus difamilast may increase the risk of skin infection.

Of the adverse events classified under the system organ class (SOC) "Infections and infestations" in the MedDRA, preferred terms (PTs) involving skin were identified and investigated. For events related to skin infection, Table 61 shows the pooled data in adult patients in phase II and III studies, Table 62 shows similarly pooled data in pediatric patients, and Table 63 shows data in the long-term treatment study.

Table 61. Events related to skin infection (pooled data in adult patients)

Adverse event	Placebo (n = 248)	Difamilast 0.3% (n = 67)	Difamilast 1% (n = 249)
All adverse events	4.0 (10)	4.5 (3)	2.0 (5)
Folliculitis	0.8 (2)	1.5 (1)	0.4 (1)
Herpes simplex	1.2 (3)	0	0.4 (1)
Kaposi's varicelliform eruption	0	0	0.4 (1)
Tinea pedis	0	0	0.4 (1)
Body tinea	0	0	0.4 (1)
Cellulitis	0.8 (2)	1.5 (1)	0
Eczema impetiginous	0	1.5 (1)	0
Paronychia	0.8 (2)	0	0
Furuncle	0.4 (1)	0	0

MedDRA/J ver.22.1, Incidence (%) (number of subjects with the event)

Table 62. Events related to skin infection (pooled data in pediatric patients)

Adverse event	Placebo (n = 107)	Difamilast 0.3% (n = 107)	Difamilast 1% (n = 110)
All adverse events	6.5 (7)	9.3 (10)	7.3 (8)
Molluscum contagiosum	0	0	2.7 (3)
Impetigo	4.7 (5)	5.6 (6)	2.7 (3)
Folliculitis	0 (0)	2.8 (3)	1.8 (2)
Paronychia	0.9 (1)	0.9 (1)	0
Hand-foot-and-mouth disease	0	0.9 (1)	0
Varicella	0.9 (1)	0	0

MedDRA/J ver.22.1, Incidence (%) (number of subjects with the event)

Table 63. Events related to skin infection (long-term treatment study)

Adverse event	Adults	Children		
	Difamilast 1% (n = 166)	Children starting with difamilast 0.3% (n = 144)	Children starting with difamilast 1% (n = 56)	All children (n = 200)
All adverse events	21.7 (36)	36.1 (52)	33.9 (19)	35.5 (71)
Folliculitis	6.0 (10)	6.3 (9)	8.9 (5)	7.0 (14)
Paronychia	4.2 (7)	4.2 (6)	3.6 (2)	4.0 (8)
Herpes simplex	3.0 (5)	0.7 (1)	3.6 (2)	1.5 (3)
Furuncle	1.8 (3)	1.4 (2)	0	1.0 (2)
Cellulitis	1.8 (3)	0	0	0
Impetigo	1.2 (2)	18.1 (26)	8.9 (5)	15.5 (31)
Kaposi's varicelliform eruption	0.6 (1)	1.4 (2)	1.8 (1)	1.5 (3)
Skin infection	0.6 (1)	0.7 (1)	1.8 (1)	1.0 (2)
Hand-foot-and-mouth disease	0.6 (1)	1.4 (2)	0	1.0 (2)
Malassezia infection	0.6 (1)	0	1.8 (1)	0.5 (1)
Skin bacterial infection	0.6 (1)	0	1.8 (1)	0.5 (1)
Fungal paronychia	0.6 (1)	0	0	0
Infected dermal cyst	0.6 (1)	0	0	0
Pustule	0.6 (1)	0	0	0
Pyoderma	0.6 (1)	0	0	0
Skin candida	0.6 (1)	0	0	0
Molluscum contagiosum	0	4.9 (7)	5.4 (3)	5.0 (10)
Varicella	0	1.4 (2)	0	1.0 (2)
Tinea infection	0	0	1.8 (1)	0.5 (1)
Herpes zoster	0	0.7 (1)	0	0.5 (1)

MedDRA/J ver.22.1, Incidence (%) (number of subjects with the event)

Adverse drug reactions of skin infection were not observed in the pooled data in adult patients. In the pooled data in pediatric patients, the concerned reactions were observed in 3.7% (4 of 107) of patients in the difamilast 0.3% group (folliculitis and impetigo in 2 patients each) and 0.9% (1 of 110) of patients in the 1% group (folliculitis) but were not in the placebo group. In the long-term treatment study, adverse drug reactions of skin infection occurred in 0.6% (1 of 166) of adult patients in the difamilast 1% group (folliculitis), 0.7% (1 of 144) of pediatric patients starting with difamilast 0.3%

(folliculitis), and 5.4% (3 of 56) of pediatric patients starting with difamilast 1% (folliculitis, Kaposi's varicelliform eruption, and tinea infection in 1 patient each).

In any of the clinical studies, no severe events related to skin infection occurred. The applicant considers that difamilast is unlikely to have a risk of severe skin infection.

In clinical studies of difamilast, application of difamilast to a site affected by skin infection was not restricted, and information about whether difamilast ointment was topically applied to the site with findings of infection was not collected. Of subjects who had an adverse event of skin infection at the application site but seemed to continue topical application of difamilast, none later experienced worsening of the event. Topical application of difamilast to the skin infection site is considered unlikely to increase the safety concerns.

The applicant considers it unnecessary to raise cautions about use of difamilast in patients with skin infection.

PMDA's view:
PMDA confirmed that in clinical studies, the incidence of skin infection did not tend to be clearly higher in the difamilast group than in the placebo group, and during the long-term treatment, the incidence of skin infection did not tend to increase, and neither serious nor severe events occurred. However, difamilast is an immunosuppressive agent and is thus supposed to have a risk of skin infection. In the clinical studies, adverse drug reactions of skin infection occurred although the incidences were not high. In addition, the clinical studies excluded patients with comorbidity of active viral skin infection and patients with a skin disease precluding appropriate assessment of atopic dermatitis, and the safety of difamilast applied to a skin infection site remained unclear because of omitted collection of the concerned information. The safety of difamilast applied to the skin infection site is therefore not confirmed. Accordingly, the package insert should include a cautionary statement that use on the skin infection site should be avoided wherever possible and information about incidences of skin infection should be continuously collected even after the market launch.

7.R.2.6 Malignant tumor

For apremilast, which is in the same class of PDE4 inhibitors as difamilast, malignant tumor was reported in a clinical study in patients with psoriasis vulgaris, and thus malignant tumor was specified as an important potential risk in the risk management plan (RMP) (Review Report "Otezla Tablets 10 mg and other 2 product items" dated March 24, 2016).

The applicant's explanation about difamilast's risk of malignant tumor:
It cannot be ruled out that apremilast leads to development of malignant tumor by acting on the immune system, but the incidence of malignant tumor in the apremilast group is similar to that in the placebo group in the concerned clinical study and is considered to not exceed the prevalence of malignant tumor in patients with psoriasis, the target disease of apremilast.

For difamilast, in 5 Japanese clinical studies (adult phase II, pediatric phase II, adult phase III, pediatric phase III, and long-term treatment studies), 9 events classified under "Neoplasms benign, malignant and unspecified (incl cysts and polyps)" were observed, of these, 8 events were "Skin neoplasm benign." In the long-term treatment study, diffuse large B-cell lymphoma (DLBCL) occurred in 1 patient, but a causal relationship to difamilast was ruled out for this event. In general, DLBCL is associated with enhanced PDE4B, and inhibition against PDE4B was reported to induce apoptosis through effects of cAMP. Therefore, difamilast, a PDE4 inhibitor, is unlikely to cause DLBCL.

PMDA's view:
Although DLBCL occurred in 1 patient in a clinical study of difamilast, a causal relationship to difamilast was ruled out. In view of this finding and information about PDE4 inhibitors including oral drugs, difamilast's risk of malignant tumor is not high at present.

7.R.3 Clinical positioning

The applicant's explanation about clinical positioning of difamilast:
The standard therapies for atopic dermatitis include pharmacotherapy, skin care, and measures against exacerbating factors, which are appropriately combined according to the severity and patient characteristics. For the pharmacotherapy, topical anti-inflammatory drugs and oral drugs are selected according to the severity and patient characteristics, but the topical anti-inflammatory drugs are mainly used. The "Guidelines for the Management of Atopic Dermatitis 2018 [in Japanese]" edited by the Japanese Dermatology Association, the Japanese Society of Allergology, and Committee for Guidelines for the Management of Atopic Dermatitis (*The Japanese Journal of Dermatology.* 2018;128:2431-502) mainly recommends topical corticosteroids and calcineurin inhibitors. These drugs, however, may cause characteristic adverse drug reactions, requiring careful consideration about the application site and duration of use. For the ointment containing delgocitinib, a JAK inhibitor, approved in January 2020, the position in treatment of atopic dermatitis will be established based on use experience in the future, but adverse drug reactions such as skin infection have been reported.

Difamilast is a PDE4 inhibitor, and difamilast ointment is a new topical agent with a new mechanism of action that is different from those of the conventional topical agents. The clinical studies demonstrated the efficacy of difamilast and indicated no particular safety problems. Therefore, difamilast offers a new treatment option for atopic dermatitis.

In view of the efficacy [see Section 7.R.1] and safety [see Section 7.R.2] of difamilast, PMDA considers that difamilast will provide a new topical treatment option for atopic dermatitis.

7.R.4 Indication

The applicant's explanation about the indication of difamilast:
In clinical practice, difamilast is expected to be used mainly in patients with atopic dermatitis overall as with the other topical agents. The phase III studies included patients with mild to moderate disease (IGA score of 2 or 3), and the long-term treatment study included patients with mild to severe or very severe disease (IGA score of 2 to 4). In the phase III and long-term treatment studies, no problematic

differences were observed in efficacy or safety among subgroups formed by severity [see Sections 7.R.1.3 and 7.R.2.2]. Based on the above, the applicant considered it appropriate to specify the proposed indication of difamilast as “atopic dermatitis.”

The phase III and long-term treatment studies demonstrated the efficacy of difamilast [see Section 7.R.1] and indicated the acceptable safety [see Section 7.R.2], therefore, PMDA considers it possible to specify the indication of difamilast as “atopic dermatitis,” as proposed for approval.

7.R.5 Dosage and administration

The applicant’s explanation about dosage regimen of difamilast:

- For adult patients

With respect to the dosage regimen in adult patients with atopic dermatitis, in the adult phase II study where difamilast 0.3% or 1% ointment was topically applied twice daily, the IGA responder rate at Week 4, the primary endpoint, in the difamilast 1% group was significantly different from that in the placebo group, and results on the other endpoints in this group also demonstrated the efficacy. In the difamilast 0.3% group, on the other hand, the IGA responder rate was not significantly different from that in the placebo group, and results on the other efficacy endpoints did not exceed those in the difamilast 1% group either. In the safety evaluation, neither difamilast 0.3% nor 1% groups presented particular safety problems [see Section 7.1.1]. Based on efficacy and safety results in the adult phase II study, the recommended dose for adults of difamilast 1% would be appropriate. The adult phase III and long-term treatment studies where difamilast 1% ointment was topically applied twice daily demonstrated the efficacy [see Section 7.R.1] and safety [see Section 7.R.2] of difamilast.

Accordingly, the dosage regimen of difamilast in adult patients with atopic dermatitis was specified as follows: Difamilast 1% ointment is topically applied twice daily.

- For pediatric patients

With respect to the dosage regimen in pediatric patients with atopic dermatitis, in the pediatric phase II study (271-102-00002) where difamilast 0.3% or 1% ointment was topically applied twice daily, the IGA responder rate at Week 4, the primary endpoint, in both difamilast 0.3% and 1% groups was significantly different from that in the placebo group, and also both groups showed the efficacy to a similar extent. In the safety evaluation, neither difamilast 0.3% nor 1% groups presented particular safety problems [see Section 7.1.2]. The above results suggested that either 0.3% or 1% might be selected as the recommended dose for pediatric patients, and thus the pediatric phase III study included 2 treatment groups where difamilast 0.3% or 1% ointment was topically applied twice daily. This phase III study demonstrated the efficacy in both difamilast 0.3% and 1% groups, and the EASI75 responder rate and change in the EASI score in the difamilast 1% group exceeded those in the 0.3% group [see Section 7.R.1]. For the safety, no clear differences were observed between the difamilast 0.3% and 1% groups [see Section 7.R.2]. The long-term treatment study was conducted with the usual starting dose of difamilast 0.3%, but the study also allowed the starting dose of difamilast 1% which was considered necessary for the pediatric patient in view of the severity and involvement of skin eruption by the investigator and a dose change from 0.3% to 1% in the pediatric patients with inadequate response. As a result, 72.0% (144 of 200) of patients started with difamilast

0.3% and 28.0% (56 of 200) patients started with difamilast 1%. Of pediatric patients starting with difamilast 0.3%, 68.1% (98 of 144) of patients changed the dose to difamilast 1%, and the IGA responder rate increased from 4.11% (3 of 73 patients) at the time of dose change to 11.94% (8 of 67 patients) 4 weeks after the dose change and reached 20.55% (15 of 73 patients) at the last assessment. For the safety, no adverse events leading to dose reduction from difamilast 1% to 0.3% occurred.

Based on the above, the dosage regimen of difamilast in pediatric patients with atopic dermatitis was specified as follows: Difamilast 0.3% ointment is topically applied twice daily, and for pediatric patients with severe disease or inadequate response, difamilast 1% ointment may be used.

- Maximum amount

In the clinical studies, 10 g per m^2 of body surface area involved was topically applied twice daily, but the maximum amount per application was not specified. Both phase III confirmatory studies in adult and pediatric patients included patients with ≥5% and ≤40% of body surface area involved, while the long-term treatment study included patients with ≥5% of body surface area involved, not specifying the upper limit. As a result, in the long-term treatment study, the mean body surface area involved at baseline in adult patients was 35.5% (median, 29.5%; minimum-maximum, 5.0%-96.0%), and the mean topical amount per application was 3.7 g (median, 3.0 g; maximum, 14.4 g). The incidence and severity of adverse events did not tend to increase with the increasing topical amount per application (Table 64). The applicant considers that difamilast, even if applied to the entire body surface, would hardly raise safety concerns.

Table 64. Incidences of adverse events in adult patients by mean amount per application in the long-term treatment study

		Mean amount of difamilast ointment per application			All adult patients (n = 166)
		≤5 g (n = 120)	>5 g and ≤10 g (n = 39)	>10 g (n = 7)	
Adverse events		75.0 (90)	61.5 (24)	85.7 (6)	72.3 (120)
Severity	Mild	56.7 (68)	48.7 (19)	42.9 (3)	54.2 (90)
	Moderate	15.8 (19)	12.8 (5)	42.9 (3)	16.3 (27)
	Severe	2.5 (3)	0	0	1.8 (3)

Incidence % (number of subjects with event)

In the pediatric patient population overall, the mean body surface area involved at baseline was 32.9% (median, 27.3%; minimum-maximum, 5.0%-98.0%), and in the preschool age subgroup (aged 2-6 years), the mean percent was 34.4% (median, 28.8%; minimum-maximum, 7.5%-94.0%). The mean topical amount of difamilast ointment per application in the pediatric patient population overall was 2.3 g (median, 1.8 g; maximum, 11.9 g), and in the preschool age subgroup, the mean topical amount was 2.0 g (median, 1.6 g; maximum, 7.1 g). The incidence and severity of adverse events did not tend to increase with the increasing topical amount per application (Table 65). The applicant considers that difamilast, even if applied to the entire body surface, would hardly raise safety concerns in the pediatric patient population including the preschool age subgroup in which the patients were small in physique.

Table 65. Incidences of adverse events in pediatric patients by mean amount per application in the long-term treatment study

		Mean amount of difamilast ointment per application						2-6 years (n = 96)	All children (n = 200)
		≤5 g		>5 g and ≤10 g		>10 g			
		2-6 years (n = 91)	Overall (n = 180)	2-6 years (n = 5)	Overall (n = 18)	2-6 years (n = 0)	Overall (n = 2)		
Adverse events		95.6 (87)	89.4 (161)	80.0 (4)	83.3 (15)	-	100 (2)	94.8 (91)	89.0 (178)
Severity	Mild	65.9 (60)	69.4 (125)	40.0 (2)	50.0 (9)	-	0	64.6 (62)	67.0 (134)
	Moderate	29.7 (27)	20.0 (36)	40.0 (2)	33.3 (6)	-	100 (2)	30.2 (29)	22.0 (44)
	Severe	0	0	0	0	-	0	0	0

Incidence % (number of subjects with event); -, Not calculated

However, the maximum amount should be mentioned in the "Precautions Concerning Dosage and Administration" section to raise caution against excessive use of difamilast in clinical practice. The topical amount for up to approximately 60% of the body surface area of a patient with atopic dermatitis irrespective of age, if specified as the maximum amount, would be able to adequately make difamilast available for most of the eligible patients and cover the area requiring the treatment in clinical practice, because ≥80% of subjects in the long-term treatment study had <60% of body surface area involved at baseline. For example, of an adult patient with a standard physique (170 cm, 63 kg), the body surface area is 1.73 m^2, and the topical amount of difamilast ointment required to cover approximately 60% of this area or 1 m^2 is close to 10 g. For school-age pediatric patients with a physique comparable to that of adults, the maximum amount of difamilast ointment would be similar to that for adult patients. Based on the above, the applicant considers it appropriate to caution that the amount of difamilast ointment per application in patients with atopic dermatitis should not exceed 10 g.

PMDA's view:
It is acceptable to apply difamilast 1% ointment to adult patients with atopic dermatitis twice daily and difamilast 0.3% ointment to pediatric patients twice daily as well as to allow use of difamilast 1% ointment in pediatric patients depending on the symptoms in accordance with the dosage regimens in the phase III and long-term treatment studies.

Concerning the maximum amount, the number of patients who topically received >10 g per application in the clinical studies is limited, but adverse events did not tend to increase with the increasing topical amount of difamilast ointment. The applicant explained that the maximum amount of difamilast ointment per application would be specified as 10 g based on the standard body surface area of adults and the baseline involvement in the long-term treatment study, in which approximately 80% of the subjects had <60% of the body surface area involved. PMDA, however, does not consider it appropriate to specify the maximum amount based on the baseline involvement in approximately 80% of the subjects in the long-term treatment study, because this study included patients who had >90% of the body surface area involved or topically received >10 g per application, indicating that a certain number of patients would require topical application of >10 g in clinical settings. On the other hand, preschool age pediatric patients with the body surface area of <1 m^2 would not require 10 g, even if the ointment is topically applied to the entire surface. This aspect also makes the maximum dose of 10 g less reasonable. The maximum amount of 10 g should not be uniformly specified irrespective of the body surface area involved and physique, and the "Precautions Concerning Dosage

and Administration" section in the package insert should include an advisory statement that an appropriate amount of difamilast ointment is 10 g per 1 m^2 as specified in the clinical study.

In addition, the "Precautions Concerning Dosage and Administration" section in the package insert should also include the following advisory statements: If skin eruption is not improved after 4 weeks of treatment with difamilast 1% ointment, treatment should be discontinued; or if the symptom is improved, the necessity of the continued treatment should be considered to ensure that difamilast 1% ointment would be switched to 0.3% ointment in pediatric patients where applicable and that difamilast would not be indiscreetly used for a long time.

Based on the above, PMDA considers that the dosage and administration should be modified as shown below; and the "Precautions Concerning Dosage and Administration" section should include advisory statements about an appropriate topical amount per application and judgement of the continued treatment.

Dosage and Administration
The usual adult dosage is an appropriate amount of the 1% product applied to the affected area twice daily.

The usual pediatric dosage is an appropriate amount of the 0.3% product applied to the affected area twice daily. According to the patient's condition, an appropriate amount of the 1% product may be applied to the affected area twice daily.

7.R.6 Use of difamilast in combination with other therapies

The applicant's explanation about the use of difamilast in combination with other therapies for atopic dermatitis:
In the phase III study, combination therapies for atopic dermatitis were prohibited, but in the long-term treatment study, concomitant topical corticosteroids, tacrolimus ointment, or biological drugs were allowed when they were necessary for the treatment owing to worsened symptoms. On the other hand, concomitant systemic corticosteroids, immunosuppressive drugs, or antimetabolites were prohibited.

In patients receiving difamilast concomitantly with topical corticosteroids or tacrolimus ointment, no problematic safety trends were observed [see Section 7.R.2.2]. During the long-term treatment study, delgocitinib ointment was approved, but no subjects used this drug. In addition, there were neither subjects who concomitantly received dupilumab (genetical recombination), human anti-human IL-4/13 receptor monoclonal antibody, nor subjects who concomitantly received phototherapy.

Difamilast in combination with dupilumab (genetical recombination), systemic corticosteroids, immunosuppressive drugs, or antimetabolites would not raise concerns about interactions and is considered to have a limited effect on the safety. With respect to phototherapy, the foreign phototoxicity study (271-12-212) and photoallergy study (271-12-213) conducted in healthy adults indicated that difamilast had neither phototoxicity nor photoallergy, raising no safety concerns.

Based on the above, the applicant considers it unnecessary to place some restrictions on or raise cautions about difamilast in combination with the other therapies for atopic dermatitis. However, because data on such combination therapy in clinical studies are limited, information about the safety of difamilast used concomitantly with the other therapies should be continuously collected through post-marketing surveillance.

PMDA's view:
In view of the applicant's explanation, it is not necessary to place restrictions on difamilast in combination with the conventional treatment for atopic dermatitis, provided that individual precautions of the concomitant therapy are followed. In addition, PMDA accepted the applicant's explanation that information about the safety of difamilast used concomitantly with the other therapies should be continuously collected through post-marketing surveillance.

7.R.7 Post-marketing investigations

The applicant's explanation about post-marketing investigations:
With respect to difamilast in combination with other drugs for atopic dermatitis, the safety information is not sufficient because of limited experience with the combination therapy in the clinical studies up to now. In particular, it cannot be ruled out that difamilast in combination with other drugs for atopic dermatitis may cause development and worsening of skin infection, and the relevant information is not sufficient for evaluation. Skin infection during concomitant use with drugs for atopic dermatitis will be specified as important missing information under safety specifications in the RMP.

The applicant will implement a post-marketing database survey using a medical information database that can provide information about patients receiving prescription of difamilast as well as terms of skin infection–related injuries and diseases and drugs used for treatment. Detailed procedures and other matters for collecting the information are under consideration.

PMDA considers that the applicant should develop the plan so that they can collect information about skin infection during use of difamilast, not limited difamilast in combination with the other drugs for atopic dermatitis, and investigate impacts of concomitant use status and combination therapies.

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 5.3.5.1-03, CTD 5.3.5.1-04, and CTD 5.3.5.2-02) 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 difamilast has efficacy in the treatment of atopic dermatitis and acceptable safety in view of its benefits. Difamilast is clinically meaningful because it offers a new treatment option for atopic dermatitis.

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

Review Report (2)

August 4, 2021

Product Submitted for Approval

Brand Name	Moizerto Ointment 0.3% Moizerto Ointment 1%
Non-proprietary Name	Difamilast
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	September 28, 2020

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy and safety

PMDA's conclusions presented in Sections "7.R.1 Efficacy" and "7.R.2 Safety" in the Review Report (1) were supported by the expert advisors at the Expert Discussion.

1.2 Indication

PMDA's conclusion presented in Section "7.R.4 Indication" in the Review Report (1) was supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA accepted the proposed indication of "atopic dermatitis."

1.3 Dosage and administration

PMDA's conclusion presented in Section "7.R.5 Dosage and administration" in the Review Report (1) was supported by the expert advisors at the Expert Discussion. In addition, the following comments were raised from the expert advisors:

- The amount per application area is not usually specified in clinical settings, and thus it is desirable to provide specific information using information materials to help determine the amount to be applied in clinical settings.

- The clinical studies have not evaluated occlusive dressing or combined application of difamilast and another drug. The efficacy and safety of these techniques remain unclear, but they are widely used in clinical settings. It is desirable to discuss whether to issue alerts regarding these techniques.

PMDA's view based on the comments from the Expert Discussion:
- Using information materials, the applicant should inform healthcare professionals and patients about the appropriate amount to be applied per area of skin eruption in an easy-to-understand manner.
- There are no clinical study results that allow assessment of the appropriateness of occlusive dressing and combined application of difamilast and another drug. From a viewpoint of safety, however, there is no evidence that supports restrictions of use of these techniques, and thus it is not necessary to prohibit them. The Clinical Studies section in the package insert should state that the clinical studies have not evaluated the safety and efficacy of occlusive dressing or combined application of difamilast and another drug.

PMDA instructed the applicant to take actions on the above, and the applicant replied that they would take the actions appropriately. In addition, PMDA instructed the applicant to modify the Dosage and Administration and Precautions Concerning Dosage and Administration sections in the package insert as shown below. The applicant responded appropriately. PMDA accepted the applicant's response.

Dosage and Administration
The usual adult dosage is an appropriate amount of the 1% product applied to the affected area twice daily.

The usual pediatric dosage is an appropriate amount of the 0.3% product applied to the affected area twice daily. According to the patient's condition, an appropriate amount of the 1% product may be applied to the affected area twice daily.

Precautions Concerning Dosage and Administration
1. An appropriate amount per 0.1 m^2 of area of skin eruption is approximately 1 g.
2. If symptoms are not improved after 4 weeks of treatment with the 1% product, discontinue the use of the product.
3. If symptoms are improved, consider whether to continue treatment in order to avoid using the product unthinkingly for a long time.
4. If the 1% product is used for a pediatric patient and symptoms are improved, consider a switchover to the 0.3% product.

1.4 Risk management plan (draft)
PMDA's conclusion presented in Section "7.R.7 Post-marketing investigations" in the Review Report (1) was supported by the expert advisors at the Expert Discussion.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for difamilast should include the safety specifications presented in Table 66, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 67.

Table 66. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Skin infection	• Malignant tumor • Embryo-fetal toxicity	• None
Efficacy specification		
• Not applicable		

Table 67. 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 • Post-marketing database survey [skin infection]	• Disseminate data gathered during early post-marketing phase vigilance • Prepare and distribute materials for healthcare professionals • Prepare and distribute materials for patients

1.5 Clinical development of the product for pediatric patients aged <2 years

The applicant is planning a clinical study of difamilast in pediatric patients with atopic dermatitis aged <2 years.

PMDA's conclusion:

In light of the prevalence of atopic dermatitis in children aged <2 years, difamilast should be developed for pediatric patients aged <2 years, and thus the applicant's development plan to conduct a clinical study in pediatric patients aged <2 years is appropriate.

2. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved after modifying the proposed indication and the dosage and administration as shown below, with the following approval condition. 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 powerful drug, and the drug product is not classified as a poisonous drug or a powerful drug.

Indication

Atopic dermatitis

Dosage and Administration

The usual adult dosage is an appropriate amount of the 1% product applied to the affected area twice daily.

The usual pediatric dosage is an appropriate amount of the 0.3% product applied to the affected area twice daily. According to the patient's condition, an appropriate amount of the 1% product may be applied to the affected area twice daily.

Approval Condition

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

Appendix

List of Abbreviations

A/G	Albumin/globulin
ALP	Alkaline phosphatase
APTT	Activated partial thromboplastin time
AUC	Area under the plasma concentration-versus-time curve
BCRP	Breast cancer resistance protein
C_{max}	Maximum concentration
CQA	Critical quality attribute
CTD	Common technical document
CYP	Cytochrome P450
DMSO	Dimethylsulfoxide
EASI	Eczema Area and Severity Index
F1	First filial generation
FAS	Full analysis set
GC	Gas chromatography
GCP	Good clinical practice
Hb	Hemoglobin
HEK293 cell	Human embryonic kidney cell line 293
Ht	Hematocrit
IC_{50}	Half maximal inhibitory concentration
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use
ICH Q1E Guideline	"Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
ICH Q3B (R2) Guideline	"Guideline on Impurities in New Drug Products" (PFSB/ELD Notification No. 0703004 dated July 3, 2006)
IGA	Investigator's global assessment
IR	Infrared absorption spectroscopy
JP	The Japanese Pharmacopoeia
JAK	Janus kinase
LC	Liquid chromatography
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
MATE	Multidrug and toxin extrusion
MDCK cell	Martin-Darby canine kidney cell
MDR	Multidrug resistance
mEASI	modified Eczema area and severity index
MedDRA/J	Medical dictionary for regulatory activities Japanese version
MS	Mass spectrometry
NC	Not calculated
NMR	Nuclear magnetic resonance spectroscopy
NZW	New Zealand White
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PDE	Phosphodiesterase
PFC	Plaque forming cell
P-gp	P-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred term in the medical dictionary for regulatory activities
PUVA	Psoralens plus UVA
QTPP	Quality target product profile
SD	Sprague Dawley

SOC	System organ class in the medical dictionary for regulatory activities
$t_{1/2}$	Elimination half-life
t_{max}	Time to reach maximum concentration
UVA	Ultraviolet A
UV/VIS	Ultraviolet-visible absorption spectroscopy